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# Intermittent hypoxia by obstructive sleep apnea is significantly associated with electro-anatomical remodeling of the left atrium preceding structural remodeling in patients with atrial fibrillation

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ABSTRACT

*Background:* Obstructive sleep apnea (OSA) is one of the risk factors for atrial fibrillation (AF). However, the mechanism underlying the atrial structural and electro-anatomical remodeling by OSA has not yet been clearly elucidated.

*Methods:* This study was conducted in 83 patients who had undergone catheter ablation for AF (49 with OSA and 34 Controls without OSA). The left atrial (LA) maps were created in all the patients using a three-dimensional electro-anatomical mapping system. The LA with a bipolar voltage of <0.5 mV was defined as the low voltage area (LVA); %LVA was defined as the ratio of the LVA to the total surface area of the LA.

*Results:* The LVA and %LVA were significantly greater in the OSA group as compared with the Control group, however, there was no difference in the LA area. The 3 % oxygen desaturation index (ODI) was significantly correlated with the %LVA (r = 0.268, P = 0.014), but not with the LA area. Multiple regression analysis with adjustments identified 3 %ODI ≥30 (3.088, 1.078–8.851, P = 0.036) as being significantly associated with the % LVA.

*Conclusions:* In patients with AF complicated by OSA, significant increase of the LVA, but not of the LA area, was observed. The intermittent hypoxia severity was significantly associated with the LVA. These results suggest that intermittent hypoxia by OSA might be one of the mechanisms of electro-anatomical remodeling of the LA, possibly preceding structural remodeling represented by LA enlargement, in patients with AF.

## 1. Introduction

Obstructive sleep apnea (OSA) is one of the most common clinically significant breathing disorders during sleep, and is well recognized as an independent risk factor for cardiovascular disease [1,2]. OSA is frequently associated with atrial fibrillation (AF) [3–7], and promotes arrhythmogenesis and impairs the treatment efficacy for AF [8–11]. The high-frequency intermittent oxygen desaturation and reoxygenation, negative intrathoracic pressure swings during sleep, atrial stretching, neurohumoral activation, and chronic concomitant conditions, such as hypertension, metabolic syndrome, and obesity, associated with OSA create progressive structural remodeling of the atrium [12–14]. This progressive atrial structural remodeling, along with the electrophysiological changes associated with the transient apnea episodes during sleep in OSA contributes to the reentry mechanism for AF and establishes a complex and dynamic arrhythmogenic substrate in the atrium during sleep. Furthermore, non-randomized studies have shown that continuous positive airway pressure used to treat OSA can help in maintaining a sinus rhythm after electrical cardioversion and catheter ablation in OSA patients with AF [15–18].

The primary mechanisms for AF are the occurrence of an atrial extrasystole from the pulmonary vein and structural and electrical

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remodeling of the atrium that serves as an arrhythmogenic substrate sustaining intra-atrial reentry [19,20]. Such remodeling corresponds electro-physiologically to a decrease in the local potential in low-voltage area (LVA) of the atrium [21]. Presence of LVA as detected by left atrial (LA) voltage mapping has been shown to be a powerful predictor of arrhythmia recurrence after AF catheter ablation [22,23]. In cases of AF with LVA, ablation of the LVA has been reported to improve the chronic phase outcomes [24].

Several previous studies have reported that OSA is associated with significant electro-anatomical remodeling of the atrium, characterized by an increase in reduced-voltage areas [13,14,25]. However, reports in regard to changes of the LA area in OSA patients are conflicting, with some studies reporting increase of the LA area [13,14] and others reporting no change of the LA area [25] in these patients. Furthermore, the precise mechanisms underlying the association between OSA and atrial remodeling remain unclear. Therefore, the present study was aimed at determining the impact of OSA, and the underlying mechanisms, on electro-anatomical and structural remodeling of the left atrium in patients with AF by applying a three-dimensional electro-anatomical mapping system.

## 2. Methods

### 2.1. Study population

A flow-chart of patient enrollment in this study is shown in Fig. 1. We retrospectively enrolled 772 consecutive patients with AF who underwent catheter ablation between April 2018 and April 2022. Patients with a prior diagnosis of OSA referred for a sleep study, or with a reduced ejection fraction (left ventricular ejection fraction ≤40 %), cardiomyopathy, significant valvular disease, or previous myocardial infarction were excluded. Cryo ablation cases and those without LVA were also excluded. Patients who had already undergone sleep tests and been diagnosed with sleep apnea were likely to have been introduced to continuous positive airway pressure (CPAP) therapy. To consider the effect of CPAP on LVA, such patients were excluded from this study. Finally, a total of 83 patients who underwent portable sleep test and three-dimensional mapping were enrolled in this study.

Among the participants, only those in whom the LVA could be mapped using the three-dimensional mapping system during AF ablation were included.

Atrial fibrillation type was defined according to the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation [26]. Paroxysmal AF was defined as AF that terminated without intervention within 7 days of onset. Persistent AF was defined as continuous AF that is sustained over 7 days. Antiarrhythmic drugs were discontinued for at least five half-lives prior to ablation in the present study. Transesophageal echocardiography or multi-detector computed tomography was performed prior to the catheter ablation in all the patients, to evaluate the LA anatomy and rule out the presence of a thrombus in the LA. The study protocol was approved by the Ethics Committee of Tokyo Medical University (T2021-0291). In this manuscript, the procedures followed were in accordance with the "Declaration of Helsinki" and the ethical standards of the responsible committee on human experimentation (the Ethics Committee of Tokyo Medical University).

### 2.2. Sleep study

All-night pulse oximetry was performed prior to the catheter ablation in all the patients, and full polysomnography (PSG) was performed using the Alice 5 Diagnostic Sleep System™ (Respironics, Inc., Murrysville, PA, USA) in patients with a 3 % oxygen desaturation index (ODI) ≥5/h (Fig. 1). Apneic and hypopneic episodes, sleep stages, and electroencephalographic arousal were scored according to the Adult OSA Task Force of the American Academy of Sleep Medicine [27]. Apnea was defined as a ≥90 % decrease in nasal flow lasting for ≥10 s. Hypopnea was defined as a decrease in nasal flow for ≥10 s, accompanied by ≥3 % oxygen desaturation or arousal. The apnea-hypopnea index (AHI) was calculated as the total number of apnea-hypopnea episodes per hour of sleep; AHI is an index of the OSA severity, and is classified as follows: AHI < 5/h, normal; 5 ≤ AHI < 15, mild OSA; 15 ≤ AHI < 30, moderate OSA; and AHI ≥ 30, severe OSA.

Patients are diagnosed as having OSA when an obstructive component accounts for more than 50 % of the apnea/hypopnea events and the AHI is ≥5/h. An episode is categorized as obstructive if the apnea occurs during respiratory effort.

### 2.3. Duration of OSA

In this study, the duration of OSA was estimated based on a questionnaire that inquired about the onset of symptoms potentially related to OSA, such as the time when snoring or apnea was first pointed out, excessive daytime sleepiness, and morning headaches. Based on these

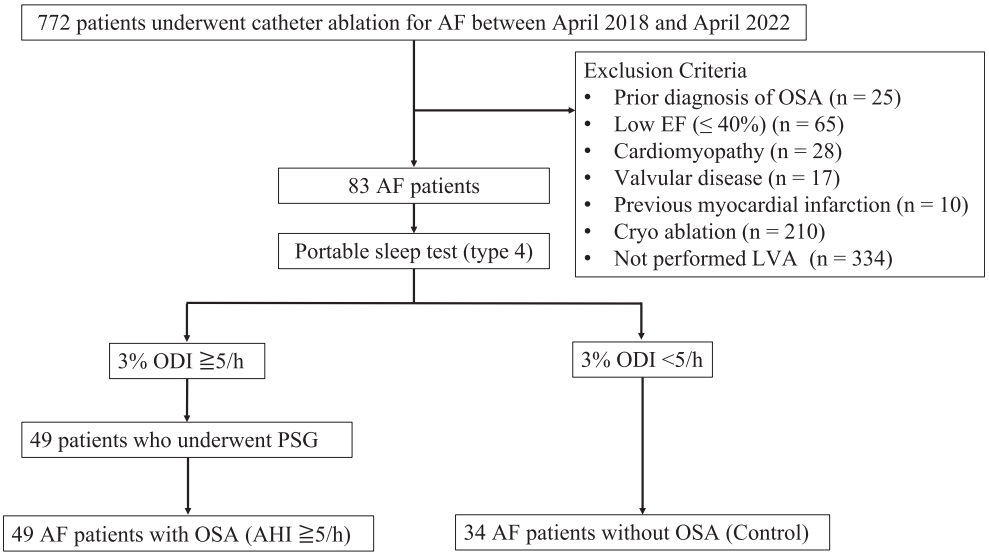


**Fig. 1.** Flow-chart of patient enrollment for this study. Abbreviations: AF, atrial fibrillation; LVA, low-voltage area of the left atrium; EF, ejection fraction; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea; PSG, polysomnography; ODI, oxygen desaturation index.

results, patients estimated to have developed symptoms within one year were defined as having "early-phase OSA", while those developing symptoms one year or more after were defined as having "late-phase OSA".

### 2.4. Electrophysiological study and electrocardiographic measurements

In all cases, LA maps were created using a three-dimensional electro-anatomical mapping system under sinus rhythm or pacing from the right atrium (cycle length, 600–800 ms). The procedure was performed under deep sedation; a sedative agent(s) was administered at the beginning of the procedure, and none of the patients in this study required tracheal intubation. For respiratory management, I-gel (Intersurgical, Wokingham, Berkshire, UK) was used for oxygen delivery. Antiarrhythmic drugs were discontinued for at least five half-lives before the ablation procedure. All patients were chronically anticoagulated for ≥4 weeks. Unfractionated heparin was administered prior to the transseptal puncture to maintain an activated clotting time of 300–400 s during the procedure. Electro-anatomical mapping was performed using Carto (Biosense Webster, Diamond Bar, CA, USA) in 24 patients, Ensite (Abbott, Chicago, IL, USA) in 37 patients, and Rhythmia (Boston Scientific, Marlborough, MA, USA) in 22 patients. Mapping was performed using a multi-electrode catheter; the density of mapping was in accordance with the physician's instructions. Maps comprised a mean of 4850 ± 3713 points [median 3190 (677, 15231)]. LVA was defined as the total area of the left atrium with a bipolar peak-to-peak voltage amplitude of <0.5 mV, and %LVA was calculated as the ratio of the LVA to the total surface area of the LA [22,23,28]. The cutoff value for %LVA was set as 5.0 % based on previous researches [29,30]. Measurements of the LA area and LVA were performed using a manual tool inside the system, after exclusion of the mitral annulus, left atrial appendage, and pulmonary veins. All the adjudication of electroanatomical maps were performed by the same two investigators, both of whom were blinded to the patient characteristics. The anatomical extent of each pulmonary vein was determined by the physician.

### 2.5. Statistical analysis

Normally distributed continuous data are expressed as the means ± standard deviation and compared using unpaired Student's t-tests. Where the outcome variables were not normally distributed, a log transformation was applied to meet the assumption of normality prior to the linear regression analysis. Categorical variables were compared between pairs of groups using the chi-squared or Fisher's exact test.

The association between the 3 % ODI and outcome variables (LVA, %LVA, LVA area, and LAVI) were summarized by determining the Pearson's correlation. Multivariate logistic regression analysis was performed using a backward stepwise approach, with adjustments for variables identified as being significant ($P < 0.05$) by univariate analysis (Model 1), and variables with significant ($P < 0.05$) differences between the two groups in Table 1 (Model 2) to determine the risk factors for %LVA ≥5%. All tests were two-sided, and the statistical significance level was set at $P < 0.05$. Analyses were conducted using IBM SPSS Statistics (version 28.0; SPSS, Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Patient characteristics (Table 1)

The characteristics of the patients enrolled in the study classified as having (OSA group) or not having OSA (Control group) are shown in Table 1. A total of 83 patients were included in this study. Of the 83 patients, 49 (59 %) had been diagnosed as having OSA (AHI ≥5/h). The mean age of overall study cohort was 63.8 ± 10.1 years, the mean BMI was 25.3 ± 4.5 kg/m$^2$, and 83 % of the patients were male. As compared with the Control group, the OSA group had a higher number of female patients, a higher BMI, and a higher prevalence of hypertension, β-blocker use and persistent AF. In the OSA group, there was a tendency for more Ensite systems, but there was no significant difference.

**Table 1**
Baseline characteristics.

| | Total (n = 83) | Control (n = 34) | OSA (n = 49) | P-value |
|---|---|---|---|---|
| Age (years) | 63.8 ± 10.1 | 63.9 ± 11.2 | 63.7 ± 9.4 | 0.938 |
| Male, n (%) | 69 (83) | 29 (85) | 40 (82) | <0.001 |
| AHI (event/h) | | – | 48.1 ± 20.2 | |
| 3 %ODI | 19.6 ± 21.1 | 2.0 ± 1.2 | 31.8 ± 19.7 | <0.001 |
| OSA duration (years) | | – | 3.9 ± 5.4 | |
| ESS | 5.7 ± 4.0 | 4.9 ± 2.0 | 6.3 ± 5.2 | 0.085 |
| BMI (kg/m$^2$) | 25.3 ± 4.5 | 23.0 ± 3.7 | 26.9 ± 4.2 | <0.001 |
| 3D Mapping system | | | | |
| Carto | 24 (29) | 12 (36) | 12 (24) | 0.627 |
| Ensite | 37 (45) | 11 (32) | 26 (53) | 0.075 |
| Rhythmia | 22 (26) | 11 (32) | 11 (23) | 0.206 |
| %LVA ≥5%, n (%) | 32 (39) | 9 (27) | 23 (47) | <0.001 |
| Persistent AF, n (%) | 39 (47) | 9 (27) | 30 (61) | 0.004 |
| Hypertension, n (%) | 48 (58) | 18 (53) | 30 (61) | 0.003 |
| Diabetes mellitus, n (%) | 12 (15) | 4 (12) | 8 (16) | 0.216 |
| Dyslipidemia, n (%) | 27 (33) | 12 (35) | 15 (31) | 0.359 |
| Current smoker, n (%) | 27 (33) | 10 (29) | 17 (35) | 0.060 |
| Coronary Artery Disease, n (%) | 5 (6) | 1 (3) | 4 (8) | 0.359 |
| $CHADS_2$ score | 1.14 ± 1.10 | 0.91 ± 1.03 | 1.31 ± 1.07 | 0.096 |
| $CHADS_2$ Vasc score | 1.75 ± 1.38 | 1.56 ± 1.41 | 1.88 ± 1.35 | 0.303 |
| β-blocker, n (%) | 39 (47) | 15 (44) | 24 (49) | 0.049 |
| Antiarrhythmic drug(s), n (%) | 30 (36) | 16 (47) | 14 (59) | 0.820 |
| Bepridil | 16 (19) | 8 (2) | 8 (16) | 0.572 |
| Cibenzoline | 3 (4) | 3 (9) | 0 (0) | 0.065 |
| Pilsicainide | 2 (2) | 2 (6) | 0(0) | 0.165 |
| Flecainide | 6 (7) | 3 (9) | 3 (6) | 0.685 |
| Amiodarone | 3 (4) | 0 (0) | 3 (6) | 0.266 |
| LVEF (%) | 60.9 ± 7.3 | 60.8 ± 5.1 | 60.9 ± 8.5 | 0.967 |
| BNP (pg/ml) | 146.0 ± 152.3 | 116.5 ± 129.7 | 166.4 ± 164.4 | 0.143 |
| CKD, n (%) | 15 (18) | 3 (9) | 12 (24) | 0.060 |

Data presented are the means± SDs and number (%) of subjects. P-value = Control vs. OSA

***Abbreviations**: AHI, apnoea hypopnoea index; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; ESS, Epworth Sleepiness Scale; BMI, body mass index; 3D, three dimensional; LVA, low voltage area; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; Cr, creatinine; CKD, chronic kidney disease

### 3.2. Atrial remodeling in the Control and OSA groups (Fig. 2)

Fig. 2 shows the findings on atrial remodeling in a box-and-whisker diagram. The OSA group had a significantly greater LVA (Control group vs. OSA group: 2.6 ± 3.2 cm$^2$ vs. 6.0 ± 6.6 cm$^2$, P = 0.003) and %LVA (Control group vs. OSA group: 3.5 % ± 4.6 % vs. 7.5 % ± 8.5 %, P = 0.008). However, there was no difference in the total LA surface area measured by the three-dimensional electro-anatomical mapping system (Control group vs. OSA group: 100.4 ± 45.6 cm$^2$ vs. 96.7 ± 44.2 cm$^2$, P = 0.716) or the left atrial volume index (LAVI) measured by ultrasound cardiography (Control group: 39.4 ± 8.4; OSA group: 40.6 ± 9.9, P = 0.711) between the two groups. Subgroup analyses (Supplement Fig. 1) revealed that the LVA was significantly greater in the male patients and patients with persistent/long-standing AF. Furthermore, in a subgroup analysis restricted to the OSA group, significant enlargement of %LVA was consistently observed in severe OSA cases. However, LA size parameters did not show significant differences (Supplement Fig. 2).

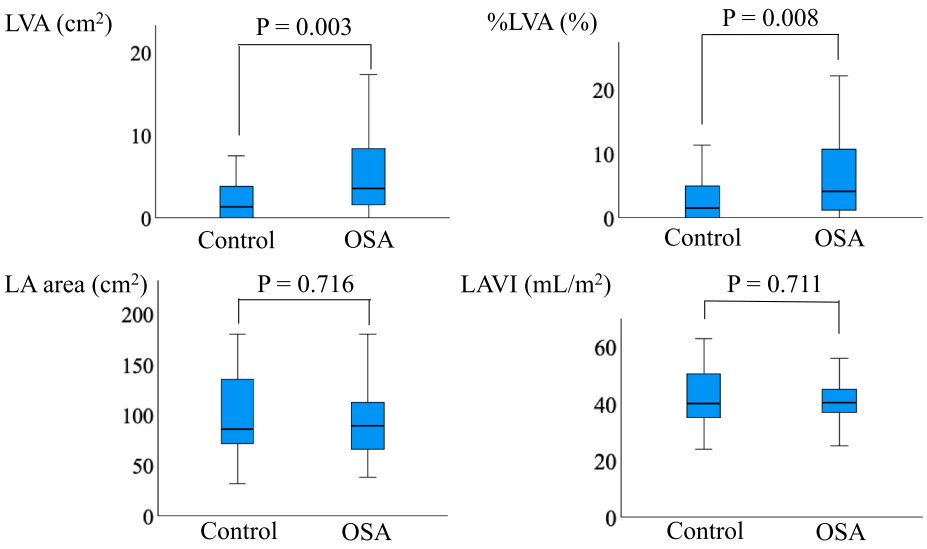


**Fig. 2.** Comparison of the LVA and LA parameters between the Control and OSA groups. Abbreviations: LVA, low-voltage area of the left atrium; LA, left atrium; LAVI, left atrial volume index; OSA, obstructive sleep apnea.

### 3.3. OSA duration and atrial remodeling (Supplement Fig. 3)

The mean OSA duration was 3.9 ± 5.4 year, with 58 cases (70 %) identified as early-phase OSA. Supplement Fig. 3 demonstrated that the comparison of %LVA and LA area between the early-phase OSA group and late-phase OSA group. %LVA was significantly higher in late-phase OSA compared to early-phase OSA (9.9 ± 10.3 % vs 4.9 ± 5.3 %, P = 0.039), but there was no significant difference in LA (132 ± 27 $cm^2$ vs 130 ± 34 $cm^2$, P = 0.872).

### 3.4. Correlation between the 3 % ODI and atrial remodeling (Fig. 3)

Fig. 3 shows the correlation between the 3 % ODI and atrial remodeling in the study subjects. Higher 3 % ODI values were associated with a higher LVA (r = 0.293, P = 0.007) and %LVA (r = 0.268, P = 0.014). On the other hand, we found no significant correlation between the 3 % ODI and the total LA surface area (r = 0.009, P = 0.936) or LAVI (r = 0.093, P = 0.408).

### 3.5. Atrial voltage abnormalities

Fig. 4 shows the anterior and posterior views of an LA voltage map. The pulmonary veins are shown in gray with no potential because the pulmonary veins were isolated. The areas indicated other than the purple areas represent areas of low voltage (defined as a bipolar amplitude <0.5 mV).

Fig. 4A shows a representative example of a patient without OSA (Control group). The voltage amplitude is normal (LA area = 135.8 $cm^2$, LVA=0.0 $cm^2$, %LVA=0.0 %). B represents a patient with severe OSA (AHI=62.0). Extensive expansion of LVA is observed in the LA anterior and posterior wall (white arrows) (LA area = 129.3 $cm^2$, LVA=12.4 $cm^2$, %LVA=9.6 %).

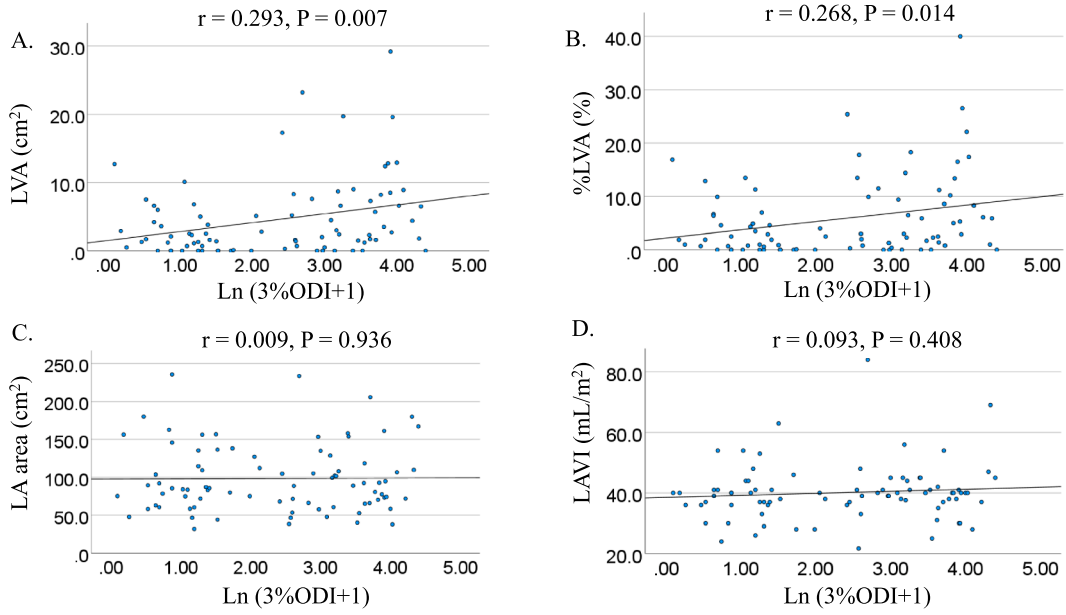


**Fig. 3.** Correlations between the 3 % ODI and left atrial remodeling. Higher values of the 3 % ODI were associated with higher values of the LVA and %LVA. On the other hand, the 3 % ODI showed no significant correlation with the LA area or the LAVI.

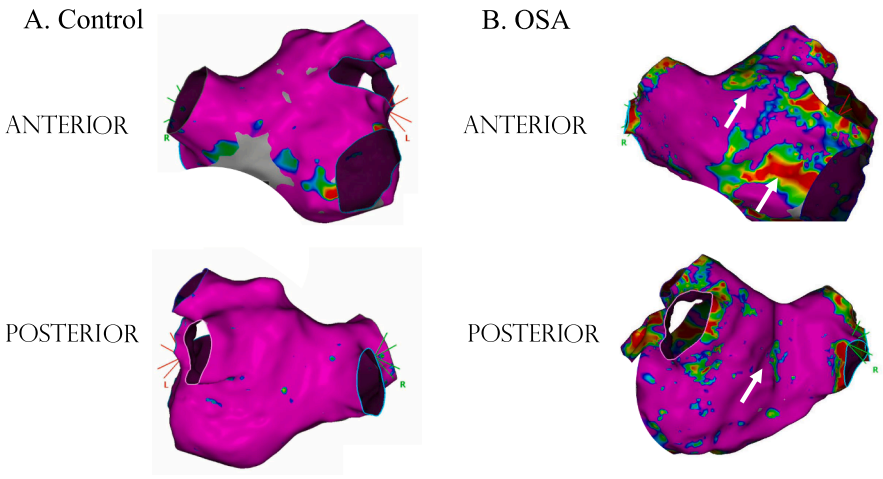


**Fig. 4.** Anterior and posterior views of the LA voltage map in a representative case. Pulmonary veins are shown in gray with no potential, because they were isolated. The areas indicated other than the purple areas, excluding the mitral annulus, left atrial appendage, and pulmonary veins, represent the LVA, defined by a bipolar voltage amplitude of <0.5 mV. A. Control group (patient without OSA). The voltage amplitude is normal (LA area = 135.8 $cm^2$, LVA=0.0 $cm^2$, %LVA=0.0 %). B. OSA group (patient with severe OSA: AHI=62.0). Extensive LVA expansion is observed in the LA anterior and posterior wall (white arrow) (LA area = 129.3 $cm^2$, LVA=12.4 $cm^2$, %LVA=9.6 %). Abbreviations: LA, left atrium; LVA, low-voltage area of the left atrium; OSA, obstructive sleep apnea.

### *3.6. Factors associated with %LVA ≥5% (Table 2)*

The proportion of subjects with %LVA ≥5% was significantly higher in the OSA group (49 %) than that in the Control group (24 %) (P = 0.014). Univariate and multivariate logistic regression analyses were performed to determine the risk factors for %LVA ≥5% (Table 2). Univariate analysis identified the gender (males had higher values) [9.789 (1.205–79.498), P = 0.033] and 3 % ODI [3.630 (1.331–9.896), P = 0.012] as being significantly associated with the %LVA ≥5%. Multivariate logistic regression analysis identified only 3 % ODI [3.088 (1.078–8.851), P = 0.036] (Model 1); [3.281 (1.067–10.093), P = 0.038] (Model 2) as being significantly associated with the %LVA ≥5%.

## 4. Discussion

This study is the first study to demonstrate that electro-anatomical remodeling precedes structural remodeling of the LA in patients with OSA, and that intermittent hypoxia is significantly associated with electro-anatomical remodeling of the LA among the mechanisms of OSA. The major findings were as follows: (1) The LVA was significantly greater in the OSA group as compared with the Control group. (2) There was no significant difference in the LA area between the OSA group and the Control group. (3) Multivariable analysis with adjustments identified the 3 % ODI as being the variable significantly associated with the LVA.

### *4.1. Prevalence of LVA*

The increase in the LVA in AF patients reflects electro-anatomical remodeling of the left atrium in these patients. The LVA is a surrogate parameter of AF progression and increase in LVA is a characteristic feature of the advanced stages of atrial cardiomyopathy. LVA is found in approximately 20 %–25 % of all patients with AF, and up to one-third of all AF patients with increase LVA show impaired rhythm outcomes after catheter ablation [31]. The prevalence of LVA varies depending on the definition of LVA in each study. Wang, et al. [32] reported that the prevalence of LVA was 62.7 % in the PAF cohort (definition of LVA: presence of a peak-to-peak bipolar voltage of <0.5 mV). On the other hand, Matsuda, et al. [33] showed that LVA were present in 21 % in patients undergoing ablation for AF (persistent AF, 51 %) (definition of LVA: a peak-to-peak bipolar voltage of <0.5 mV covering ≥5 $cm^2$ of the LA). In this study, we defined LVA as covering ≥5 % of the LA based on previous researches [29,30]. The prevalence of LVA in this study was 27 % in the Control group, which is consistent with previous researches,

**Table 2**
Factors associated with %LVA ≥5%.

| For %LVA≥5% | | | | | | |
|---|---|---|---|---|---|---|
| | Univariate | | Multivariate (Model 1) | | Multivariate (Model 2) | |
| | OR (95 % CI) | P-value | OR (95 % CI) | P-value | OR (95 % CI) | P-value |
| 3 %ODI≥30/h | 3.630 (1.331–9.896) | 0.012 | 3.088 (1.078–8.851) | 0.036 | 3.281 (1.067–10.093) | 0.038 |
| Age ≥65 (years) | 0.504 (0.202–1.255) | 0.141 | | | | |
| Male | 9.789 (1.205–79.498) | 0.033 | 6.800 (0.812–56.935) | 0.077 | 5.799 (0.640–52.526) | 0.104 |
| BMI ($kg/m^2$) ≥25 | 1.074 (0.443–2.607) | 0.874 | | | 0.609 (0.210–1.762) | 0.360 |
| Persistent AF | 1.494 (0.615–3.632) | 0.376 | | | 1.156 (0.399–3.347) | 0.790 |
| OSA duration | 1.063 (0.980–1.153) | 0.140 | | | | |
| LAVI ($mL/m^2$) ≥34 | 0.833 (0.185–3.750) | 0.812 | | | | |
| Current smoking | 1.134 (0.440–2.926) | 0.794 | | | | |
| Hypertension | 1.429 (0.567–3.598) | 0.449 | | | 1.139 (0.339–3.825) | 0.833 |
| Diabetes mellitus | 1.181 (0.340–4.109) | 0.793 | | | | |
| CKD | 1.760 (0.553–5.597) | 0.338 | | | | |
| β-blocker use | 2.265 (0.919–5.583) | 0.076 | | | 1.408 (0.506–3.918) | 0.513 |

*Abbreviations: OR, odds ratio; CI, Confidence interval. Other abbreviations as in Table 1.
Model 1: Adjusted for Male.
Model 2: Adjusted for Male, BMI (kg/m2) ≥25, Persistent AF, Hypertension, and β-blocker use.

and 47 % in the OSA group, which was significantly higher (Table 1).

### 4.2. Measurement of LA Area/Volume

In this study, LA enlargement was evaluated using the LA surface area measured by the three-dimensional electro-anatomical mapping system and the LAVI measured by ultrasound cardiography. The LA surface area lacks a standard reference value, making comparison with healthy individuals difficult. However, according to the results of LAVI, a standard indicator of LA enlargement, obtained by echocardiography, the average LAVI was 39.4 ± 8.4 in the Control group and 40.6 ± 9.9 in the OSA group, both exceeding the cut-off value of 34 [34], but there was no significant difference between the two groups. Therefore, while the overall population in this study had mild LA enlargement, the lack of a significant difference between the Control and OSA groups suggests that there may not be an additive effect of OSA on LA enlargement.

### 4.3. OSA and the atrial substrate for AF

Acute apnea-associated atrial electrophysiological changes associated with intermittent hypoxia, intrathoracic pressure changes, and sympathovagal activation combine to serve as a trigger for AF and a complex and dynamic substrate for AF. Repeated episodes of long-term OSA are eventually associated with structural remodeling and disturbances of electrical conduction in the atrium [12]. However, the natural progression of OSA-mediated atrial remodeling in humans is not yet clearly understood and may well depend on the duration and severity of OSA.

In this study, the OSA group had a significantly greater LVA, but the LA area did not differ significantly between the OSA group and Control group. These results suggest that the physiological changes associated with OSA may have led to electro-anatomical remodeling of the left atrium, as represented by the increase in LVA, but that most patients probably had relatively short-term OSA and structural remodeling represented by LA enlargement had not occurred yet. Therefore, in AF patients in which electro-anatomical mapping shows an increase of the LVA without concomitant increase of the LA area, the possibility of concomitant early-phase OSA may need to be considered, and evaluation and intervention for OSA may be indicated.

### 4.4. Mechanisms of the increase in LVA in patients with OSA

Repetitive episodes of apnea/hypopnea in OSA, associated with intermittent hypoxia, negative intrathoracic pressure swings, atrial stretch, and neurohumoral activation are believed to be associated with cardiac structural and electric remodeling. In animal models, repetitive episodes of apnea/hypopnea in OSA have been shown to be associated with atrial fibrosis and important changes in connexin-43 expression and distribution, resulting in slowing of atrial conduction and vulnerability to arrhythmias, including AF [35].

However, among the pathophysiological changes associated with OSA, it remains unclear which components might be involved in the atrial remodeling in humans. In this study, our finding of a significant association between the 3 % ODI and the LVA suggests that in OSA, among the associated pathophysiological changes, recurrent intermittent hypoxia may be the primary contributor to electro-anatomical remodeling of the atrium.

### 4.5. Other predictors of LVA in patients with AF

Previous studies have reported that expansion of the LVA is often associated with LA volume enlargement [36]. However, the LVA expansion was not found to be associated with the LA size in this study. As previously mentioned, one possible reason for this discrepancy is that the patients in this study had relatively early-phase OSA and might have developed LV enlargement over time.

Other factors that contribute to expansion of the LVA include female sex, advanced age, and longer duration of AF [37]. In particular, the AF phenotype is considered as a major factor in predicting the LVA. However, in our study, only the 3 % ODI and male sex were found to be significantly associated with the LVA (Table 2). The patients of this study were cases deemed as being suitable candidates for ablation. Therefore, even in patients with persistent AF, the duration of AF in most patients was <1 year. Thus, the duration of AF may explain the absence of the correlation of the AF phenotype with the LVA. A previous study reported that OSA associates with marked atrial remodelling, predominantly among paroxysmal AF cohorts with severe OSA [25]. This result was consistent with our findings.

### 4.6. Diagnosis and duration of OSA

This is a study based on the clinical course of usual AF ablation therapy. Therefore, it is ethically challenging to perform additional PSG on cases with a 3 % ODI of less than 5. The absence of this screening could lead to undiagnosed OSA cases within the control group, potentially confounding the results. However, in this study, the correlation between portable sleep test-ODI and PSG-ODI had good correlation ($r = 0.786$, $P < 0.001$, data not shown), so the absence of this PSG does not lead to diametrically opposed results.

The duration of OSA was estimated by questionnaires, which asked about the first time snoring or apnea was pointed out, or when the patient first became aware of excessive daytime sleepiness. There is no standard definition for early-phase OSA. We defined onset within one year as early-phase OSA in this study. As shown in the Supplement Fig. 3, LVA was significantly higher in late-phase OSA compared to early-phase OSA, but there was no significant difference in LA. However, the large standard deviation of OSA duration indicates that the reported duration of OSA is susceptible to bias based on questionnaire responses. Further research is needed to accurately assess the relationship between the duration of OSA and LVA.

### 4.7. Study limitations

This study had several limitations. (1) This study was a retrospective study conducted on patients at a single center, which could have led to a bias in participant selection. Therefore, further studies on larger sample sizes should be conducted for a more robust conclusion. (2) The duration of OSA was assessed through patient interviews, which may have led to some degree of inaccuracy in assessing the OSA duration. (3) The changes in autonomic nervous activity and intrathoracic pressure associated with OSA, which were assumed to explain the effect of OSA on the LVA, were not measured, and their involvement remains uncertain. (4) The Control group of patients did not undergo PSG, so that the exact AHI in the Control group patients remains unknown. The absence of the PSG in Control group could lead to undiagnosed OSA cases within the control group, potentially confounding the results. (5) It is well known that the size of LVA is affected by the mapping system, but in this study, the evaluations were mixed with three different systems, and the evaluation methods are not standardized. This distribution of the three different mapping systems may introduce any potential bias or variability. (6) In this study, the changes in LVA before and after CPAP therapy, a treatment for severe OSA, have not been investigated. (7) In this study, LA enlargement was evaluated using the LA surface area measured by the three-dimensional electro-anatomical mapping system and the LAVI measured by ultrasound cardiography, but we did not perform quantification using CT scans. (8) The assessment of electrical remodeling of LA was conducted only through LVA, other parameters like fractionation and conduction velocity were not examined.

## 5. Conclusions

In patients with AF complicated by OSA, a significant expansion of

the LVA was observed, with no evidence, however, of an increase of the LA area. The intermittent hypoxia severity was significantly associated with the LVA. These results suggest that intermittent hypoxia by OSA might be one of the mechanisms of electro-anatomical remodeling of the LA, possibly preceding structural remodeling represented by LA enlargement, in patients with AF. Therefore, in AF patients with expansion of the LVA but no LA enlargement, the possibility of concomitant OSA may need to be considered, and evaluation and intervention for OSA may be indicated.

## CRediT authorship contribution statement

**Yasuyuki Takada:** Writing – review & editing, Writing – original draft, Investigation. **Kazuki Shiina:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation. **Shunichiro Orihara:** Validation, Software, Formal analysis, Data curation. **Yoshifumi Takata:** Supervision, Data curation. **Takamichi Takahashi:** Investigation. **Junya Kani:** Investigation. **Takahiro Kusume:** Investigation. **Muryo Terasawa:** Investigation. **Hiroki Nakano:** Validation, Methodology. **Yukio Saitoh:** Supervision, Project administration, Investigation, Conceptualization. **Yoshinao Yazaki:** Investigation. **Hirofumi Tomiyama:** Supervision, Conceptualization. **Taishiro Chikamori:** Supervision, Conceptualization. **Kazuhiro Satomi:** Supervision, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

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