A pacemaker transthoracic impedance sensor with an advanced algorithm to identify severe sleep apnea: The DREAM European study

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BACKGROUND Sleep apnea (SA) is associated with cardiovascular diseases and is highly prevalent in patients with pacemakers (PMs).

OBJECTIVE To validate a transthoracic impedance sensor with an advanced algorithm (sleep apnea monitoring) for identifying severe SA.

METHODS Patients with indications for PM (VVI/DDD) were enrolled regardless of symptoms suggesting SA. Severe SA diagnosis was acknowledged when the full polysomnography gave an apnea-hypopnea index (PSG-AHI) of $\geq$30 events/h. The PSG-AHI was compared with the respiratory disturbance index evaluated by the SAM algorithm (SAM-RDI) compiled from the device during the same diagnosis night, and the performance of the device and the SAM algorithm was calculated to identify patients with severe SA. The agreement between methods was assessed by using Bland and Altman statistics.

RESULTS Forty patients (mean age 73.8 $\pm$ 19.1 years; 67.5% men; body mass index 27.7 $\pm$ 4.4 kg/m^2) were included. Severe SA was diagnosed by PSG in 56% of the patients. We did not retrieve SAM-RDI data in 14% of the patients. An optimal cutoff value for the SAM-RDI at 20 events/h was obtained by a receiver operator characteristic curve analysis, which yielded a sensitivity of 88.9% (95% confidence interval [CI] 65.3%–98.6%), a positive predictive value of 88.9% (95% CI 65.3%–98.6%), and a specificity of 84.6% (95% CI 54.6%–98.1%) (n = 31). The Bland-Altman limits of agreement for PSG-AHI (in events per hour) were [−14.1 to 32.4].

CONCLUSION The results suggest that an advanced algorithm using PM transthoracic impedance could be used to identify SA in patients with PMs outside the clinic or at home.

KEYWORDS Bradycardia; Pacemaker; Minute ventilation; Sleep apnea; Sleep apnea diagnosis

ABBREVIATIONS **CI** = confidence interval; **NPV** = negative predictive value; **PM** = pacemaker; **PPV** = positive predictive value; **PSG** = polysomnography; **PSG-AHI** = apnea-hypopnea index evaluated by polysomnography; **SA** = sleep apnea; **SAM** = sleep apnea monitoring; **SAM-RDI** = respiratory disturbance index evaluated by the sleep apnea monitoring algorithm

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Introduction

Sleep apnea (SA) is common in middle-age general population, and its prevalence increases up to 20% above 70 years.[1] A great number of clinical prospective cohorts and epidemiological studies demonstrated that obstructive SA constitutes an independent risk factor to cardiovascular morbidities and mortality. Obstructive SA is now implicated as a risk factor for hypertension, stroke, coronary artery disease, congestive heart failure, and arrhythmias.[2,3] SA has been proposed to be causally related to arrhythmias and sudden cardiac death.[4,5] A high prevalence of SA in patients with cardiac implants[6] requires a specific diagnosis strategy

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because SA recognition might represent a potential therapeutic target for reducing occurrence and recurrence of arrhythmia.

Patients referred for SA diagnosis usually present with associated symptoms such as snoring, apneas, and/or excessive daytime sleepiness. Patients with cardiovascular disorders are frequently nonsleepy and less symptomatic.[6,7] Appropriate screening/diagnosis tools are lacking or have not been validated in these at-risk populations. Up to now, polysomnography (PSG) remains the "gold standard" to diagnose SA but is challenged by waiting lists of sleep laboratories and high related costs.[8] Rate-responsive pacemakers (PMs) use minute ventilation sensors to adjust heart rate and have demonstrated the capability to detect breathing variations by using transthoracic impedance measurements. Previous studies have suggested to use this information as a screening tool for detecting SA.[9–11] The primary goal of the DREAM study was to assess the accuracy of a novel advanced algorithm using transthoracic impedance and minute ventilation (sleep apnea monitoring [SAM] algorithm) to detect severe SA in unselected population of bradycardia patients with newly implanted PMs. The validation of the SAM algorithm was performed against full sleep studies scored in an expert core laboratory. The secondary goal was to determine the prevalence of moderate to severe SA in our population.

Methods

Study design

The DREAM study (Clinicaltrials.gov identifier: NCT01537718) is a European prospective multicenter study in new patients who were eligible for the implantation of a single- or a dual-chamber PM according to the available guidelines.[12] Patients were consecutively included, regardless of symptoms suggesting SA. The study has been approved by ethics committees and regulatory health authorities of different countries involved in the study. All patients signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and all applicable laws and regulations. All adverse events occurring during the course of the study were reported, followed up, and reviewed to identify any potential relationship between the PM device and safety.

Study population and follow-up

Patients were implanted with a single- or a dual-chamber PM (REPLY 200 SR or DR, Sorin CRM SAS, Clamart, France). The choice of the right atrial (when applicable) and right ventricular leads was left at investigators' discretion. Bipolar leads were not mandatory, except when a single-chamber device was implanted. Patients were followed up for 3 months. Three visits were scheduled: at prehospital discharge and 1 month and 3 months after implantation. During these visits and at any unscheduled visits, the cardiologist performed routine checks of the PM and lead(s).

Between 1-month and 3-month visits, patients spent 1 night at the Sleep Laboratory of the University Hospital they had been admitted to undergo PSG. Polysomnography recordings were standardized between the different participating centers and included measurements of electroencephalograms, chin electromyogram, electrocardiogram, electrooculogram, pulse oximetry, nasal pressure, and thoracic and abdominal movements. The central reading of PSGs was done in an expert core laboratory (University Hospital, Grenoble, France) according to the AASM scoring rules.[13]

The PM device data obtained using the SAM algorithm (time window 0:00–5:00) were downloaded in the morning after PSG.

Objectives and study outcomes

The main objective of the study was to evaluate the performance of the SAM algorithm in comparison to PSG by using the following 2 approaches:

1. An event-based approach, which assessed the performance of the SAM algorithm toward the detection of abnormal respiratory events, as determined from investigators' interpretation of PSG;
2. An index-based approach, which assessed the performance of the SAM algorithm toward the diagnosis of SA severity, as determined from the apnea-hypopnea index derived from PSG scoring. In this approach, the apnea-hypopnea index evaluated by PSG (PSG-AHI) and the respiration disturbance index evaluated by the SAM algorithm (SAM-RDI) were compared and an agreement between the methods was assessed.

The prevalence of SA in the study population was determined by using the PSG-AHI.

Events detection by PSG and device-based feature (SAM algorithm)

PSG scoring was the responsibility of a central core laboratory (JLP, Sleep Laboratory of the CHU, Grenoble, France). The central core laboratory took care of the quality of tracings and avoided between centers variability in AHIs evaluation. The central core laboratory was blinded for the SAM-RDI results. PSG measurements were scored according to current guidelines.[13] The PSG-AHI was defined as the hourly average number of abnormal breathing events during sleep. The severity of SA was rated by using the following definitions: PSG-AHI $<$ 15 events/h: no or mild SA; 15 events/h $\leq$ PSG-AHI $<$ 30 events/h: moderate SA; PSG-AHI $\geq$ 30 events/h: severe SA.

A previous version of the SAM algorithm has been described previously.[11] Briefly, a PM sensor derives minute ventilation from transthoracic impedance measurements. A current pulse was injected between the PM can and one of the pacing electrodes. Voltage (proportional to impedance) was measured between the can and another electrode located

on the same or on another lead. Transthoracic impedance varies with respiratory movements, body posture, and cardiac contractions. Only relative impedance was considered; therefore, the sensor measurements were independent from the lead and the can position. An appropriate filtering (low-pass filter at 0.5 Hz and a band-pass filter at 0.05–0.5 Hz) was applied on the transthoracic impedance signal. Each respiratory cycle's amplitude and period were measured from the impedance signal; and the minute ventilation value and the index were calculated as the ratio, or average of the ratio, of amplitude and period.

The SAM algorithm detects the following events: apnea (absence of a significant respiratory cycle for >10 seconds) and marked hypopnea (sustained, >10 seconds, reduction of the respiratory amplitude by at least 50% compared to the mean minute ventilation of preceding validated respiratory cycles). After PM interrogation, a respiratory disturbance index evaluated by the SAM algorithm (SAM-RDI), corresponding to the mean number of detected events per hour of the estimated sleep, was automatically computed.

Compared to the previous version of the algorithm, respiratory cycles with unexpected baseline motion (potentially due to patient's changes in body position, yawning, or coughing) and cycles presenting an abnormal signal-to-noise ratio were tracked and were excluded from the analysis. Another significant improvement is the management of repeated flow cycles with artifacts: in the case of frequent cycle exclusions (more than 4 cycles excluded over the last 16) within or preceding the suspicion of an apnea or hypopnea, the detection of the event was discarded from the final SAM-RDI. An analysis of the total number of excluded cycles was performed at the end of the night, and no SAM-RDI was provided when excluded cycles exceeded 400 cycles/h overnight. The signal processed by the SAM algorithm was then synchronized with the recorded PSG tracing (Figure 1).

For the event-based approach, the first 40 events recorded by PSG for each patient (presenting at least 40 PSG events) were matched with the events recorded by the device.

For the index-based approach, performances of the SAM algorithms were assessed on patients with implanted devices with appropriate data for PSG-AHI and SAM-RDI calculation, that is, completed PSG and valid data from PSG and the SAM algorithm, respectively, during the evaluation night.

Statistical analysis

Study data were reported in the case report forms by the investigators, and device outputs were extracted on Excel files. A database was built-up on Oracle Clinical Database (Clinical Release 4.6), and the global study database was frozen on June 4, 2013, and exported to SAS software. Quantitative variables were expressed as mean ± SD.

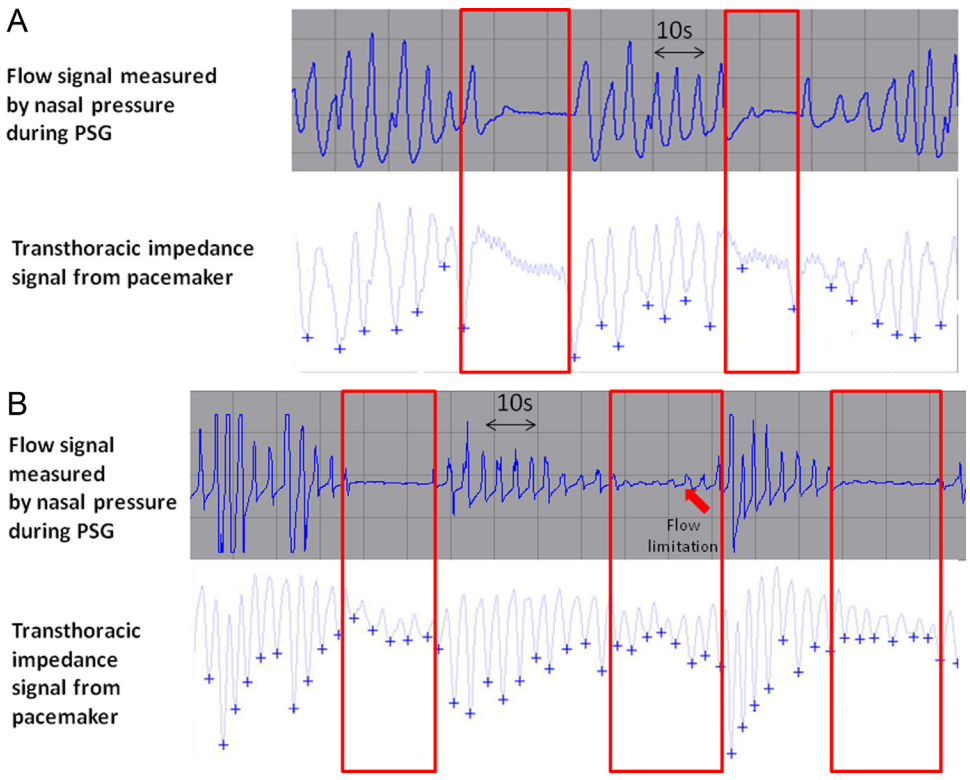

Figure 1 Nasal pressure measurements during polysomnography (PSG) and corresponding sleep apnea monitoring (SAM) recordings of transthoracic impedance from the minute ventilation sensor. **A:** Two typical apneas are framed. Apneas are identified clearly on the nasal pressure signal during PSG as a drop in the peak signal excursion by $\geq 90\%$ of pre-event baseline. Note the concurrent reduction of the amplitude of the thoracic impedance signal from the pacemaker. **B:** Hypopnea events are framed. Hypopneas in adults are scored when the peak signal excursions drop by $\geq 30\%$ of pre-event baseline using nasal pressure. Note the simultaneous reduction of the amplitude of the thoracic impedance signal from the pacemaker.

Qualitative variables are presented as the number of patients and percentage.

The occurrence and severity of SA were evaluated in patients with implanted devices who completed PSG. The device performance for severe SA identification was evaluated by the area under the receiver operator characteristic curve (Wald method) at different RDI cutoffs and compared with the area under the random guess line by using a χ^2 test. The optimal cutoff point (SAM-RDI) to discriminate the 2 populations (patients with severe and nonsevere SA) was determined by the best trade-off between sensitivity and specificity. Confidence intervals (CIs) were calculated for sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) by using the Clopper-Pearson exact method. An agreement between the 2 indexes was evaluated by using a scatter plot and Bland and Altman statistics.[14] All statistical analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, NC).

Results

Study population and study flow

A total of 40 patients were enrolled in the DREAM study between March 13, 2012, and July 25, 2012, in 5 centers in France and Spain. Their mean age was 73.8 ± 19.1 years, and mean body mass index was 27.7 ± 4.4 kg/m^2; most patients were men (67.5%). Detailed demographic characteristics and implantation statistics are summarized in Table 1.

Three patients (7.5%) withdrew their consent before undergoing PSG, and 1 patient (2.5%) experienced an acute cardiac failure during his examination through PSG. Consequently, 36 patients (90%) completed their overnight PSG recordings and were analyzed for SA diagnosis. The SAM-RDI was not available for 5 (14%) patients owing to signal artifacts for the study night. Therefore, 31 patients were analyzed for performances of SAM algorithms.

Table 1 Demographic characteristics (N = 40)

Age (y)	73.8 ± 10.1
Sex: male	27 (67.5)
Body mass index (kg/m^2)	27.7 ± 4.4
Indication for implantation	
AVB III/II	20 (50.0)
Syncope	6 (15.0)
Brady-tachy syndrome	5 (12.5)
Sinus node dysfunction	9 (22.5)
Atrial rhythm disorders at inclusion	
Paroxysmal atrial fibrillation	8 (20.5)
Persistent/permanent atrial fibrillation	6 (15.4)
Underlying cardiac diseases	
Coronary artery disease	6 (15.0)
Valvular heart disease	2 (5.0)
Cardiomyopathy	9 (22.5)
Hypertension	25 (62.5)
Cardiac failure	16 (40.0)
Other comorbidities	
Diabetes	5 (12.5)
Current smoker	8 (20.0)
Implanted device	
REPLY 200 single chamber	10 (25.0)
REPLY 200 dual chamber	30 (75.0)
Initial implant	33 (88.5)
Replacement	7 (17.5)

Values are presented as mean ± SD or as n (%). AVB III/II: atrioventricular block 3rd degree/2nd degree.

SA prevalence

A wide range of the PSG-AHI values between 4 and 82 events/h were obtained from PSG performed overnight, and the diagnosis of moderate to severe SA (PSG-AHI > 15 events/h) was made in 78% of our unselected population of patients with PMs (n = 36), with 56% receiving a diagnosis of severe SA (PSG-AHI > 30 events/h).

Performance of the SAM algorithm

Event-based approach

The event-by-event comparison between PSG and SAM data (1802 abnormal respiratory events studied) provided a sensitivity of 60.4% (95% CI 57.6%–63.2%) and a PPV of 50.6% (95% CI 48.0%–53.3%).

Index-based approach

In the index-based approach, the SAM-RDI ranged from 0.0 to 70.5 events/h. The area under the receiver operator characteristic curve was 0.91 (95% CI 0.80–1.00; $P < .001$; Figure 2). The optimal SAM-RDI cutoff value for detecting patients with severe SA (PSG-AHI > 30 events/h) was 20 events/h. With this optimal cutoff value (SAM-RDI > 20 events/h), 16 of 18 patients who received the diagnosis of severe SA through PSG were accurately detected by the SAM algorithm (sensitivity 88.9%, 95% CI 65.3%–98.6%; specificity 84.6%, 95% CI 54.6%–98.1%; PPV 88.9%, 95% CI 65.3%–98.6%; NPV 84.6%, 95% CI 54.6%–98.1%).

A scatter plot (Figure 3) and Bland and Altman statistics (Figure 4) indicated a good agreement between the 2 methods. The difference (systematic error or bias) between the PSG-AHI and the SAM-RDI was 9.2 events/h. In patients with severe SA (SAM-RDI ≥ 20 events/h), the mean difference was 14.3 events/h.

Discussion

Main findings

In our unselected population of patients with PMs, we found a prevalence of 78% in moderate to severe SA and 56% in severe SA. An optimal cutoff of 20 events/h for the SAM-RDI value was validated to identify severe SA with a sensitivity of 88.9% (95% CI 65.3%–98.6%), a PPV of 88.9% (95% CI 65.3%–98.6%), and a specificity of 84.6% (95% CI 54.6%–98.1%).

Prevalence of SA in patients with cardiac implants

In a population of patients newly implanted for symptomatic sinus dysfunction, permanent atrioventricular block, or severe heart failure, the prevalence rate of SA was up to 59%, with 27% of the patients suffering from severe disease.[6] The prevalence of symptoms of disordered breathing was 32.3% in a population implanted for bradyarrhythmia.[15] In the

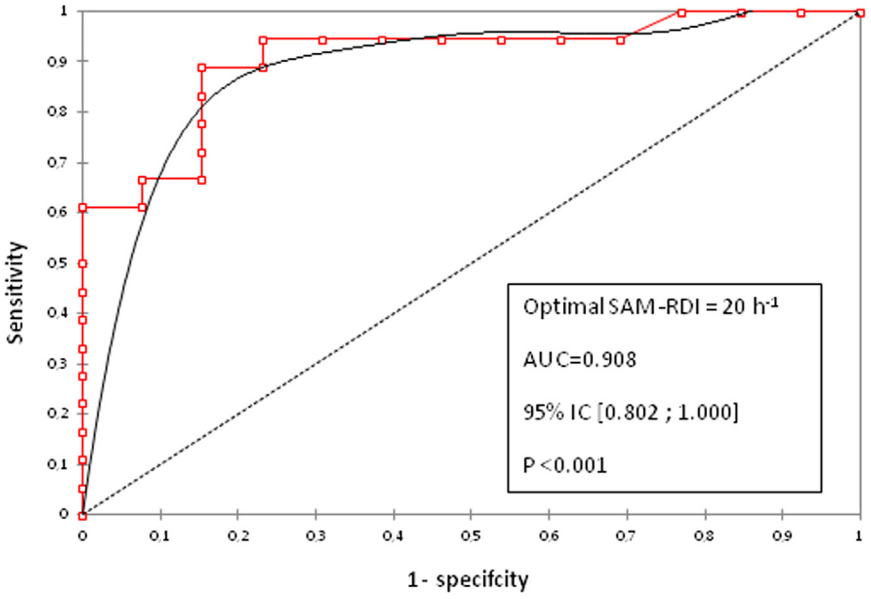

Figure 2 Receiver operator characteristic curve for the detection of severe sleep apnea (defined as PSG-AHI > 30 events/h). The sensitivity is plotted against (1 − specificity) at different SAM-RDI cutoffs (in red). The smoothed curve is shown in black. Statistics are provided with the optimal SAM-RDI cutoff of 20 events/h found to provide the best trade-off between sensitivity and specificity. AUC = area under the curve; PSG-AHI = apnea-hypopnea index evaluated by polysomnography; SAM-RDI = respiratory disturbance index evaluated by the sleep apnea monitoring algorithm.

current DREAM study, we even reported a highest prevalence rate of 78% for the moderate to severe spectrum of the disease, which included 56% of the patients exhibiting severe SA. This result is consistent with the study of Shalaby et al,[10] which gave prevalence rates of 67% and 53%, respectively, in a population aged 69 ± 12 years. In our DREAM study, population was older (73.8 ± 10.1 years) than that in the 2 studies mentioned previously (63 ± 8 and 62.2 ± 12.2 years), and this certainly partially explain the highest prevalence of SA in the DREAM cohort. The diagnosis method used by Fietze et al[15] differed significantly from other studies, since SA was searched by using simplified tools (MESAM IV device, MAP, Munich, Germany) based on heart rate, snoring and oxygen saturation without information on sleep quality or duration, or direct measurements of airflow. This diagnosis procedure clearly underestimated hypopnea. In summary, all available studies exhibited an undiagnosed SA rate above 50% in patients implanted with PMs. This figure has recently been expended in patients implanted with cardioverter-defibrillators.[16–18]

Performance of the SAM algorithm in perspective

The index-based approach is the most clinically relevant approach for identifying patients with severe SA. A

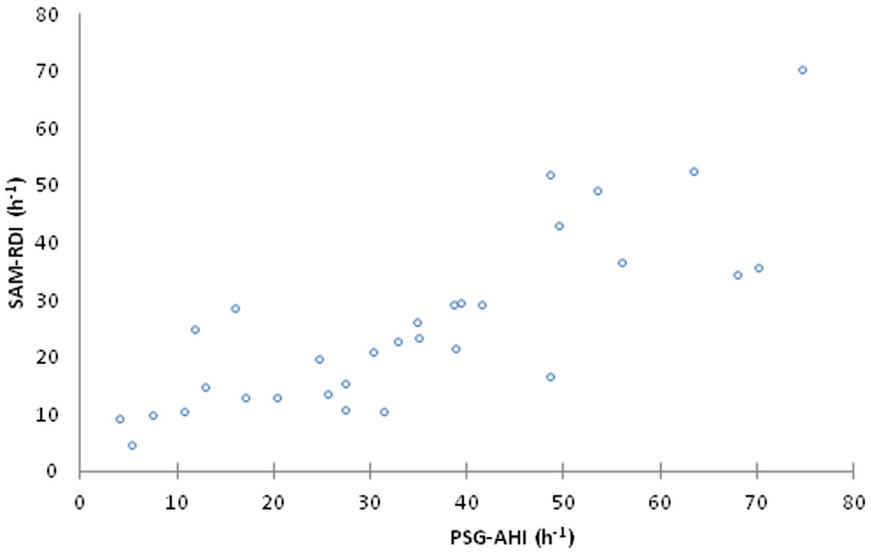

Figure 3 Scatter plot between the respiratory disturbance index evaluated by the SAM algorithm (SAM-RDI, in events/h) and the apnea-hypopnea index evaluated by polysomnography (PSG-AHI, in events/h). PSG-AHI = apnea-hypopnea index evaluated by polysomnography; SAM = sleep apnea monitoring; SAM-RDI = respiratory disturbance index evaluated by the sleep apnea monitoring algorithm.

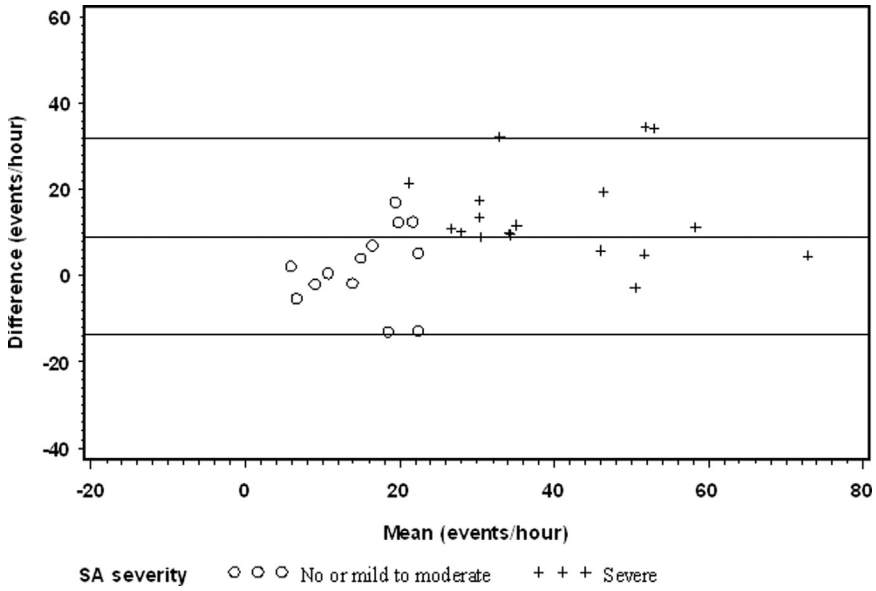

Figure 4 Bland-Altman plot (y axis: difference between the PSG-AHI and the SAM-RDI; x axis: mean of the SAM-RDI and PSG-AHI), showing mean of the differences (bias) presented with the 2SD interval. Mean = 9.2 ± 11.6; limits of agreement (2SD) = [−14 to 32.4]. SA = sleep apnea; PSG-AHI = apnea-hypopnea index evaluated by polysomnography; SAM-RDI = respiratory disturbance index evaluated by the sleep apnea monitoring algorithm.

preliminary version of the SAM algorithm (developed in Talent PM, ELA Medical) had been studied by Defaye et al[11] in patients with PMs. A cutoff RDI value of 30.6 events/h was found to yield 75% sensitivity, 94% specificity, 75% PPV, and 94% NPV. The advanced algorithm presented here showed higher performances (89% sensitivity while maintaining a high specificity). This was mainly achieved through improved management of nonphysiological artifacts of the minute ventilation signal. Five of 36 patients with PSG data had no SAM-RDI provided owing to the new artifact exclusion management. However, this significant failure rate corresponded to data acquired during a single night. In clinical practice, this concern will be solved by the night after night measurements of the SAM-RDI, which will provide correct SA screening information for nearly all the patients.

To our knowledge, 2 other device-based respiratory sensor–equipped PMs have been studied for the diagnosis of SA. Shalaby et al[10] reported a good correlation between the PM-AHI and the PSG-AHI ($r = .80$; $P < .01$) and identified patients with moderate to severe SA, with an index-based sensitivity of 89.3%, a specificity of 66.7%, and a PPV of 73.5%. From the individual data reported by Scharf et al,[9] we have extrapolated on the whole population a sensitivity of 78%, a specificity of 92.3%, a PPV of 87.5%, and an NPV of 85.7%.

These studies including our own are limited by their relatively small sample size; evaluation in larger populations is needed to fully validate these diagnostic tools and their cost-effective benefits. Also, further technological developments will certainly improve the reliability of the system by allowing us to better estimate sleep duration via combined activity sensor and algorithms.

Study limitations

The evaluation of the performance presented herein was not conducted on a training set and an evaluation data set of patients. This can be considered as a significant design limitation. The DREAM study should be considered as the first validation step of this new technology, and further prospective multicenter studies or registries are required.

Transthoracic impedance measurements of ventilation are qualitative estimates of ventilation. They do not allow a quantitative flow measurement, which constitutes a limitation for subtle hypopnea recognition. Also, this system does not assess directly the severity of nocturnal hypoxia, which is the landmark of SA. However, the duration of abnormal respiratory events is available and reflects the severity of intermittent hypoxia. Both sleep macrostructure and microarousals are not detected by the device. To address this limitation, the patient's sleep period can be adjusted in accordance with patient's sleep habits (programmed between 0:00 and 5:00 in the DREAM study to ensure a high probability of sleep during the recording period). Finally, an interesting evolution in the development of the sensor would be to discriminate the central from obstructive apnea events by looking at different specific ventilatory patterns.[19]

Clinical implications and perspectives

As the prevalence of SA is up to 65% in the different population with indications for cardiac implants, awareness of cardiologist should increase in this field. More than three-quarters (78%) of the unselected patients of the DREAM study were diagnosed with moderate to severe SA by using the gold standard method, that is, PSG. This new transthoracic impedance-derived PM for severe SA

screening/diagnosis and follow-up is now commercially available in various implantable devices; it may improve the management of patients in routine cardiology practice. An ongoing registry, the Registry of Sleep Apnea Monitoring and Atrial Fibrillation in Pacemaker Patients (Clinicaltrials.gov identifier: NCT01922726), will provide a long-term evaluation of the effect of this systematic SA screening on clinical outcomes in patients with implantable cardiac devices. The night after night measurements after implantation would help understand the evolution of severe SA, together with different therapeutic interventions.

Conclusions

The DREAM study showed that a transthoracic impedance sensor with an advanced algorithm, the SAM algorithm, could be used to identify severe SA in patients with PMs.

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