



Cardiac remodeling, autonomic parameters, and clinical factors associated with obstructive sleep apnea: a case-control study

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Abstract

Background. Obstructive sleep apnea (OSA) is associated with substantial cardiovascular morbidity through mechanisms involving intermittent hypoxia, sympathetic activation, oxidative stress, and progressive cardiac remodeling. The present study aimed to comprehensively evaluate clinical characteristics, echocardiographic abnormalities, autonomic function, and independent factors associated with OSA in a case-control population.

Methods. This observational, case-control study included 108 adults recruited from a tertiary sleep laboratory, 54 patients with OSA and 54 controls selected using frequency matching for age and sex and considered at low risk for OSA based on STOP-Bang screening. Clinical characteristics, cardiovascular risk factors, transthoracic echocardiographic parameters, structural cardiac abnormalities, and 24-hour Holter-derived autonomic indices were compared between groups. Continuous variables were analyzed using the Mann-Whitney U test, categorical variables using Pearson's chi-square or Fisher's exact test, and univariable and multivariable binary logistic regression analyses were performed to identify variables independently associated with OSA.

Results. Compared with controls, patients with OSA had significantly higher prevalences of obesity, smoking, hypertension, diabetes mellitus, and ischemic heart disease (IHD). Echocardiography demonstrated larger left atrial and right ventricular diameters, higher pulmonary artery systolic pressure (PASP), and increased frequencies of left ventricular hypertrophy (LVH), diastolic dysfunction, and moderate tricuspid regurgitation (TR). Among the Holter-derived autonomic parameters, the root mean square of successive differences between adjacent normal-to-normal intervals (RMSSD) was significantly lower in patients with OSA in the unadjusted comparison. In multivariable linear regression analyses, the association between OSA and RMSSD was attenuated and did not reach statistical significance, while OSA was not independently associated with the standard deviation of normal-to-normal intervals (SDNN). In univariable logistic regression analyses, obesity, smoking, hypertension, diabetes mellitus, ischemic heart disease, left ventricular hypertrophy, and diastolic dysfunction were significantly associated with OSA. After multivariable adjustment, obesity [adjusted odds ratio (OR) 10.86, 95% confidence intervals (CI) 2.99–39.47], smoking (adjusted OR 4.88, 95% CI 1.32–18.14), ischemic heart disease (adjusted OR 19.17, 95% CI 1.65–222.41), and left ventricular hypertrophy (adjusted OR 3.54, 95% CI 1.01–12.40) remained independently associated with OSA.

Conclusions. OSA was associated with structural cardiovascular abnormalities and an unadjusted difference in the Holter-derived autonomic parameter RMSSD, whereas neither RMSSD nor SDNN showed a statistically significant independent association with OSA after multivariable adjustment. Obesity, smoking, ischemic heart disease, and left ventricular hypertrophy were independently associated with the presence of OSA, underscoring the close relationship between sleep-disordered breathing and cardiovascular disease. Comprehensive cardiovascular evaluation may improve risk stratification and support earlier identification of patients at increased cardiovascular risk.

Keywords: obstructive sleep apnea, cardiac remodeling, left ventricular hypertrophy, autonomic parameters, echocardiography

Introduction

Obstructive sleep apnea (OSA) is one of the most common sleep-related breathing disorders, affecting nearly one billion adults worldwide, including approximately 425 million individuals with moderate-to-severe disease requiring treatment [1]. Its prevalence continues to increase in parallel with the global obesity epidemic, making OSA an important and growing public health challenge [1,2]. Characterized by recurrent episodes of upper-airway collapse during sleep, OSA induces intermittent hypoxemia, sleep fragmentation, recurrent arousals, and marked intrathoracic pressure swings that trigger sustained sympathetic activation, oxidative stress, and systemic inflammation [3,4]. Consequently, OSA is now recognized as an independent risk factor for cardiovascular morbidity and mortality and has been associated with hypertension, coronary artery disease, heart failure, atrial fibrillation, stroke, pulmonary hypertension, and increased cardiovascular mortality [4–6].

The cardiovascular burden of OSA extends far beyond the respiratory system and arises from the interaction of mechanical, autonomic, inflammatory, and metabolic mechanisms. Recurrent hypoxia-reoxygenation cycles, repeated arousals, and exaggerated intrathoracic pressure fluctuations promote chronic sympathetic activation, endothelial dysfunction, oxidative stress, systemic inflammation, and neurohumoral dysregulation, ultimately leading to vascular injury and progressive cardiac remodeling [3,4,6–9]. These pathophysiological processes provide the biological basis for the strong association between OSA and cardiovascular disease and support the concept that OSA should be regarded as a systemic cardiovascular disorder rather than an isolated sleep-related breathing disorder [4,6].

Cardiovascular remodeling associated with OSA involves both structural and functional abnormalities affecting the left and right heart. Previous echocardiographic studies have demonstrated increased left ventricular mass, impaired diastolic function, atrial enlargement, right ventricular remodeling, and elevated pulmonary artery pressures, highlighting the broad cardiovascular impact of sleep-disordered breathing [10–13]. In parallel, autonomic dysfunction, characterized by reduced heart rate variability and sympathetic predominance, has emerged as an additional mechanism contributing to arrhythmogenesis and adverse cardiovascular outcomes in patients with OSA [14–17]. Although these cardiovascular manifestations have been extensively investigated, previous studies have frequently focused on individual aspects of cardiovascular involvement, such as echocardiographic remodeling or autonomic dysfunction, rather than evaluating these domains simultaneously within the same study population. The present study therefore aimed to provide an integrated characterization of the cardiovascular phenotype associated with OSA by simultaneously assessing clinical and cardiometabolic characteristics, comprehensive transthoracic echocardiographic findings involving both left-

and right-sided cardiac chambers, pulmonary hemodynamic parameters, and 24-hour Holter-derived autonomic indices in a case-control study using frequency matching for age and sex. The objective was therefore to characterize the coexistence of these cardiovascular abnormalities and their independent associations with OSA within a unified analytical framework. In addition, univariable and exploratory multivariable logistic regression analyses were used to identify clinical and structural characteristics independently associated with OSA.

Methods

Study design and population

This observational, case-control study using frequency matching for age and sex included 108 adult participants recruited during the predefined study period from the Dr. Constantin Papilian Military Clinical Emergency Hospital. Consecutive patients with suspected OSA underwent objective sleep evaluation based on clinical assessment and STOP-Bang screening. Participants with a STOP-Bang score ≥ 3 were considered at increased risk for OSA and underwent objective sleep evaluation using Type 3 portable respiratory monitoring. Of the patients evaluated, 54 participants with moderate or severe OSA confirmed by polygraphy were included in the OSA group. Patients with mild OSA were not included in the final analytical cohort. Subsequently, 54 control participants were selected using frequency matching to achieve a 1:1 ratio with the OSA group with respect to the overall distribution of age and sex. No individual OSA-control pairs were established or retained. Control participants were selected based on a STOP-Bang score ≤ 2 , corresponding to the predefined low-risk category. They were considered clinically unlikely to have OSA, and objective sleep testing was not routinely performed in the control group. Demographic characteristics, anthropometric measurements, cardiovascular risk factors, medical history, Holter electrocardiographic data, and transthoracic echocardiographic parameters were collected for all participants. Exclusion criteria included severe renal impairment (eGFR < 30 mL/min/1.73 m²), active or previous malignancy, persistent, paroxysmal, or permanent atrial fibrillation or other major cardiac arrhythmias, and advanced heart failure (NYHA functional class III–IV). Patients receiving medications with a substantial potential to influence autonomic tone or heart rate variability, including digoxin, antiarrhythmic drugs, or non-dihydropyridine calcium-channel blockers, were also excluded. Beta-blocker therapy was not considered an exclusion criterion because it represented standard cardiovascular therapy in the study population. Patients with regular or evening alcohol consumption were excluded from both groups because alcohol consumption may affect upper airway collapsibility and cardiac autonomic function, potentially acting as a confounding factor in the assessment of OSA and autonomic parameters.

Clinical assessment

Baseline clinical assessment included demographic characteristics (age and sex), anthropometric measurements, including body mass index (BMI) and obesity status, with obesity defined as a BMI ≥ 30 kg/m², smoking status, hypertension, diabetes mellitus, and ischemic heart disease. Clinical characteristics and medical history were obtained from hospital records and standardized patient interviews.

Polygraphic evaluation

Overnight Type 3 portable respiratory monitoring was performed in participants with suspected OSA using the Nox T3 system (Nox Medical, Reykjavík, Iceland). In accordance with established diagnostic pathways, participants with a STOP-Bang score ≥ 3 were considered at increased risk for OSA and underwent objective sleep evaluation. Respiratory recordings were initially scored automatically using the manufacturer's software and subsequently reviewed and manually corrected by a certified sleep specialist in accordance with the American Academy of Sleep Medicine (AASM) scoring criteria [18,19]. The diagnosis of OSA was established based on the apnea-hypopnea index (AHI). OSA severity was categorized as mild ($5 \leq \text{AHI} < 15$ events/hour), moderate ($15 \leq \text{AHI} < 30$ events/hour), or severe ($\text{AHI} \geq 30$ events/hour). For the present case-control analysis, only participants with moderate or severe OSA were included in the OSA group. Participants with mild OSA were not included in the final analytical cohort in order to maintain a clearer distinction between the OSA and control groups. Accordingly, the final OSA group comprised patients with moderate-to-severe OSA. Respiratory events were also classified according to their type as obstructive, central, or mixed. AHI and oxygen desaturation index (ODI) were recorded for participants undergoing polygraphic evaluation. Controls were selected according to predefined low-risk STOP-Bang screening criteria (score ≤ 2) and did not undergo objective sleep testing.

Holter electrocardiographic assessment

Twenty-four-hour ambulatory electrocardiographic Holter monitoring was performed using the BTL-08 H600 system (BTL Industries Ltd.) and analyzed using the BTL CardioPoint-Holter software. Before automated parameter derivation, recordings were visually reviewed by an experienced cardiologist, and artifacts and non-sinus beats were excluded from heart rate variability analysis [20,21]. The following time-domain parameters were analyzed from normal-to-normal (NN) intervals: mean RR interval, standard deviation of NN intervals (SDNN), and the root mean square of successive differences between adjacent NN intervals (RMSSD). RMSSD was reported in milliseconds and was calculated as the square root of the mean of the squared differences between successive NN intervals. In the primary software output, RMSSD was labeled as "heart rate variability (HRV)"; this vendor-specific label has been replaced throughout the manuscript with the standard term RMSSD to avoid ambiguity. SDNN reflects overall heart

rate variability over the recording period, whereas RMSSD primarily reflects short-term beat-to-beat variability and is predominantly influenced by parasympathetic cardiac modulation. Maximum, minimum, and mean heart rates were also recorded. Time-domain parameters were selected because they provided complementary information on overall (SDNN) and short-term (RMSSD) heart rate variability in the 24-hour ambulatory recordings.

Echocardiographic evaluation

Comprehensive transthoracic echocardiography was performed by an experienced cardiologist using a commercially available ultrasound system in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging. The following continuous parameters were evaluated: left atrial diameter, right atrial diameter, right ventricular diameter, tricuspid annular plane systolic excursion (TAPSE), and pulmonary artery systolic pressure (PSAP). In addition, categorical echocardiographic variables, including left ventricular hypertrophy (LVH), left ventricular diastolic dysfunction, regional wall motion abnormalities, and tricuspid regurgitation (TR) severity, were recorded. Left ventricular hypertrophy was recorded as a predefined categorical echocardiographic variable (present/absent) based on the clinical echocardiographic assessment. The underlying continuous left ventricular mass index values were not available in the analytical dataset. Left ventricular diastolic dysfunction was defined according to the American Society of Echocardiography / European Association of Cardiovascular Imaging (ASE/EACVI) recommendations using the following parameters: average E/e' ratio > 14 , septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s, left atrial volume index > 34 mL/m², and peak tricuspid regurgitation velocity > 2.8 m/s. Diastolic dysfunction was considered present when at least three of these four criteria were positive; when only two criteria were available, the classification was considered indeterminate. Tricuspid regurgitation severity was assessed by ECG using an integrated qualitative and semi-quantitative approach in accordance with contemporary ASE/EACVI recommendations and was categorized as mild, moderate, or severe [22,23]. Assessment incorporated the overall appearance of the regurgitant jet on color Doppler and relevant Doppler and structural findings, when technically available.

Quality control and device calibration

All diagnostic examinations were performed using equipment maintained within the institutional clinical setting according to applicable institutional procedures and manufacturer recommendations. Routine technical checks and maintenance were performed as part of standard clinical practice throughout the study period. Standardized acquisition and measurement procedures were used for polygraphy, echocardiography, and Holter monitoring to minimize technical and operator-related variability.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro-Wilk test. Since most variables were not normally distributed, continuous data are presented as median and interquartile range (IQR) and were compared using the Mann-Whitney U test. Categorical variables are presented as frequencies and percentages and were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Effect size for categorical associations was assessed using Cramer's V.

Univariable binary logistic regression analyses were performed to evaluate variables associated with the presence of obstructive sleep apnea (OSA). Because frequency matching was used, unconditional binary logistic regression was performed. Variables selected for the multivariable logistic regression model were those that demonstrated statistically significant associations with OSA in the univariable analyses and were considered suitable for inclusion in the multivariable model. Variables for which logistic regression could not be reliably estimated because of sparse data or complete separation were not included. Variables reaching statistical significance in the univariable analyses were subsequently entered simultaneously into an exploratory multivariable binary logistic regression model using the Enter method. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Model discrimination was assessed using the Nagelkerke R^2 , overall classification accuracy, and receiver operating characteristic (ROC) curve analysis with calculation of the area under the curve (AUC) and its 95% confidence interval. Calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test. Given the exploratory nature of the multivariable

analysis, the resulting estimates were interpreted cautiously and considered hypothesis-generating rather than definitive.

Separate multivariable linear regression models were performed with RMSSD and SDNN as dependent variables to assess their associations with OSA after adjustment for potential demographic and cardiometabolic confounders. Each model included OSA status, age, sex, obesity, smoking, hypertension, diabetes mellitus, and ischemic heart disease as independent variables. Unstandardized regression coefficients (B), standardized regression coefficients (β), 95% confidence intervals (CIs), and p-values were reported. Multicollinearity was assessed using tolerance and variance inflation factor (VIF) values. Model assumptions were evaluated by inspection of the distribution of standardized residuals, normal probability plots, and scatterplots of standardized predicted values against standardized residuals. A two-sided p-value < 0.05 was considered statistically significant.

The study included 108 participants (54 patients with OSA and 54 controls selected using frequency matching with respect to age and sex) recruited during the predefined study period. No formal a priori sample size calculation was performed before recruitment.

Results

Clinical characteristics of the study population

Baseline demographic and clinical characteristics of the study population are summarized in table I. As expected, age and sex distributions were comparable between the two groups. In contrast, patients with OSA had a substantially higher cardiometabolic risk burden, with higher prevalences of obesity, hypertension, diabetes mellitus, ischemic heart disease, and active smoking. The largest effect size was observed for obesity (Cramer's V = 0.57).

Table I. Clinical characteristics of the study population stratified by obstructive sleep apnea status.

Variable	Controls (n = 54)	OSA (n = 54)	p value
Age, years	59.5 (50.0–65.0)	59.5 (51.0–66.0)	0.813
Male sex, n (%)	43 (79.6)	43 (79.6)	1.000
Obesity, n (%)	18 (33.3)	48 (88.9)	<0.001
Smoking, n (%)	8 (14.8)	23 (42.6)	0.001
Hypertension, n (%)	42 (77.8)	52 (96.3)	0.004
Diabetes mellitus, n (%)	4 (7.4)	14 (25.9)	0.010
Ischemic heart disease, n (%)	1 (1.9)	15 (27.8)	<0.001
OSA severity, n (%)	-	-	-
Mild OSA ($5 \leq \text{AHI} < 15$ events/hour)	-	0 (0.0)	-
Moderate OSA ($15 \leq \text{AHI} < 30$ events/hour)	-	16 (29.6)	-
Severe OSA ($\text{AHI} \geq 30$ events/hour)	-	38 (70.4)	-
AHI, events/hour	-	49.1 (22.47–67.30)	-
Apnea subtype, n (%)	-	-	-
Obstructive apnea	-	54 (100.0)	-
Central apnea	-	0 (0.0)	-
Mixed apnea	-	0 (0.0)	-

Continuous variables are presented as median (interquartile range [IQR]) and were compared using the Mann-Whitney U test. Categorical variables are presented as number (percentage) and were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Statistical significance was defined as $p < 0.05$.

The final OSA group comprised exclusively patients with moderate or severe disease, as patients with mild OSA were not included in the analytical cohort. All patients with OSA had obstructive events, with no central or mixed apnea identified (Table I).

Continuous cardiovascular remodeling markers according to OSA status

Continuous echocardiographic and Holter-derived parameters are summarized in table II. Compared with controls, patients with OSA exhibited significant differences in several echocardiographic and Holter-derived parameters. Echocardiographic assessment demonstrated several statistically significant differences between the OSA and control groups, involving right-sided cardiac dimensions and functional parameters. Right atrial diameter was lower in patients with OSA than in controls (27 vs. 29 mm, $p < 0.001$), whereas TAPSE was higher (26 vs. 17 mm, $p < 0.001$). The difference in right ventricular diameter was small in absolute terms (24 vs.

23 mm), despite statistical significance ($p < 0.001$). These findings should therefore be interpreted in the context of their absolute magnitude and clinical reference ranges. Regarding autonomic function, RMSSD was significantly lower in patients with OSA, while no significant between-group differences were observed for RR interval, SDNN, maximum heart rate, minimum heart rate, or mean heart rate (Table II).

To further investigate whether the observed differences in heart rate variability were independently associated with OSA, separate multivariable linear regression models were performed for RMSSD and SDNN, adjusting for age, sex, obesity, smoking, hypertension, diabetes mellitus, and ischemic heart disease. Both models were statistically significant overall. After adjustment, OSA showed a negative but non-significant association with RMSSD and was not independently associated with SDNN (Table III).

Table II. Continuous echocardiographic and Holter-derived parameters according to obstructive sleep apnea status.

Variable	Controls (n = 54)	OSA (n = 54)	p value
Left atrial diameter, mm	28.0 (28.0–30.0)	30.0 (28.0–32.0)	0.002
Right atrial diameter, mm	29.0 (28.0–31.0)	27.0 (26.8–28.0)	<0.001
Right ventricular diameter, mm	23.0 (22.0–23.0)	24.0 (23.0–24.0)	<0.001
TAPSE, mm	17.0 (17.0–18.0)	26.0 (22.0–28.0)	<0.001
PSAP, mmHg	22.0 (12.0–32.0)	33.0 (29.0–36.0)	<0.001
RR interval, ms	860.5 (777.0–903.3)	858.0 (815.5–897.5)	0.766
SDNN, ms	125.0 (108.0–160.5)	120.5 (98.8–138.3)	0.083
RMSSD, ms	30.0 (23.5–34.3)	23.0 (19.8–28.3)	<0.001
Maximum heart rate, bpm	120.5 (107.8–134.0)	114.0 (102.8–128.3)	0.127
Minimum heart rate, bpm	53.0 (46.0–57.3)	53.0 (47.8–56.3)	0.837
Mean heart rate, bpm	71.5 (66.0–78.3)	71.0 (66.8–78.3)	0.905

Continuous variables are presented as median (interquartile range [IQR]) and were compared using the Mann-Whitney U test. Abbreviations: TAPSE, tricuspid annular plane systolic excursion; PSAP, pulmonary artery systolic pressure; SDNN, standard deviation of normal-to-normal RR intervals; RMSSD, root mean square of successive differences between adjacent NN intervals. Statistical significance was defined as $p < 0.05$.

Table III. Multivariable linear regression analyses of autonomic parameters according to OSA status.

Predictor	RMSSD B (95% CI)	β	p-value	SDNN B (95% CI)	β	p-value
OSA	-3.578 (-7.272 to 0.116)	-0.217	0.057	-13.197 (-30.739 to 4.345)	-0.185	0.139
Age	-0.273 (-0.410 to -0.136)	-0.361	<0.001	-0.763 (-1.414 to -0.112)	-0.233	0.022
Sex	2.046 (-1.484 to 5.576)	0.100	0.253	13.697 (-3.067 to 30.461)	0.154	0.108
Obesity	-3.005 (-6.524 to 0.514)	-0.177	0.093	-12.639 (-29.349 to 4.072)	-0.172	0.137
Smoking	-1.717 (-5.051 to 1.617)	-0.094	0.309	1.816 (-14.018 to 17.650)	0.023	0.820
Hypertension	-2.245 (-6.700 to 2.209)	-0.091	0.320	-1.517 (-22.672 to 19.638)	-0.014	0.887
Diabetes mellitus	-1.692 (-5.658 to 2.274)	-0.076	0.399	-3.743 (-22.577 to 15.091)	-0.039	0.694
IHD	3.400 (-0.940 to 7.740)	0.146	0.123	17.244 (-3.368 to 37.855)	0.171	0.100

Model statistics: RMSSD model: $F(8,99) = 5.444$, $p < 0.001$, adjusted $R^2 = 0.140$; SDNN model: $F(8,99) = 2.448$, $p = 0.018$, adjusted $R^2 = 0.098$. RMSSD and SDNN were entered as dependent variables in separate multivariable linear regression models. B, unstandardized regression coefficient; β , standardized regression coefficient; CI, confidence interval; IHD, ischemic heart disease; OSA, obstructive sleep apnea.

Structural cardiovascular abnormalities according to OSA status

Structural and functional echocardiographic abnormalities are summarized in table IV. Patients with OSA had a higher prevalence of left ventricular hypertrophy and diastolic dysfunction than controls. Regional left ventricular wall motion abnormalities were observed only among patients with OSA. Tricuspid regurgitation severity also differed significantly between groups, with moderate regurgitation more frequently observed in patients with OSA (Table IV).

Factors associated with obstructive sleep apnea

Univariable binary logistic regression analysis was performed to evaluate the association between

demographic, clinical, and echocardiographic variables and the presence of OSA (Table V). Obesity, smoking, hypertension, diabetes mellitus, ischemic heart disease, diastolic dysfunction, and left ventricular hypertrophy were significantly associated with OSA, whereas male sex was not. The corresponding effect estimates and model performance measures are presented in table V.

Multivariable logistic regression analysis

An exploratory multivariable logistic regression model was constructed using variables that demonstrated statistically significant associations with OSA in the univariable analyses. The overall model was statistically significant, and calibration and classification performance are presented in table VI.

Table IV. Structural and functional cardiac abnormalities according to obstructive sleep apnea status.

Variable	Controls (n = 54)	OSA (n = 54)	p value
Left ventricular hypertrophy	14 (25.9%)	42 (77.8%)	<0.001
Diastolic dysfunction	30 (55.6%)	43 (79.6%)	0.008
Wall motion abnormalities (dyskinesia)	0 (0.0%)	6 (11.1%)	0.027 a
Tricuspid regurgitation			<0.001 b
None	22 (40.7%)	0 (0.0%)	
Mild	20 (37.0%)	25 (46.3%)	
Moderate	12 (22.2%)	29 (53.7%)	

Data are presented as n (%). Categorical variables were compared using Pearson's chi-square test unless otherwise specified. a Fisher's exact test was used for wall motion abnormalities because expected cell counts were <5. b p value refers to the overall comparison of tricuspid regurgitation severity between groups. Statistical significance was defined as a two-sided p-value <0.05.

Table V. Univariable logistic regression analysis for factors associated with obstructive sleep apnea.

Variable	Odds ratio (95% CI)	p value	Nagelkerke R ²	Overall classification accuracy (%)
Male sex	1.00 (0.39–2.55)	1.000	0.000	50.0
Obesity	16.00 (5.77–44.37)	<0.001	0.395	77.8
Smoking	4.27 (1.69–10.75)	0.002	0.124	63.9
Hypertension	7.43 (1.58–35.04)	0.011	0.107	59.3
Diabetes mellitus	4.38 (1.34–14.33)	0.015	0.084	59.3
Ischemic heart disease	20.39 (2.58–160.91)	0.004	0.192	63.0
Diastolic dysfunction	3.13 (1.33–7.34)	0.009	0.087	62.0
Left ventricular hypertrophy	10.00 (4.13–24.21)	<0.001	0.329	75.9

Odds ratios were obtained from univariable binary logistic regression models with obstructive sleep apnea as the dependent variable. Nagelkerke R² and overall classification accuracy are presented as measures of model performance. Left ventricular wall motion abnormalities were not included because the logistic regression model did not converge due to complete separation.

Table VI. Multivariable logistic regression analysis for factors associated with obstructive sleep apnea.

Variable	β	Adjusted OR (95% CI)	p value
Obesity	2.385	10.86 (2.99–39.47)	<0.001
Smoking	1.586	4.88 (1.32–18.14)	0.018
Hypertension	0.455	1.58 (0.20–12.41)	0.666
Diabetes mellitus	0.834	2.30 (0.40–13.35)	0.352
Ischemic heart disease	2.953	19.17 (1.65–222.41)	0.018
Left ventricular diastolic dysfunction	-0.143	0.87 (0.21–3.54)	0.842
Left ventricular hypertrophy	1.264	3.54 (1.01–12.40)	0.048

Binary logistic regression using the Enter method. Variables significant in univariable analysis were entered simultaneously into the multivariable model. Adjusted odds ratios (OR) with 95% confidence intervals (CI) are presented. Model performance: Omnibus X² = 65.674 (p < 0.001); Cox & Snell R² = 0.456; Nagelkerke R² = 0.607; Hosmer-Lemeshow X² = 4.236 (p = 0.835); overall classification accuracy = 83.3%.

After multivariable adjustment, obesity, smoking, ischemic heart disease, and left ventricular hypertrophy remained independently associated with OSA, whereas hypertension, diabetes mellitus, and left ventricular diastolic dysfunction were no longer statistically significant (Table VI). The apparent discriminatory performance of the final multivariable logistic regression model was further assessed using receiver operating characteristic (ROC) curve analysis. The model showed high apparent discriminatory ability, with an area under the curve (AUC) of 0.905 (95% CI: 0.848–0.962; $p < 0.001$). The corresponding ROC curve is presented in figure 1.

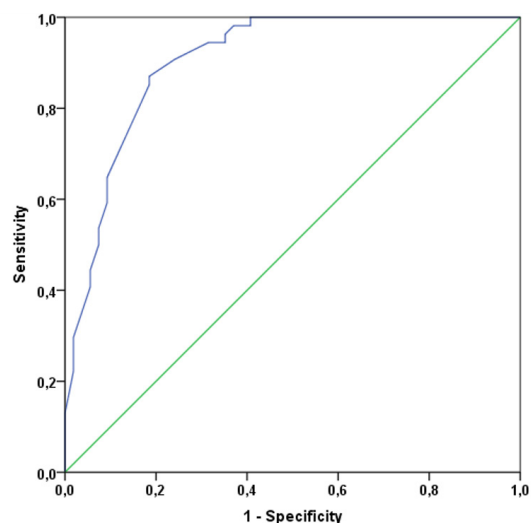


Figure 1. Receiver operating characteristic curve of the final multivariable logistic regression model for obstructive sleep apnea.

Discussion

The present study demonstrates that OSA is associated with a multidimensional cardiovascular phenotype encompassing cardiometabolic risk and structural cardiac abnormalities, while differences in the Holter-derived autonomic parameter RMSSD were observed in unadjusted analyses. Importantly, obesity, smoking, ischemic heart disease, and left ventricular hypertrophy remained independently associated with OSA after multivariable adjustment. These findings reinforce the close relationship between sleep-disordered breathing and cardiovascular disease while highlighting the contribution of both clinical and structural factors.

The clinical profile observed in the present cohort is consistent with the well-established association between OSA and cardiometabolic risk factors, with obesity showing the strongest independent association with OSA. This finding is in agreement with previous evidence identifying obesity as an important modifiable risk factor associated with the development and severity of OSA [3,24]. Excess adipose tissue deposition within the tongue and upper

airway, particularly in individuals with central obesity, may promote pharyngeal narrowing, increased upper-airway collapsibility, and impaired neuromuscular compensation during sleep, thereby facilitating recurrent obstructive respiratory events [24,25]. Beyond these anatomical effects, obesity is associated with systemic inflammation, insulin resistance, and sustained sympathetic activation, which may contribute to both OSA pathophysiology and its cardiovascular manifestations [11,26–29]. Collectively, these mechanisms provide a plausible biological context for the strong association between obesity and OSA observed in the present study, while the case-control design does not allow determination of temporal or causal relationships between these factors.

The associations with smoking and ischemic heart disease further support the complex interplay between OSA and cardiovascular disease. Previous studies have linked smoking with sleep-disordered breathing through mechanisms involving upper-airway inflammation, oxidative stress, impaired neuromuscular control, and alterations in sleep architecture [30–34]. Similarly, the association between OSA and ischemic heart disease may involve recurrent hypoxia-reoxygenation, endothelial dysfunction, oxidative stress, systemic inflammation, and sympathetic activation [4,5,35]. These mechanisms were not directly assessed in the present study and should therefore be regarded as potential pathophysiological explanations rather than mechanisms demonstrated by our data.

Cardiac remodeling represents an important component of the cardiovascular phenotype associated with OSA. The structural abnormalities observed in the present study are broadly consistent with previous echocardiographic evidence and may reflect the cumulative effects of recurrent nocturnal hypoxia, sympathetic overactivity, neurohumoral activation, and altered cardiac loading conditions [7,9,10,36,37]. Among these abnormalities, left ventricular hypertrophy remained independently associated with OSA after multivariable adjustment, consistent with evidence indicating that LVH is one of the most reproducible structural manifestations associated with OSA across different patient populations [10]. In contrast, the lack of an independent association between diastolic dysfunction and OSA after adjustment suggests that diastolic abnormalities may be substantially influenced by coexisting conditions, particularly obesity, hypertension, and metabolic abnormalities. These findings emphasize the multifactorial nature of cardiac remodeling in patients with OSA and suggest that structural myocardial changes may provide complementary information beyond functional abnormalities alone.

The right-sided findings provide further support for the involvement of pulmonary vascular and right ventricular pathways in OSA [4,5,7,38,39]. The relatively high prevalence of moderate tricuspid regurgitation in

the OSA group, despite the relatively modest resting PSAP values, warrants cautious interpretation. Tricuspid regurgitation in OSA may reflect predominantly functional changes related to right-sided loading conditions, including intermittent increases in intrathoracic pressure and transient nocturnal changes in pulmonary vascular loading, which may not be fully captured by a single daytime resting echocardiographic PSAP measurement. In addition, the high prevalence of obesity in this cohort may have influenced echocardiographic image quality and the assessment of regurgitation severity. Therefore, some degree of measurement variability or overestimation of TR severity cannot be excluded. The observed prevalence should consequently be interpreted in the context of the selected cardiovascular cohort and the limitations of conventional resting echocardiographic assessment. Pulmonary hypertension has been proposed as a potential consequence of chronic nocturnal hypoxemia, with hypoxia-induced pulmonary vasoconstriction, endothelial dysfunction, and vascular remodeling potentially contributing to increased pulmonary vascular resistance and right ventricular afterload [4,5,7]. These hemodynamic alterations may contribute to right ventricular remodeling and functional tricuspid regurgitation through right ventricular enlargement and annular dilatation [38]. However, the right-sided echocardiographic findings in the present study did not demonstrate uniform right-sided chamber enlargement or established right ventricular systolic dysfunction. Although significant differences in right atrial diameter and TAPSE were observed, right atrial diameter was lower in patients with OSA than in controls, while TAPSE was higher rather than reduced. The higher TAPSE therefore does not support impaired longitudinal right ventricular systolic function as assessed by this parameter. These findings should be interpreted in the context of the known dependence of conventional right ventricular indices on loading conditions and the complex geometry of the right ventricle. The higher TAPSE observed in the OSA group may reflect preserved or potentially augmented longitudinal right ventricular excursion in response to altered loading conditions, although this interpretation remains speculative and cannot be established from the observational case-control design [36,39,40]. More advanced imaging techniques, including right ventricular strain analysis, have demonstrated greater sensitivity for detecting subclinical right ventricular dysfunction and may provide a more comprehensive assessment of right-heart involvement in OSA than conventional parameters alone [36,40]. Importantly, the pulmonary vascular and right-heart findings observed in the present study should be interpreted in the context of the higher burden of cardiometabolic comorbidities in the OSA group, which may independently influence pulmonary pressures and cardiac remodeling. The mechanisms discussed above therefore represent potential pathophysiological explanations rather than mechanisms

directly demonstrated by the present study.

The unadjusted reduction in RMSSD observed in the present study is consistent with previous evidence suggesting that RMSSD may provide information on autonomic modulation that is not captured by conventional heart rate parameters [14,16,41,42]. Recurrent nocturnal respiratory events, intermittent hypoxemia, and sleep fragmentation may activate peripheral and central chemoreflex pathways, promoting sympathetic overactivity that can persist beyond sleep [7,8,43]. This autonomic imbalance has been implicated in hypertension, myocardial remodeling, myocardial ischemia, and cardiac arrhythmias and may therefore represent an important link between OSA and adverse cardiovascular outcomes [7,8,43,44]. Although SDNN did not differ significantly between study groups, previous investigations have shown that individual RMSSD indices are influenced by multiple clinical factors, including age, cardiovascular comorbidities, and medication use, which may partly account for variability between studies, particularly in relatively small cohorts [14,16,42]. Importantly, in the adjusted analysis, the association between OSA and RMSSD was attenuated and did not reach conventional statistical significance ($p = 0.057$), while OSA was not independently associated with SDNN ($p = 0.139$). These findings suggest that the autonomic differences observed in the unadjusted comparison may be partly influenced by age and the accompanying cardiometabolic profile. Therefore, the observed reduction in RMSSD should be interpreted cautiously and should not be considered an independent association with OSA after adjustment for these factors.

Taken together, the multivariable findings highlight the coexistence of cardiometabolic risk factors, structural myocardial remodeling, and sleep-disordered breathing. These findings are consistent with the current understanding of OSA as a multisystem disorder resulting from the interaction of anatomical, metabolic, inflammatory, and neurohumoral mechanisms rather than an isolated respiratory condition [7,45]. From a clinical perspective, the coexistence of obesity, smoking, ischemic heart disease, and echocardiographic evidence of left ventricular hypertrophy should increase clinical suspicion for previously unrecognized OSA, particularly in cardiovascular practice, where the condition remains substantially underdiagnosed despite its high prevalence among patients with established cardiovascular disease [4,45]. Earlier recognition of this clinical profile may facilitate timely referral for polygraphic evaluation and implementation of appropriate therapeutic strategies, potentially improving long-term cardiovascular risk stratification and patient management [4].

Limitations

The present study has several strengths. The frequency-matched case-control design minimized the influence of two major demographic determinants of cardiovascular remodeling. More importantly, the

simultaneous assessment of clinical and cardiometabolic characteristics, comprehensive transthoracic echocardiography, pulmonary hemodynamic parameters, and Holter-derived autonomic indices enabled an integrated characterization of the cardiovascular phenotype associated with OSA within the same study population. While the individual abnormalities identified are consistent with previously reported manifestations of OSA, the added value of the present study lies in demonstrating their coexistence and examining their independent associations within a unified clinical, structural, and autonomic framework. This comprehensive approach extends previous investigations that primarily focused on isolated echocardiographic or autonomic parameters and allowed the identification of independent clinical and structural characteristics associated with OSA within the same study population. Several limitations should also be acknowledged. The observational case-control design precludes establishing causal relationships between OSA and the observed cardiovascular abnormalities. In addition, the study was conducted at a single tertiary referral center, which may limit the generalizability of the findings. Detailed equipment-specific calibration records were not incorporated into the study database, although the diagnostic systems were used and maintained within routine institutional clinical practice. Therefore, minor temporal variations in equipment performance cannot be completely excluded. Furthermore, the OSA cohort was restricted to patients with moderate-to-severe disease, as patients with mild OSA were not included in the final analytical cohort. This limits the generalizability of the findings to patients with milder forms of OSA. The relatively small number of patients with moderate OSA also limited the feasibility and statistical robustness of severity-stratified analyses. Although AHI was used to characterize OSA severity, the primary analysis was designed to compare participants with OSA versus controls rather than to evaluate severity-dependent associations within the OSA group. Therefore, potential dose-response relationships between continuous AHI values and cardiovascular parameters were not assessed. Future studies with larger cohorts and a broader spectrum of OSA severity should investigate these relationships. An additional limitation concerns the ascertainment of OSA status in the control group. While OSA was objectively confirmed by polygraphy in the case group, controls were selected using a predefined low-risk STOP-Bang criterion (score ≤ 2) and did not undergo objective sleep testing. Because the STOP-Bang questionnaire incorporates BMI and hypertension as individual components, the use of this criterion for control selection may have influenced the distribution of these characteristics between the study groups. Therefore, the associations of obesity and hypertension with OSA should be interpreted in the context of the control-selection strategy. Therefore, the presence of undiagnosed or

asymptomatic OSA, particularly milder disease, cannot be definitively excluded in the control group. This potential misclassification should be considered when interpreting the observed between-group differences. Another limitation is the potential for confounding by concomitant cardiovascular medication, particularly beta-blocker therapy, which may influence heart rate variability parameters. Detailed patient-level medication data, including beta-blocker use, dose, and treatment duration, were not systematically available in the analytical database and therefore could not be used to adjust the HRV analyses or perform medication-specific sensitivity analyses. Although cardiovascular comorbidities such as hypertension and ischemic heart disease were included as covariates in the multivariable analyses, these variables cannot be considered reliable surrogates for individual beta-blocker exposure. Consequently, medication-related residual confounding cannot be completely excluded. The observed differences in RMSSD and SDNN should therefore be considered strictly exploratory and hypothesis-generating rather than definitive evidence of OSA-related autonomic dysfunction. The higher prevalence of obesity, hypertension, diabetes mellitus, and ischemic heart disease in the OSA group represents an additional potential source of residual confounding, as these conditions may independently influence left ventricular remodeling, diastolic function, pulmonary pressures, and autonomic regulation. Although multivariable adjustment was performed for both the autonomic and OSA-association analyses, residual confounding cannot be completely excluded, particularly given the modest sample size and the imbalance in cardiometabolic characteristics between the groups. The adjusted autonomic analyses showed attenuation of the association between OSA and RMSSD, which did not reach conventional statistical significance, while no independent association was observed between OSA and SDNN. In view of the potential influence of concomitant medication and residual cardiometabolic confounding, these findings should be interpreted cautiously and considered exploratory. Another limitation concerns the interpretation of absolute echocardiographic chamber dimensions in the context of the high prevalence of obesity in the OSA group. Approximately 89% of patients with OSA were classified as obese, and body size may influence absolute atrial and ventricular dimensions. Therefore, unindexed chamber measurements may not fully distinguish physiological size-related differences from pathological cardiac remodeling. Indexed parameters, particularly left atrial volume index and left ventricular mass index, may provide a more standardized assessment of chamber remodeling in populations with a high prevalence of obesity. However, these indexed measurements were not available as continuous variables in the present analytical dataset. Left ventricular hypertrophy was available only as a predefined categorical variable and was therefore analyzed as such.

Future studies should incorporate body-size-indexed echocardiographic measurements, with appropriate consideration of the potential limitations of conventional body-surface-area indexing in patients with severe obesity. The relatively modest sample size may have reduced statistical power for selected analyses and contributed to the wide confidence intervals observed for certain regression estimates. The multivariable logistic regression analysis should therefore be considered exploratory, given the relatively small number of outcome events in relation to the number of predictor parameters. The model included seven parameters and 54 OSA events, corresponding to approximately 7.7 events per predictor parameter, which is below the commonly cited 10-events-per-parameter rule of thumb. Consequently, potential overfitting, model instability, and imprecision of individual effect estimates cannot be excluded, as reflected by the particularly wide confidence interval observed for ischemic heart disease (adjusted OR 19.17, 95% CI: 1.65–222.41). In addition, variable selection was based on statistical significance in univariable analyses rather than on a prespecified clinical or causal framework. This data-driven approach may introduce selection bias and unstable coefficient estimates and may have resulted in clinically relevant confounders being excluded from the multivariable model. Taken together, these considerations support interpreting the multivariable findings as exploratory and hypothesis-generating rather than definitive. No formal *a priori* sample size calculation was performed before recruitment, which should also be considered when interpreting the statistical power of secondary and exploratory analyses.

Conclusion

Obstructive sleep apnea was associated with a broad spectrum of cardiovascular abnormalities, including structural cardiac remodeling and an unadjusted reduction in RMSSD. Compared with controls, patients with OSA exhibited a higher prevalence of traditional cardiovascular risk factors, differences in cardiac morphology, higher pulmonary artery systolic pressure, more frequent left ventricular hypertrophy and diastolic dysfunction, and reduced RMSSD in the unadjusted comparison. In the exploratory multivariable analysis, obesity, smoking, ischemic heart disease, and left ventricular hypertrophy were independently associated with the presence of OSA. Importantly, after adjustment for age, sex, obesity, smoking, hypertension, diabetes mellitus, and ischemic heart disease, the association between OSA and RMSSD was attenuated and did not reach conventional statistical significance, while OSA was not independently associated with SDNN. The main contribution of this study is the integrated characterization of structural cardiac remodeling, pulmonary hemodynamic involvement, and autonomic parameters within the same frequency-matched case-control population by age and sex. These findings support an association between OSA

and an adverse cardiovascular phenotype and highlight the potential value of comprehensive cardiovascular assessment in patients with suspected or confirmed sleep-disordered breathing. However, given the observational case-control design, the modest sample size, and the substantial burden of cardiometabolic comorbidities, these findings do not establish causal relationships between OSA and the observed cardiovascular abnormalities. Further prospective studies are warranted to clarify the temporal and pathophysiological relationships between OSA, cardiac remodeling, pulmonary hemodynamics, and autonomic regulation.

Author Contributions

Conceptualization, C.V.Z.B. and L.M.P.; methodology, C.V.Z.B.; software, D.C.M. and R.M.P.; validation, L.M.P.; formal analysis, D.C.M. and L.M.P.; investigation, C.V.Z.B. and R.M.P.; resources, L.M.P.; data curation, C.V.Z.B., R.M.P. and D.C.M.; writing-original draft preparation, C.V.Z.B., D.C.M. and R.M.P.; writing-review and editing, D.C.M. and L.M.P.; visualization, D.C.M. and R.M.P.; supervision, L.M.P.; project administration, C.V.Z.B.; funding acquisition, C.V.Z.B.

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Ethical Considerations

The study protocol was approved by the Ethics Committee of Iuliu Hațieganu University of Medicine and Pharmacy Cluj-Napoca (Approval No. 119/17.05.2022). All participants provided written informed consent prior to enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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