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Impact of sleep apnea on cardioembolic risk in patients with atrial fibrillation: data from the ESADA cohort

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Abstract

Background: An accurate determination of the cardio-embolic risk in patients with atrial fibrillation (AF) is crucial to prevent consequences like stroke. Obstructive sleep apnea (OSA) is a known risk factor for both AF and stroke. We aim to explore a possible association between OSA and an increased cardioembolic risk in patients with AF.

Methods: we assessed data from the ESADA cohort where patients with known AF and OSA were included. Parameters of OSA severity and hypoxic burden like lowest SpO2 and 4% oxygen desaturation index (ODI4) were analysed. Patients were stratified according to their cardioembolic risk estimated with the CHA2DS2-VASc score.

Results: From the initial cohort of 14,646 patients, a final set of 363 were included in the analysis. Indices of hypoxic burden during sleep were associated with increased CHA2DS2-VASc score (ODI4 17.9 vs 29.6 vs 30.5 events/hour and lowest SpO2 81.2 vs 77.8 vs 77.5% for low, moderate and high cardioembolic risk respectively, $p<0.05$)

Conclusions: These results support the potential role of OSA-related hypoxia in the risk for cardioembolic complications such as stroke in patients with AF.

Background

Atrial fibrillation (AF) is the most common supra-ventricular arrhythmia worldwide and is one of the causes of ischemic stroke.(1)
Obstructive sleep apnea (OSA) is a well recognized risk factor for cardiovascular diseases and is an independent predictor of stroke in patients with AF. (2)
OSA and AF often coexist and a causal relationship between the two has been proposed: OSA may promote AF by the repetitive cycles of intermittent hypoxia causing an imbalance of cardiac autonomic modulation.
In AF patients, assessment of thromboembolic risk, and subsequent use of appropriate therapy is crucial for stroke prevention. The risk stratification involves the use of CHA2DS2-VASc score which includes demographic data and cardiovascular risk factors that are shared with many other co-morbid conditions.(3) Although OSA has a significant impact on AF recurrence (4), it is not formally included in the CHA2DS2-VASc score.
The aim of the present study is to explore the association between OSA and an increased cardio-embolic risk in patients with AF, in a large sample of patients recruited from a Pan-European cohort (European Sleep Apnea Database - ESADA).

Patients and methods

The ESADA Study started in 2007 and collect data prospectively from unselected adult patients with suspected OSA referred to European sleep centres. (5)
Demographic data (age, smoking history and alcohol consumption), anthropometric measurements (age, height and body weight), information on sleepiness measured by the Epworth Sleepiness Scale (ESS), data about cardiovascular co-morbidities, in particular AF, are recorded.
OSA is diagnosed by means of polygraph or polysomnography and the following indices are calculated: apnea–hypopnea index (AHI), 4% oxygen desaturation index (ODI4), mean and lowest oxyhaemoglobin saturation (SpO2), and time spent with SpO2 < 90%. CHA2DS2-VASc score was calculated by assigning 1 point for each of the following conditions: heart failure (HF), type 2 diabetes mellitus, hypertension, vascular disease, female sex, and age 65-74 years; and 2 points for a history of ischemic stroke/transient ischemia attack (TIA) and age above 75 years. Based on ESC guidelines on AF, the total CHA2DS2-VASc score can be further classified into 3 risk categories: low, moderate and high risk of cardio-embolic events. (7)

Statistical analysis

Quantitative variables are summarized as means (± standard deviation, SD), whilst qualitative variables as absolute and relative (percentage) frequencies. Analysis of different subgroups of patients according to their CHA2DS2-VASc risk were performed with Kruskal-Wallis test, pairwise comparisons were performed using Wilcoxon rank sum test. Variables with significant correlation with CHA2DS2-VASc risk were then analyzed in a multivariate regression and stepwise regression.

Results

Cross-sectional data from 14,646 patients were included in the study: 8205 patients were excluded after participating centres data quality check, eventually, 14283 patients without AF were excluded. From the total sample a cohort of 363 OSA patients with confirmed AF and OSA was analyzed and the main patient characteristics are summarized in Table 1. The distribution of CHA2DS2-VASc score is the following: 43 patients (11.8%) with score 0, 103 patients (28.4%) with score 1, 88 patients (24.2%) with score 2, 72 patients (19.8%) with score 3, 36 patients (9.9%) with score 4, 15 patients (4.1%) with score 5, 4 patients (1.1%) with score 6, 2 patients (0.6%) with score 7.

Table 1: main characteristics of the studied patients. Data are expressed as mean (standard deviation) or as absolute numbers (percentage).

	Study goup OSA and AF
Subjects, n (% males)	363 (76%)

Age, years	63.7 (9.7)
BMI, kg/m2	32.2 (6.3)
Systolic Blood Pressure, mmHg	133.1 (18.7)
Diastolic Blood Pressure, mmHg	81.0 (10.9)
Heart Rate, bpm	69.8 (12.6)
Waist, cm	112.8 (15.3)
Hip, cm	113.8 (14.4)
Neck, cm	42.5 (4.1)
Insulin dependent diabetes, n (%)	14 (3.9%)
Non-insulin dependent diabetes, n (%)	58 (16.0%)
Ischemic heart disease, n (%)	42 (11.6%)
AHI, events/hour	29.4 (22.5)
AHI <5/hour, events (%)	41 (11.4%)
AHI 5-15/hour, events (%)	83 (23.1%)
AHI 15-30/hour, events (%)	84 (23.4%)
AHI >30/hour, events (%)	151 (42.1%)
ODI4, events/hour	28.8 (23.3)
Mean SaO_2, %	92.2 (3.3)
Lowest SaO_2, %	78.1 (10.1)
Time SpO_2 below 90%, min	57.4 (81.8)
ESS (points)	9.2 (5.1)

Table 2: Main characteristics of patients in the 3 different cardio-embolic risk categories. *= ≥2 vs 0 and vs 1, #=1 vs ≥2, $=0 vs 1 and vs ≥2, &= 0 vs ≥2. Data are expressed as mean (standard deviation).

	CHADVASC score			**p-value**
	0	**1**	**≥2**	
Age, yrs	51.3 (10.2)	59.9 (7.4)	67.9 (7.4)	0.23
BMI, kg/cm^2	29.2 (4.9)	32.4 (6.6)	32.6 (6.2)	<0.05$
SBP, mmHg	125.0 (11.4)	131.6 (19.8)	135.4 (18.8)	<0.001&
DBP, mmHg	79.9 (8.9)	82.7 (12.4)	80.3 (10.4)	0.28
HR, bpm	67.2 (13.3)	71.3 (13.5)	69.5 (11.8)	0.27
Neck, cm	42.4 (3.8)	43.5 (4.2)	41.9 (4.0)	<0.05#
AHI, events/h	22.3 (19.9)	29.7 (22.6)	30.6 (22.7)	0.08
ODI4, events/h	17.9 (17.1)	29.6 (22.5)	30.5 (24.1)	<0.05$
Mean SaO_2, %	93.2 (2.0)	92.2 (3.1)	92 (3.6)	0.08
Lowest SaO_2, %	81.2 (9.6)	77.8 (9.8)	77.5 (10.3)	<0.05$
Time SpO_2 below 90%, min	17.2 (34.0)	73.4 (90.1)	58.3 (82.7)	0.321

ODI4, but not AHI, was significantly increased in category Chadvasc score 1 and ≥2 when compared to the low cardioembolic risk category (Kruskal-Wallis chi-squared = 9.6436, df = 2, p-value = 0.008, table 2). Similarly, lowest SpO2 was significantly reduced in the high CHA2DS2-VASc risk score categories (Figure 1).

The multivariate regression analysis identified ODI4, BMI and lowest SpO2 as predictors of cardio-cardio-embolic risk and when co-linear variables were removed, only lowest SpO2 resulted significant in the stepwise regression (intercept 3.86, beta coefficient -0.02, p<0.01)

Discussion

The main finding of this cross sectional analysis of patients with known AF is that OSA severity is associated with increased cardioembolic risk. In fact, ODI4, a measure of intermittent hypoxia, but not the event matrix AHI, showed a significant association with CHA2DS2-VASc score suggesting a potential role of OSA-related hypoxia in the risk of developing cardio embolic complications such as stroke in patients with OSA and AF.

To our knowledge, this is the largest cohort of patients with OSA and AF assessed by means of either cardiorespiratory polygraphy or nocturnal polysomnography. Our results confirm the data by Szymanski and co-authors obtained in a smaller cohort of hospitalized patients (8) that showed an increased cardioembolic risk estimated with CHA2DS2-VASc score among patients with AF and OSA compared with patients with AF alone.

The interest of our study is related to the fact that, while the role of hypoxia in the development of AF is well known, much less is known about the impact of hypoxia on cardioembolic risk in humans. Animal studies showed that mice with either a HIF1a gene knockout or a HIF1a gain-of-function mutation exhibited a downregulation of protein S levels and therefore an increased thrombin production, consistent with a prothrombotic effect. (9)

We have to acknowledge a few limitations of our study. Its cross-sectional nature makes it difficult to establish a causal relationship between OSA and cardioembolic risk. In addition to this, giving the multi centric nature of this ESADA sub-study, it has been impossible to verify the reliability of the AF diagnosis in all patients by means of an actual ECG tracing or a long-term thumb ECG assessment.

Conclusion

The analysis of the ESADA cohort confirms that OSA severity is associated with an increased cardioembolic risk in patients with atrial fibrillation. In particular, ODI4 and lowest SpO2 showed a significant association with CHA2DS2-VASc score suggesting a potential role of hypoxia in the risk of developing cardio embolic complications such as stroke in patients with OSA and AF.

Figure 1: bar chart showing lowest SpO2 in the 3 cardioembolic risk categories.

Disclosures: none.

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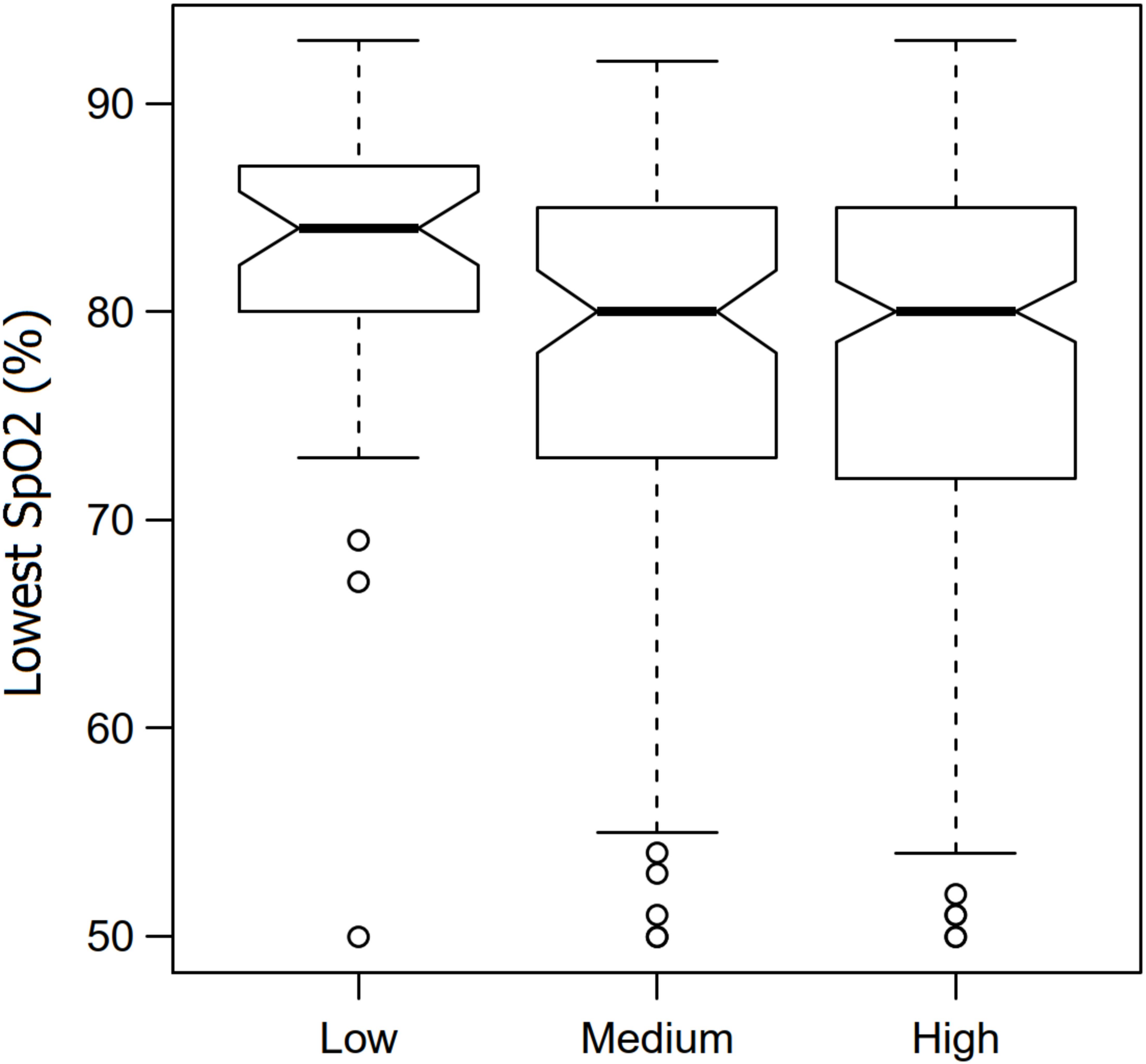
Lowest SpO2 (%)
90
80
70
60
50
Low
Medium
High