Original article

Successful screening of sleep-disordered breathing using a pacemaker-based algorithm in Japan

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A R T I C L E   I N F O

A B S T R A C T

Background: Recent pacemakers with transthoracic impedance sensors have a specific algorithm identifying sleep apnea (SA). Our aim was to evaluate the algorithm in Japanese patients.
Methods: Consecutive patients implanted with a pacemaker with sleep apnea monitoring algorithm at our hospital were enrolled prospectively. After implantation, patients underwent polysomnography (PSG). The respiratory disturbance index measured by pacemaker (RDI-PM) was extracted in the morning after PSG.
Results: Forty-five patients were recruited; 78% of patients underwent overnight PSG completely, and among them RDI-PM was invalid for one patient. Then the analysis was performed in 34 patients. Moderate/severe SA (apnea hypopnea index, AHI $\geq$ 15 events/h) and severe SA (AHI $\geq$ 30 events/h) by PSG were diagnosed in 65% and 41% of patients. The mean AHI-PSG and RDI-PM were 30.4 $\pm$ 22.6 and 21.7 $\pm$ 14.2 events/h, respectively. There was a significant positive correlation between AHI-PSG and RDI-PM (r = 0.543; p = 0.001). The correlation was stronger in the severe SA group (r = 0.664; p = 0.010), in a group whose apnea index was higher than hypopnea index (r = 0.822; p = 0.002), and in a group whose central sleep apnea (CSA) index was higher than obstructive sleep apnea index (r = 0.977; p < 0.001). RDI-PM cut-off value for identifying severe SA was 22 (area under the curve, 0.682; sensitivity, 64%; specificity, 75%).
Conclusions: The pacemaker-based algorithm is a useful screening tool for SA in Japanese individuals, especially in the severe SA group, apnea-dominant group, and CSA-dominant group.

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Introduction

Sleep apnea (SA) is an independent risk factor associated with various cardiovascular diseases [1]. Obstructive sleep apnea (OSA) has been demonstrated as a risk factor for hypertension [2], coronary artery disease [3], congestive heart failure [4], arrhythmias [5,6], recurrence of atrial fibrillation after pulmonary vein isolation [7], appropriate shock rates of life-threatening ventricular arrhythmia in implantable cardioverter-defibrillators during the night [8], and sudden cardiac death [9]. And congestive heart failure is related to these cardiac diseases [10]. Several population-based cohort studies have shown that approximately 1 in 5 adults has at least mild OSA with an apnea hypopnea index (AHI) $\geq$ 5, and 1 in 15 adults has moderate or severe OSA with an AHI $\geq$ 15 [1,11]. In Japan, Hida et al. reported that the prevalence of 159 healthy workers who had apnea index more than 10 episodes/h was 7.5% [12]. However, the prevalence of SA with an AHI $\geq$ 10 in pacemaker-implanted patients has been reported to be as high as 59% [13]. Our previous study involving Japanese pacemaker-implanted patients reported that the prevalence of moderate to severe SA (AHI $\geq$ 15) was as high as 58% [14]. These patients usually lack typical symptoms such as excessive daytime sleepiness, and more than 85% of them remain undiagnosed [11].

Rate-responsive pacemakers have a specific algorithm to detect breathing disorders by applying the measurements of impedance

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changes in minute ventilation sensors [15,16], which might be able to screen undiagnosed SA in patients with pacemakers (PMs) outside the clinic. The DREAM European study, which was conducted in France and Spain, has shown the accuracy and usefulness of a sleep apnea monitoring (SAM) algorithm installed in Sorin/Livanova pacemakers (REPLY 200DR or KORA 250DR; CRM SAS, Clamart, France) for detecting SA by comparing polysomnography (PSG) results [17], which is the gold standard for diagnosing SA.

Despite the small physique of Japanese, the prevalence of SA is considered to be equivalent to Caucasians. Especially in pacemaker-implanted patients, a high prevalence of SA was known although most of them were asymptomatic. A screening for SA using transthoracic impedance by pacemaker targeted for Japanese patients is an important issue, but there are no data in Japanese patients to date. In this study, the primary goal was to evaluate the correlation between the respiratory disturbance index measured by pacemakers with SAM algorithm (RDI-PM) and the AHI measured by PSG (AHI-PSG) in Japanese patients. The secondary goal was to calculate the cut-off value for severe SA in Japanese patients.

Methods and materials

Study design

This study was a single-center, cross-sectional, prospective, and observational study performed to evaluate the accuracy of the SAM algorithm installed in Sorin/Livanova pacemakers to detect sleep-disordered breathing. The study was approved by the ethics committee of our hospital under the approved number of B140904007, and all patients provided informed consent.

Pacemaker-detected SA

The SAM algorithm installed in Sorin/Livanova pacemakers has been developed and updated from previous versions [18]. The pacemaker injects a current and measures the voltage between the proximal atrial tip electrode and the can. When the atrial lead is unipolar or when the proximal atrial tip is broken, the current is injected between the can and the distal ventricular tip electrode. Therefore, the impedance is calculated by the following formula: $Zth\ (\Omega) = dV\ (V)/I\ (A)$; Zth is the transthoracic impedance, V is the voltage, and I is the current. Each respiratory cycle is recognized as the peak-to-peak of the impedance.

The SAM algorithm defines apnea as the absence of the respiratory cycle for more than 10 s; it defines hypopnea as a reduction in respiratory amplitude by at least 50% for more than 10 s compared to the mean minute ventilation of the preceding respiratory cycles. The pacemaker counts the total number of apnea and hypopnea instances during 5 h; this time period can be set according to each patient's usual sleeping time from 22:00 h to 06:00 h. Then, the RDI is calculated as the mean number of detected events per hour. If there are more than 400 unstable or noisy cycles per hour, then the RDI at night is considered invalid and is not displayed. The daily RDI values are recorded for up to 6 months.

PSG-detected SA

PSG defines apnea as the absence of airflow in the nose and mouth for more than 10 s during sleep. Hypopnea is defined as 30% reduction of airflow in the nose and mouth lasting more than 10 s and accompanied by a 3% desaturation in pulse oximetry or arousal response [19]. The severity of SA is determined as follows: mild,

5 to <15 events per hour; moderate, 15 to <30 events per hour; and severe, ≥30 events per hour.

OSA is an apnea due to complete collapse of the pharynx accompanied by respiratory efforts during sleep [19,20]. Central sleep apnea (CSA) is due to complete withdrawal of the central respiratory drive to the muscles used for respiration [20,21].

In this study, PSG (Alice PDx 2007; Philips Respironics, Murrysville, PA, USA) included measurements of electroencephalograms, electrooculograms, chin electromyograms, electrocardiograms, pulse oximetry, nasal and mouth airflow using both pressure and thermistor sensor, and thoracic and abdominal movements. The PSG analysis was conducted according to the scoring rules of the American Academy of Sleep Medicine (2007 version) [19].

Study subjects

The subjects were consecutive patients who underwent implantation of dual-chamber pacemakers (REPLY200DR or KORA250DR) at our hospital regardless of SA symptoms. The type of implantation included initial implantation and generator replacement. Indications for pacemaker implantation were in accordance with the available guidelines [22].

Exclusion criteria

Patients who did not agree to undergo PSG were excluded. Patients who could not complete the PSG examination were excluded. Patients whose RDI-PM during PSG examination were invalid due to too much noise were excluded.

Study method

After pacemaker implantation, the SAM algorithm was set to start. The monitored 5-h period was programmed from 22:00 h to 06:00 h according to each patient's declaration of individual sleep time. And then, patients underwent PSG one night during the same hospitalization period. The RDI-PM data were extracted in the morning after PSG.

Statistical analysis

Differences between AHI calculated using PSG and RDI calculated using a pacemaker were assessed according to Bland–Altman statistics [23]. The correlation between AHI-PSG and RDI-PM was calculated using Pearson's correlation coefficient and partial correlation coefficient. Bonferroni procedure for multiple tests were conducted for comparing PSG results by SA severity. The performance of the pacemaker during identification of severe SA was evaluated by the area under the receiver-operating characteristic (ROC) curve. The optimal cut-off point (RDI-PM) used to discriminate patients with severe SA from the others was determined by the best trade-off between sensitivity and specificity. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for that cut-off were calculated.

All statistical analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY, USA). The significance level was set at 0.05.

Results

Study population and study flow

A total of 45 patients underwent implantation with Sorin/Livanova pacemakers from October 2014 to February 2017 at our hospital. Among them, 8 patients withdrew their consent before

Table 1
Demographic characteristics (N = 34).

Age (years)	71.2 ± 15.8
Male	18/34
Body mass index (kg/m^2)	23.4 ± 7.5
Indication of implantation	
Sinus node dysfunction	17/34
Atrial ventricular block	17/34
Comorbidities	
Hypertension	20/34
Paroxysmal/Persistent fibrillation	13/34
Permanent fibrillation	1/34
Coronary heart disease	2/34
Chronic heart failure	2/34
Diabetes	8/34
Cardiac function	
Left ventricular ejection fraction (%)	69.2 ± 7.1
LVDd (mm)	45.6 ± 5.1
LAD (mm)	36.9 ± 7.4
BNP (pg/ml)	50.1 ± 60.0
Epworth sleepiness score	6.9 ± 3.5
Type of implantation	
Initial implantation	21/34
Replacement	13/34

LVDd, left ventricular end-diastolic diameter; LAD, left atrium diameter; BNP, brain natriuretic peptide.

undergoing PSG; therefore, 37 patients underwent overnight PSG. Two patients could not complete the PSG examination.

According to individual sleep time, the 5-h period measured by pacemaker was set at 23:00–04:00 h in one patient, at 01:00–06:00 h in one patient, and at 00:00–05:00 h in the other patients. During the PSG night, RDI-PM was invalid in one patient.

Therefore, 34 patients were analyzed to evaluate the SAM algorithm to detect SA. No patients received continuous positive airway pressure treatment. Clinical characteristics of the patients are summarized in Table 1.

SA prevalence

PSG analysis showed the mean AHI was 30.4 ± 22.6 events per hour, ranged between 2 and 72 events per hour. Of a total of 34 patients (18 males; average age, 71.2 ± 15.6 years; average body mass index, 23.5 ± 3.8 kg/m^2), 22 (65%) were diagnosed with moderate and severe SA (AHI ≥ 15 events per hour) and 14 (41%) were diagnosed with severe SA (AHI ≥ 30 events per hour).

PSG analysis revealed that the mean apnea index was 15.6 ± 18.0 events per hour (51.3% of AHI), and that the mean hypopnea index was 14.8 ± 11.0 events per hour (48.7% of AHI). Apnea types

were as follows: CSA, 3.4 ± 8.7 events per hour (11.2% of AHI); OSA, 9.9 ± 12.6 events per hour (32.6% of AHI); and mixed sleep apnea, 2.1 ± 4.0 events per hour (6.8% of AHI) (Table 2).

Differences between RDI-PM and AHI-PSG

The mean RDI-PM was 21.7 ± 14.2 events per hour (Table 2). Bland–Altman statistics showed a good agreement between the two methods (Fig. 1). The difference between AHI-PSG and RDI-PM for each patient was 8.57 ± 19.1 events per hour.

Correlation of AHI-PSG and RDI-PM during the same night

For the 34 patients, there was a significant correlation between the AHI-PSG and RDI-PM (r = 0.543; n = 34; p = 0.001) (Fig. 2A). The correlation coefficients were 0.539 (n = 22; p = 0.010) for the moderate and severe SA group (AHI ≥ 15) and 0.664 (n = 14; p = 0.010) for the severe SA group (AHI ≥ 30) (Table 3A, Fig. 2B).

Correlation of RDI-PM and arousal index by PSG

The Pearson's correlation coefficient between the RDI-PM and the arousal index according to PSG was significant (0.620; n = 34; p < 0.001) (Table 3B).

Sub-group analysis by type of event – apnea versus hypopnea

For the patient group whose apnea index was higher than the hypopnea index (HA group), the correlation coefficient between AHI-PSG and RDI-PM was strongly significant at 0.822 (n = 11; p = 0.002). For the patient group whose hypopnea index was higher than the apnea index (LA group), the correlation coefficient was 0.254 (n = 23; p = 0.241). The partial correlation coefficient between RDI-PM and AHI-PSG by removing BMI factor in HA group and LA group were r = 0.781 (p = 0.008) (Fig. 2C), r = 0.238 (p = 0.286), respectively.

Sub-group analysis by type of event – CSA versus OSA

Four patients were excluded because their CSA index and OSA index were equivalent. For the patient group whose CSA index was higher than the OSA index (HC group), the correlation coefficient between AHI-PSG and RDI-PM was strongly significant at 0.977 (n = 7; p < 0.001). For the patient group whose CSA index was lower than the OSA index (LC group), the correlation coefficient was 0.491 (n = 23; p = 0.017). The partial correlation coefficient by

Table 2
Results of polysomnography and RDI measured by pacemaker.

Polysomnography	Total (n = 34)[*]	Mild SA (n = 9)	Moderate SA (n = 8)	Severe SA (n = 14)	p-Value[**]
AHI-PSG (/h)	30.4 ± 22.6	9.0 ± 1.6	22.7 ± 5.0	54.1 ± 12.2	<0.001[a)]
Apnea index (/h)	15.6 ± 18.0	1.2 ± 1.7	8.6 ± 5.1	32.3 ± 16.8	<0.001[b)]
CSA index (/h)	3.4 ± 8.7	0.5 ± 0.7	1.7 ± 2.8	6.9 ± 12.8	0.191
OSA index (/h)	9.9 ± 12.6	0.6 ± 1.0	5.3 ± 4.6	20.7 ± 13.7	<0.001[b)]
Mixed apnea index (/h)	2.1 ± 4.0	0.1 ± 0.3	0.6 ± 0.6	4.6 ± 5.4	0.013[b)]
Hypopnea index (/h)	14.8 ± 11.0	7.8 ± 1.9	14.1 ± 5.9	22.3 ± 12.4	0.003[c)]
3% ODI index (/h)	26.0 ± 20.6	7.6 ± 3.5	19.1 ± 8.0	46.6 ± 13.7	<0.001[a)]
Arousal index (/h)	21.2 ± 16.7	5.2 ± 3.1	17.3 ± 7.1	35.0 ± 14.0	<0.001[b)]
Sleep efficiency (%)	74.2 ± 16.3	87.2 ± 10.0	75.5 ± 18.1	64.4 ± 11.9	0.002[c)]
Pacemaker					
RDI-PM (/h)	21.7 ± 14.2	15.0 ± 12.0	20.4 ± 11.1	28.1 ± 16.0	–

AHI-PSG, apnea-hypopnea index measured by polysomnography; CSA, central sleep apnea; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; RDI-PM, the respiratory disturbance index measured by pacemaker; SA, sleep apnea. SA severity; mild, defined as 5 ≤ AHI < 15; moderate, defined as 15 ≤ AHI < 30; severe, defined as AHI ≥ 30.
[*] Three patients were diagnosed non-SA.
[**] Bonferroni procedure for multiple test were conducted. a) mild SA < moderate SA < severe SA, b) mild SA < severe SA, and c) mild SA > severe SA.
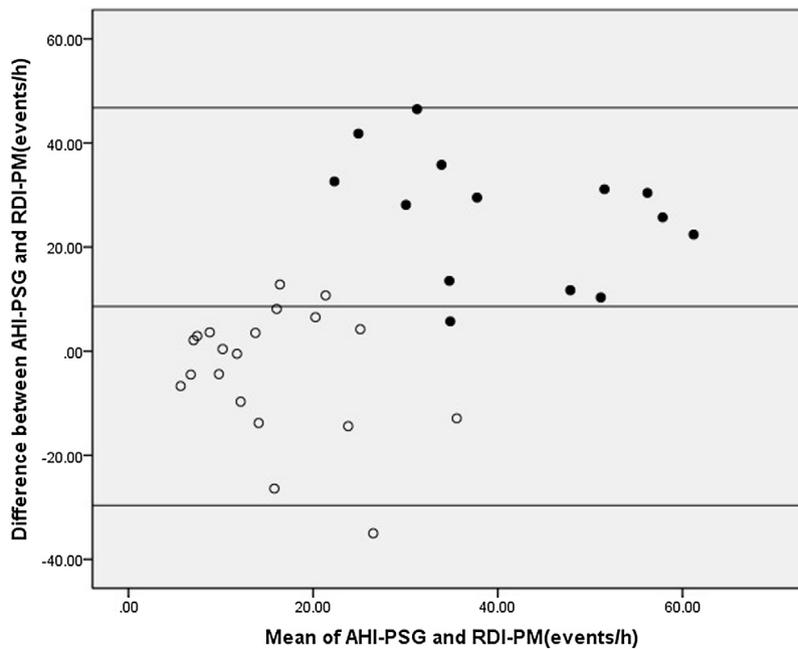
Fig. 1. Bland–Altman plots of differences between AHI-PSG and RDI-PM. These plots show the means of the differences (presented with a 2-SD interval). The y-axis shows differences between the two methods. The x-axis shows the mean of AHI-PSG and RDI-PM. SA severity: ○ No or mild to moderate, ● Severe. Mean difference = 8.57 ± 19.10; +2 SD = 46.77; −2 SD = −29.63. AHI-PSG, apnea-hypopnea index measured by polysomnography; RDI-PM, the respiratory disturbance index measured by pacemaker; SA, sleep apnea; SD, standard deviation.

removing BMI factor between RDI-PM and AHI-PSG by removing BMI factor in HC group and LC group were $r = 0.979$ ($p = 0.001$) (Fig. 2D) and $r = 0.484$ ($p = 0.022$), respectively.

Cut-off value for detecting severe SA

Fourteen patients (41%; 7 males; average age, 80.4 ± 7.2 years) were diagnosed with severe SA (AHI, 54.1 ± 12.2; RDI, 28.1 ± 16.0) by PSG. The RDI cut-off value for detecting severe SA using a pacemaker was 22. Using this value, 9 out of 14 patients had accurate detection (64% sensitivity, 75% specificity, 64% PPV and 75% NPV, area under the curve 0.682, 95% CI: 0.48–0.88) (Fig. 3).

Discussion

Our study showed feasible SA detection capability using pacemakers and a high prevalence (65%) of moderate and severe SA for pacemaker-implanted patients. Our results were similar to those of the DREAM European study; however, the BMI values for our patients were relatively low (23.4 vs. 27.7 in the DREAM European study [17]). Japanese people have craniofacial morphology features such as a short mandibular body and mandibular retrusion, specific hyoid bone position, and specific airway shape that contribute to the high prevalence of OSA despite their lack of obesity [24]. The SA detection capability of pacemakers was shown in spite of difference in physique. In addition, our patients had fewer symptoms of daytime sleepiness. Johns reported that the Epworth Sleepiness Scores (ESS) for moderate (AHI 15 to <30) and severe SA (AHI ≥ 30) were 11.5 ± 4.2 and 16.0 ± 4.4, respectively, for Australian individuals [25]. For our patients, the ESS were 9.6 ± 3.9 for the moderate SA group and 6.2 ± 3.5 for the severe SA group, which were relatively low and did not reflect the severity of SA. This may lead to delayed diagnosis of SA. It is meaningful for non-obese Japanese patients to have such a screening method by pacemaker.

A significant correlation was found between AHI-PSG and RDI-PM, and the r values were strengthened in the severe group ($n = 14$; $r = 0.664$; $p = 0.010$). Because there is no need for treatment for

mild SA, it is acceptable that severe cases have higher detectability. RDI-PM was also correlated with arousal index according to PSG ($n = 34$; $r = 0.620$; $p < 0.001$), suggesting that sleep quality is degraded for patients with high RDI-PM.

Pacemakers ignore sleep status because they are not able to detect electroencephalogram measurements. Therefore, this is considered the most likely cause of the difference between AHI-PSG and RDI-PM. The AHI is calculated by dividing the total sum of apnea and hypopnea events by the total sleeping time. In this study, the mean sleep efficiency was 74.2% in our patients. Therefore, the RDI-PM is often lower than AHI-PSG.

According to the sub-group analysis, the correlation coefficient was strengthened in the HA group ($n = 11$; $r = 0.822$; $p = 0.002$) and in the HC group ($n = 7$; $r = 0.977$; $p < 0.001$) (Table 3A). Although it was difficult to exclude various confounding factors due to a small number of subjects, the noticeable difference of correlation coefficients including partial correlation coefficient between HA and LA group, and between HC and LC group can support the good correlation in apnea-dominant group and CSA-dominant group. Some factors attributed to characteristics of pacemaker-based measurement were considered. To detect hypopnea by thoracic impedance, a rate of change in thoracic movement is relatively small compared to apnea, and it is determined when accompanied with desaturation of 3% in pulse oximetry or arousal response by PSG, pacemakers might be limited in their ability to identify hypopnea. CSA is accompanied by complete absence of respiration and thoracic-abdominal movements, which can explain the good correlation between the two methods. On the other hand, OSA is caused by obstruction of the pharynx and is accompanied by respiratory effort. Remaining thoracic movements may affect impedance measurement compared to CSA. Moreover, negative intrathoracic pressure and increased venous return during OSA causes increased intrapulmonary vasculature blood, resulting in thoracic impedance reduction [20]. This mechanism can be a modifier that reduces the rate of thoracic impedance change.

For our patients, the RDI cut-off value for detecting severe SA was 22 with 64% of sensitivity and 75% of specificity. As previously described, there is high prevalence of moderate to
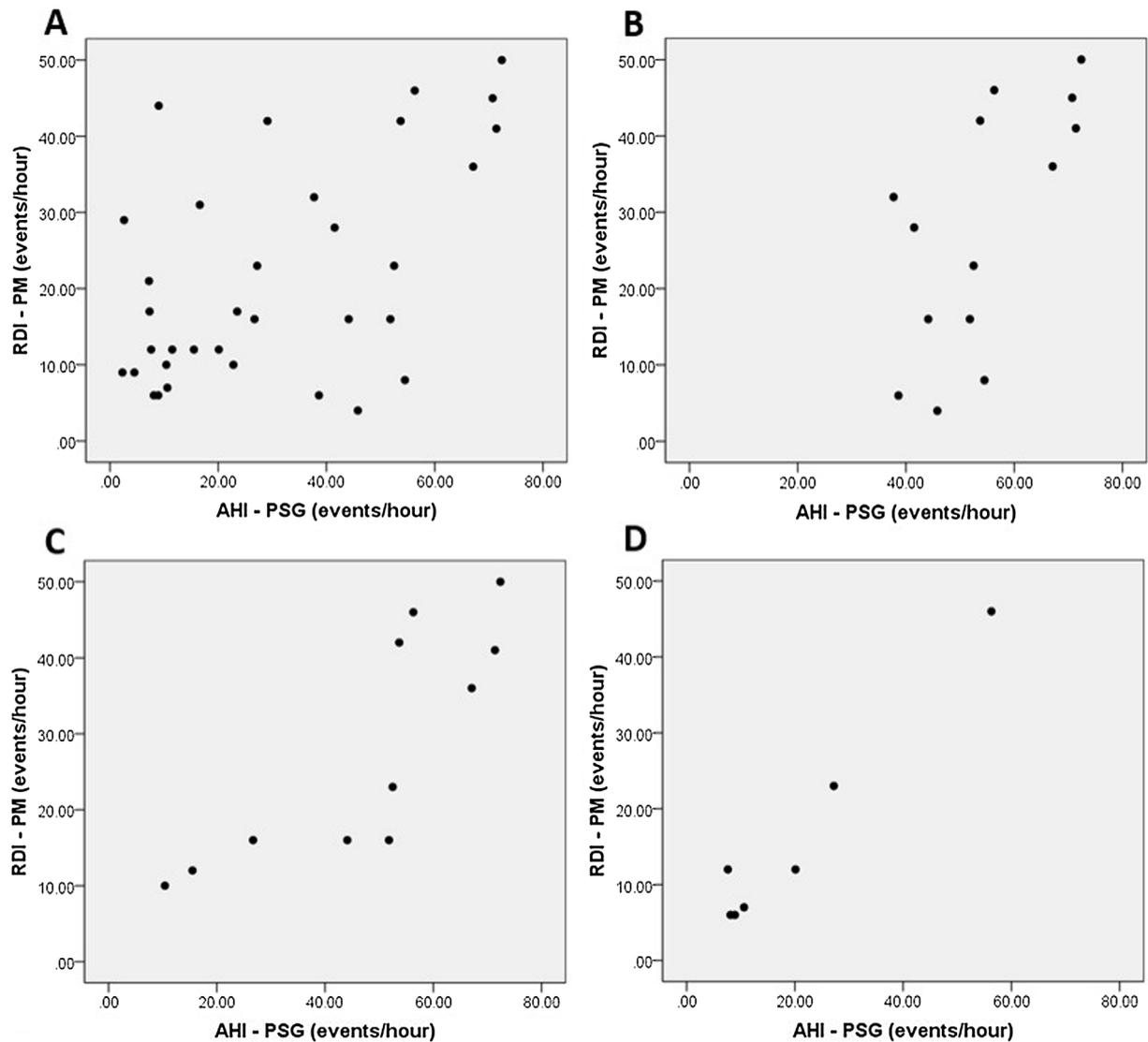
Fig. 2. (A) Scatter plot between the AHI-PSG and RDI-PM for the total patients ($r = 0.543$, $p = 0.001$, $n = 34$). (B) Severe SA group ($r = 0.664$, $p = 0.010$, $n = 14$). (C) HA group ($r = 0.822$, $p = 0.002$, $n = 11$). (D) HC group ($r = 0.977$, $p < 0.001$, $n = 7$). AHI-PSG, apnea-hypopnea index measured by polysomnography; HA group = a group whose apnea index was higher than the hypopnea index measured by PSG; HC group = a group whose central sleep apnea index was higher than the obstructive sleep apnea index measured by PSG; RDI-PM, the respiratory disturbance index measured by pacemaker; SA, sleep apnea.

Table 3A
Correlation coefficient between AHI-PSG and RDI-PM.

	AHI-PSG	RDI-PM	r	p
Total patients ($n = 34$)	30.4 ± 22.6	21.7 ± 14.2	0.543	0.001
Moderate/severe SA ($n = 23$)	41.3 ± 19.2	24.5 ± 14.8	0.578	0.004
Severe SA ($n = 14$)	54.2 ± 12.2	28.1 ± 16.0	0.664	0.010

Table 3B
Correlation coefficient between arousal index based on PSG and RDI-PM.

	AI-PSG	RDI-PM	r	p
Total patients ($n = 34$)	21.2 ± 16.7	21.7 ± 14.2	0.620	<0.001

AHI-PSG, apnea-hypopnea index measured by polysomnography; AI, arousal index; RDI-PM, the respiratory disturbance index measured by pacemaker; SA, sleep apnea. SA severity: moderate, defined as $15 \leqq AHI < 30$; severe, defined as $AH \geqq 30$.
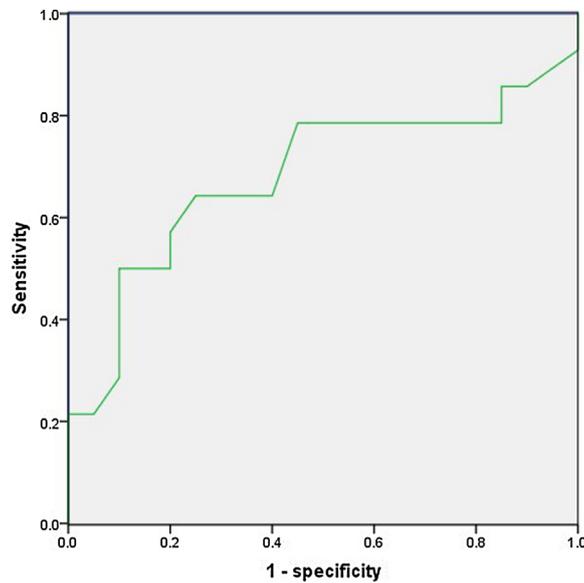
Fig. 3. Receiver-operator characteristic curve for the detection of severe sleep apnea defined AHI ≥30 events per hour by PSG. The cut-off value of RDI-PM for detecting severe sleep apnea was 22, with 64% sensitivity, 75% specificity, 64% PPV, 75% NPV, and an AUC of 0.682 (95% CI: 0.48–0.88). AHI-PSG, apnea-hypopnea index measured by polysomnography; AUC, area under the curve; CI, confidence interval, NPV, negative predictive value; PPV, positive predictive value; RDI-PM, the respiratory disturbance index measured by pacemaker.

severe SA in pacemaker-implanted patients, most of whom were asymptomatic and undiagnosed. It is infeasible to perform PSG for all pacemaker-implanted patients, but the SAM-algorithm can display RDI without any additional inspections. Due to its convenience, the relative low sensitivity can be acceptable for screening.

Based on our results, the pacemaker algorithm enabled us to recognize sleep disorders, especially in the severe SA group, apnea-dominant group (HA group), and CSA-dominant group (HC group). It can be a useful screening tool for undiagnosed SA in Japanese individuals with pacemaker implants.

Although PSG has been the most reliable standard for diagnosing SA, it is costly and time-consuming [26]. Furthermore, it is difficult to repeat over time. However, for pacemaker-implanted patients, we can obtain the daily RDI records for up to 6 months. The daily fluctuations are considered as an advantage point compared to PSG which can help us to understand sleep apnea severity that might be affected by some cardiac disease conditions. It has been reported that CSA is especially increased in heart failure patients [27]. The SAM algorithm might be a useful tool for monitoring daily RDI and even for predicting heart failure development if the RDI worsens. Because it has not been clarified whether SA onset precedes the beginning of heart failure development, a long-term observation, focused on heart failure patients involving resynchronization therapy devices is needed.

Study limitations

Our study had some limitations. It was a single-center study and the number of subjects was too small to conduct interaction across subgroup analysis. To conduct partial correlation coefficient as a substitute analysis, only one factor could be removed because of small subgroup subjects. The influence of various confounding factors was not completely excluded. Further investigation with more subjects is needed.

Our patients included those with not only initial implantation but also generator replacement. Since PSG was performed during the same hospitalization period when pacemaker implantation was performed,

the influence immediately after the operation on the lead impedance measurements cannot be denied; for example, pocket edema, myocardial inflammation, and hematoma around the lead tip.

Conclusion

The SAM algorithm is a useful screening tool for SA in Japanese individuals with pacemakers, especially in the severe SA group, apnea-dominant group, and CSA-dominant group.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

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