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Association Between Device-Detected Sleep-Disordered Breathing and Implantable Defibrillator Therapy in Patients With Heart Failure

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ABSTRACT

BACKGROUND Sleep-disordered breathing is highly prevalent in heart failure (HF) and has been suggested as a risk factor for malignant ventricular arrhythmias. The Respiratory Disturbance Index (RDI) computed by an implantable cardioverter-defibrillator (ICD) algorithm accurately identifies severe sleep apnea.

OBJECTIVES In the present analysis, the authors evaluated the association between ICD-detected sleep apnea and the incidence of appropriate ICD therapies in patients with HF.

METHODS We enrolled 411 HF patients who had received an ICD endowed with an algorithm that calculates the RDI each night. In this analysis, the weekly mean RDI value was considered. The endpoint was the first appropriate ICD shock.

RESULTS The median follow-up was 26 months (25th to 75th percentile: 16-35 months). During follow-up, 1 or more ICD shocks were documented in 58 (14%) patients. Patients with shocks were younger (age 66 $\pm$ 13 years vs 70 $\pm$ 10 years; $P = 0.038$), and had more frequently undergone implantation for secondary prevention (21% vs 10%; $P = 0.026$). The maximum RDI value calculated during the entire follow-up period did not differ between patients with and without shocks (55 $\pm$ 15 episodes/h vs 54 $\pm$ 14 episodes/h; $P = 0.539$). However, the ICD-detected RDI showed considerable variability during follow-up. The overall median of the weekly RDI was 33 episodes/h (25th to 75th percentile: 24-45 episodes/h). A time-dependent Cox regression model revealed that a continuously measured weekly mean RDI of ≥45 episodes/h was independently associated with shock occurrence (HR: 4.63; 95% CI: 2.54-8.43; $P < 0.001$), after correction for baseline confounders (age, secondary prevention).

CONCLUSIONS In HF patients, appropriate ICD shocks were more likely to be delivered during periods when patients exhibited more sleep-disordered breathing. (Arrhythmias Detection in a Real World Population [RHYTHM DETECT]; NCT02275637) (J Am Coll Cardiol EP 2022;8:1249–1256) © 2022 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CRT-D = cardiac resynchronization therapy implantable cardioverter-defibrillator

CSA = central sleep apnea

HF = heart failure

ICD = implantable cardioverter-defibrillator

OSA = obstructive sleep apnea

RDI = Respiratory Disturbance Index

SA = sleep apnea

SDB = sleep-disordered breathing

Sleep-disordered breathing (SDB) is frequent in heart failure (HF).[1] Although obstructive sleep apnea (OSA) is the most common type of SDB and is characterized by transient mechanical obstruction of the upper airways, central sleep apnea (CSA), ie, altered central respiratory control, is more common in HF patients. Sleep-disordered breathing has been associated both with the development of arrhythmias[2,3] and with a higher risk of sudden cardiac death.[4] Using data from implantable cardioverter-defibrillators (ICDs), several studies have investigated the impact of SDB on the incidence of ventricular arrhythmias in HF patients, and have found that both OSA and CSA are independent predictors of life-threatening ventricular arrhythmias.[5-8] Some modern pacemakers and ICDs are equipped with automated algorithms that measure thoracic impedance to detect sleep apnea (SA) events.[9,10] Their ability to continuously monitor the severity of SDB is potentially an opportunity to risk-stratify patients dynamically during follow-up.

The objective of this analysis was to investigate the association between ICD-detected SDB and the incidence of appropriate ICD therapies in patients with HF.

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METHODS

PATIENT SELECTION. The study was a prospective, nonrandomized, multicenter evaluation of patients receiving an ICD or cardiac resynchronization therapy implantable cardioverter-defibrillator (CRT-D) endowed with the ApneaScan (Boston Scientific) diagnostic feature. Consecutive HF patients with reduced left ventricular ejection fraction (≤35% at the time of implantation) who had received a device in accordance with standard indications[11] and who were enrolled in the LATITUDE (Boston Scientific) remote monitoring platform were enrolled at 27 study centers (full list of participating centers in the Supplemental Appendix) and followed up in accordance with the standard practice of the participating centers. Data on the clinical events that occurred during follow-up were collected at the study centers within the framework of a prospective registry. The Institutional Review Boards approved the study, and all patients provided written informed consent for data storage and analysis.

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 changes to count respiration. At night, the algorithm automatically detects apnea/hypopnea events by counting the interbreath time intervals that exceed a minimum baseline value. After verifying the signal quality and validating the respiratory interval measurement, the algorithm defines an apnea episode as 2 consecutive deep breaths with an interval of >10 s between breaths, and a hypopnea episode as an interval >10 s between deep breaths, which additionally contains consecutive small breaths. The total number of apnea and hypopnea events is stored and the Respiratory Disturbance Index (RDI) is calculated by dividing the number of events by the programmed sleep duration. Measurements are suspended during other ICD activities (eg, capacitor charge, shock, lead impedance measurements). At least 2 hours of valid data must be obtained to calculate the RDI value on the day. The RDI is presented as a daily trend on device interrogation. Development of the ApneaScan algorithm is based on data from a published study.[9]

STUDY ENDPOINTS. The objective of the present analysis was to investigate the association between the RDI values calculated by the ICD algorithm and the incidence of therapies delivered by the ICD. The episodes considered in the analysis were spontaneous ventricular tachyarrhythmias detected and treated by the implanted device and subsequently validated by the local investigator. The primary endpoint was the first appropriate ICD shock therapy. The secondary endpoint was the first ICD therapy (antitachyarrhythmia pacing or shock) for ventricular tachycardia or ventricular fibrillation.

STATISTICAL ANALYSIS. Descriptive statistics are reported as mean ± SD for normally distributed continuous variables or as median (25th to 75th percentile) in the case of skewed distribution. Normality of distribution was tested by means of the nonparametric Kolmogorov-Smirnov test. Categorical data are expressed as percentages. Analysis of the time to the first episode was made using the Kaplan-Meier method. Cox proportional hazards models were used to determine the association between patients' baseline characteristics and the occurrence of the endpoints during the follow-up period, and to estimate the HRs and the 95% CIs of an episode. The weekly RDI value was also treated as a time-varying covariate in time-dependent Cox models. All variables displaying statistical significance ($P < 0.05$) were entered into a multivariate regression analysis.

The model was adjusted for those baseline variables that proved to be associated with the occurrence of endpoints on univariate analysis. A P value <0.05 was considered significant for all tests. All statistical analyses were performed by means of R: a language and environment for statistical computing (R Foundation for Statistical Computing).

RESULTS

STUDY POPULATION. From December 2017 to June 2021, 411 patients received an ICD or CRT-D and were enrolled. **Table 1** shows the baseline clinical variables of all patients in analysis. All patients received a device programmed to 2 detection zones: one beginning at ≥170 beats/min in 87% of patients for ventricular tachycardia, with a ≥5-second delay before delivery of antitachycardia pacing or shock in 93% of patients; the other beginning at ≥200 beats/min in 93% of patients for faster tachycardia, with a ≤2.5-second delay in 85% of patients. No patient was reported to receive continuous positive airway pressure therapy during the observation period.

FOLLOW-UP. The median follow-up was 26 months (25th to 75th percentile: 16-35 months). During follow-up, 1 or more ICD shocks were documented in 58 (14%) patients. **Figure 1** shows the Kaplan-Meier analysis of time to the first ICD shock. An ICD therapy (antitachyarrhythmia pacing or shock) for ventricular tachycardia or ventricular fibrillation was delivered in 100 (24%) patients (**Figure 1**).

The ICD-detected RDI values recorded in all patients during the entire follow-up period were stored on the remote monitoring platform. The RDI showed considerable variability during follow-up in the overall population (**Figure 2**) and in individual patients (Supplemental Figure 1). The overall median of the weekly RDI was 33 episodes/h (25th to 75th percentile: 24-45 episodes/h), and it resulted higher in secondary prevention (35 episodes/h [25th to 75th percentile: 26-46 episodes/h]) than in primary prevention patients (33 episodes/h [25th to 75th percentile: 24-44 episodes/h]) ($P < 0.001$). The distribution of weekly RDI values stratified by primary or secondary prevention is reported in Supplemental Figure 2. The weeks during which the ICDs delivered shocks or any therapy for ventricular tachycardia or ventricular fibrillation were most frequently those in which the device detected higher RDI values in the overall population (**Figure 2**) and in the groups stratified by primary or secondary prevention (Supplemental Figure 3). The median RDI was 47 episodes/h (25th to 75th percentile: 27-51 episodes/h) during weeks with shocks and 33 episodes/h (25th to 75th percentile: 24-44 episodes/h) during weeks with no shocks ($P = 0.026$). However, the maximum RDI value calculated during the entire follow-up period did not differ between patients with and without shocks (55 ± 15 episodes/h vs 54 ± 14 episodes/h; $P = 0.539$). Comparison of the shock rate during weeks with mean RDI >45 episodes/h (ie, the 75th percentile of the RDI distribution) (0.20 shocks/y; 95% CI: 0.13-0.28 shocks/y) with that with RDI ≤45 episodes/h (0.04 shocks/y; 95% CI: 0.03-0.07 shocks/y) yielded an incidence rate ratio of 4.53 (95% CI: 2.43-8.62; $P < 0.001$). Similarly, the rate of shocks or antitachyarrhythmia pacing during weeks with mean RDI >45 episodes/h was 0.25 events/y (95% CI: 0.17-0.36 events/y) and that during the remaining weeks was 0.11 events/y (95% CI: 0.08-0.15 events/y), with an incidence rate ratio of 2.33 (95% CI: 1.43-3.76; $P < 0.001$).

TABLE 1 Demographics and Baseline Clinical Parameters (N = 411)

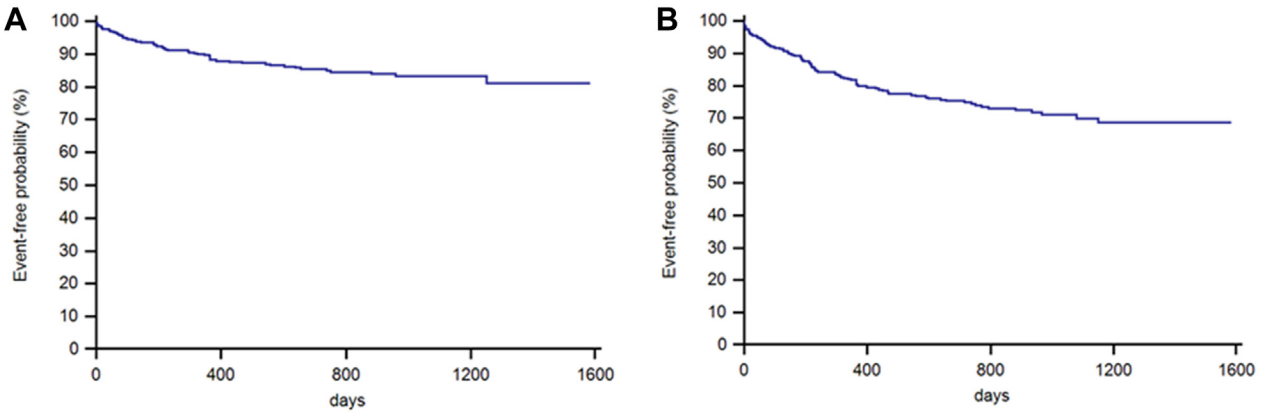
Age, y	69 ± 10
Male	317 (77)
Body mass index, kg/m^2	26 ± 4
Ischemic heart disease	193 (47)
NYHA functional class	
I	19 (5)
II	250 (61)
III	134 (33)
IV	8 (2)
LV ejection fraction, %	32 ± 8
History of atrial fibrillation	136 (33)
Secondary prevention	49 (12)
CRT device	297 (72)
Diabetes	113 (27)
Chronic kidney disease	107 (26)
Pulmonary disease	70 (17)
Hypertension	223 (54)
β-blocker use	377 (92)
Diuretic use	367 (89)
Antiarrhythmic use	86 (21)
ACE inhibitor, ARB, or ARNI use	386 (94)
Weekly RDI, episodes/h	33 (24-45)
Maximum RDI, episodes/h	54 ± 14

Values are mean ± SD, n (%), or median (25th to 75th percentile).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; CRT = cardiac resynchronization therapy; LV = left ventricular; NYHA = New York Heart Association; RDI = Respiratory Disturbance Index.

ASSOCIATION BETWEEN RDI AND ENDPOINT OCCURRENCE. The results of the regression analysis of variables associated with ICD shock and any ICD therapy occurrence are shown in **Table 2**. On applying a Cox regression model, the maximum device-detected RDI was not associated with the occurrence of shocks. However, on using a time-dependent Cox model, the continuously measured weekly mean RDI

FIGURE 1 Time to Primary and Secondary Endpoint



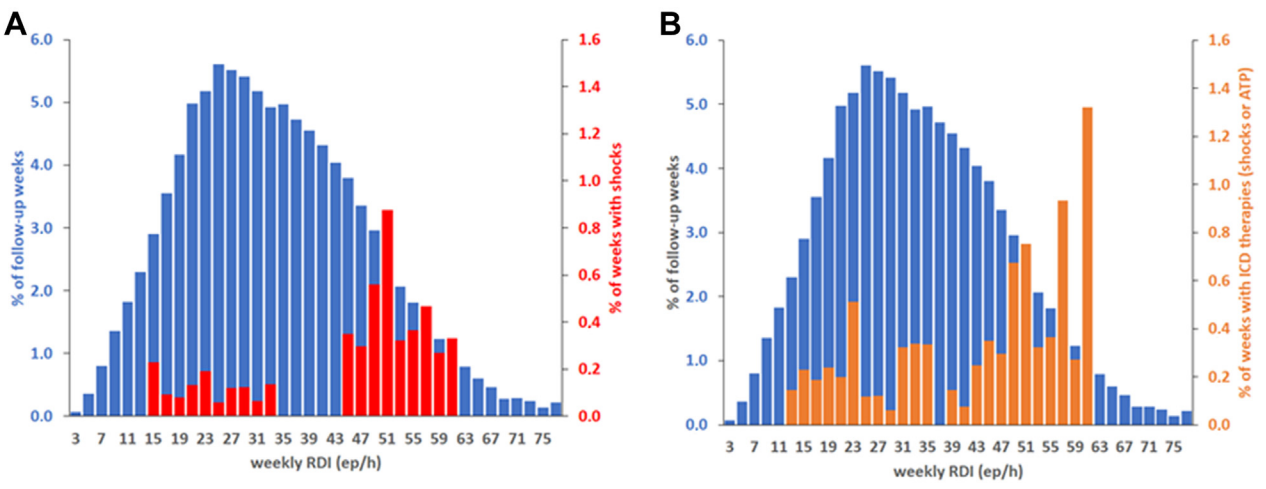
(A) Time to first implantable cardioverter-defibrillator shock delivered during follow-up. **(B)** Time to first implantable cardioverter-defibrillator therapy (antitachyarrhythmia pacing or shock) for ventricular tachycardia or ventricular fibrillation.

was associated with the occurrence of shock (HR: 1.03; 95% CI: 1.01-1.05; $P = 0.026$) and of any ICD therapy (antitachyarrhythmia pacing or shock) (HR: 1.02; 95% CI: 1.00-1.04; $P = 0.035$). After correction for age and implantation for secondary prevention, the association was confirmed between RDI as a continuous variable and shocks (HR: 1.04; 95% CI: 1.01-1.08; $P = 0.032$) or any ICD therapy (HR: 1.03; 95% CI: 1.00-1.07; $P = 0.038$). With a dichotomous approach, a weekly mean RDI >45 episodes/h was associated with the occurrence of shock (HR: 4.54; 95% CI: 2.50-8.22; $P < 0.001$). This association was confirmed (HR:4.63, 95% CI: 2.54-8.43; $P < 0.001$) after correction for age and implantation for secondary prevention (Figure 3). A weekly mean RDI >45 episodes/h was also associated with the occurrence of any ICD therapy (HR: 2.36; 95% CI: 1.48-3.77; $P < 0.001$), as reported in Figure 3.

DISCUSSION

In the present study of patients with HF, we analyzed the association between the incidence of appropriate ICD therapies and SDB, as evaluated by an automatic

FIGURE 2 Distribution of Weekly RDI Values



Blue bars indicate overall median value 33 episodes/h (25th to 75th percentile: 24-45 episodes/h). **(A)** Distribution of follow-up weeks with implantable cardioverter-defibrillator shocks according to the weekly Respiratory Disturbance Index (RDI) value **(red bars)**. **(B)** Distribution of follow-up weeks with any implantable cardioverter-defibrillator therapy according to the weekly RDI value **(orange bars)**.

ICD algorithm based on the measurement of thoracic impedance. We found an association between RDI values continuously measured by the ICD and the occurrence of shocks and any ICD therapy delivered during a follow-up of more than 2 years (**Central Illustration**).

SDB is common in patients with HF, with a reported prevalence of 50% to 70%.[1,12] Multiple consequences of SDB, eg, hemodynamic, autonomic, and biochemical alterations, are all plausible promoters of heart rhythm disorders.[13] Indeed, SDB has been associated both with the development of arrhythmias[2,3] and with a higher risk of sudden cardiac death.[4] A growing number of studies have assessed the clinical impact of SDB on the incidence of appropriate ICD therapy, a surrogate for malignant ventricular arrhythmia.[5-8] A meta-analysis of 9 prospective cohort studies[14] confirmed that, in patients with HF and reduced ejection fraction, the risk of appropriate ICD therapy is higher among patients with SDB, as assessed by means of traditional tools, ie, single-night attended or unattended polysomnography, cardiorespiratory polygraphy, or pulse oximetry.

It has previously been demonstrated that the device-computed RDI accurately identifies severe SA in patients with implanted pacemakers[9] and ICDs,[10] and that it is equally accurate in patients with predominant CSA and OSA.[10] Therefore, the availability of the algorithm in pacemakers and ICDs constitutes an opportunity to screen patients at risk of SA. Indeed, diagnosing and treating apnea is a relevant issue in the management of HF patients,[15] but the limited access to polysomnography is known to result in undiagnosed[16] and undertreated SA, as well as excessively long waiting lists.[17]

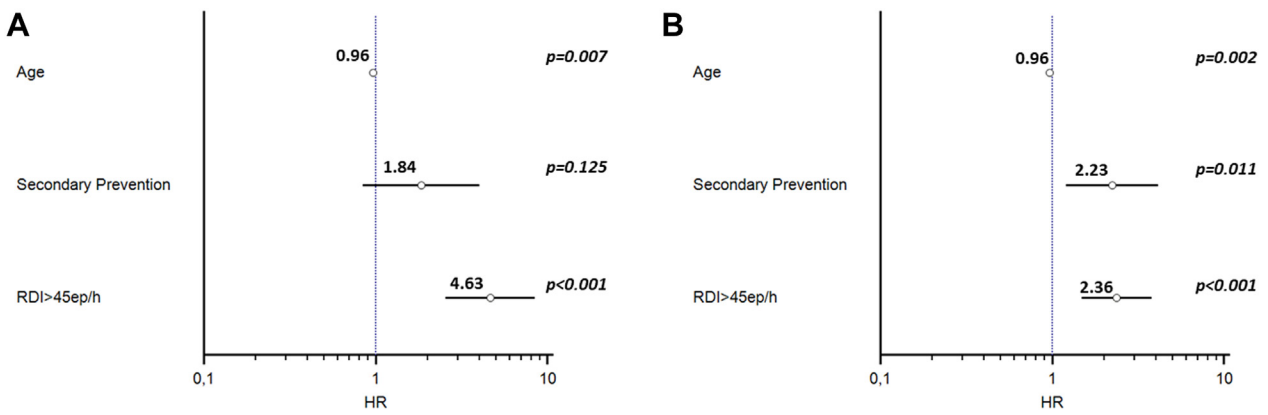
The availability of these algorithms in implantable devices offers the opportunity to automatically monitor SDB in the long-term, and this may present additional advantages. Indeed, in pacemaker patients, we previously observed considerable

TABLE 2 Univariate Analysis of Baseline Variables Associated With Occurrence of Shock and Any ICD Therapy (Antitachyarrhythmia Pacing or Shock)

	Shock			Any ICD therapy		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age	0.97	0.95-0.99	0.007	0.97	0.95-0.99	0.003
Male	0.94	0.51-1.75	0.855	0.47	0.73-1.98	0.467
Body mass index	0.99	0.91-1.07	0.740	0.99	0.93-1.05	0.696
Ischemic heart disease	0.96	0.57-1.6	0.873	0.82	0.55-1.22	0.325
NYHA functional class	1.26	0.82-1.95	0.295	1.18	0.84-1.64	0.344
Ejection fraction	0.98	0.95-1.02	0.355	0.99	0.97-1.02	0.590
History of atrial fibrillation	1.01	0.59-1.73	0.973	1.34	0.90-1.99	0.157
Secondary prevention	2.05	1.09-3.85	0.027	2.49	1.55-3.99	<0.001
CRT device	0.59	0.35-1.01	0.057	0.69	0.46-1.05	0.084
Diabetes	0.81	0.45-1.48	0.500	0.97	0.62-1.50	0.889
Chronic kidney disease	1.02	0.57-1.84	0.942	1.03	0.66-1.61	0.891
Pulmonary disease	1.17	0.61-2.24	0.647	1.20	0.73-1.98	0.467
Hypertension	0.60	0.36-1.01	0.058	0.65	0.44-1.01	0.054
β-blocker use	1.23	0.45-3.37	0.691	1.22	0.57-2.63	0.609
Diuretic use	0.80	0.37-1.76	0.587	0.98	0.51-1.88	0.961
Antiarrhythmic use	1.37	0.77-2.44	0.279	1.44	0.93-2.22	0.103
ACE inhibitor, ARB, or ARNI use	0.70	0.28-1.74	0.443	0.80	0.39-1.63	0.540
Maximum RDI	1.00	0.98-1.02	0.778	1.00	0.99-1.01	0.949

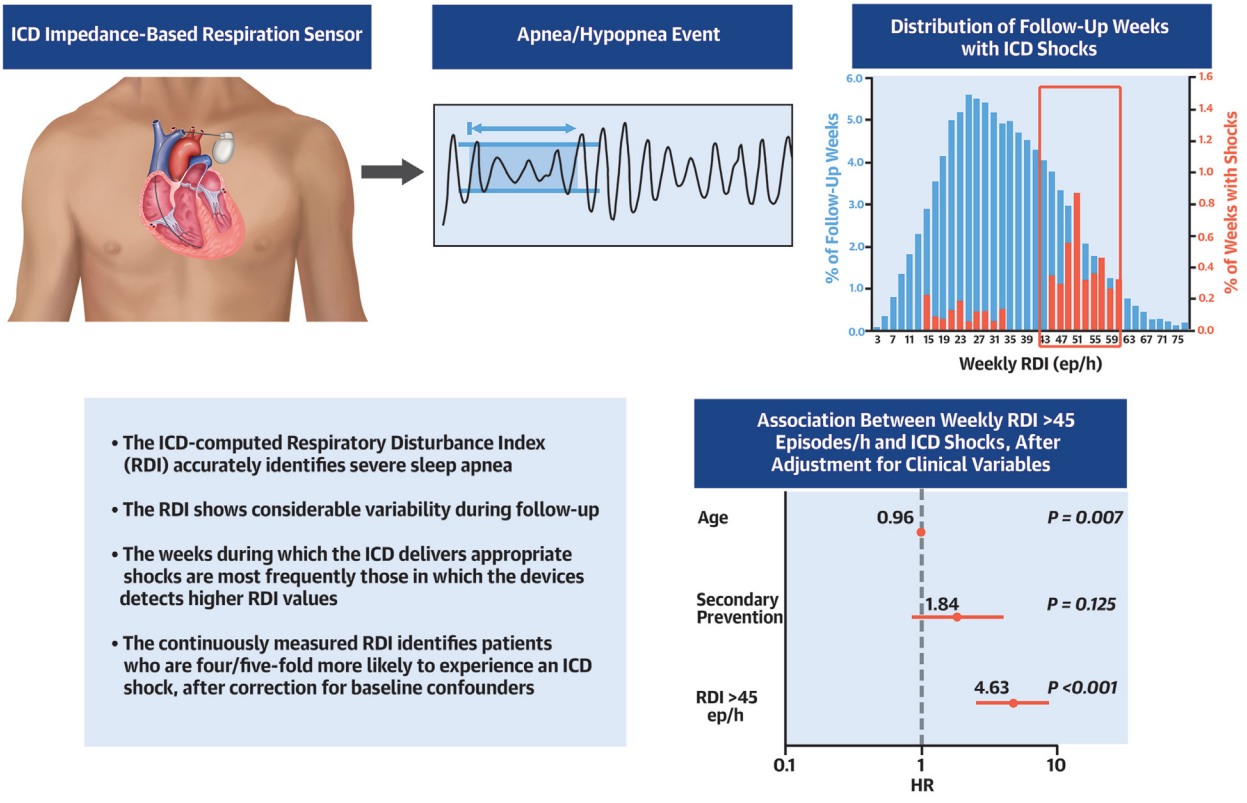
ICD = implantable cardioverter-defibrillator; other abbreviations as in Table 1.

FIGURE 3 Results of the Time-Dependent Cox Model



(A) Association between weekly mean Respiratory Disturbance Index >45 episodes/h and implantable cardioverter-defibrillator shock, after adjustment for clinical variables. **(B)** Association between weekly mean Respiratory Disturbance Index >45 episodes/h and implantable cardioverter-defibrillator therapy (antitachyarrhythmia pacing or shock), after adjustment for clinical variables.

CENTRAL ILLUSTRATION **Appropriate ICD Shocks are More Likely To Be Delivered During Periods When Patients Exhibit More Sleep-Disordered Breathing, as Measured By Automated ICD Algorithms**



The continuous and automatic assessment of sleep apnea with ICDs allows physicians to identify patients with periods of significantly increased risk of ventricular tachyarrhythmias.

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variability in device-detected SA.[18] This suggests that a single overnight sleep study may not be representative of SA severity and may result in the misclassification of severe SA, as is also hypothesized by other authors.[19] The wide dispersion of RDI values recorded in the present analysis confirms these observations in a population of HF patients. Moreover, we also observed that the maximum RDI value calculated during the entire follow-up period was not associated with the study endpoints, unlike the continuously measured weekly RDI value. This suggests that the RDI can dynamically stratify patients during follow-up. Indeed, in this study the rate of ICD shocks was 4.5× higher when the patient had RDI values >45 episodes/h, demonstrating that dynamic assessment using RDI could identify time intervals when HF patients are at significantly increased risk of arrhythmias. Moreover, this finding seems to confirm that, in the context of SDB, ventricular arrhythmias may be triggered by transient causes, such as the increased sympathetic tone or the electro-mechanical feedback induced by myocardial stretch caused by hyperventilation.[20]

The availability of a reliable tool that can automatically detect SDB may also facilitate the adoption of targeted therapeutic strategies and the monitoring of their efficacy. For example, there is growing evidence that continuous positive airway pressure can reduce apneic events, sympathetic activity,[21] and the shift of intrathoracic pressure and ventricular unloading.[22] Thus, treating OSA by means of continuous positive airway pressure can lower the risk of arrhythmia occurrence[23] and reduce the frequency of ventricular ectopy during sleep in patients with OSA and HF.[24] Similarly, therapy with adaptive servo-ventilation has been shown to reduce appropriate

ICD therapies in HF patients with Cheyne-Stokes respiration.[25] Nevertheless, the impact of SDB treatments on reducing the risk of sudden death requires verification.

The continuous monitoring of SA may also be able to improve adherence to continuous positive airway pressure treatment, which is a well-known issue,[26] and to monitor the effects of cardiac treatments on the severity of SDB. Indeed, a reduction in SA severity might follow effective cardiac resynchronization therapy in HF patients,[27] and patients undergoing catheter ablation for ventricular arrhythmias are at higher risk of tachycardia recurrence if they are also affected by SA.[28]

In the present analysis, the overall median RDI value was high (33 episodes/h), as was the individual maximum RDI (54 ± 14 episodes/h). Similarly, in a previous study,[18] we showed that the optimal mean RDI value for the prediction of atrial fibrillation in pacemaker patients was ≥46 episodes/h, ie, a value significantly higher than the apnea-hypopnea index (≥30 episodes/h) commonly adopted to diagnose severe SA by means of standard polysomnography.[29] This result is consistent with previous findings, which showed an agreement between the apnea-hypopnea index and RDI values recorded during the sleep-study night.[10] Indeed, in that study, the RDI value was shown to be affected by a positive bias of 11 episodes/h. In agreement with these findings, and to maintain specificity (ie, to avoid too frequent warnings from the algorithm), in the present analysis we adopted a cutoff value of 45 episodes/h (ie, the 75th percentile of the RDI distribution) for the definition of weeks with high RDI.

In our study, high RDI during follow-up identified patients who were 4-/5-fold more likely to experience an ICD shock, after correction for baseline confounders. We found a similar association between device-detected severe SDB and any ICD therapy (antitachyarrhythmia pacing or shock), but with a lower HR (HR: 2.36). This value is higher, but quite in line with that calculated in a meta-analysis[14] that estimated the impact of SDB (assessed by means of traditional tools) on the same endpoint of shock or antitachyarrhythmia pacing (1.55, 95% CI: 1.32-1.83).

Although the present findings refer to the monitoring of patients who already have ICDs, they support the concept of including the evaluation of SDB in a possible score for the assessment of the risk of sudden cardiac death at the time of ICD implantation. Indeed, many risk scores have been proposed to improve the accuracy of current ICD indications based only on the ejection fraction, but none of these has included SDB as a possible risk factor.[30-33]

STUDY LIMITATIONS. First, its observational design may have introduced an inherent bias. Second, we have not performed conventional polysomnography to confirm diagnosis of sleep apnea and the algorithm for SDB detection does not distinguish between obstructive and central sleep apnea. Third, the rate-detection settings and ICD programming were left to the discretion of the implanting physicians, according to their knowledge of the individual patient's arrhythmia history. Different individual rate settings can affect the frequency of ICD therapy, which could have influenced our analysis.

CONCLUSIONS

In HF patients with an ICD, device-diagnosed SDB identifies patients who are more likely to receive appropriate ICD therapies.

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Drs Campari and Valsecchi are employees of Boston Scientific, Inc. Dr Boriani has received small speaker fees from Boston, Biotronik, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The reader will enhance his/her ability to make informed diagnostic and therapeutic decisions and provide effective health management by making use of the information provided by modern cardiac devices.

TRANSLATIONAL OUTLOOK: SDB is common in patients with HF. The accuracy of pacemaker and ICD algorithms for the detection of sleep apnea has been demonstrated. We found an association between ICD-detected sleep apnea and the occurrence of ventricular arrhythmias, suggesting that the availability of these tools may facilitate the adoption of targeted therapeutic strategies and the monitoring of their efficacy. Nonetheless, additional studies are required to verify the efficacy of these strategies and to promote their adoption into standard practice.

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APPENDIX For supplemental figures, please see the online version of this paper.

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