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ORIGINAL RESEARCH

Association Between Central Sleep Apnea and Left Atrial Enlargement in Snoring Patients with Preserved Ejection Fraction

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Background: Central sleep apnea (CSA) significantly impacts cardiovascular health, linking it to left atrial enlargement, atrial fibrillation, and impaired cardiac function in heart failure patients with reduced ejection fraction (EF). However, the relationship between CSA and left atrial size in individuals with preserved EF remains underexplored.

Objective: This study aims to examine the relationship between left atrial size and CSA in snoring patients with preserved EF.

Methods: An observational study was conducted involving 341 consecutive snoring patients from a cardiology department who underwent overnight polysomnography (PSG) and echocardiography. Patients with EF below 50%, pulmonary diseases or neuromuscular disorders were excluded. CSA was defined as a central apnea-hypopnea index (CAHI) of five or more events per hour. Inverse probability of treatment weighting (IPTW) and logistic regression models were employed to evaluate the relationship between CSA and left atrial size.

Results: Among the 341 patients, 33 (9.68%) were diagnosed with CSA, with a higher prevalence in males (10.0%) than females (8.91%). Left atrial enlargement (LAE) was observed in 172 patients (50.44%), predominantly in females (71.29%). CSA patients demonstrated significantly higher apnea-hypopnea index (AHI) (49.2/h vs 26.75/h, $p < 0.01$) and oxygen desaturation index (ODI) (44.9 vs 22.85, $p < 0.01$), alongside more sleep time with oxygen saturation < 90% (6.6% vs 2.35%, $p = 0.01$). Echocardiographic evaluations revealed that CSA patients had a greater left atrial anterior-posterior diameter(LAD-ap 42.73 ± 13.01 mm vs 38.15 ± 4.58 mm, $p < 0.01$) and a higher frequency of LAE (69.7% vs 48.38%, $p = 0.02$). Males with CSA had a significantly increased risk of LAE (OR: 4.54; 95% CI: 1.45–14.2) after IPTW adjustment, with significant associations persisting among those with risk factors such as smoking and dyslipidemia.

Conclusion: This study highlights a significant association between CSA and left atrial enlargement in males with preserved EF, suggesting that CSA may contribute to atrial remodeling even without reduced ejection fraction.

Keywords: central sleep apnea, left atrial enlargement, preserved ejection fraction

Introduction

Sleep-disordered breathing (SDB), comprising obstructive sleep apnea (OSA), central sleep apnea (CSA), as well as CSA-Cheyne-Stokes respiration, poses detrimental impacts on cardiovascular and neuroendocrine systems, compromising quality of life and emotional well-being. The physiological pressure of SDB will lead to persistent biological effects, which will eventually lead to changes in cardiovascular basement substances and increase the risk of cardiac arrhythmia.[1] OSA has been associated with increased risks of cardiovascular diseases and strokes, highlighting the urgent need for effective management strategies. For instance, Zhao et al identified a J-shaped relationship between weight-adjusted

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waist index and cardiovascular disease risk in hypertensive patients with OSA,[2] while Cai et al demonstrated that the body roundness index enhances the predictive value of cardiovascular disease risk in similar populations.[3]

CSA, which is characterized by respiratory pauses resulting from central nervous system dysregulation or complete neuromuscular paralysis, is often observed in patients with heart failure, atrial fibrillation, and cerebrovascular disease. CSA receives comparatively less attention than OSA, but potentially more severe, due to hypoventilation and hypoxia.[4] Previous researches had demonstrated that in patients with heart failure and reduced ejection fraction (HFrEF), CSA was associated with an enlarged left atrial size,[5,6] the presence of atrial fibrillation,[7] a decreased left ventricular ejection fraction (LVEF)[8] and elevated levels of brain natriuretic peptide (BNP).[9] The application of continuous positive airway pressure (CPAP) therapy for the treatment of CSA has been shown to enhance LVEF and improve performance on the 6-minute walk test.[10] Additionally, patients with CSA may experience greater benefits from valve replacement surgery for rheumatic heart disease in terms of cardiac function improvement.[11] Moreover, it has been established that CSA is correlated with an increased risk of developing atrial fibrillation in individuals without heart failure, underscoring its clinical significance (OR=3.00, [95% CI, 1.40–6.44]).[12] These findings suggested that CSA was linked to left atrial pathologies, atrial arrhythmias, and diminished cardiac function; however, the underlying mechanisms and processes involved in disease progression remained poorly understood.

Prior studies had indicated a potential correlation between left atrial size and OSA,[13] however, the relationship between left atrial size and CSA remained inadequately investigated, particularly in individuals with preserved left ventricular ejection fraction (LVEF). The current study aims to address this gap by examining the association between left atrial size and CSA in subjects with preserved ejection fraction, thereby contributing to the existing body of knowledge in this area.

Materials and Methods

We conducted an observational study involving consecutive snoring patients from the cardiology department who underwent overnight polysomnography (PSG), echocardiography and laboratory blood test from March 1st, 2016, to June 30th, 2024. The patient is an inpatient in the cardiology department, admitted due to hypertension, coronary heart disease, heart failure, and other related conditions. For patients who exhibit symptoms of snoring, it is recommended that they undergo sleep monitoring. Patients with left ventricle ejection fraction below 50% measured by echocardiography, those with pulmonary diseases (including chronic obstructive pulmonary disease, asthma, lung cancer, and pneumonia occurring within three months), or individuals with neuromuscular disorders were excluded from the study (Figure 1). All included patients were undergoing their first sleep monitoring examination and none of them had previously received treatment for OSA, including the use of a ventilator. PSG was utilized to diagnose and classify SDB events. Echocardiography was employed to measure the left atrial anterior-posterior diameter, ejection fraction, and left ventricular diastolic function. Blood samples were collected for various biochemical analyses. The Body Mass Index (BMI) was calculated by dividing an individual's weight, measured in kilograms, by their body surface area, expressed in square meters. The research was approved by the ethics committee at Peking University International Hospital, with the ethics identifier 2023-KY-0083-02. Due to the exclusive use of anonymized data for analysis, individual consent was exempted and the waiver of informed consent was approved by the ethics committee at Peking University International Hospital.

Echocardiography

All participants underwent transthoracic echocardiography, during which parameters such as LVEF, left atrial anterior-posterior diameter, left ventricular end diastolic diameter (LVEDD), the degree of mitral regurgitation, and left ventricular diastolic function were documented in accordance with current guideline.[14] In this study, left atrial enlargement (LAE) was defined as an anterior-posterior diameter of the left atrium of 40 mm or greater in men and 35 mm or greater in women.[15]

Sleep Evaluation

All enrolled patients underwent overnight polysomnography (using either Alice6 from Philips Respironics, Inc. or E-Series from Compumedics, Inc). in a sleep laboratory. PSG was conducted in accordance with the guidelines

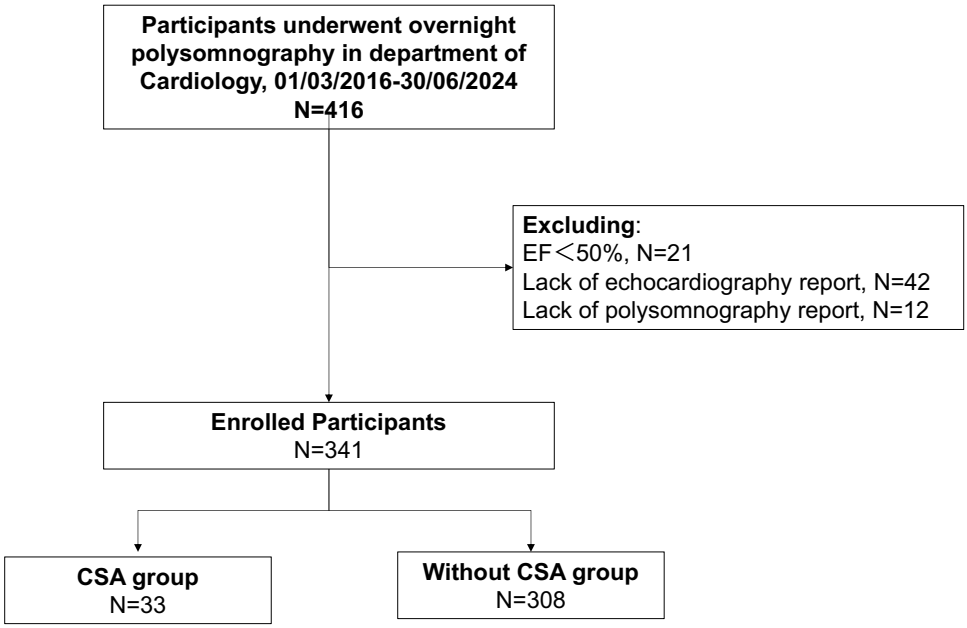

Figure 1 Flowchart of Patient Inclusion and Exclusion.

established by the American Academy of Sleep Medicine,[16] which included the recording of various physiological signals. These signals encompassed electroencephalographic activity (F3M2, F4M1, C3M2, C4M1, O1M2, O2M1), bilateral electro-oculographic activity, chin muscle electromyography, oronasal thermistor airflow, nasal pressure, rib cage and abdominal excursions, electrocardiogram (lead 1), snoring, body position, bilateral anterior tibialis electromyography, as well as heart rate and oxygen saturation measurements via pulse oximetry. Following the AASM's 2012 scoring manual,[17] an experienced sleep technologist manually scored the PSG data, aided by computer software, to identify sleep events. Apneas were scored when there was a 90% or greater reduction in airflow from baseline lasting for 10 seconds or more on the oronasal thermistor trace. Obstructive apneas were defined by the presence of respiratory effort during the event, whereas central apneas lacked such effort. Mixed apneas initially exhibited absent respiratory effort but later demonstrated it. Hypopneas were defined as a 30% or greater reduction in respiratory signal lasting for 10 seconds or more, accompanied by a 3% or greater decline in oxygen saturation or an arousal. The Obstructive Apnea-Hypopnea Index (OAHI) and Central Apnea-Hypopnea Index (CAHI) were documented for each participant in the study. The classification of obstructive sleep apnea (OSA) severity was determined by the OAHI, which measures the frequency of obstructive apneas and hypopneas per hour of sleep. The stratification of OSA severity based on OAHI values was as follows: mild OSA was indicated by an OAHI of 5 to 15 events per hour; moderate OSA was characterized by an OAHI of 15 to 30 events per hour; and severe OSA was defined as an OAHI exceeding 30 events per hour.[18]

In the context of this research, a diagnosis of central sleep apnea (CSA) was established when the CAHI reached a threshold of ≥5 events per hour. Participants were subsequently divided into two groups: those with a CAHI of ≥5 events per hour and those with a CAHI of <5 events per hour, thereby enabling a comparative analysis.

Covariates

Covariates included demographic information, comorbidities, laboratory test results, echocardiographic data, and polysomnography (PSG) reports, all sourced from electronic medical records. The variables collected encompassed sex, age, BMI, hypertension, diabetes mellitus, coronary heart disease, history of myocardial infarction, history of stroke, alcohol intake, cigarette smoking, atrial fibrillation (AF), hyperlipidemia (defined as either current use of lipid-lowering medication or abnormal lipid test results), peripheral arterial atherosclerosis; proteinuria; triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate (eGFR), thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), hemoglobin (HGB), red cell distribution width (RDW), uric acid (UA), ejection fraction (EF), left

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atrial anterior-posterior diameter (LAD-ap), LVEDD, AHI, OAHI, CAHI, oxygen saturation of arterial blood hemoglobin (SaO2), duration of arterial oxygen saturation <90% (T90%), the frequency of oxygen desaturation events per hour with a desaturation of at least 3% (3%ODI) and lowest blood oxygen saturation (LSaO2). The time interval between the echocardiographic examination and the sleep monitoring was less than 3 weeks. All laboratory test results were obtained within 1 month of the sleep monitoring.

Statistical Analysis

The Kolmogorov–Smirnov test was employed to assess the normality of continuous data. For normally distributed data, a two-sided *t*-test was utilized for comparisons, with results expressed as mean ± standard deviation (SD). In contrast, for data that did not conform to a normal distribution, the Wilcoxon–Mann–Whitney test was applied, and results were presented as median with interquartile range. Categorical variables were reported as frequencies and percentages, with differences in proportions analyzed using the chi-square or Fisher's exact tests.

Correlation analyses between CAHI and clinical variables were conducted using Spearman correlation coefficient. A logistic regression model was employed to evaluate the association between CSA and left atrial enlargement, with results reported as odds ratios (ORs) accompanied by 95% confidence intervals (CIs). A series of models were executed to further elucidate these associations: (1) Model 1: unadjusted; (2) Model 2: adjusting age and sex; (3) Model 3: adjusting age, sex, BMI, smoking history, alcohol consumption, and disease history (hypertension, diabetes, dyslipidemia, coronary heart disease, MI, stroke, atrial fibrillation, peripheral arterial atherosclerosis); and (4) Model 4: adjusting age, sex, BMI, smoking history, alcohol consumption, disease history, lab test (proteinuria, TC, eGFR, FT3, HGB, RDW), EF, LVEDD, mitral regurgitation, and sleep status (severe OSAS, mean SaO2). Covariates for the logistic regression model were chosen based on similar criteria, including baseline disparities, inclusion in previous comparable studies, and expert judgment. Variance Inflation Factor (VIF) analysis was conducted to address potential multi-collinearity in models, where VIF less than 10 means no multi-collinearity.

To account for potential confounding factors and to better estimate the independent relationship between left atrial anteroposterior diameter and CSA, we employed propensity score weighting techniques. A logistic regression model was formulated, utilizing the occurrence of CSA as the dependent variable. The independent variables incorporated into the model including sex, age, alcohol consumption, diabetes mellitus, dyslipidemia, coronary heart disease, previous stroke, atrial fibrillation, atherosclerosis (peripheral atherosclerosis detected by ultrasound, including arteries of the extremities and carotid arteries, etc), TC, LDL-C, eGFR, FT3, HGB and RDW. The selection of variables for the propensity score was primarily guided by the differences between two groups, their association with both exposure and outcomes, and the exclusion of potential intermediate variables in the causal pathway. Individual's predicted probability from this model served as their propensity score. Using these scores, we calculated the inverse probability of treatment weighting (IPTW) stabilized weights. To ensure that the weighted sample size matches the original population size, let PS denote the propensity score for an observation unit, and Pt denote the proportion of the entire population that received the treatment. The weight for individuals in the treatment group is Pt/PS, and for those in the control group, it is (1-Pt)/(1-PS). Standardized mean difference (SMD) of baseline characteristics before and after IPTW was calculated and showed in supplementary Figure 1. All above analysis was repeated among dataset after IPTW.

Given the increased incidence of CSA among males,[19] our methodology included conducting separate analyses stratified by sex for all previously mentioned analyses. Additionally, we performed subgroup analyses among males based on the presence of the following risk factors: age≥50 years, BMI < 28 kg/m2, smoking, alcohol consumption, hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, history of myocardial infarction, history of stroke, atrial fibrillation, proteinuria, and mitral regurgitation. Subgroup analyses were all conducted based on full adjustment model. The statistical analyses were carried out utilizing SAS software, version 9.4 (SAS Institute Inc). A two-sided P value threshold of less than 0.05 was established to determine the significance of all comparisons.

Results

Baseline Characteristics

The study comprised a total of 341 patients, of whom 33 (9.68%) were diagnosed with CSA. Among the participants, 24 (10.0%) of the males and 9 (8.91%) of the females were identified with CSA, while 172 (50.44%) of the total cohort exhibited left atrial enlargement (LAE), with 72 (71.29%) of these cases being female (refer to supplementary Table 1). Baseline characteristics of the study population before and after IPTW were presented in Table 1.

Table 1 Patient Characteristics in the CSA and Without CSA Groups Before and After IPTW

Variables	Before IPTW			After IPTW		
	With CSA N=33	Without CSA N=308	*p value*	With CSA N=33	Without CSA N=308	*p value*
Demographics						
Age, years	62.33±12.26	53.46±14.3	<0.01*	55.11±14.38	53.44±14.32	0.53
Sex, n (%)			0.76			0.70
Male, n (%)	24(72.73)	216(70.13)		24(73.18)	216(70.05)	
Female, n (%)	9(27.27)	92(29.87)		9(26.82)	92(29.95)	
BMI, kg/m^2	28.22±3.32	28.99±4.56	0.23	28.02±4.56	28.94±4.56	0.25
Smoking history, n (%)	17(51.52)	161(52.27)	0.93	17(51.98)	161(51.37)	0.95
Alcohol consumption, n (%)	10(30.3)	119(38.64)	0.35	10(24.95)	119(37.2)	0.15
Disease History						
Hypertension, n (%)	26(78.79)	258(83.77)	0.47	26(90.02)	258(83.53)	0.32
Diabetes, n (%)	17(51.52)	102(33.12)	0.04*	17(17.91)	102(34.2)	0.05
Dyslipidemia, n (%)	31(93.94)	254(82.47)	0.09	31(95.1)	254(83.68)	0.07
Coronary heart disease, n (%)	20(60.61)	99(32.14)	<0.01*	20(26.86)	99(33.93)	0.40
History of MI, n (%)	5(15.15)	18(5.84)	0.04*	5(5.89)	18(6.19)	0.95
History of stroke, n (%)	12(36.36)	26(8.44)	<0.01*	12(7.81)	26(10.68)	0.60
Atrial fibrillation, n (%)	5(15.15)	11(3.57)	<0.01*	5(4.39)	11(4.62)	0.95
Atherosclerosis, n (%)	31(93.94)	242(78.57)	0.04*	31(69.6)	242(79.62)	0.17
Lab test						
Proteinuria, n (%)	7(21.21)	24(7.79)	0.01*	7(5.49)	24(8.17)	0.58
TC, mmol/L	4.25±1.25	4.51±1.05	0.18	4.15±.153	4.49±.495	0.06
TG, mmol/L	1.85±1.07	2.31±2.19	0.23	1.731.08	2.28±.284	0.11
LDL-C, mmol/L	2.55±0.99	2.67±0.93	0.52	2.39±.398	2.66±.663	0.04*
eGFR	72.43±25.11	94.24±19.49	<0.01*	89.81±19.49	92.44±19.49	0.48
TSH, ulU/mL	1.92(1.33, 2.72)	1.82(1.31, 2.68)	0.51	1.53(1.24, 3.73)	1.83(1.31, 2.72)	0.51
FT3, pmol/L	4.2(3.8, 4.8)	4.8(4.4, 5.3)	<0.01*	5.02(4.1, 5.3)	4.8(4.4, 5.28)	<0.01*
FT4, pmol/L	16.6(14.8, 18.2)	16.31(15, 17.9)	0.69	16.8(15.6, 18.9)	16.3(15, 17.9)	0.69
HGB, g/L	135.7±24.63	143.67±16.88	0.08	136.56/L6.93	143.15/L7.25	0.03*
RDW, fL	43.52±7.35	41.61±3.1	0.01*	41.185/L48	41.755/L14	0.47
UA, mmol/L	417.73±127.30	400.06±106.73	0.38	443.673L/L.48	402.573L/L91	0.10
Polysomnography parameters						
AHI, events/h	49.2(32.9, 60)	26.75(13.2, 46.75)	<0.01*	37.1(22.6, 56.9)	26.8(13.3, 47.8)	<0.01*
CAHI, events/h	15.3(7.4, 22.8)	0.2(0.0.8)	<0.01*	7.5(5.3, 16.4)	0.2(0, 0.8)	<0.01*
OAHI, events/h	22.3(16.7, 39.5)	25.8(13.1, 45.8)	0.55	17.6(16.7, 39.5)	25.9(13.2, 45.9)	0.55
OSAS			0.09			0.01*
None	5(15.15)	18(5.84)		5(9.35)	18(5.61)	
Mild	3(9.09)	66(21.43)		3(3.75)	66(21.03)	
Middle	12(36.36)	95(30.84)		12(54.4)	95(31.35)	
Severe	13(39.39)	129(41.88)		13(32.5)	129(42.01)	

(*Continued*)

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Table 1 (Continued).

Variables	Before IPTW			After IPTW		
	With CSA N=33	Without CSA N=308	*p value*	With CSA N=33	Without CSA N=308	*p value*
Mean SaO_2, %	93.21±3.01	93.87±2.43	0.15	93.93SaO1)	93.83SaO1	0.75
T90%	6.6(2.3, 21.3)	2.35(0.3, 15.1)	0.01*	4.4(1.8, 11.9)	2.4(0.3, 15.2)	0.01*
$LSaO_2$, %	79.64±8.96	81.27±9.36	0.34	81.89±9.36	81.25±9.36	0.58
3%ODI	44.9(27.55, 60.4)	22.85(8.9, 39.95)	<0.01*	36.9(15.5, 55.1)	22.9(9.4, 39.4)	<0.01*
Echocardiography						
EF, %	64.02±5.95	66.37±5.41	0.02*	65.41±5	66.29±6.2	0.36
LAD-ap, mm	42.73±13.01	38.15±4.58	<0.01*	39.75±4.58	38.33±4.58	0.11
Left atrial enlargement, n(%)	23(69.7)	149(48.38)	0.02*	23(74.84)	149(50.69)	0.01*
LVEDD, mm	48±5.38	48.07±4.39	0.94	46.88, mm1	48.07, mm2	0.13
LV diastolic dysfunction, n (%)	25(75.76)	182(59.09)	0.06	25(50.89)	182(61.57)	0.22
Mitral Regurgitation, n (%)			0.02*			0.45
None	22(66.67)	264(85.71)		22(76.71)	264(84.98)	
Mild	10(30.3)	37(12.01)		10(20.27)	37(12.69)	
Middle	1(3.03)	3(0.97)		1(3.02)	3(1.08)	
Severe	0(0)	1(0.32)		0(0)	1(0.32)	

Note: *p<0.05.

Abbreviations: BMI, body mass index; MI, myocardial infarction; TG, Triglycerides; TC, Total cholesterol; LDL-C, Low-density lipoprotein cholesterol; eGFR, Estimated Glomerular Filtration Rate; TSH, Thyroid Stimulating Hormone; FT3, Free Triiodothyronine; FT4, Free Thyroxine; HGB, Hemoglobin; RDW, Red cell distribution; UA, Uric Acid; AHI, apnea-hypopnea index; CAHI, Central Apnea-Hypopnea Index; OAHI, Obstructive Apnea-Hypopnea Index; OSAs, obstructive sleep apnea severity; SaO_2, oxygen saturation of arterial blood hemoglobin; T90%, time with arterial oxygen saturation<90%; $LSaO_2$, lowest blood oxygen saturation; 3%ODI, the number of oxygen desaturation events per hour with a desaturation of at least 3%; EF, ejection fraction; LAD-ap, Left Atrium Anterior-Posterior Diameter; LVEDD, left ventricular end diastolic diameter; LV, left ventricle.

Prior to IPTW, patients with CSA were significantly older (62.33±12.26 vs 53.46±14.3 years, p<0.01) and had a higher prevalence of diabetes (51.52% vs 33.12%, p=0.04), coronary heart disease (60.61% vs 32.14%, p<0.01), history of myocardial infarction (15.15% vs 5.84%, p=0.04), history of stroke (36.36% vs 8.44%, p<0.01), atrial fibrillation (15.15% vs 3.57%, p<0.01), peripheral arterial atherosclerosis (93.94% vs 78.57%, p=0.04) and protein urine (21.21%vs, 7.79%, p=0.01). Furthermore, these patients demonstrated lower levels of eGFR and FT3, alongside elevated RDW. After IPTW, the demographic and clinical characteristics between the CSA and non-CSA groups were well balanced, with no statistically significant differences observed in most variables.

Association Between CAHI and Clinical Characteristics

No statistically Spearman correlation was found between CAHI and LAD-ap in both male and female subjects (Table 2). Among males, statistically significant inverse correlations were observed between eGFR ($r = -0.26$, $p < 0.01$), FT3 ($r = -0.16$, $p = 0.01$), EF ($r = -0.20$, $p < 0.01$), Mean SaO2 ($r = -0.14$, $p = 0.03$), and LSaO2 ($r = -0.20$, $p < 0.01$) with CAHI. These findings suggested that diminished renal function, lower FT3 levels, reduced EF, and decreased oxygen saturation were associated with increased severity of CSA in males. In female subjects, a significant inverse correlation was observed between FT4 ($r = -0.23$, $p = 0.02$) and LSaO2 ($r = -0.22$, $p = 0.02$) with CAHI, indicating lower free thyroxine levels and lower lowest oxygen saturation were associated with more severe CSA in females.

Association Between CSA and Left Atrial Size

Subjects with CSA had significantly higher AHI (49.2/h vs 26.75/h, p<0.01), 3%ODI (44.9 vs 22.85, p<0.01), and a greater proportion of sleep time with oxygen saturation<90% (6.6% vs 2.35%, p=0.01). As for echocardiography indicators, patients with CSA exhibited higher LAD-ap (42.73±13.01 mm vs 38.15±4.58 mm, p<0.01), more frequent left atrial enlargement (69.7% vs 48.38%, p=0.02), lower EF (64.02±5.95 vs 66.37±5.41, p=0.02), and higher prevalence of mitral regurgitation (p=0.02) (Table 1).

No multi-collinearity was found among CSA and other covariates (refer to supplementary Table 2). No statistically significant associations were observed in logistic regression models prior to IPTW. However, after IPTW, statistically significant odd ratios were found among males. Males with CSA had higher risk of left atrial enlargement both in un-adjusting model and adjusting models. In the full model, the odd ratio was 4.54 (95% CI: 1.45, 14.2) (Table 3 and supplementary Table 3). No significant associations were identified in female subjects (Table 3). The positive associations were still significant among male who had history of smoking, no alcohol consumption, dyslipidemia, and those who had no history of coronary artery disease, MI, stroke, atrial fibrillation, proteinuria or mitral regurgitation (Figure 2).

Discussion

The principal finding of this study highlights a novel and independent association between CSA and left atrial enlargement in patients with preserved ejection fraction, aligning with previous research conducted in heart failure populations with reduced EF.[5,6] Notably, this represents the first documented significant correlation between CSA and left atrial dimensions in individuals with preserved left ventricular systolic function, thereby enhancing the understanding of the complex relationship between sleep-disordered breathing and cardiac remodeling.

CSA and Left Atrial Enlargement

Our findings not only reinforce the connection between LAE and atrial fibrillation (AF) in the context of preserved EF but also suggest that CSA may play a pivotal role in this pathological continuum. The severity of CSA, as noted in

Table 2 Correlations Between Clinical Variables and CAHI

	Male		Female	
	Spearman r	**p value**	**Spearman r**	**p value**
TC	−0.04	0.50	0.12	0.22
TG	−0.07	0.28	0.08	0.42
LDL-C,	−0.03	0.67	0.18	0.08
eGFR	−0.26	<0.01	−0.15	0.12
TSH	0.07	0.27	−0.03	0.73
FT3	−0.16	0.01	−0.23	0.02
FT4	−0.10	0.13	0.14	0.15
HGB	−0.08	0.24	−0.14	0.18
RDW	0.09	0.16	−0.03	0.80
UA	0.08	0.25	0.15	0.12
EF	−0.20	<0.01	0.10	0.30
LAD-ap	0.09	0.14	0.10	0.33
LVEDD	0.03	0.64	0.05	0.61
OAHI	0.15	0.02	0.30	<0.01
AHI,	0.32	<0.01	0.44	<0.01
Mean SaO_2	−0.14	0.03	−0.13	0.20
T90%	0.20	<0.01	0.18	0.08
$LSaO_2$	−0.20	<0.01	−0.22	0.02
3%ODI	0.31	<0.01	0.44	<0.01

Abbreviations: TG, Triglycerides; TC, Total cholesterol; LDL-C, Low-density lipoprotein cholesterol; eGFR, Estimated Glomerular Filtration Rate; TSH, Thyroid Stimulating Hormone; FT3, Free Triiodothyronine; FT4, Free Thyroxine; HGB, Hemoglobin; RDW, Red cell distribution; UA, Uric Acid; EF, ejection fraction; LAD-ap, Left Atrium Anterior-Posterior Diameter; LVEDD, left ventricular end diastolic diameter; OAHI, Obstructive Apnea-Hypopnea Index; AHI, apnea-hypopnea index; SaO_2, oxygen saturation of arterial blood hemoglobin; T90%, time with arterial oxygen saturation<90%; $LSaO_2$, lowest blood oxygen saturation; 3%ODI, the number of oxygen desaturation events per hour with a desaturation of at least 3%.

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Table 3 Logistic Regression Analysis to Explore Odds Ratios of CSA for Left Atrial Enlargement

	Male		Female	
	OR (95% CI)	p value	OR (95% CI)	p value
Before IPTW				
Model1	3.07(1.26, 7.49)	0.01	1.45(0.28, 7.45)	0.65
Model2	2.47(0.99, 6.18)	0.05	1.23(0.23, 6.56)	0.81
Model3	1.96(0.68, 5.6)	0.21	1.16(0.19, 7.27)	0.87
Model4	1.54(0.49, 4.84)	0.46	1.17(0.11, 12.38)	0.9
After IPTW				
Model1	2.97(1.24, 7.14)	0.01	4.54(0.42, 49.54)	0.21
Model2	2.9(1.19, 7.03)	0.02	4.48(0.41, 48.96)	0.22
Model3	3.23(1.19, 8.78)	0.02	5.33(0.43, 65.98)	0.19
Model4	4.54(1.45, 14.2)	0.01	3.99(0.19, 82.06)	0.37

Notes: Model 1: unadjusted. Model 2: adjusting age and sex. Model 3: adjusting age, sex, BMI, smoking history, alcohol consumption, and disease history (hypertension, diabetes, dyslipidemia, coronary heart disease, MI, stroke, atrial fibrillation, peripheral arterial atherosclerosis). Model 4: adjusting age, sex, BMI, smoking history, alcohol consumption, disease history, lab test (proteinuria, TC, eGFR, FT3, HGB, RDW), EF, LVEDD, mitral regurgitation, and sleep status (severe OSAS, mean SaO2).
Abbreviation: IPTW, inverse probability of treatment weighting.

previous studies like that by Nobuhiko Haruki, inversely correlates with left atrial reservoir and conduit function, hinting at a potential causal mechanism whereby impaired LA phasic function either stems from or exacerbates CSA.[20]

CSA, as a subtype of sleep-disordered breathing (SDB), introduces a cascade of nocturnal perturbations, including hypoxemia, arousal reactions, and repetitive surges of sympathetic activity. These events foster oxidative stress,[21]

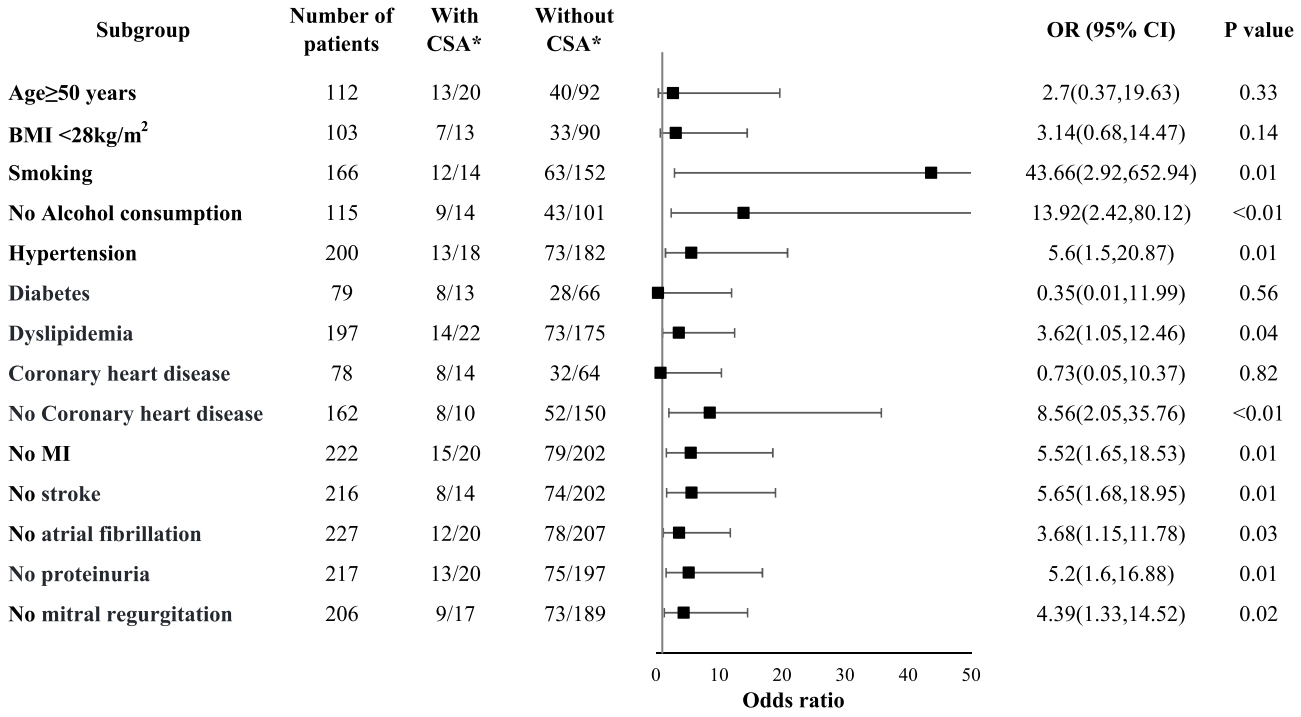

Figure 2 Subgroup analysis of association between CSA and left atrial enlargement after IPTW adjustment. * *Number of patients having left atrial enlargement/number of total patients. OR (95% CI) was calculated based on logistic model adjusting age, sex, BMI, smoking history, alcohol consumption, disease history, lab test (proteinuria, TC, eGFR, FT3, HGB, RDW), EF, LVEDD, mitral regurgitation, and sleep status (severe OSAS, mean SaO_2).*
Abbreviation: CSA, central sleep apnea.

a known driver of cardiac remodeling,[22] and atrial fibrillation.[23] By inducing tissue hypoxia, disrupting sleep architecture, and activating the sympathetic nervous system,[24,25] CSA adversely impacts cardiovascular function. Notably, the intermittent nature of PaCO2 fluctuations and arousal episodes, more pronounced in CSA than OSA, may prime the heart for arrhythmogenic structural and electrical remodeling via sympathetic overactivation.[26,27]

Interventions targeting SDB, such as continuous positive airway pressure (CPAP) and adaptive servoventilation therapy, have been shown to reduce left atrial size in patients with SDB[28,29] Furthermore, a high prevalence of CSA has been documented in AF patients with preserved EF,[30,31] with case reports illustrating the temporal link between paroxysmal AF and subsequent CSA, reinforcing the idea that CSA/LAE may precede AF.[32]

LAE, an independent predictor of stroke and mortality,[33] can precede left ventricular diastolic dysfunction, establishing a bidirectional relationship between SDB and heart failure with preserved ejection fraction (HFpEF). SDB may induce diastolic dysfunction, while HFpEF, can precipitate sleep apnea.[34] This vicious cycle involves multiple mechanisms, including left atrial overload, ventricular remodeling, pulmonary hypertension, and AF, which collectively contribute to the development of HFpEF.

Male Sex, CSA and Left Atrial Enlargement

To our knowledge, this is the first study to demonstrate sex disparities in the association between CSA and LAE. In the male patients, CSA was significantly and independently related to left atrial enlargement.

In general population with CSA, males typically outnumber females.[35,36] A study of the Veterans Health Administration (VHA) national administrative databases demonstrated that male sex was independent predictor of CSA (odds ratio [OR] = 2.31, 95% confidence interval [CI]: 1.94–2.76, $p < 0.0001$).[37] Moreover, left atrial anteroposterior diameter and left atrial volume are larger in men than in women.[38,39] However, the relationship between CSA and LAE does not provide direct evidence of causality or that sex is a mediating variable between them. We need more in-depth data analysis and statistical modeling to explore the underlying connections and causal relationships among these factors.

The sex disparity in the CSA-LAE relationship can be attributed to several interrelated factors. Firstly, hormonal differences play a significant role. Estrogen has been shown to have cardioprotective effects and may influence cardiac structure and function differently in females compared to males. For instance, fluctuations in estrogen levels can impact myocardial remodeling and vascular tone, potentially moderating the effects of CSA on LAE.[40,41] Secondly, studies have demonstrated that male pulmonary veins exhibit a heightened amplitude of isoproterenol-elicited delayed afterdepolarizations, leading to increased susceptibility to arrhythmias. This heightened electrophysiological response in males may exacerbate the impact of CSA on LAE, making men more vulnerable to associated cardiovascular complications.[42] Additionally, differences in sleep architecture between genders could further elucidate this relationship. Research indicates that men and women may experience variations in sleep stages and overall sleep quality, which could influence the severity and frequency of CSA episodes. These differences may result in varying degrees of hypoxia and hemodynamic changes, ultimately impacting left atrial size and function.[43,44] Moreover, lifestyle factors, such as body composition and the prevalence of comorbidities like hypertension and obesity, often differ between sexes and could also mediate the relationship between CSA and LAE. Understanding these multifactorial influences is crucial in elucidating the complexities of the CSA-LAE relationship.

The correlation between CSA and left atrial enlargement in male patients could enhance cardiovascular risk stratification. Clinicians should consider incorporating CSA measurements into routine assessments for male patients with risk factors for atrial enlargement and related complications, such as atrial fibrillation or heart failure. Given the gender differences in the relationship between CSA and left atrial enlargement, it may be beneficial to develop gender-specific clinical guidelines, recognizing that they may present unique patterns of cardiovascular risk and disease progression compared to female patients. These findings could also lead to targeted therapeutic interventions. For example, specific lifestyle modifications, pharmacological treatments, or monitoring strategies could be implemented for male patients.

In the absence of coronary artery disease, CSA still emerges as a distinct risk factor for LA enlargement. This suggests that CSA can independently influence cardiac structure and function, highlighting its role as a potential target

for intervention. The lack of pre-existing cardiovascular conditions means that CSA may exert a more pronounced effect on atrial structure, as there are no competing pathologies. The left atrium may be particularly vulnerable to the effects of CSA in the absence of other cardiovascular stressors, leading to a more pronounced enlargement in these patients. However, the reason behind asks for further investigation.

Implications for Clinical Practice

Acknowledging sleep health as a modifiable cardiovascular risk factor underscores the urgency to screen patients for CSA. While the mechanisms underpinning CSA in both AF and HF are likely intertwined, effective management of comorbidities and prevention of central respiratory events could stabilize gas exchange, dampen sympathovagal imbalance, and potentially mitigate or reverse structural changes predisposing to AF. Although the efficacy of CSA treatment in reducing AF burden remains underexplored, this represents a promising area for future research, especially among high-risk populations with coexisting CSA and AF, regardless of their heart failure status.

The present study may have significant implications for the management of patients with left atrial dilatation. Numerous clinical guidelines recommend assessing sleep-disordered breathing as a coexisting condition in individuals with heart failure. However, a definitive diagnosis requires polysomnography (PSG), which can be financially burdensome, time-consuming, and may not be readily available in all settings. Our findings indicate a significant independent correlation between central sleep apnea (CSA) and left atrial enlargement (LAE), particularly among male patients. Consequently, evaluating left atrial dimensions that cannot be solely attributed to other comorbidities is essential for identifying individuals at heightened risk for CSA. Given the limited availability of extensive screening studies, the most effective methods for determining which patients should be referred for PSG remain unclear. Unlike OSA, which may present with specific indicators suggestive of its diagnosis, CSA lacks definitive signs or symptoms that reliably predict its occurrence, particularly in patients without heart failure.[45]

The correlation between CSA and left atrial enlargement (LAE) in individuals with preserved left ventricular systolic function underscores the importance of early detection and intervention. Identifying CSA at an early stage can facilitate timely management strategies that may mitigate the adverse effects on cardiac remodeling and function. Given that LAE is an independent predictor of stroke and mortality, early recognition of CSA could play a crucial role in preventing the progression to more severe cardiovascular complications.

Moreover, the relationship between CSA and atrial fibrillation (AF) highlights the need for proactive screening in patients with preserved ejection fraction. By addressing CSA early, clinicians can potentially reduce the incidence of AF and its associated risks, thereby improving patient outcomes.

Interventions such as continuous positive airway pressure (CPAP) therapy have demonstrated efficacy in reducing left atrial size and improving overall cardiovascular health in patients with sleep-disordered breathing. This reinforces the notion that early detection and treatment of CSA can lead to meaningful clinical benefits, including the preservation of left atrial function and a reduction in the risk of arrhythmias.

Limitations

While our investigation into the relationship between CSA and left atrial size offers valuable insights, several limitations must be acknowledged to ensure the interpretation of our findings is grounded in a comprehensive understanding of their contextual constraints.

Firstly, the adoption of a nonstandard definition of CSA poses a significant challenge to the generalizability of our results. The standard criteria for defining Central Sleep Apnea (CSA) typically require a Central Apnea Hypopnea Index (CAHI) of ≥5 events per hour, accompanied by a proportion of central sleep apnea events exceeding 50% of the total respiratory events. However, the incidence of CSA is relatively low, which poses challenges in conducting comprehensive studies and ensuring adequate sample sizes. Given these limitations, our study temporarily adopts the CAHI index alone as a proxy for CSA phenomena. This approach allows us to focus specifically on the subset of patients who exhibit CSA events and investigate their relationship with left atrial size. Additionally, we acknowledge that the overly strict diagnostic criteria may inadvertently exclude a significant population of patients with meaningful CSA. The lack of a universally accepted definition for CSA can introduce variability in both the identification and categorization of

patients, thereby limiting the extent to which our findings can be applied to broader populations. This underscores the need for future studies to adopt standardized criteria to facilitate comparison and replication of results.

Another limitation arises from the fact that Left Atrial Volume Index (LAVI) was not reported in our study due to the low number of participants who completed the necessary testing. Instead, we relied solely on left atrial anteroposterior diameter. The measurement of the left atrial anteroposterior diameter relies on the assumption that the left atrium is a perfect sphere, which is rarely the case in clinical practice. This geometric simplification can lead to inaccuracies in assessing true left atrial size, potentially underestimating or overestimating enlargement. Besides, the findings may not be easily comparable to other studies that utilize LAVI as the standard measurement for left atrial enlargement. This inconsistency could limit the generalizability of the results and complicate the integration of this research into broader clinical contexts. Nonetheless, the simplicity and accessibility of this anteroposterior diameter measurement make it an attractive alternative in settings with limited resources.

Furthermore, a significant limitation of our research is the lack of comprehensive BNP or NT-proBNP measurements among the enrolled patients. Only a small proportion of participants had their BNP or NT-proBNP levels evaluated, and given that these two biomarkers cannot be directly compared, we opted not to analyze this aspect in our study. The absence of BNP data poses challenges in accurately assessing cardiac function among our study population. BNP levels are known to reflect heart failure status and can provide insights into the severity of left ventricular/atria dysfunction. In the context of preserved ejection fraction, distinguishing between patients with and without heart failure is crucial, as it may influence prognosis, CSA incidence, and left atrial size. Without BNP measurements, differentiating these aspects becomes difficult, potentially impacting our understanding of the relationship between CSA and left atrial dimensions in this specific population. Future studies should aim to include both BNP and NT-proBNP measurements to better elucidate these relationships and enhance prognostic stratification in patients with preserved ejection fraction.

To strengthen our conclusions, larger-scale studies encompassing a more diverse patient population, particularly with a greater proportion of women, are imperative. While we observed a sex-independent association between LAE and CSA, the small number of female participants limits the certainty of our findings' applicability to women. This sex disparity leads to a pronounced overrepresentation of males in the CSA cohort, which may potentially introduce biases into our findings. The imbalanced sex distribution, therefore, underscores the importance of considering sex as a critical variable in interpreting our results and highlights the need for future studies to strive for more sex-balanced recruitment strategies to ensure the robustness and generalizability of findings pertaining to CSA and its associated outcomes.

Lastly, the observational nature of our study design restricts our ability to infer causal relationships between left atrial volume increase and augmented CSA. The enrolled patients were all individuals who underwent sleep monitoring due to snoring and cannot be considered representative of the general population. Future interventional studies are needed to elucidate the specific physiologic and molecular pathways that might mediate this association, thereby advancing our understanding of the complex interplay between sleep-disordered breathing and cardiac remodeling.

Conclusion

In conclusion, our study reinforces the independent role of CSA in left atrial enlargement, especially in men, shedding light on the complex interplay between sleep-disordered breathing and cardiac remodeling. This finding underscores the importance of sleep health assessment and management in the prevention and treatment of cardiovascular diseases, including atrial fibrillation.

Looking forward, future research should focus on elucidating the underlying mechanisms that contribute to the gender differences observed in the CSA-LAE relationship. Investigating the impact of hormonal variations, sleep architecture, and lifestyle factors on this relationship could provide valuable insights for targeted interventions. Additionally, clinical studies exploring the effects of specific treatments for CSA—such as continuous positive airway pressure (CPAP) therapy—on cardiac remodeling and arrhythmogenesis in different genders could advance our understanding and management of cardiovascular health.

By emphasizing gender-specific factors in cardiovascular health, we can move towards more personalized and effective healthcare strategies. Ultimately, addressing these gaps in research will not only enhance our understanding

of the associations between CSA and LAE but also improve clinical outcomes for patients at risk of cardiovascular complications.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy considerations and the protection of individual rights, but are available from the corresponding author on reasonable request.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Due to the retrospective nature of the study, ethics committee at Peking University International Hospital waived the need of obtaining informed consent.

Author Contributions

Xinghe Sun: Conceptualization, Methodology, acquisition of data, interpretation, Writing-Original draft preparation.

Chaoqun Wu: Conception, study design, execution, analysis and draft preparation.

Yang Wang: Visualization, execution and writing-original draft preparation.

Yinghui Gao: Supervision. conception, study design, drafted and critically reviewed the article.

All Authors have agreed on the article submitted to this journal. They reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All of them agree to take responsibility and be accountable for the contents of the article.

Xinghe Sun and Yang Wang are joint first authors.

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