Arrhythmia/Electrophysiology

Diagnosis of Sleep-Related Breathing Disorders by Visual Analysis of Transthoracic Impedance Signals in Pacemakers

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Background—Minute ventilation sensors of cardiac pacemakers measure ventilation by means of transthoracic impedance changes between the pacemaker case and the electrode tip. We investigated whether this technique might detect sleep-related breathing disorders.

Methods and Results—In 22 patients, analog waveforms of the transthoracic impedance signal measured by the pacemaker minute ventilation sensor over the course of a night were visualized, scored for apnea/hypopnea events, and compared with simultaneous polysomnography. Analysis of transthoracic impedance signals correctly identified the presence or absence of moderate to severe sleep apnea (apnea/hypopnea index, AHI >20 h⁻¹) in all patients (receiver operating characteristics, ROC=1.0). The ROC for AHI scores of ≥5 h⁻¹ and ≥10 h⁻¹ showed an area under the curve of 0.95, P<0.005, and 0.97, P<0.0001, respectively. Accuracy over time assessed by comparing events per 5-minute epochs was high (Cronbach α reliability coefficient, 0.85; intraclass correlation, 0.73). Event-by-event comparison within ±15 seconds revealed agreement in 81% (κ, 0.77; P<0.001).

Conclusions—Detection of apnea/hypopnea events by pacemaker minute ventilation sensors is feasible and accurate compared with laboratory polysomnography. This technique might be useful to screen and monitor sleep-related breathing disorders in pacemaker patients. (Circulation. 2004;110:2562-2567.)

Key Words: pacemakers ▪ diagnosis ▪ sleep apnea syndromes

The estimated prevalence of sleep apnea is 2% to 4% in the general population1 and up to 50% in patients with congestive heart failure.2 Because sleep-disordered breathing (SDB) is associated with a number of cardiovascular diseases,3 including hypertension,4 heart failure,5,6 and coronary artery disease,7 it may be frequent in patients with implanted pacemakers or intracardiac defibrillators. However, many patients with SDB remain undiagnosed.

Diagnosis of SDB requires multichannel recordings in the sleep laboratory. One method to measure respiration is impedance pneumography.8,9 After injection of an electrical transthoracic current, the changes in electric conductance (transthoracic impedance) are measured, which depend on the ratio of gas/fluid volumes. This principle is used in minute ventilation sensors of cardiac pacemakers. In a previous study, we have shown that impedance minute ventilation measured by pacemaker sensors is closely correlated with oral-nasal airflow.10 Consequently, the sensor might also detect disturbances of ventilation during sleep. This study was designed to test the feasibility of SDB detection on the basis of a visual analysis of transthoracic impedance waveforms measured by the pacemaker minute ventilation sensor. Analysis of SDB by pacemakers might be an ideal tool to screen for sleep apnea and monitor treatment effects of cardiac pacing.11,12 As reference, we used simultaneous clinical standard multichannel polysomnography.13

Methods

Study Design

This study included 22 patients at 2 institutions who provided informed written consent approved by the local medical ethics committees and had had a rate-responsive pacemaker with a minute ventilation sensor (Medtronic Kappa 400) implanted at least 6 months earlier (Table 1). Sleep apnea had been diagnosed previously in 2 patients. The rate-response function was programmed “on” to activate the minute ventilation sensor. Patients reported to the sleep laboratory at 8 PM and were instrumented for a standard overnight sleep study. The lights were turned off between 10 and 11 PM. Each center scored the clinical polysomnography, and 1 investigator analyzed the transthoracic impedance tracing data in a blinded manner.

Measurements

Polysomnographic recording systems (Institution B Alice 4, Respiration; Vangard, Vangard Inc) included derivations of electroen-
TABLE 1. Patient Characteristics (n=22)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>14/8</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>65.6±13.4</td>
</tr>
<tr>
<td>Body mass index, kg/m² (range)</td>
<td>28±5.8 (20–41)</td>
</tr>
<tr>
<td>Ejection fraction, % (range)</td>
<td>47±16 (15–60)</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>18 (81)</td>
</tr>
<tr>
<td>Valvular</td>
<td>7</td>
</tr>
<tr>
<td>CAD</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>HOCM</td>
<td>1</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>1</td>
</tr>
<tr>
<td>AV node ablation + NICM</td>
<td>2</td>
</tr>
<tr>
<td>Sternotomy because of previous open-heart surgery, n (%)</td>
<td>7 (32)</td>
</tr>
</tbody>
</table>

Pacemaker lower rate of
- 50/min                                     1
- 60/min                                     8
- 70/min                                     11
- 75/min                                     1
- 80/min                                     1

Impedance of the MV-sensor electrode        525±266 Ω
Location of MV-sensor electrode, atrial/ventricular 20/2
Epworth sleepiness scale (range)            7.6±5.4 (0–16)

Previous diagnosis of sleep apnea, n (%)   2 (9)

CAD indicates coronary artery disease; HOCM, hypertrophic obstructive cardiomyopathy; and MV, minute ventilation.

cephalogram (C3A2, C4A1), electro-oculogram (LEA2, REA1), submental electromyogram, ECG, pulse oximetry, rib cage and abdominal excursions by strain gauges, nasal pressure recording for measurement of ventilation,14 microphones, body position by accelerometer, and audiovisual monitoring by a low-light camera.15 An electrical signal for time synchronization of the recording systems was set manually at the beginning of the recording.

The transthoracic impedance of the minute ventilation sensor is obtained by injecting a biphasic current pulse (1 mA, 15 μs, 16 Hz) into the chest cavity via the proximal electrode of the pacemaker lead and measuring the resulting voltage change between the device case and the distal electrode at a 16-Hz sampling rate. The raw signal was telemetered by use of a modified DR-180 Holter monitor (Rozinn Medical, model RZ152, modified by Northeast Monitoring), filtered with a bandpass from 0.05 to 0.8 Hz, processed, and visualized by use of a commercially available software (MatLab, MathWorks). The processed transthoracic impedance was visualized as an analog waveform and scored manually for apnea/hypopnea events and compared with polysomnographic recordings (Figure 1).

Data Analysis

Different blinded investigators scored polysomnographic and transthoracic impedance tracings. A hypopnea/apnea event on the transthoracic impedance signal was defined by an amplitude decrease >50% from baseline for at least 10 seconds’ duration and was compared with polysomnographic recordings. According to previously published guidelines, a hypopnea/apnea event had to fulfill 1 of the 2 following criteria for at least 10 seconds: (1) a clear decrease of >50% from baseline in the amplitude of a valid measure of breathing, ie, nasal pressure swings (or excursions of the rib cage and abdominal strain-gauge signals if nasal pressure swings were absent because of oral breathing), and (2) an amplitude reduction of a valid measure of breathing during sleep that did not reach 50% but was associated with either an oxygen desaturation of >3% or an arousal.16 The apnea/hypopnea index (AHI) was calculated as the number of such events per hour.

Agreement of the 2 methods was assessed by comparing AHI indices according to Bland and Altman.6 Because 2 different recording systems were used (Vanguard or Alice 4 and Holter-DR), time correlation was not precise within seconds. Therefore, the reliability of the method over the entire sleep study duration was assessed by comparing 5-minute epochs with any events as well as the number of apnea/hypopnea events per 5-minute epoch.

In addition, an event-by-event analysis was performed to compare the transthoracic impedance signal to a single-channel reference signal (nasal pressure only) without use of the oxygen saturation criterion. Only tracings from 1 institution experienced in validation of nasal pressure recordings were of sufficient quality for this single-channel analysis.14 For both methods, events were defined by a decrease in amplitude of at least 50% and were considered identical when occurring within a ±15-second window.

Statistical Analysis

Continuous variables are expressed as mean±SD. Differences on AHI scorings between the 2 methods were assessed according to Cohen’s k statistics. Epoch-by-epoch apnea/hypopnea scores from these 2 different methods were compared by intraclass correlation coefficients. Receiver operating characteristic (ROC) curves were used to test the diagnostic accuracy of impedance signal analysis for the detection of sleep apnea syndrome at various AHI cutoffs.14 Statistical significance was assumed at a value of P<0.05. All analyses were performed by use of a commercially available statistical package (SPSS for Windows 9.0).

Results

The mean polysomnographic recording duration was 8.3±0.1 hours. The mean sleep time was 5.3±1.4 hours. Visual analysis of impedance signal waveforms was feasible in all patients (Figure 1) for 6.2±1.8 hours. However, in 2 patients, telemetry errors led to technical loss of maximal 40% of total time. The patients had a wide range of AHI, from 0 to 79.2 h−1 (mean, 24±21 h−1) and reported an Epworth sleepiness score of 7.6±5.4 (Table 1). A significant number of apnea/hypopnea events (AHI >5/min) was found in 17 of 22 (80%) patients and was correctly diagnosed in 16 of 17 (94%) on impedance signal scoring (Table 2). The diagnosis of moderate to severe SDB (AHI >20 h−1) was made in 12 patients (45%) and was identified with 100% sensitivity and specificity on impedance signal scoring (Figure 2). Among these 12 patients, 10 were newly diagnosed with SDB and 4 had not reported typical symptoms. The severity of SDB was not related to the degree of left ventricular dysfunction (Table 2).

Comparison of the Two Methods

Compared with clinical polysomnographic scoring, the analysis of the transthoracic impedance signal waveform showed a significant correlation of AHI (Pearson’s r=0.869, P<0.001, Figure 2). The difference of AHI between the 2 methods (ie, the bias) was on average −1.5±0.6 h−1 (P<0.05) and was increasing with higher AHI (Figure 3). The limits of agreement of AHI (2 SD of the mean difference) were ±20.8 h−1, but when the 3 patients with the highest AHI by polysomnography (79, 57, and 46 h−1) were omitted from the analysis, the limits of agreement were 0±12.2 h−1.

Diagnostic accuracy at various cutoff levels was evaluated by ROC. The area under the curve for detection of an AHI of
≥5 h⁻¹ was 0.95±0.05, P<0.005. The corresponding areas for an AHI of ≥10 h⁻¹ and ≥15 h⁻¹ were both 0.966±0.37, P<0.0001. For the cutoff level of AHI ≥20 h⁻¹, all patients were correctly classified by the pacemaker (ROC=1.0, 100% specificity and sensitivity).

A total of 1637 five-minute epochs were analyzed in all patients over the entire recording time. Of those, 803 epochs included at least 1 apnea/hypopnea event on PSG. The transthoracic impedance signal correctly identified 724 epochs (90%), accounting for a sensitivity of 82±21%, a specificity of 74±18%, and a positive and negative predictive value of 76%. The measure of agreement on Cohen’s κ statistics was 0.69±0.018 (P<0.001). The intraclass correlation coefficient of AHI scores per 5-minute epoch was 0.73 (P<0.001). This suggests that 73% of the AHI variation per 5-minute epoch on impedance scoring was related to variation in the reference polysomnographic scoring.

On the basis of polysomnographic findings, the differentiation between predominantly obstructive versus central type of SDB was made in 15 patients (Table 2). Identification of apnea/hypopnea events on transthoracic impedance analysis was feasible for both central and obstructive events; however, the differentiation between the 2 types of events was not possible. When matching apnea/hypopnea events per 5-minute epoch, the transthoracic impedance analysis was more sensitive to central than obstructive epochs (93% versus 83%, P=NS) but with a lower specificity (67% versus 71%, P=NS). Events were more likely to be overscored in central...
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TABLE 2. Detection of Hypopnea/Apnea on Pacemaker Impedance Signal Analysis Compared With Polysomnographic Recordings

<table>
<thead>
<tr>
<th>No.</th>
<th>Institution</th>
<th>Duration, h</th>
<th>AHI PSG</th>
<th>AHI PM</th>
<th>Difference in AHI</th>
<th>Predominant Pattern</th>
<th>BMI, kg/m²</th>
<th>EF</th>
<th>Indication for PM</th>
<th>Thoracotomy</th>
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<td>1</td>
<td>B</td>
<td>4.8</td>
<td>79.2</td>
<td>48.4</td>
<td>−30.8</td>
<td>Obstructive</td>
<td>NA</td>
<td>NA*</td>
<td>SND</td>
<td>−</td>
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<tr>
<td>2</td>
<td>B</td>
<td>5.3</td>
<td>56.6</td>
<td>33.2</td>
<td>−23.4</td>
<td>Obstructive</td>
<td>25</td>
<td>0.25</td>
<td>AVB</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>4.9</td>
<td>45.8</td>
<td>60.2</td>
<td>14.4</td>
<td>Central</td>
<td>35</td>
<td>0.29</td>
<td>SND+AVB</td>
<td>−</td>
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<tr>
<td>4</td>
<td>B</td>
<td>4.2</td>
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<td>31.2</td>
<td>−10.3</td>
<td>Obstructive</td>
<td>39</td>
<td>0.55</td>
<td>SND</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>7.6</td>
<td>40.5</td>
<td>39.6</td>
<td>−0.9</td>
<td>Central</td>
<td>28</td>
<td>0.40</td>
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<tr>
<td>6</td>
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<td>38.9</td>
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<td>33</td>
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<td>B</td>
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<td>35.4</td>
<td>37.7</td>
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<td>27</td>
<td>0.2</td>
<td>SND</td>
<td>−</td>
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<tr>
<td>8</td>
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<td>25</td>
<td>0.35</td>
<td>AVB</td>
<td>−</td>
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<tr>
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<td>26.6</td>
<td>−3.5</td>
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<td>30</td>
<td>0.6</td>
<td>AVB</td>
<td>−</td>
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<tr>
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<td>30.9</td>
<td>2.3</td>
<td>Obstructive</td>
<td>25</td>
<td>0.6</td>
<td>AVB</td>
<td>−</td>
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<td>22.1</td>
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<td>26</td>
<td>0.65</td>
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<tr>
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<td>41</td>
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<td>AVB</td>
<td>−</td>
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<td>25</td>
<td>0.6</td>
<td>AVB</td>
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</tr>
<tr>
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<td>7.9</td>
<td>18.0</td>
<td>10.1</td>
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<td>0.6</td>
<td>SND+AVB</td>
<td>+</td>
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<td>13.9</td>
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<td>AVB</td>
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<td>9.8</td>
<td>4.4</td>
<td>Central</td>
<td>23</td>
<td>0.55</td>
<td>SND</td>
<td>+</td>
</tr>
<tr>
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<td>A</td>
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<td>3.8</td>
<td>4.1</td>
<td>0.3</td>
<td>Central</td>
<td>22</td>
<td>0.55</td>
<td>SND</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>A</td>
<td>7.0</td>
<td>3.1</td>
<td>14.0</td>
<td>10.9</td>
<td>Central</td>
<td>22</td>
<td>0.15</td>
<td>SND</td>
<td>−</td>
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<tr>
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<td>6.8</td>
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<td>Central</td>
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<td>SND</td>
<td>−</td>
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<tr>
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<td>7.7</td>
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<td>Central</td>
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<td>0.60</td>
<td>AVB</td>
<td>−</td>
</tr>
<tr>
<td>Average</td>
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<td>6.2</td>
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<td>22.5</td>
<td>−1.5</td>
<td>Central</td>
<td>27.5</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>±1.8</td>
<td>±21</td>
<td>±16</td>
<td>±11</td>
<td></td>
<td></td>
<td>±6</td>
<td>±16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No EF available; no history of heart disease other than SND.

PSG indicates polysomnography; BMI, body mass index; PM, pacemaker; AHI, apnea/hypopnea index; SND, sinus node dysfunction; AVB, atrioventricular block; and EF, ejection fraction.

SDB and underscored in obstructive SDB (mean AHI difference, 5.4 ± 7.9 versus 6.9 ± 11.6, P < 0.05). The lowest correlation was found in patient 19. This patient had emphysema with a predominantly abdominal breathing pattern while the atrial lead was used for minute ventilation sensing. Another problem was abrupt changes in the signal-to-noise ratio during changes of sleeping position to a certain posture, such as the lateral decubitus position on the side of the device implant. In 2 patients, the impedance signal was often interrupted because of telemetry errors caused by body movements, and ~40% of their sleep study had to be excluded. The accuracy of the transthoracic impedance signal analysis was not related to the body mass index of the patients or the electrode impedance of the sensing pacemaker lead.

To compare impedance tracings to a single-channel respiration tracing without use of the oxygen saturation criterion, the identification and matching of single events was performed referencing to nasal airflow only. Because of technical reasons, this comparison could be performed only at 1 institution. Of 1276 events on nasal pressure tracings, 1033 (81%) were identified within ±15 seconds on impedance tracings (223 were false-positive and 5775 were true-negative 30-second intervals; sensitivity, 81%; specificity, 52%; positive predictive value, 82%; negative predictive value, 95%), leading to an agreement of 0.77 on κ statistics.

Discussion

Main Findings

This study demonstrates the usefulness of the transthoracic impedance signal recorded by pacemaker minute ventilation sensors to detect pauses and transient reductions in ventilation during sleep. The apnea/hypopnea events identified by analysis of the pacemaker signal led to the identification of 94% of patients with an AHI > 5 and to the correct diagnosis of moderate to severe sleep apnea (AHI > 20 h⁻¹) with 100% sensitivity and specificity.

The correlation between AHI derived from impedance signal analysis and polysomnography was 0.87 (P < 0.001, Figure 2), and precision decreased only in 3 patients with AHI > 40. Excluding these patients, the bias of AHI was 0 ± 12 h⁻¹. The measure of agreement between the 2 methods was 0.7 on κ statistics, which is similar to other home-based PSG recording systems and satisfactory for clinical screening purposes and for monitoring treatment effects. The intraclass correlation coefficient of 0.73 indicates that 73% variation in apnea/hypopnea scores per 5-minute epoch during the entire sleep study was related to variation in reference PSG scores.
Technical Aspects

Analog waveforms of transthoracic impedance signals measured by pacemaker minute ventilation sensors reflect changes in thoracic geometry and fluid/gas volume relationship similar to impedance pneumography. The technical problems of impedance pneumography include changes in skin electrical conductivity. The pacemaker has the advantage of using stable internal electrodes with a constant surface, and its correlation to measured ventilation has been excellent. A sampling rate of 16 Hz allows adequate tracking of respiration on an analog waveform. The raw signal reflecting changes in intrathoracic gas volume is a linear dimension, whereas the first derivative would be a surrogate of a flow signal, ie, of changes in volume over time reflecting ventilation, which was preferable for visual analysis. Transthoracic impedance signals are not a surrogate of respiratory inductive plethysmography by thoracic or abdominal sensors but rather of ventilation itself. Therefore, the differentiation between central and obstructive events cannot be made, because the ventilation is decreased in both. For the same reason, however, detection of SDB was possible in both patients with predominantly central and obstructive SDB.

The results of an event-by-event comparison referencing to nasal pressure tracings showed that more than 80% of episodes identified by both methods were identical. Thus, a declining amplitude in impedance signal waveforms actually corresponds to a simultaneous decrease in ventilation visualized on nasal airflow.

Clinical Implications

This method could be used for screening and monitoring sleep-related breathing disorders in patients having a rate-responsive pacemaker with a minute ventilation sensor. The ROC curves starting at 0.95 for AHI >5 h⁻¹ and reaching 1.0 for AHI >20 h⁻¹ indicate sufficient accuracy in detecting and excluding SDB. The development of automatic detection algorithms will allow screening of pacemaker patients, which needs to be tested in larger patient series. Because the transthoracic impedance signal is measured constantly when the minute ventilation sensor is programmed on, SDB might be detected incidentally during routine pacemaker follow-up. When monitoring of sleep-related breathing disorders becomes feasible in pacemaker patients, the therapeutic effect of different atrial pacing algorithms can be assessed. Finally, in patients with congestive heart failure and intracardiac defibrillators or pacemakers, periodic respiration during daytime (Cheyne-Stokes respiration) could be detected, providing important independent prognostic information. This monitoring could be used to guide heart failure therapy either by continuous positive airway pressure or, more elegantly, by atrial and biventricular pacing algorithms. Thus, the present study suggests the potential for novel applications of pacemaker technology in screening, monitoring, and treatment of sleep-related breathing disorders.

Limitations

The main limitation of this feasibility study is the small number of patients with a high prevalence of SDB. Larger studies are under way to confirm these results by use of automatic download and detection algorithms. We did not differentiate between hypopnea and apnea events, because the physiological consequences are similar. Impedance waveforms were scored false-positive in central events or periodic respiration without desaturation, when the patient was lying on the side of pacemaker implant. Abrupt changes in signal-to-noise ratio were found when changes in sleeping position directed ventilation to the lung opposite to the pacemaker implant side. We also encountered this problem...
when calibrating the minute ventilation sensor in different postures. An autocalibration algorithm guided by the activity sensor might overcome this issue.

In this study, we analyzed only effective sleep time diagnosed on polysomnography. In clinical application, sleep time might not be directly available from pacemaker information and might have to be retrieved from the patient’s diary. Alternatively, we have proposed an algorithm using mechanical activity variance for the detection of sleep, which could be used for automatic detection of resting periods.

Technical Limitations
Because we used 2 different recording systems, the polysomnograph and the DR 180 Holter, time synchronization was performed manually. Major time correlation errors were generated by data filtering and processing in 2 different systems at 1 institution. However, matching the number of episodes per 5-minute epoch over the entire registration period, which obtained similar results from both institutions, compensated for this issue.

The cardiac activity on transthoracic impedance signals can be seen in Figure 1 and needs to be filtered for automatic detection. In 2 patients, major parts of the recordings were excluded because of Holter telemetry errors caused by body movements. This problem will be resolved by future internal recording storage and download software.

Conclusions
Transthoracic impedance signals from pacemaker minute ventilation sensors can be used for detection and quantification of hypopnea/apnea events. The agreement with reference polysomnographic scorings is promising for future application in screening and monitoring of sleep-related breathing disorders. This study opens a wide field of applications for future pacemaker generations in various groups of patients.

Disclosure
Christoph Scharf has received research support from Medtronic; Yong K. Cho is an employee of Medtronic; and Bruce L. Wilkoff has received honoraria for speaking engagements and research for and is an advisor to Medtronic.

References
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Christoph Scharf, Yong K. Cho, Konrad E. Bloch, Corinna Brunckhorst, Firat Duru, Kryzstof Balaban, Nancy Foldvary, Lynn Liu, Richard C. Burgess, Reto Candinas and Bruce L. Wilkoff

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