Implantable cardioverter-defibrillator–computed respiratory disturbance index accurately identifies severe sleep apnea: The DASAP-HF study ⓔ

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BACKGROUND Sleep apnea (SA) is a relevant issue in the management of patients with heart failure for risk stratification and for implementing treatment strategies.

OBJECTIVE The purpose of this study was to evaluate in patients with implantable cardioverter-defibrillators (ICDs) the performance of the respiratory disturbance index (RDI) computed by the ApneaScan algorithm (Boston Scientific Inc., Natick, MA) as a discriminator of severe SA.

METHODS ICD-indicated patients with left ventricular ejection fraction ≤35% were enrolled. One month after implantation, patients underwent a polysomnographic study. We evaluated the accuracy of the RDI for the prediction of severe SA (apnea-hypopnea index [AHI] ≥30 episodes/h) and the agreement between RDI and AHI during the sleep study night.

RESULTS Two hundred sixty-five patients were enrolled to obtain the required sample of 173 patients with AHI and RDI data for analysis. The mean AHI was 21 ± 15 episodes/h and severe SA was diagnosed in 38 patients (22%), while the mean RDI was 33 ± 13 episodes/h. On the basis of the receiver operating characteristic curve analysis of RDI values, the area under the curve was 0.77 (95% confidence interval [CI] 0.70–0.83; $P < .001$). At an RDI value of 31 episodes/h, severe SA was detected with 87% (95% CI 72%–96%) sensitivity and 56% (95% CI 48%–66%) specificity. RDI closely correlated with AHI recorded during the same night ($r = 0.74$; 95% CI 0.57–0.84; $P < .001$), and the Bland-Altman agreement analysis revealed a bias of 11 episodes/h, with limits of agreement being −10 to 32 episodes/h.

CONCLUSION The RDI accurately identified severe SA and demonstrated good agreement with AHI. Therefore, it may serve as an efficient tool for screening patients at risk of SA.

KEYWORDS Heart failure; ICD; Respiratory disturbances; Sleep apnea; Thoracic impedance

Introduction

Sleep-disordered breathing is the most common comorbidity in heart failure (HF), occurring in 30%–80% of the affected patients.[1,2] Obstructive sleep apnea (SA) is more common and occurs both in the general population and in the population with HF, whereas central SA is closely

associated with HF.[3] SA has been associated with the development of hypertension[4] and arrhythmias[5–7] and has been shown to have a negative prognostic value in HF.[8] In particular, SA is an independent risk factor for malignant ventricular arrhythmias, which require appropriate implantable cardioverter-defibrillator (ICD) therapies in patients with HF.[9]

Although polysomnography is the diagnostic gold standard, access to this procedure is limited and frequently clinically significant SA remains undiagnosed.[10] Alternative methods of monitoring sleep-related breathing disorders are therefore needed in patients with cardiovascular diseases at higher risk of SA. Recently, automated algorithms based on the continuous measurement of thoracic impedance have been developed to detect advanced sleep-disordered breathing.[11] Some modern pacemakers and ICD are equipped with these algorithms and provide indices for the continuous quantification of the severity of SA.

The Diagnosis of Sleep Apnea in Patient With Heart Failure (DASAP-HF) study aimed at evaluating in patients with an ICD the performance of the respiratory disturbance index (RDI) computed by the ApneaScan algorithm (Boston Scientific Inc., Natick, MA) as a discriminator of severe SA.

Methods
Patient selection
The study was a prospective, nonrandomized, multicenter evaluation of patients implanted with an ICD or cardiac resynchronization therapy with ICD (CRT-D) endowed with the ApneaScan diagnostic feature (the list of centers is reported in Appendix 1). Patients had to present with current ICD or CRT-D indications[12,13] and with left ventricular systolic dysfunction, that is, left ventricular ejection fraction ≤35%. Patients already receiving CRT, those unavailable to attend scheduled follow-up visits at the center, or those with a life expectancy of <12 months were all excluded. The ethics committees approved the study, and all patients gave written informed consent.

Study design
Devices and pacing leads were implanted by means of standard techniques. Baseline evaluation included demographic characteristics and medical history, clinical examination, 12-lead electrocardiogram, and echocardiographic evaluation. At 1 month after enrollment, patients underwent an in-clinic visit. If RDI values were measured and stored by the device within 7 days before the visit, a sleep study was scheduled within 7 days. Otherwise, a new visit was planned after 2 months (3 months from the enrollment). After the sleep study, the implanted device was interrogated and stored data were retrieved.

Sleep study recording
Each patient underwent an unattended home nocturnal recording by means of a portable SA monitor (Embletta, Broomfield, CO) equipped with multiple sensors, in agreement with the current American Academy of Sleep Medicine guidelines for the detection of respiratory events.[14] The parameters recorded were oronasal airflow and air temperature, thoracoabdominal movements through plethysmography, O_2 saturation by a finger pulse oximeter, body position and movement, and snoring. Recordings were evaluated by a core laboratory, blinded to the values recorded by the implanted device. *Apnea* was defined as a drop in the peak thermal sensor excursion by >90% of the baseline value and lasting ≥10 seconds, and *hypopnea* was defined as a >50% reduction in oronasal airflow lasting ≥10 seconds together with a >3% drop in oxygen saturation. The apnea-hypopnea index (AHI) was computed as the number of apneas and hypopneas divided by the sleep time analyzed, minus movement time and standing position time. For the purposes of the present study, *SA* was defined as severe if the AHI was ≥30 episodes/h during the sleep study night.[11,15]

Device characteristics
Commercially available ICD/CRT-Ds and transvenous leads were used in this study. Devices were equipped with the ApneaScan diagnostic feature, which continuously measures thoracic impedance by sending a low-voltage signal from the lead and the ICD can. As thoracic impedance varies with respiratory movements, changes in impedance are used to create a waveform that is used to count respiration. At the time of device programming, the diagnostic feature is enabled and a programmable time period when the patient is expected to be sleeping is set. At night, the algorithm automatically detects apnea-hypopnea events by assessing the amount of time between breaths that exceed a minimum baseline value. The baseline is a weighted average of tidal volumes, which is continually updated to account for small changes. In case of sudden large increases or decreases in the respiratory sensor signal after postural changes, the algorithm quickly readjusts the baseline. After verification of the signal quality and validation of the respiratory interval measurement, the algorithm defines an apnea episode as 2 consecutive large breaths, where the time between breaths is >10 seconds, and a hypopnea episode as an interval between large breaths >10 seconds, which additionally contains consecutive small breaths. The total number of apnea and hypopnea events is stored, and the RDI is calculated by dividing the number of events by the programmed sleep duration. Data collection begins 1 hour after the programmed start time and ends 1 hour before the end of the sleep duration, so that data are not collected while the patient is expected to fall asleep and wake-up. Moreover, measurements are suspended during other ICD activities (eg, capacitor charge, shock, and lead impedance measurements). At least 2 hours of valid data must be obtained to calculate the RDI value of the day. The RDI is presented as a daily trend on device interrogation. The development of the ApneaScan algorithm is based on data from a published study.[11]

SA prediction and analysis

The primary objective of this study was to evaluate the performance of the device-calculated RDI value as a binary discriminator of severe SA. For the analysis, the average RDI value calculated by the algorithm over a 1-week period preceding the sleep study was used.

The secondary objective was to assess the performance of the RDI as a diagnostic tool by evaluating the agreement between RDI and AHI values. The RDI value recorded during the same diagnosis night was then compared with the AHI.

Statistical analysis

Continuous data were expressed as mean ± SD. Categorical data were expressed as number (percentage). For the primary objective, a receiver operating characteristic (ROC) curve analysis was conducted to assess the performance of the RDI as a predictor for SA (determined by the sleep study on the basis of an AHI cutoff of 30 episodes/h). In our analysis, we optimized sensitivity and specificity simultaneously; that is, we regarded the value resulting in the maximum product of sensitivity and specificity on the curve as the optimal cutoff. The sensitivity and specificity of the RDI were also specified, along with 95% confidence interval (CI), for an RDI cutoff of 32 episodes/h (nominal cutoff for severe SA in the ApneaScan algorithm).

The sample size for the analysis (170 patients) was estimated on the basis of the assumption that the study would have 90% power to detect a difference from the area under the curve (AUC) of 0.5 (equivalently RDI had no predictive value), with 0.68 expected AUC and 20% prevalence of SA. Considering 30% of unavailable RDI values and 15% of sleep studies not adequately performed or not scheduled on time, a maximum sample of 320 subjects was considered to allow the analysis of the primary objective. Nonetheless, the enrollment was interrupted as soon as the target of 170 patients in the analysis was achieved.

The performance of the RDI as a diagnostic tool was determined by comparing all available RDI and AHI values recorded during the sleep study night. Agreement between the 2 indices was computed as the bias (mean), with limits of agreement computed as bias ± 2SD when differences followed normal distribution.[16] Normality was tested by means of the Kolmogorov-Smirnov 1-sample test. Statistical correlations between variables were tested by means of linear regression analysis. A P value of <.05 was considered significant for all tests. All statistical analyses were performed by means of Statistica software, version 7.1 (StatSoft, Inc., Palo Alto, CA).

Results
Study population

A total of 265 patients were enrolled in the study between March 31, 2014 and July 6, 2016 at 13 centers in Italy and Spain. Nine patients died before the visit at 1 or 3 months. In 75 patients no RDI values were recorded by the ICD within 7 days before the visit, while 8 patients did not undergo the
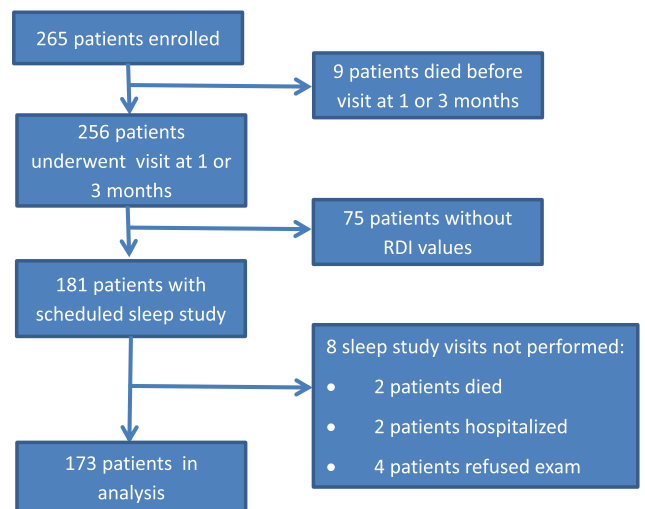

Figure 1   Patient disposition.

scheduled sleep study. The remaining 173 patients underwent home nocturnal recording, and stored data were retrieved from the implanted device (Figure 1). Table 1 lists baseline clinical variables.

Sleep study and SA detection

The mean AHI value on the polygraphic recording was 21 ± 15 episodes/h, and severe SA was diagnosed in 38 patients

Table 1   Demographic characteristics and baseline clinical parameters (N = 173)

Parameter	Value
Age (y)	68 ± 10
Sex: male	139 (80)
Body mass index (kg/m²)	27 ± 8
Primary prevention	152 (88)
NYHA class III–IV	91 (53)
QRS duration (ms)	126 ± 38
Sinus rhythm	133 (77)
Ischemic heart disease	91 (53)
Hypertension	38 (22)
History of atrial fibrillation	31 (18)
Pulmonary diseases	60 (35)
COPD	22 (13)
Chronic kidney disease	17 (10)
Diabetes	47 (27)
LV ejection fraction (%)	29 ± 5
LVESV (mL)	84 ± 74
LVEDV (mL)	122 ± 99
Creatinine level (mg/dL)	1.08 ± 0.62
ACE-inhibitor use	151 (87)
Aldosterone antagonist use	100 (58)
β-Blocker use	165 (96)
Diuretic use	162 (94)
Antiarrhythmic drug use	44 (25)
CRT-D device	87 (50)

Values are presented as mean ± SD or as n (%).

ACE = angiotensin-converting enzyme; CRT-D = cardiac resynchronization therapy–defibrillator; COPD = chronic obstructive pulmonary disease; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association.
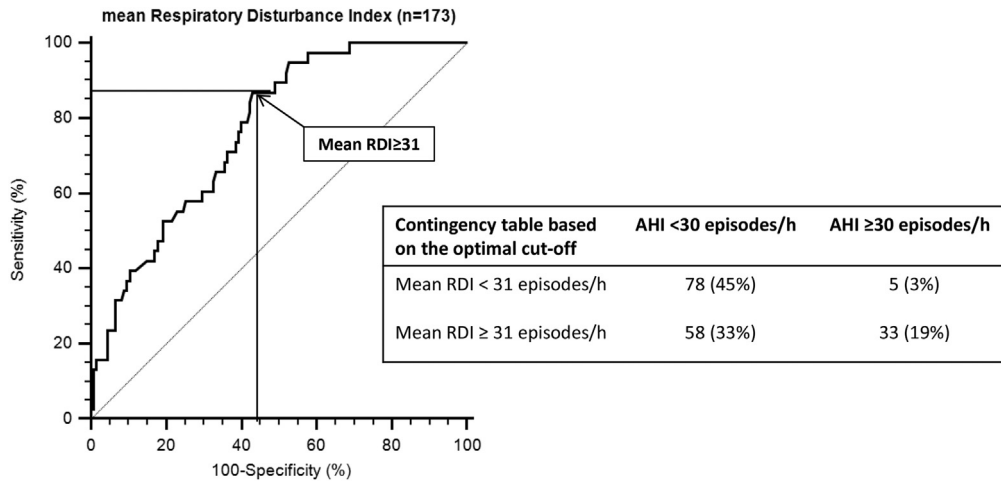
Figure 2 Receiver operating characteristic curve analysis of the RDI. Sensitivity and specificity were 87% (95% confidence interval 72%–96%) and 56% (95% confidence interval 48%–66%), respectively, at 31 episodes/h. AHI = apnea-hypopnea index; RDI = respiratory disturbance index.

(22%) (AHI ≥30 episodes/h). Among patients with severe SA, 19 (50%) had a predominance of central apnea, 16 (42%) obstructive apnea, and 3 (8%) mixed apnea.

Primary end point

The mean RDI value recorded by the implanted devices during the week preceding the study night was 33 ± 13 episodes/h. On the basis of the ROC curve analysis of RDI values for the prediction of severe SA, the AUC was 0.77 (95% CI 0.70–0.83; $P < .001$) (Figure 2). The cutoff that best identified severe SA and maximized sensibility and specificity was 31 episodes/h. It enabled severe SA to be detected with 87% (95% CI 72%–96%) sensitivity and 56% (95% CI 48%–66%) specificity. When a cutoff of 32 episodes/h (nominal cutoff for severe SA in the ApneaScan algorithm) was adopted, the sensitivity and specificity were 79% (95% CI 63%–90%) and 58% (95% CI 50%–67%), respectively. Two examples of RDI values in patients with and without severe SA are presented in Figure 3.

The results of the ROC curve analysis of RDI values for the prediction of severe SA in specific subgroups are presented in Table 2. The RDI was equally accurate in detecting severe SA across subgroups.

Secondary end point

The performance of the RDI as a diagnostic tool was determined by comparing the RDI and AHI values during the sleep study night. In 49 (28%) of the 173 patients in the analysis, the RDI and AHI values were available for the same night. The mean AHI value was 20 ± 15 episodes/h, and the RDI was 31 ± 14 episodes/h. The RDI value closely correlated with the AHI value ($r = 0.74$; 95% CI 0.57–0.84; $P < .001$). The Bland-Altman agreement analysis between RDI and AHI values during the sleep study night revealed a bias between measurements of 11 episodes/h, with limits of agreement being −10 to 32 episodes/h. The regression line of differences showed an intercept coefficient of 13.0 (95% CI 6.4–19.7; $P < .001$) and a slope coefficient

of −0.07 (95% CI −0.30 to 0.16; $P = .561$) (Figure 4). The agreement analysis performed in patients with nonsevere SA revealed a bias between measurements of 14 episodes/h, with limits of agreement being −3 to 31 episodes/h. In this subgroup, the correlation coefficient between RDI and AHI values was 0.64 (95% CI 0.41–0.79; $P < .001$). In patients with severe SA, the bias between measurements was −1 episodes/h, with limits of agreement being −22 to 21 episodes/h. In this subgroup, the correlation coefficient between RDI and AHI values was 0.80 (95% CI 0.30–0.96; $P = .009$) (Figure 4).

Discussion

The present study demonstrated that the device-computed RDI was able to accurately predict severe SA in patients who received an ICD/CRT-D endowed with the ApneaScan algorithm. Moreover, good agreement was seen between RDI
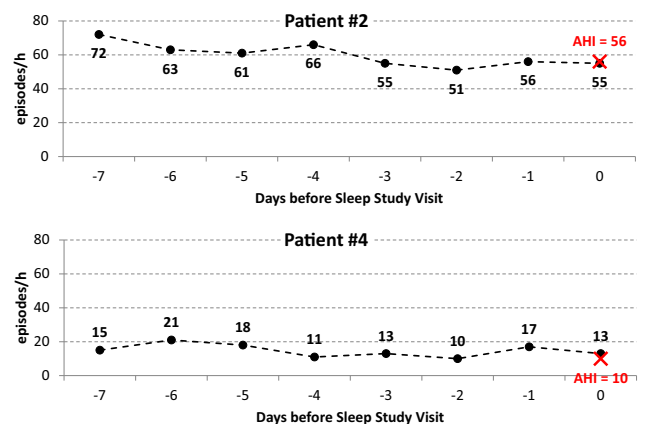

Figure 3 Examples of respiratory disturbance index values in patients with and without severe sleep apnea (AHI = 56 episodes/h and AHI = 10 episodes/h, respectively). The data collected before the sleep study visit were available on device interrogation and presented as a daily trend. AHI = apnea-hypopnea index.

Table 2 Results of the receiver operating characteristic curve analysis of RDI values for the prediction of severe sleep apnea in specific subgroups

Variable	Area under the curve	95% confidence interval	P
CRT-D recipient (n = 87)	0.75	0.64–0.83	<.001
No CRT-D recipient (n = 86)	0.78	0.68–0.87	<.001
Diagnosed pulmonary diseases (n = 60)	0.80	0.61–0.92	<.001
Undiagnosed pulmonary diseases (n = 113)	0.74	0.64–0.81	<.001
Predominant central apnea (n = 61)	0.73	0.60–0.84	.001
Predominant obstructive apnea (n = 72)	0.77	0.65–0.86	<.001

CRT-D = cardiac resynchronization therapy–defibrillator; RDI = respiratory disturbance index.

estimates and AHI values measured during the same night by means of a standard home nocturnal polygraphic recording.

Sleep-related breathing disorders are frequent in patients with cardiovascular disease.[17] Cardiac arrhythmias are more frequent in persons with obstructive SA and increase with the number of apneic episodes.[18] Nocturnal arrhythmias have been shown to occur in up to 50% of patients with obstructive SA, the most common being nonsustained ventricular tachycardia, sinus arrest, atrioventricular conduction block, and frequent premature ventricular contractions.[6,7] Moreover, obstructive SA has been shown to affect a higher proportion of patients with a history of atrial fibrillation than of the general population.[19]

According to the recommendations from American[20,21] and European[22] guidelines, clinical judgment should be used to screen for sleep-disordered breathing in patients with HF. However, although patients who are hospitalized with an admission diagnosis of acute HF have a high likelihood of testing positive for sleep-disordered breathing,[23,24] sleep studies are rarely performed in hospitals as routine clinical care. The reasons why few HF programs investigate coexisting SA are that most patients with HF do not complain of daytime sleepiness or other features of SA[25] and that the diagnosis of SA requires overnight polysomnography performed in a sleep laboratory. During the test, multiple physiological variables are recorded continuously. These variables generally include sleep staging by means of an electroencephalogram, electromyogram, electro-oculogram, respiration, and snoring. Through these signals, disordered breathing and its effect on sleep and oxygenation can be precisely quantified.[14] Access to polysomnography is limited, as it requires special institutions
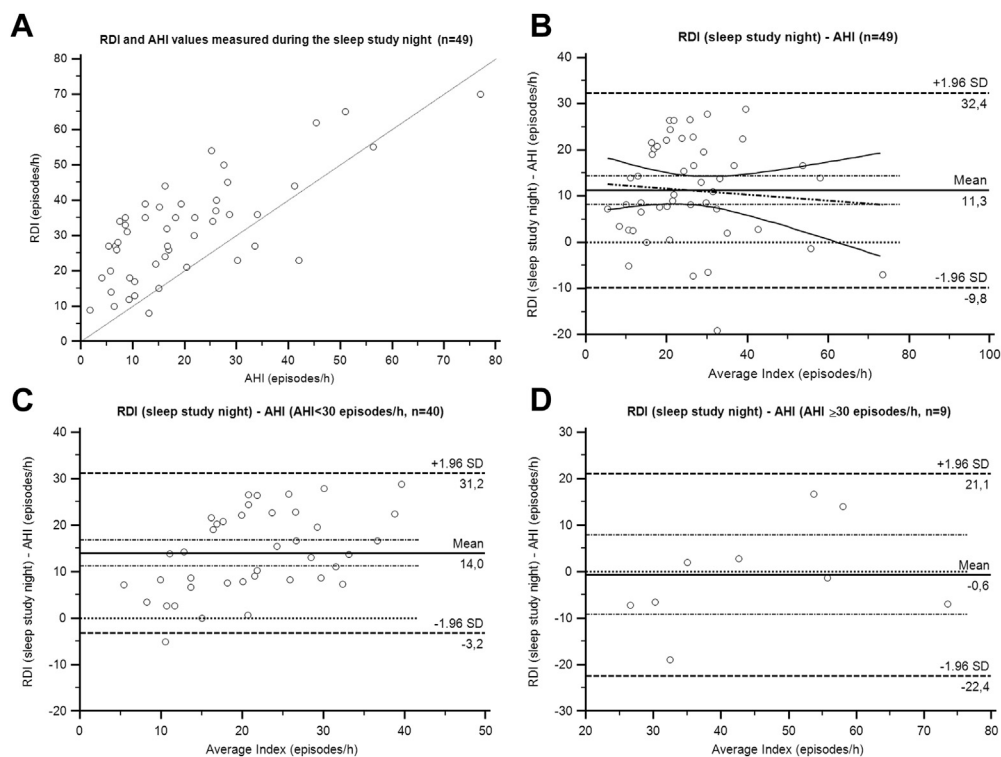

Figure 4   **A:** Diagram showing RDI and AHI values measured during the sleep study night in 49 patients. **B:** Bland-Altman plots. RDI-AHI is the difference between indices; average index is their mean. The solid line indicates the bias and the dashed lines the limits of agreement between indices. The regression line of differences is shown with its 95% confidence interval. **C:** Bland-Altman plot for patients with non-severe SA (AHI <30 episodes/h). **D:** Bland-Altman plot for patients with severe SA (AHI ≥30 episodes/h). AHI = apnea-hypopnea index; RDI = respiratory disturbance index.

and trained technicians and is relatively expensive. This problem of timely access results in undiagnosed and under-treated SA, as well as excessively long waiting lists.[26,27] Indeed, in clinical practice, >85% of patients with clinically significant and treatable obstructive SA are not diagnosed by means of standard methods.[28,29] This is confirmed by the high proportion of patients with a history of undiagnosed severe SA (22%) in our series.

Alternative methods for screening patients for sleep-disordered breathing have been proposed, though their sensitivity and specificity have not always been assessed. Some of these options include questionnaires, overnight oximetry, and devices combining limited respiratory assessment. Recently, some modern pacemakers and ICDs have been equipped with automated algorithms for the automatic detection of advanced sleep-disordered breathing.[11] In the present study, we measured the performance of one such algorithm in a population of patients with no prior diagnosis of sleep-disordered breathing. We enrolled unselected patients with systolic HF with current ICD/CRT-D indications, thus ensuring the external validity of our results.

The average RDI value calculated by the ICD over a 1-week period accurately identified patients with severe disordered breathing on the polygraphic recording subsequently performed. Therefore, the ICD diagnostics may serve as an efficient tool for screening patients at risk of SA. Patients identified by the automatic algorithm may therefore subsequently undergo standard polysomnography to confirm the diagnosis, determine the type of SA, and then guide the treatment decision. In our analysis, the RDI was equally accurate in detecting severe SA across prespecified subgroups. Indeed, the accuracy of the algorithm seemed high regardless of CRT, previous diagnosis of pulmonary disorders, or type of SA. The ApneaScan algorithm is currently available in the European market, and the results of the DASAP-HF study are completely in line with the intended use statement, that is, providing data that, along with other clinical information, could be used to identify and follow changes in patients who may be at high risk of sleep-disordered breathing. While for the actual diagnosis of SA, the manufacturer suggests to rely only on standard clinical methods such as polysomnography.

In the present study, we also demonstrated good agreement between AHI and RDI values recorded during the sleep study night, showing good performance of the algorithm as a diagnostic tool. Nonetheless, we showed a systematic bias toward overestimation of the RDI (11 episodes/h). In particular, the RDI performed well, with no bias between measurements, in patients with frequent SA episodes. However in patients with less frequent SA episodes (AHI <30 episodes/h), the RDI value was affected by a positive bias and the correlation with the AHI was lower. This could be ascribed to the sensitivity value adopted by the algorithm to detect breathing events or to the gradual adjustments in the reference tidal volume continuously performed by the system to account for possible postural changes. Another possible source of error could be an imprecise setting of the

sleep time at ICD implantation. Indeed, the system collects data during a fixed time period when the patient is expected to be sleeping. Further refinements of the algorithm may include integration of multiple sensors to automatically assess sleep time.[30] Although the automatic detection of respiratory disturbances by ICDs should not be intended as a comprehensive alternative to a standard sleep study, this last finding supports the possible use of the RDI as a tool for the continuous monitoring of respiratory disturbances.

Recently, Mazza et al[31] investigated the relationship between the ApneaScan-measured RDI and the occurrence of atrial fibrillation in patients who received a pacemaker endowed with the algorithm. Their findings suggest an additional potential use of the diagnostics, as device-detected severe SA was independently associated with a higher risk of new-onset atrial fibrillation. In particular, severe SA on follow-up data review identified patients who were about twice more likely to experience an atrial fibrillation episode in the next 3 months. The long-term follow-up of patients enrolled in the DASAP-HF study will allow to confirm this preliminary result and extend it by testing the association between ICD-detected SA and the clinical outcome.

Study limitations

The present study lacked a test set for independent validation of the algorithm performance, and therefore the RDI cutoff value for severe SA identification must be interpreted with caution. Although the present study allowed to demonstrate the ability of the RDI to screen patients at risk of severe SA, it did not assess the clinical impact of its adoption. Specific screening protocols should be implemented and tested to verify the effectiveness and efficiency of this novel tool in clinical practice.

Conclusion

The ICD-computed RDI accurately identified severe SA and demonstrated good agreement with AHI values measured during the same night by ambulatory polygraphy. The RDI may serve as an efficient tool for screening patients at risk of severe SA. The ability of ICDs to continuously and remotely monitor respiratory disturbances could allow both the evolution of SA and the possible impact of therapeutic interventions to be assessed.

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Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2017.09.038.

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