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Association between implantable defibrillator-detected sleep apnea and atrial fibrillation: The DASAP-HF study

Giuseppe Boriani MD, PhD[1] | Igor Diemberger MD, PhD[2] | Ennio C. L. Pisanò MD[3] | Paolo Pieragnoli MD[4] | Alessandro Locatelli MD[5] | Alessandro Capucci MD[6] | Antonello Talarico MD[7] | Massimo Zecchin MD[8] | Antonio Rapacciuolo MD, PhD[9] | Marcello Piacenti MD[10] | Ciro Indolfi MD, PhD[11,12] | Miguel A. Arias MD[13] | Catia Checchinato MD[14] | Maria T. La Rovere MD[15] | Gianfranco Sinagra MD, PhD[8] | Michele Emdin MD, PhD[10] | Renato P. Ricci MD[16] | Antonio D'Onofrio MD[17]

[1]Department of Biomedical, Metabolic and Neural Sciences, Cardiology Division, University of Modena and Reggio Emilia, Modena, Italy

[2]Department of Experimental, Diagnostic and Specialty Medicine, Institute of Cardiology, Policlinico S.Orsola-Malpighi, University of Bologna, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[3]Cardiology Division, Vito Fazzi Hospital, Lecce, Italy

[4]Cardiology Division, University of Florence, Florence, Italy

[5]Cardiology Division, "Bolognini" Hospital, Seriate, BG, Italy

[6]Clinica di Cardiologia e Aritmologia, Università Politecnica delle Marche, Ancona, Italy

[7]Cardiology Division, Ospedale SS. Annunziata, Cosenza, Italy

[8]Cardiovascular Department, Ospedali Riuniti, University of Trieste, Trieste, Italy

[9]Cardiology Division, Federico II University, Naples, Italy

[10]Cardiology Division, Institute of Life Science, Scuola Superiore Sant'Anna and Fondazione Toscana Gabriele Monasterio, Pisa, Italy

[11]Division of Cardiology, "Magna Graecia" University, Catanzaro, Italy

[12]Mediterranea Cardiocentro, Naples, Italy

[13]Arrhythmia Unit, Hospital Virgen de la Salud, Toledo, Spain

[14]Cardiology Division, Ospedale Santa Croce, Moncalieri, TO, Italy

[15]Division of Cardiac Rehabilitation, Istituti Clinici Scientifici Maugeri, IRCCS, Istituto Scientifico di Montescano, Montescano, Pavia, Italy

[16]Italian Heart Rhythm Society (AIAC), Rome, Italy

[17]Unità Operativa di Elettrofisiologia, Studio e Terapia delle Aritmie, Ospedale Monaldi, Naples, Italy

Correspondence
Giuseppe Boriani, MD, PhD, Department of Biomedical, Metabolic and Neural Sciences, Cardiology Division, University of Modena and Reggio Emilia, Policlinico di Modena, Via del Pozzo, 71, 41124 Modena, Italy.
Email: giuseppe.boriani@unimore.it

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Abstract

Introduction: The Respiratory Disturbance Index (RDI) computed by an implantable cardioverter defibrillator (ICD) algorithm accurately identifies severe sleep apnea (SA). In the present analysis, we tested the hypothesis that RDI could also predict atrial fibrillation (AF) burden.

Methods: Patients with ejection fraction ≤35% implanted with an ICD were enrolled and followed up for 24 months. One month after implantation, patients

Abbreviations: AF, atrial fibrillation; AHI, apnea hypopnea index; CI, confidence interval; CRT-D, cardiac resynchronization therapy ICD; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; RDI, Respiratory Disturbance Index; SA, sleep apnea.

underwent a polysomnographic study. The weekly mean RDI value was considered, as calculated during the entire follow-up period and over a 1-week period preceding the sleep study. The endpoints were as follows: daily AF burden of ≥5 min, ≥6 h, ≥23 h.

Results: Here, 164 patients had usable RDI values during the entire follow-up period. Severe SA (RDI ≥ 30 episodes/h) was diagnosed in 92 (56%) patients at the time of the sleep study. During follow-up, AF burden ≥ 5 min/day was documented in 70 (43%), ≥6 h/day in 48 (29%), and ≥23 h/day in 33 (20%) patients. Device-detected RDI ≥ 30 episodes/h at the time of the polygraphy, as well as the polygraphy-measured apnea hypopnea index ≥ 30 episodes/h, were not associated with the occurrence of the endpoints, using a Cox regression model. However, using a time-dependent model, continuously measured weekly mean RDI ≥ 30 episodes/h was independently associated with AF burden ≥ 5 min/day (hazard ratio [HR]: 2.13, 95% confidence interval [CI]: 1.24–3.65, $p = .006$), ≥6 h/day (HR: 2.75, 95% CI: 1.37–5.49, $p = .004$), and ≥23 h/day (HR: 2.26, 95% CI: 1.05–4.86, $p = .037$).

Conclusions: In heart failure patients, ICD-diagnosed severe SA on follow-up data review identifies patients who are from two- to three-fold more likely to experience an AF episode, according to various thresholds of daily AF burden.

KEYWORDS

atrial fibrillation, heart failure, ICD, respiratory disturbances, sleep apnea

1 | INTRODUCTION

1.1 | Implantable cardioverter defibrillator (ICD)-detected sleep apnea (SA) and atrial fibrillation (AF)

Sleep-disordered breathing is frequent in heart failure (HF)[1] and has been associated with the development of arrhythmias.[2–4] Multiple factors such as hypoxemia, sympathetic activation, and systemic inflammation that occur in obstructive sleep apnea (SA) may also be mechanisms that predispose to the development of AF. Indeed, a higher proportion of patients with a history of AF have been shown to have obstructive SA in comparison with the general population.[5] Some modern pacemakers and ICDs are equipped with automated algorithms based on the continuous measurement of thoracic impedance to detect advanced SA.[6] The Diagnosis of Sleep Apnea in Patient with HF (DASAP-HF) study demonstrated that the ICD-computed Respiratory Disturbance Index (RDI) computed by the ApneaScan™ algorithm (Boston Scientific Inc.) accurately predicts severe SA in patients who received an ICD or a cardiac resynchronization therapy ICD (CRT-D).[7] The objective of this analysis of the DASAP-HF study was to investigate the association between AF and ICD-detected SA during the 24 months post-enrollment follow-up period.

2 | METHODS

2.1 | Patient selection

The study was a prospective, nonrandomized multicenter evaluation of patients implanted with an ICD or CRT-D endowed with the ApneaScan™ diagnostic feature. Patients had to present with current ICD or CRT-D indications,[8] and with left ventricular systolic dysfunction, that is, left ventricular ejection fraction ≤3 5%. Patients already on CRT, those unavailable to attend scheduled follow-up visits at the center, or with a life expectancy <12 months were all excluded. The Ethical Committees approved the study and all patients gave written informed consent.

2.2 | Study design

Devices and pacing leads were implanted by means of standard techniques. Baseline evaluation included demographics and medical history, clinical examination, 12-lead electrocardiogram, and echo-cardiographic 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. The sleep study consisted of an unattended home nocturnal recording by means of a portable SA monitor (Embletta) equipped with multiple sensors, in agreement with current American Academy of Sleep Medicine guidelines for the detection of respiratory events.[9] Recordings were evaluated by a Core Lab and SA was defined as severe if the Apnea Hypopnea Index (AHI) was ≥30 episodes/h during the sleep-study night.[6,10] After the sleep study, the implanted device was interrogated and stored data were retrieved. During follow-up, patients were conventionally followed up by means of in-clinic visits or underwent remote device monitoring. The decision to adopt remote monitoring was based on the physician's and patient's preference, and the physician's evaluation of the patient's potential compliance with remote follow-up instead of scheduled routine in-office follow-up visits. Remotely monitored patients received a communicator and were enrolled in the LATITUDE (Boston Scientific) remote monitoring platform. For the present analysis of the association between AF and ICD-detected SA, only remotely monitored patients were included and the device data stored during the entire follow-up period were downloaded from the platform.

2.3 | 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 assessing the amount of time between breaths that exceed a minimum baseline value. After verification of the signal quality and validation of the respiratory interval measurement, the algorithm defines an apnea episode as two consecutive large breaths, where the time between breaths is >10 s, and a hypopnea episode as an interval between large breaths >10 s, 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. Measurements are suspended during other ICD activities (e.g., capacitor charge, shock, lead impedance measurements). At least 2 h 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. Development of the ApneaScan™ algorithm is based on data from a published study.[6]

2.4 | Study endpoints

The short-term objective of the DASAP-HF study was to evaluate the performance of the device-calculated RDI value as a binary discriminator of severe SA and the results have already been published.[7] The objective of the long-term analysis described in the present paper was to investigate the association between the RDI values calculated by the ICD algorithm and the incidence of AF during the 24 months post-enrollment follow-up period. The incidence and duration of AF were derived from device data, which comprise the total time spent by the patient in AF on each day of the follow-up period. Patients were considered to have experienced AF episodes if the device detected a cumulative AF duration ≥ 5 min, ≥6 h, and ≥23 h, in agreement with previous studies.[11]

2.5 | Statistical analysis

All enrolled subjects who satisfied the inclusion/exclusion criteria and with RDI values recorded by the ICD during the entire follow-up period were used in the analysis. Weekly average RDI values were considered, as calculated by the algorithm over a 1 week period preceding the sleep study and during the entire follow-up period. Measures were stratified according to an RDI value ≥ or <30 episodes/h. Continuous data were expressed as mean ± SD for normally distributed variables, or medians with 25th to 75th percentiles in the case of skewed distribution. Normality of distribution was tested by means of the nonparametric Kolmogorov–Smirnov test. Categorical data were expressed as percentages. The analysis of time to first event was done by means of the Kaplan–Meier method. Cox proportional hazards models were used to determine the association between the occurrence of events during the follow-up period and baseline characteristics, and to estimate the hazard ratios (HRs) and the 95% confidence intervals (CIs) of an event. In the analysis, follow-up periods ended at the time of the first AF event or were censored at the end of follow-up. To account for the intrapatient variability of the RDI value over follow-up, weekly average RDI values were also treated as a time-varying covariate by means of time-dependent Cox models, that is, splitting the analysis time into weekly intervals and stratifying the models for these time intervals. The models were corrected for those baseline variables that proved to be associated with the occurrence of events on univariate analysis. All variables associated with a statistical significance such as $p < .05$ were considered for multivariate regression analysis. A p <.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).

3 | RESULTS

3.1 | Study population and SA detection

A total of 265 patients were enrolled in the study between March 2014 and July 2016 at 13 centers in Italy and Spain. Seventeen patients did not undergo the scheduled sleep study because of refusal, ongoing hospitalization or death. Out of the remaining patients, 173 had RDI values recorded by the ICD within 7 days before the scheduled sleep study visit and were included in the published analysis of the short-term study phase. Out of these patients, 164 had usable RDI values stored during the entire follow-up period in the remote monitoring platform. The baseline characteristics of these patients did not differ from those of the

TABLE 1 Demographics and baseline clinical parameters

Parameter	Total (*N* = 164)
Age, years	67 ± 10
Male, *n* (%)	123 (75)
Body mass index, km/m^2	27 ± 4
NYHA Class III–IV, *n* (%)	74 (45)
QRS duration, ms	132 ± 30
Sinus rhythm at implantation, *n* (%)	148 (90)
Ischemic heart disease, *n* (%)	82 (50)
Hypertension, *n* (%)	39 (24)
History of atrial fibrillation, *n* (%)	44 (27)
Pulmonary disease, *n* (%)	63 (38)
Diabetes, *n* (%)	60 (37)
Creatinine, mg/dl	1.18 ± 0.45
Ejection fraction, %	29 ± 5
LVESV, ml	130 ± 60
LVEDV, ml	182 ± 77
LAD, mm	46 ± 8
CRT-D device, *n* (%)	99 (60)
$CHADS_2$ score	1.7 ± 0.9
CHA_2DS_2-VASc score	3.1 ± 1.4
Mean RDI at the time of sleep study, ep/h	31 ± 15
AHI at sleep study recording, ep/h	21 ± 16
ACE-inhibitor use, *n* (%)	136 (83)
Aldosterone antagonist use, *n* (%)	91 (56)
β-Blocker use, *n* (%)	149 (91)
Diuretic use, *n* (%)	143 (87)
Antiarrhythmic drug use, *n* (%)	36 (22)
Anticoagulant/antiplatelet, *n* (%)	137 (84)

Abbreviations: AHI, apnea/hypopnea index; CRT, cardiac resynchronization therapy; LAD, left atrial diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; RDI, respiratory disturbance index.

101 patients excluded. Table 1 shows baseline clinical variables of the study group. On implantation, 44 (27%) patients presented with a history of AF. Antiarrhythmic medications were used by 36 (22%) patients on hospital discharge. The mean AHI measured at sleep study recording was 21 ± 16 episodes/h. The mean RDI value over the week preceding the sleep study was 31 ± 15 episodes/h and severe SA (RDI ≥ 30 episodes/h) was diagnosed by the ICD in 80 (49%) patients. Overall, an average value of RDI ≥ 30 episodes/h was measured during 35% of the entire follow-up period of the study group. At least one weekly mean RDI value ≥ 30 episodes/h was measured during follow-up in 143 (87%) patients. Among the

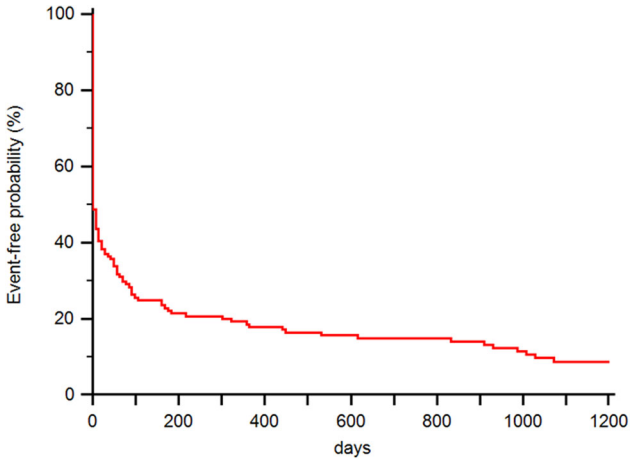

FIGURE 1 Time to first severe sleep apnea implantable cardioverter defibrillator (ICD)-detection (weekly mean Respiratory Disturbance Index [RDI] value ≥ 30 episodes/h).

84 patients with undetected severe SA during the sleep study week, 63 (75%) presented with severe SA during follow-up. The time to first severe SA ICD-detection is reported in Figure 1.

3.2 | Follow-up and AF occurrence

The 164 patients in analysis were followed over a median follow-up of 25 months (25–75 percentile: 24–25 months). During follow-up, 17 (10%) patients died for any cause. AF burden ≥ 5 min/day was documented in 70 (43%) patients, ≥6 h/day in 48 (29%) patients, and ≥23 h/day in 33 (20%) patients. Figure 2 shows the Kaplan–Meier analysis of time to first event of AF burden ≥ 5 min, ≥6 h, and ≥23 h.

The results of the regression analysis of baseline variables associated with AF occurrence, according to various thresholds of daily AF burden (≥5 min, ≥6 h, ≥23 h), are shown in Table 2. It is noteworthy that device-detected RDI ≥ 30 episodes/h at the time of the polysomnographic study, as well as the polygraphy-measured AHI ≥ 30 episodes/h, were not associated with the occurrence of the endpoints, using a Cox regression model. However, using a time-dependent Cox model, continuously measured weekly mean RDI ≥ 30 episodes/h was independently associated with AF burden ≥ 5 min/day (HR: 2.13, 95% CI: 1.24–3.65, $p = .006$), ≥6 h/day (HR: 2.75, 95% CI: 1.37–5.49, $p = .004$), and ≥23 h/day (HR: 2.26, 95% CI: 1.05–4.86, $p = .037$), after correction for history of AF, left atrial diameter, and gender (Figure 3). Repeating the analysis in patients with no history of AF at baseline, the association between weekly mean RDI ≥ 30 episodes/h and AF was confirmed: AF burden ≥ 5 min/day (HR: 2.43, 95% CI: 1.17–5.07, $p = .018$), ≥6 h/day (HR: 4.53, 95% CI: 1.49–13.76, $p = .008$), and ≥23 h/day (HR: 4.33, 95% CI: 1.02–19.85, $p = .048$). The association was also confirmed treating the RDI value as a continuous variable: AF burden ≥ 5 min/day (HR: 1.02, 95% CI: 1.00–1.04, $p = .013$), ≥6 h/day (HR: 1.03, 95% CI: 1.00–1.05, $p = .027$), and ≥23 h/day (HR: 1.03, 95% CI: 1.00–1.08, $p = .049$).

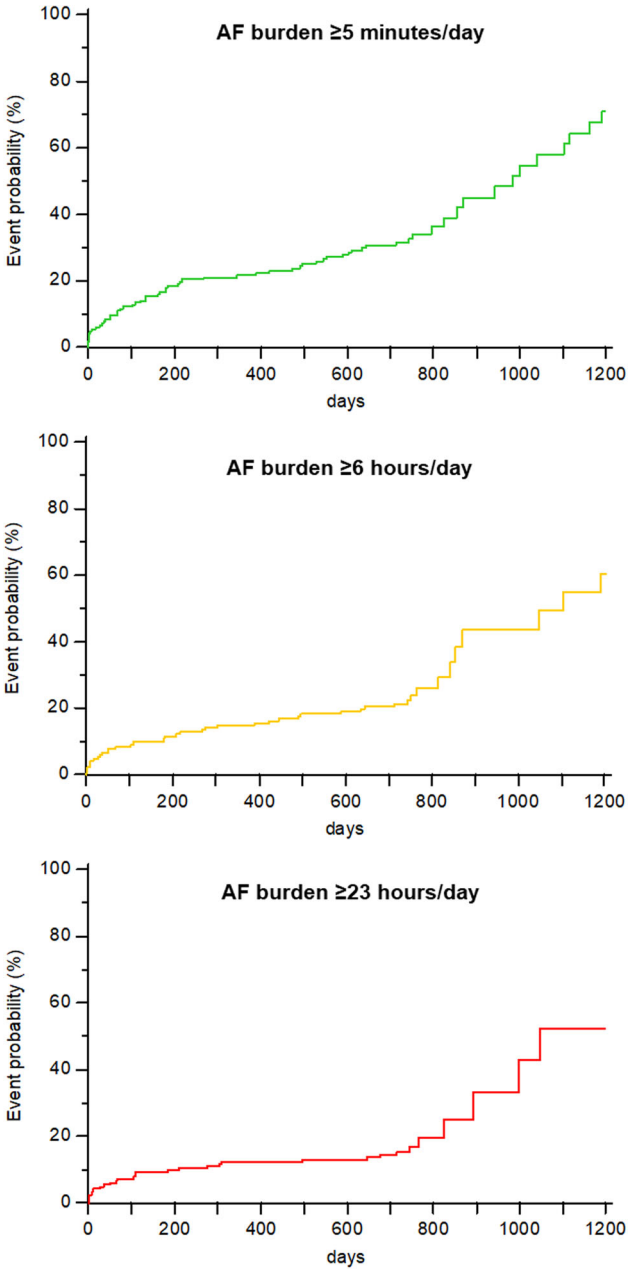

FIGURE 2 Time from the implantation to the first episode of atrial fibrillation (AF) burden ≥ 5 min/day (top panel), ≥6 h/day (mid panel), ≥23 h/day (bottom panel).

4 | DISCUSSION

The DASAP-HF study previously demonstrated that a device-computed RDI accurately identifies severe SA in HF patients implanted with an ICD. In the present analysis, we demonstrated an association between RDI values continuously measured by the ICD and AF occurrence during a follow-up of more than 2 years.

A high proportion of patients with HF and systolic dysfunction experience breathing disorders both during nighttime and during short-term laboratory recording.[12–14] Diagnosing and treating apnea is a relevant issue in the management of HF patients.[15] Indeed, a large body of clinical data indicates that HF patients with SA, as detected by conventional polysomnography, have an increased risk of mortality independent of traditional risk factors.[15,16] However, the standard diagnosis of SA by means of the overnight polysomnography requires special institutions and trained technicians. The limited access to polysomnography is known to result in undiagnosed (>85% of patients with clinically significant and treatable obstructive SA)[17] and undertreated SA, as well as excessively long waiting lists.[18] Therefore, the availability of accurate algorithms for the automatic detection of advanced SA in pacemakers and ICDs represents an opportunity for screening patients at risk of SA.[6] Indeed, in our previous analysis the average RDI value calculated by the ICD over a 1 week period identified patients with severe disordered breathing (AHI ≥ 30 episodes/h) on the polygraphic recording subsequently performed, with 87% sensitivity and 56% specificity.[7]

The association between SA and AF has been previously demonstrated. A higher prevalence of SA has been shown in patients undergoing cardioversion for AF than in patients with no history of AF[5] and SA has been identified as predictor of AF over a follow-up of 4 years in patients with no AF at baseline.[19] Our results demonstrate that the ICD-measured RDI may allow stratification of HF patients with ICDs for AF risk, extending preliminary results obtained in pacemaker recipients.[20,21] Importantly, the verification of severe SA at the time of the polysomnographic study did not predict the occurrence of AF during a follow-up of more than 2 years, but we demonstrated the association between AF and the continuously measured weekly RDI values, using a time-dependent model. This suggests the ability of the RDI to dynamically stratify patients during follow-up, extending preliminary observations based on quarterly evaluations.[20]

The incidence of AF detected in this study was in line with that reported in previous studies on patients with pacemakers and ICDs.[22] Very short pacemaker- and ICD-detected atrial high-rate episodes are usually considered clinically irrelevant, but longer episodes (≥5 min/day) are associated with an increased risk of clinical AF,[11,23,24] ischemic stroke,[23–25] major adverse cardiovascular events,[26] and cardiovascular death.[27] Although studies are awaited to define the optimal management, careful monitoring of patients with atrial high-rate episodes is recommended, because of the high risk of progression to longer episodes and clinical AF.[11,28,29]

In this study, severe SA during follow-up identified patients who were from two- to threefold more likely to experience an AF episode, according to various thresholds of daily AF burden (≥5 min, ≥6 h, ≥23 h). More than a mere risk stratification, the dynamic nature of the association between respiratory disturbances and AF seems to confirm the causal mechanisms that have been proposed to explain the link between obstructive SA and AF, that is, the nocturnal oxygen desaturation,[2] the diastolic dysfunction,[30,31] the systemic inflammation,[32] and the autonomic imbalance during SA.[33]

In a recent high-density mapping study, AHI ≥ 30 episodes/h indicated a threshold at which atrial remodeling in paroxysmal AF became more advanced. In contrast, significant remodeling was

TABLE 2 Univariate analysis of baseline variables associated with AF occurrence

	AF burden of ≥5 min/day			AF burden of ≥6 h/day			AF burden of ≥23 h/day		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.02	0.99–1.04	0.232	1.01	0.99–1.04	0.331	1.03	0.99–1.08	0.113
Male gender	1.85	1.02–3.36	0.046	2.89	1.32–6.33	0.008	2.37	0.91–6.18	0.079
Body mass index	0.98	0.93–1.04	0.566	0.99	0.93–1.07	0.967	1.01	0.93–1.10	0.804
NYHA class	1.08	0.69–1.67	0.747	1.01	0.61–1.69	0.961	1.01	0.54–1.89	0.976
Ischemic heart disease	0.78	0.49–1.26	0.321	0.92	0.52–1.63	0.776	0.67	0.33–1.35	0.262
Ejection fraction	0.98	0.94-1.03	0.524	1.01	0.95–1.07	0.709	1.01	0.94–1.09	0.715
Left atrial diameter	1.07	1.03–1.13	0.002	1.10	1.04–1.17	0.001	1.11	1.04–1.19	0.002
History of AF	2.88	1.71–4.84	<0.001	5.05	2.71–9.41	<0.001	5.02	2.47–10.19	<0.001
Hypertension	1.35	0.76–2.42	0.313	1.36	0.69–2.70	0.375	2.01	0.96–4.22	0.066
Pulmonary disease	0.99	0.60–1.63	0.976	0.92	0.48–1.75	0.795	0.60	0.27–1.33	0.209
Diabetes	1.19	0.73–1.93	0.485	1.19	0.67–2.11	0.564	1.47	0.73–2.96	0.279
Creatinine	1.11	0.67–1.86	0.685	1.42	0.80–2.51	0.232	1.72	0.90-3.29	0.102
CRT	1.23	0.75–2.00	0.412	1.27	0.70–2.29	0.428	1.42	0.68–2.96	0.348
$CHADS_2$ score	1.05	0.83–1.33	0.658	1.04	0.78–1.38	0.806	1.26	0.89–1.79	0.192
CHA_2DS_2-VASc score	1.02	0.87–1.21	0.783	0.98	0.80–1.20	0.873	1.07	0.83–1.37	0.625
Mean RDI* ≥ 30 ep/h	1.29	0.77–2.14	0.336	1.92	0.94–3.90	0.074	1.27	0.58–2.77	0.547
AHI** ≥ 30 ep/h	0.95	0.46–1.97	0.898	1.06	0.46–2.45	0.888	1.25	0.45–3.44	0.668

Abbreviations: AF, atrial fibrillation; AHI, apnea hypopnea index; CI, confidence interval; CRT, cardiac resynchronization therapy; HR, hazard ratio; NYHA, New York Heart Association; RDI, Respiratory Disturbance Index.

*Mean RDI at the time of sleep study.

**AHI at sleep study recording.

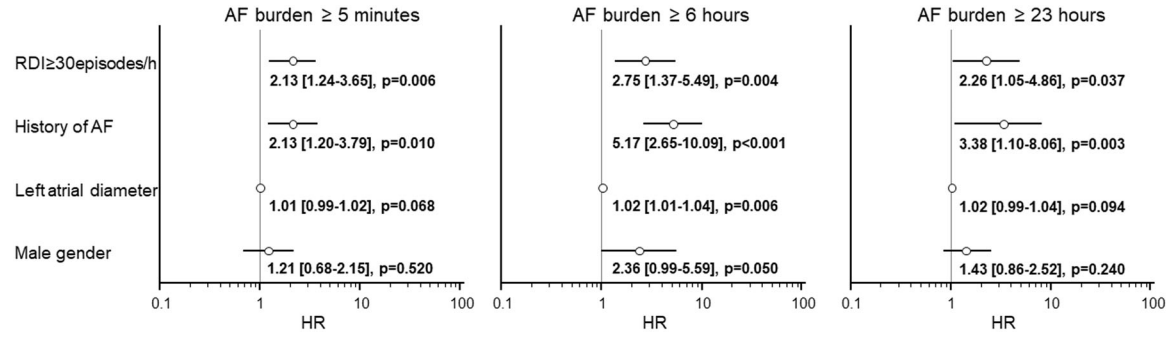

FIGURE 3 Results of the time-dependent Cox model. Association between weekly mean Respiratory Disturbance Index (RDI) ≥ 30 episodes/h and atrial fibrillation (AF) burden ≥ 5 min/day, ≥6 h/day, and ≥23 h/day, after adjusting for clinical variables.

observed across all SA categories in persistent AF.[34] According to the authors, their findings explain the poorer efficacy of rhythm control strategies among AF cohorts with increasingly severe SA[35] and highlight paroxysmal AF cohorts with severe SA as a group well poised to derive maximal antiarrhythmic benefit from obstructive SA treatment, in agreement with previous evidence.[36] The availability of a reliable tool which allows automated detection of advanced SA together with continuous monitoring of the burden of AF may facilitate the management of cardiovascular risk factors and concomitant diseases advocated by current guidelines,[22] in addition to appropriately approach risk stratification for ischemic stroke[37] with institution of an adequate antithrombotic treatment.[38,39] Moreover, observational studies suggested that SA is associated with a reduced efficacy of catheter- and pharmacological- based rhythm control strategies, and that treatment with continuous positive airway pressure has a positive impact on AF recurrences after electrical cardioversion and improves catheter ablation outcomes.[40–43] All these data suggest that information on SA and AF

burden may integrate the clinical assessment of an individual patients and facilitate resulting in improved decision making.

4.1 | Limitations

The limitations of our study should be acknowledged. First, its observational design may have introduced an inherent bias. Second, of all patients enrolled in the study, only remotely monitored patients were included in the analysis to extract device data stored during the entire follow-up period from the platform. This resulted in a smaller sample size. Moreover, the algorithm for SA detection does not distinguish between obstructive SA and central SA and, also, did not take into the effect of treatments directed to correct SA.

5 | CONCLUSIONS

In HF patients implanted with an ICD, device-diagnosed severe SA is associated with a higher risk of AF. In particular, severe SA during follow-up identifies patients who are from two- to threefold more likely to experience an AF episode, according to various thresholds of daily AF burden.

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CONFLICT OF INTEREST

G. Boriani reported speaker's fees of small amount from Bayer, Boehringher, Boston, Daiichi, outside the submitted work. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Giuseppe Boriani http://orcid.org/0000-0002-9820-4815
Igor Diemberger http://orcid.org/0000-0002-3823-3809

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