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ORIGINAL ARTICLE

Relationship between diastolic ventricular dysfunction and subclinical sleep-disordered breathing in atrial fibrillation ablation candidates

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Abstract Sleep-disordered breathing (SDB) is recognized as a primary factor or mediator of atrial fibrillation (AF). We hypothesized that the severity of SDB among AF ablation candidates would be associated with left ventricular diastolic dysfunction (LVDD) even for subclinical SDB. A total of 246 patients hospitalized for initial pulmonary vein isolation (PVI) were analyzed. Known SDB cases were excluded. We measured the oxygen desaturation index (ODI) by pulse oximetry overnight as an indicator of SDB, and classified SDB severity by 3 % ODI as normal (ODI < 5 events/h), mild (ODI ≤ 5 to <15 events/h), or moderate-to-severe (ODI ≥15 events/h). The LVDD was assessed by echocardiography using combined categories with tissue Doppler imaging and left atrial (LA) volume measurement. Among the participants, 42 patients (17.1 %) had LVDD. The prevalence of LVDD increased with the SDB severity from 8.6 % (normal) to 12.7 % (mild) to 40.0 % (moderate-to-severe SDB) ($p < 0.0001$). In the multivariate logistic regression analysis, the odds ratio of having LVDD in the moderate-to-severe SDB group (ODI ≥ 15) vs. normal group (ODI < 5) was 5.96 (95 % CI, 2.10–19.00, $P = 0.006$). The presence of moderate-to-severe SDB in AF ablation candidates adversely affected LV diastolic function even during a subclinical state of SDB.

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Keywords Atrial fibrillation · Sleep-disordered breathing · Left ventricular diastolic dysfunction · Left atrial remodeling

Introduction

Sleep-disordered breathing (SDB), including obstructive sleep apnea (OSA) and central sleep apnea (CSA), is prevalent in approximately half of patients with atrial fibrillation (AF) [1, 2]. Untreated OSA is associated with a higher risk of the recurrence of AF after medical therapy [3], electrical cardioversion [4], or AF ablation [5–7]. While moderate-to-severe OSA causes structural and functional changes in left ventricular (LV) function compared to that in healthy subjects [8, 9], the severity of CSA is also associated with the incidence of AF among patients with LV dysfunction [10]. Most previous studies of these relationships between SDB and LV dysfunction in AF were evaluated in patients already diagnosed with SDB; however, the impact during the subclinical period of SDB has not been elucidated. We conducted a prospective cross-sectional study of the association between the severity of previously undiagnosed SDB among AF ablation candidates and adverse cardiac structural remodeling, particularly regarding left atrium (LA) dilatation and LV diastolic function parameters which are associated with AF ablation failure.

Materials and methods

Study population

The study was conducted under a prospective, single-center observational design using a prospective registry. We

recruited 269 consecutive Japanese non-mitral valvular AF patients hospitalized at our institution as candidates for de novo pulmonary vein isolation (PVI) from December 2011 to May 2014. We excluded 5 patients from analysis due to the use of positive airway pressure (CPAP) for known SDB, and 18 due to inappropriate oxygen desaturation data ($n = 5$) and concomitant disease affecting ventricular diastolic function, such as post-cardiac surgery, creatinine level >=2.0, moderate aortic valve disease, and hypertrophic cardiomyopathy ($n = 13$; Fig. 1). The study was conducted in the remaining 246 patients. The study protocol was approved by the ethical committee of Tenri Hospital and all patients provided written informed consent to all procedures associated with the study.

Pulse oximetry

The evening before the AF ablation procedure, all patients underwent a medical interview, physical examination, and oxyhemoglobin saturation (SaO_2) monitoring. This monitoring was conducted with a high-resolution pulse oximeter (PULSOX-Me300; Minolta Co, Osaka, Japan), which has emerged as a simplified screening tool via a finger probe pulse oximeter for SDB [11]. A sleep diary was recorded to minimize any potential overestimation of sleep duration. The sampling frequency of the PULSOX- Me300 oximeter was 1 Hz during the memory interval for an average time of 3 s each. The resolution for SpO_2 was 0.1 %. The algorithm for analyzing the PULSOX-Me300 data was compatible with that implemented in commercially available software (DS-Me, Minolta Co, Osaka, Japan). In this study, we used a 3 % oxygen desaturation index (ODI) as the SDB cutoff value, as described in previous studies. This ratio has 80 % sensitivity and 95 % specificity for detecting an apnea–hypopnea index (AHI) of ≥5 events/h by polysomnography (PSG) using a cutoff threshold of a 3 % ODI = 5, and an 85 % sensitivity and 100 % specificity for detecting an AHI of ≥20 using a 3 % ODI = 15 [12, 13]. To classify the severity of the SDB, we subdivided the patients into three groups according to 3 % ODI level, namely ODI < 5 events/h as the normal SDB group, 5 ≤ ODI < 15 as the mild SDB group, and 15 ≤ ODI as the moderate-to-severe SDB group (50 patients) (Fig. 1).

Echocardiographic measurements

All transthoracic echocardiographic data were obtained and analyzed by the same echocardiography specialist before the procedure. Two-dimensional echocardiographic images of the LA and LV were obtained in accordance with the American Society of Echocardiography (ASE) recommendations [14]. The mitral inflow velocity and tissue Doppler imaging (TDI) signals were adjusted to provide a smooth velocity distribution without introducing any noise at a 100-mm/s sweep speed. LV ejection fraction (LVEF) was assessed by the modified Simpson's method. The early (E) and late (A) diastolic peak velocities from the apical 4-chamber (4C) view, and E-wave deceleration time were also measured. The peak early mitral annular velocities (e') were derived by tissue Doppler analysis at the septal and lateral margin of the mitral annulus in the apical 4C view. The E/e' was then calculated as an index of the LV filling pressure at both annular sites. Although the baseline data were managed to be acquired during sinus rhythm,

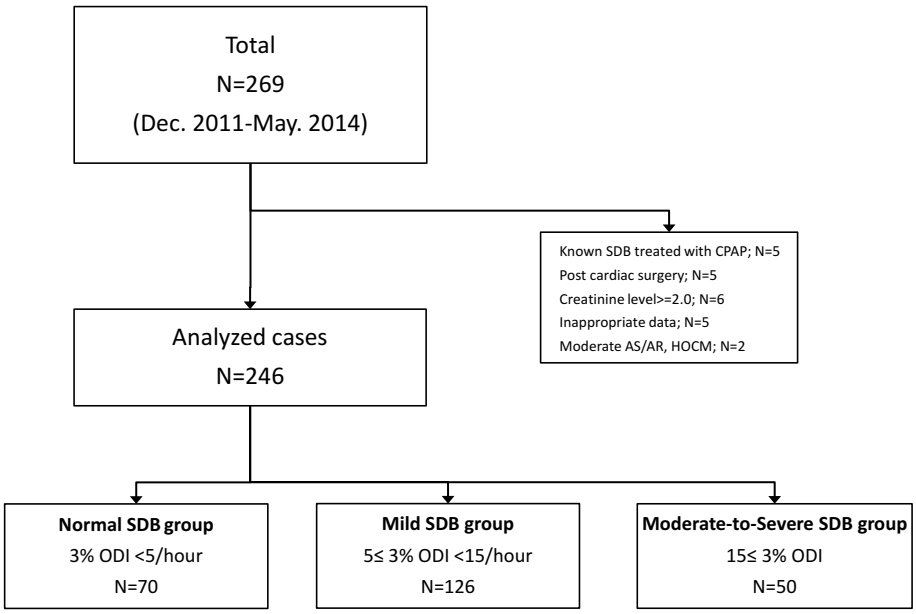

Fig. 1 Flowchart of the subjects in the study

measurements in persistent AF cases were obtained from a single cardiac cycle with an RR interval corresponding to a heart rate of 70–80 beats/min during an AF rhythm [15].

LA volume and LV diastolic function

LA volume was estimated by the biplane area-length method, using measurements in the apical 4- and 2-C views at end-systole. LA volume index was calculated as the LA volume divided by the body surface area [16]. In this study, an enlarged LA was defined as a left atrial volume index (LAVI) of $\geq$34 mL/m^2 in accordance with previous studies [17, 18].

Furthermore, left ventricular diastolic dysfunction (LVDD) was evaluated using combined categories with tissue Doppler measurements of the septal and lateral mitral annulus and LA volume, which was the first screening step before grading the LV diastolic function with the recent ASE recommendations [18]. An LVDD case was defined as a patient who met all three of the following criteria, a septal annular *e*' of <8 cm/s, lateral annular *e*' of <10 cm/s, and an enlarged LA. All patients who were not classified as LVDD cases were treated as having normal LV diastolic function.

Statistical analysis

Data were collected and entered prospectively in a computer database. Continuous variables were summarized as the mean and standard deviation or median and interquartile ranges (IQR), depending on the normality of the distribution. Comparisons were made with the χ^2 or Fisher's exact test for categorical variables, as appropriate, and with the Wilcoxon rank-sum test for continuous variables. A value of $P \leq 0.05$ was considered statistically significant. To identify independent predictors of an enlarged LA and LVDD, univariate and multivariate logistic regression analyses were performed using 11 relevant clinical factors, namely age; gender; AF evolution time (< or $\geq$24 months); body mass index (BMI); AF type; history of hypertension (HT), diabetes mellitus (DM) or congestive heart failure (CHF); use of angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB); brain natriuretic peptide (BNP) level; and left ventricular ejection fraction (LVEF) (< or $\geq$50 %), and three groups categorized according to the severity of the SDB. Variables with a *P* value $\leq$0.10 in the univariate models were included in the multivariate analyses. In univariate and multivariate logistic regression analyses, the normal SDB group was used as reference. Odds ratios and corresponding 95 % confidence intervals (CIs) were also computed where appropriate. Statistical analyses were performed with JMP version 10.02 software (SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient characteristics

Of the 246 study patients, SDB was detected in 176 patients (71.5 %), grouped as 126 (51.2 %) with mild SDB and 50 (20.3 %) with moderate-to-severe SDB (Fig. 1). The baseline characteristics and echocardiographic parameters of all patients and in three groups categorized by the severity of SDB are shown in Tables 1 and 2. The baseline characteristics, including age, gender, CHA_2DS_2-VASc score [19], β-blocker utilization, and LVEF, were similar among the three groups. The prevalence of hypertension and use of ACEI/ARB were significantly lower in the normal SDB group than in the mild and moderate-to-severe SDB groups ($P < 0.0001$ and $p = 0.015$, respectively). Therefore, baseline blood pressure was well controlled (systolic/diastolic blood pressure; 125/74 mmHg; median). In contrast, in the moderate-to-severe SDB group, left ventricular hypertrophy exhibited a greater progression than in the normal SDB group regarding the septal wall thickness ($p = 0.018$) and posterior wall thickness ($p = 0.048$). In addition, SDB was positively associated with body mass index (BMI) ($p = 0.0001$), and patients were more likely to have nonparoxysmal AF ($p = 0.0012$). The severity of SDB was linearly associated with the BNP level with each cutoff ($p = 0.0005$). Further, LAVI, the ratio of the early transmitral filling velocity (*E*) and early diastolic mitral annular velocity (*e*'), significantly differed between the normal and moderate-to-severe SDB group for both the septal and lateral velocities (LAVI; $p = 0.0008$, septal *E*/*e*'; $p = 0.0004$, lateral E/e'; $p = 0.0003$, respectively).

LA volume, LV diastolic dysfunction, and SDB

Figure 2 shows the prevalence of patients with an enlarged LA or LADD in the three groups according to SDB severity. An enlarged LA was observed in 126 (51.2 %) of all subjects, and this ratio gradually increased with increasing SDB severity ($p < 0.0001$). LVDD was observed in 42 (17.1 %) of all subjects, and similarly gradually increased with SDB severity ($p < 0.0001$). Among the three groups, the incidence of both enlarged LA and LVDD was significantly higher in the moderate-to-severe SDB group (76.0 and 40.0 %, respectively) than in the other two groups.

Multivariate analysis of predictors of enlarged LA and LVDD

Table 3 demonstrates the univariate- and multivariate-adjusted OR and 95 % CI for the selected cardiovascular risk factors associated with enlarged LA. A multivariate

Table 1 Clinical characteristics of patients with or without sleep-disordered breathing

3 % ODI cutoff, events/hour		ODI < 5	5 ≤ ODI < 15	15 ≤ ODI
Clinical and demographic indices, median (IQR)	All patients ($n = 246$)	Normal SDB group ($n = 70$)	Mild SDB group ($n = 126$)	Moderate-to-severe SDB group ($n = 50$)
Age (years)	65 (59–70)	63 (58–70)	65 (59–70)	67 (61–70)
Male, n (%)	189 (76.8)	49 (70.0)	97 (77.0)	43 (86.0)*
Total duration of AF history (months)	24.0 (9–60)	31.0 (13–70)	16.5 (6–51)*	25.0 (9–60)
CHA2DS2-VASc score	2 (1–3)	1.5 (1–3)	2 (1–3)	2 (1–3)
Body mass index (kg/m^2)	23.6 (22–25)	22.9 (20–24)	23.6 (21–25)*	25.2 (23–27)‡
Non-paroxysmal AF, n (%)	88 (35.8)	15 (21.4)	27 (34.6)*	27 (54.0)‡
Systolic blood pressure (mmHg)	125 (116–136)	124 (114–135)	125 (117–136)	126 (117–137)
Diastolic blood pressure (mmHg)	74 (69–82)	73 (70–80)	75 (68–84)	75 (69–83)
Heart rate, beats per minute	71 (62–80)	70 (61–79)	72 (63–80)	70 (63–83)
Hypertension, n (%)	131 (53.3)	25 (35.7)	68 (54.0)*	38 (76.0)‡
Diabetes mellitus, n (%)	31 (12.6)	6 (8.6)	17 (13.5)	8 (16.0)
History of CHF, n (%)	20 (8.1)	9 (12.9)	9 (7.1)	2 (4.0)
Current drug therapy				
ACE inhibitors/ARB, n (%)	80 (32.5)	16 (22.9)	40 (31.8)	24 (48.0)†
β-Blockers, n (%)	98 (39.8)	24 (34.3)	50 (39.7)	24 (48.0)
S-Cre (mg/dl)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–1.0)
BNP (pg/dl)	71.6 (29–145)	42.9 (17–97)	74.7 (37–145)†	111.7 (34–199)‡

ODI oxygen desaturation index, *AF* atrial fibrillation, *LAD* left atrial dimension, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blockers, *CHF* congestive heart failure, *S-Cre* serum creatinine, *BNP* brain natriuretic peptide

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, compared with 3 % ODI < 5 category

regression analysis after adjusting for the age revealed that moderate-to-severe SDB was the strongest independent predictor of enlarged LA [odds ratios (OR); 2.95, 95 % confidence intervals (95 % CI); 1.08–8.76, $p = 0.034$], followed by BMI ≥ 25 kg/m^2 (OR; 2.35, 95 % CI; 1.13–5.09, $p = 0.022$). Table 4 shows the univariate- and multivariate-adjusted analyses for the selected cardiovascular risk factors associated with LVDD. The multivariate analysis showed that only the presence of moderate-to-severe SDB was independently associated with LVDD (OR; 5.96, 95 % CI; 2.10–19.00, $p = 0.0006$).

Discussion

Main findings

In this study, we found that SDB, even in subclinical settings, was commonly present in patients who were candidates for AF ablation. It also showed that the prevalence of an enlarged LA and LVDD increased with increasing severity of SDB, and that moderate-to-severe SDB was an independent predictor of enlarged LA and LVDD. These findings suggest that subclinical moderate-to-severe SDB had adversely affected the LA remodeling as well as LV diastolic function before the procedure.

LA volume, LV diastolic dysfunction, and SDB

Among findings, pulse oximetry revealed that 20.3 % of AF ablation candidates had moderate-to-severe SDB (3 % ODI level of ≥15) even in their subclinical state. Our present study revealed that the coexistence of SDB with a pulse oximeter as well as obesity (BMI ≥ 25 kg/m^2) independently associated with LA anatomical remodeling among consecutive AF patients who had not been subjectively recognized as having sleep apnea (not only OSA) before AF ablation. Furthermore, moderate-to-severe SDB was the strongest factor of LVDD among AF patients. Although several studies reported that SDB causes LA remodeling and LV diastolic function, these studies were focused on patients with known SDB strictly diagnosed by OSA history and PSG among a male or obese cohort [20–22]. In contrast, we demonstrated these relationships among AF ablation candidates. It is well known that LVDD is a powerful predictor of LA enlargement and AF, and reflects the duration and severity of an increased LA pressure [23]. The concomitance of LVDD and an enlarged LA is an independent risk factor for the outcome of AF ablation [24]. On the other hand, SDB has been independently recognized to be related to the outcome after PVI [5–7]. Therefore, our findings suggested that this negative link between SDB and a poor

Table 2 Echocardiographic parameters in subjects with or without sleep-disordered breathing

3 % ODI cutoff, events/hour		ODI < 5	5 ≤ ODI < 10	15 ≤ ODI	*P* value
Echocardiographic parameter, median (IQR)	All patients ($n = 246$)	Normal SDB group ($n = 70$)	Mild SDB group ($n = 126$)	Moderate-to-severe SDB group ($n = 50$)	
LAD (mm)	38 (33–42)	36 (32–39)	38 (33–43)†	41.5 (39–44)‡	<.0001
LAV (ml)	57.5 (44–76)	50 (38–69)	58 (45–77)*	72 (56–85)‡	0.0001
LAVI (ml/cm^2)	34.2 (25–44)	30.0 (23–39)	34.1 (25–43)	39.4 (34–50)‡	0.0008
LVEF (%)	65.4 (61–69)	66.1 (59–69)	65.8 (61–70)	63.3 (59–68)	0.28
LVEDV (ml)	81.9 (65–98)	80.2 (63–100)	81.1 (66–98)	84.5 (71–98)	0.59
LVESV (ml)	27.4 (22–37)	26.9 (21–37)	27.4 (22–36)	27.9 (23–39)	0.36
SWT (mm)	9 (8–10)	8 (8–9)	9 (8–10)	10 (8–11)†	0.018
PWT (mm)	9 (8–10)	8 (8–10)	9 (8–10)	9 (8–10)†	0.048
E (cm/s)	73 (62–86)	72 (61–86)	71 (62–84)	80 (65–97)*	0.065
A (cm/s)[§]	67 (52–79)	62 (50–74)	68 (54–81)	71 (55–85)*	0.080
E/A[§]	1.01 (0.8–1.3)	1.01 (0.9–1.4)	1.03 (0.8–1.3)	0.94 (0.8–1.4)	0.44
Dct (ms)	199.5 (167–236)	204 (173–239)	197 (166–230)	195 (168–245)	0.55
e' (septal), cm/s	8.4 (7–10)	9.0 (7–11)	8.4 (7–10)	7.8 (6–10)	0.12
e' (lateral), cm/s	10.2 (9–13)	10.3 (9–13)	10.5 (9–13)	10.0 (8–12)	0.14
E/e' (septal)	9.0 (7–11)	8.3 (7–10)	8.7 (7–11)	10.0 (9–12)‡	0.0004
E/*e'* (lateral)	6.9 (6–9)	6.6 (5–8)	6.6 (5–9)	8.2 (7–10)‡	0.0003

ODI oxygen desaturation index, *LAD* left atrial dimension, *LAV* left atrial volume, *LAV* left atrial volume index, *LVEF* left ventricular ejection fraction, *EDV* end-diastolic volume, *ESV* end-systolic volume, *SWT* left ventricular septal wall thickness, *PWT* left ventricular posterior wall thickness, *E* early transmitral filling velocity, *e*' early diastolic mitral annular velocity

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, compared with a 3 % ODI < 5 category

[§] Only for patients with sinus rhythm during ultrasound cardiography

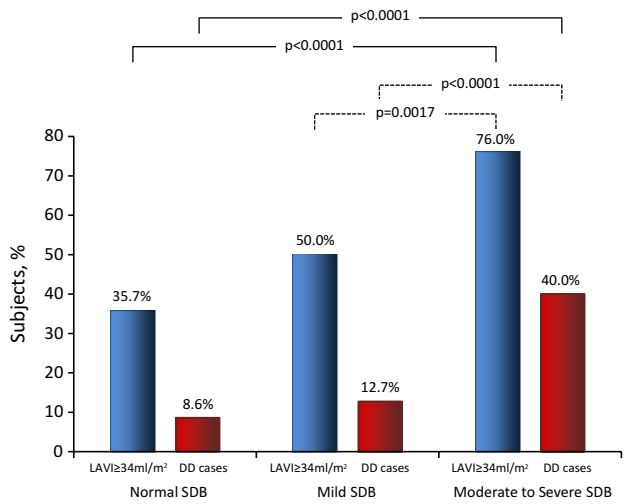

Fig. 2 Unadjusted proportion of an enlarged LA and LVDD conditions by the severity of the ODI

prognosis of PVI might be related to the LA remodeling based on preexisting LVDD caused by SDB. In the present study, HT and LV hypertrophy, which are major factors in LVDD, were found to be more likely in moderate-to-severe SDB group. This finding is consistent with previous studies reported that SDB was independently associated with HT and LV hypertrophy, which leads to LVDD [25–27]. Recently, SDB has been recognized not only as a risk factor for LV remodeling, but also for LA remodeling. The pathophysiological interaction between SDB and LV remodeling or between SDB and LA remodeling remains complex, and it might differ depending on the type of SDB [25, 28]. However, awareness of a relationship with subsequent nocturnal hypertension due to excessive sympathetic activation, inflammation, oxidative stress, negative intrathoracic pressure swing, and endothelial dysfunction has recently increased as a new pathophysiological insight between SDB and LV remodeling [29–31]. Additionally, recent works demonstrated that the SDB is independently associated with atrial electrical remodeling as well as anatomical remodeling [32, 33]. They also speculated that intermittent chronic hypoxemia, hypercapnia, and increased plasmatic catecholamine levels may represent direct proarrhythmogenic injury to the atrial tissue. Therefore, not only a pressure overload due to LVDD, but also subsidiary factors related to SDB cause atrium tissue remodeling.

Epidemiological data have demonstrated that SDB has prognostic implications for AF among patients both with and without cardiovascular diseases [1, 2, 34]. On this

Table 3 Univariate and multivariate models of clinical factors associated with LAVI $\geq$ 34 ml/m^2

Variables	Univariate regression analysis		Multivariate regression analysis	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Age (years)	1.05 (1.02–1.09)	0.0002	1.06 (1.02–1.09)	0.0007
Male gender	1.30 (0.70–2.49)	0.41		
AF evolution time ≥24 months	1.16 (0.69–1.96)	0.57		
BMI $\geq$ 25 kg/m^2	2.66 (1.43–5.21)	0.0018	2.35 (1.13–5.09)	0.022
Non-PAF	2.41 (1.36–4.39)	0.0023	1.58 (0.77–3.27)	0.21
HT	1.27 (0.75–2.14)	0.37		
DM	3.33 (1.33–10.16)	0.0086	2.34 (0.85–7.58)	0.10
History of CHF	1.77 (0.66–5.61)	0.27		
ACEI/ARB usage	1.50 (0.85–2.69)	0.16		
BNP (pg/ml)	1.01 (1.00–1.01)	<0.0001	1.00 (0.99–1.01)	0.20
LVEF < 50 %	4.94 (1.36–31.69)	0.012	4.42 (0.99–31.87)	0.052
SDB group				
Normal SDB group	1 (reference)		1 (reference)	
Mild SDB group	1.53 (0.85–2.78)	0.16	1.12 (0.58–2.17)	0.73
Moderate-to-severe SDB group	5.80 (2.41–15.69)	<.0001	2.95 (1.08–8.76)	0.034

PAF paroxysmal atrial fibrillation, *HT* hypertension, *DM* diabetes mellitus, *CHF* congestive heart failure, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BNP* brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *SDB* sleep-disordered breathing

Table 4 Univariate and multivariate models of clinical factors associated with LV diastolic dysfunction

Variable	Univariate regression analysis		Multivariate regression analysis	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Age (years)	1.03 (0.99–1.07)	0.15		
Male gender	0.62 (0.24–1.40)	0.26		
AF evolution time ≥24 months	1.28 (0.66–2.52)	0.46		
BMI $\geq$ 25 kg/m^2	1.94 (0.96–3.85)	0.065	1.26 (0.57–2.68)	0.56
Non-PAF	1.27 (0.64–2.50)	0.49		
HT	1.36 (0.70–2.71)	0.37		
DM	0.69 (0.20–1.89)	0.50		
History of CHF	1.70 (0.53–4.70)	0.35		
ACEI/ARB usage	1.35 (0.66–2.66)	0.40		
BNP pg/ml	9.05 (1.69–48.95)	0.011	1.00 (0.99–1.00)	0.39
LVEF < 50 %	3.51 (1.22–9.55)	0.021	2.99 (0.90–9.39)	0.072
SDB group				
Normal SDB group	1 (reference)		1 (reference)	
Mild SDB group	1.55 (0.60–4.50)	0.37	1.47 (0.56–4.34)	0.45
Moderate-to-severe SDB group	7.11 (2.72–21.13)	<0.0001	5.96 (2.10–19.00)	0.0006

PAF paroxysmal atrial fibrillation, *HT* hypertension, *DM* diabetic mellitus, *CHF* congestive heart failure, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BNP* brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *SDB* sleep-disordered breathing

basis, the development of subclinical SDB might precede several known risk factors of LVDD, and play a crucial role in LA enlargement and LVDD among AF ablation candidates prior to the onset of AF. Previous uncontrolled studies indicate that CPAP induces reverse atrial remodeling in patients with severe SDB [35, 36]. Furthermore, CPAP significantly provides an overall lower arrhythmia recurrence rate and improves outcomes following PVI [5–7, 37]. Pulse oximetry can, therefore, be incorporated into clinical pathways as a simple and efficient initial diagnostic tool for the evaluation for SDB in many patients referred for AF ablation.

SDB and progressing sustained AF

In this study, we found that non-paroxysmal AF was more common in the SDB groups and that paroxysmal AF was more common in the normal SDB group, despite the longer total duration of AF history in the normal SDB patients. While the risk factors associated with incident AF have been reported, few studies have examined whether these AF risk factors differ with regard to the development of non-paroxysmal AF rather than paroxysmal AF. Indeed, OSA is increasingly recognized as a potential risk factor for the development of AF, and SDB is more frequently observed in non-paroxysmal AF patients [38]. However, our findings suggested that the severity of SDB might be preferentially associated with early development toward non-paroxysmal AF.

There is some speculation of the relationship between SDB and the progression to sustained forms of AF. One is that SDB might produce multifocal triggers in arrhythmogenic veins (PVs and/or non-PV) [7]. A second is that SDB is associated with anatomical and/or electrical adverse remodeling. Actually, current studies have shown that inter-atrial conduction or intra-atrial conduction abnormalities, which should contribute to the maintenance of AF, are associated with OSA [22, 34, 35]. However, our candidates for AF ablation were intentionally excluded if they had severe LA enlargement over 150 ml/m^2, suggesting that the former speculation might be preferable in our setting. Frequent elevations in end-diastolic pressure due to accumulated stress from the SDB can initiate repetitive arrhythmias from PV [1]. Furthermore, the prevalence of non-PV triggers of AF is higher in SDB patients [7]. This complex interplay between the mechanical–electrical feedback mechanisms might provoke sustained AF [39, 40].

Limitations

Several limitations of our study warrant mention. First, while diastolic dysfunction, a common accompaniment of aging, is associated with HT, obesity, diabetes, and coronary artery disease, the cross-sectional design of this single-center study did not permit us to establish causation between the diastolic dysfunction and SDB. Additionally, the lack of a convenient, inexpensive, and accurate method for determining the diastolic dysfunction affected the reproducibility of echocardiographic data, especially for the composite objects of paroxysmal and non-paroxysmal AF. Secondly, we did not show precise data for the type or severity of SDB using PSG, the standard examination for SDB. A different mechanism of SDB for the occurrence of diastolic dysfunction might affect the results. The existence of central sleep apnea, which should be more common in the patients with persistent AF, might not have been properly diagnosed. Because OSA may be more related to genesis of AF and CSA would be considered more as the result of AF (e.g., a higher LA pressure). Accordingly, a degree of residual confounding may have been present, despite our multivariate adjustment.

Conclusions and clinical implications

The presence of moderate-to-severe SDB in candidates for AF ablation adversely affected LV diastolic function in these patients, even when the SDB was in a subclinical state. We recommend that pulse oximeter testing becomes a routine part of the procedural work-up before AF ablation.

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References

1. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK (2004) Association of atrial fibrillation and obstructive sleep apnea. Circulation 110:364–367
2. Digby GC, Baranchuk A (2012) Sleep apnea and atrial fibrillation; 2012 Update. Curr Cardiol Rev 8:265–272
3. Monahan K, Brewster J, Wang L, Parvez B, Goyal S, Roden DM, Darbar D (2012) Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter. Am J Cardiol 110:369–372
4. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, Shamsuzzaman AS, Somers VK (2003) Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 107:2589–2594
5. Bitter T, Nölker G, Vogt J, Prinz C, Horstkotte D, Oldenburg O (2012) Predictors of recurrence in patients undergoing cryoballoon ablation for treatment of atrial fibrillation: the independent role of sleep-disordered breathing. J Cardiovasc Electrophysiol 23:18–25
6. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, Kramer DB, Zimetbaum PJ, Buxton AE, Josephson ME, Anter E (2013) Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol 62:300–305
7. Patel D, Mohanty P, Di Biase L, Shaheen M, Lewis WR, Quan K, Cummings JE, Wang P, Al-Ahmad A, Venkatraman P, Nashawati E, Lakkireddy D, Schweikert R, Horton R, Sanchez J, Gallinghouse J, Hao S, Beheiry S, Cardinal DS, Zagrodzky J, Candy R, Bailey S, Burkhardt D, Natale A (2010) Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure. Circ Arrhythm Electrophysiol 3:445–451
8. Kim SH, Cho GY, Shin C, Lim HE, Kim YH, Song WH, Shim WJ, Ahn JC (2008) Impact of obstructive sleep apnea on left ventricular diastolic function. Am J Cardiol 101:1663–1668
9. Butt M, Dwivedi G, Shantsila A, Khair OA, Lip GYH (2012) Left ventricular systolic and diastolic function in obstructive

sleep apnea: impact of continuous positive airway pressure therapy. Circ Heart Fail 5:226–233
10. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, T¨opfer V (2007) Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 9:251–257
11. Takeda T, Nishimura Y, Satouchi M, Kamiryo H, Takenaka K, Kasai D, Urata Y, Kobayashi K, Shimada T, Yoshimura S, Nishiuma T, Yokoyama M (2006) Usefulness of the oximetry test for the diagnosis of sleep apnea syndrome in Japan. Am J Med Sci 331:304–308
12. Ling IT, James AL, Hillman DR (2012) Interrelationships between body mass, oxygen desaturation, and apnea-hypopnea indices in a sleep clinic population. Sleep 35:89–96
13. Nakamata M, Kubota Y, Sakai K, Kinefuchi S, Nakayama H, Ohdaira T, Sato M, Shinoda H, Kouno M (2003) The limitation of screening test for patients with sleep apnea syndrome using pulse oximetry (in Japanese with English abstract). J Jpn Soc Respir Care 12:401–406
14. Nagueh SF, Kopelen HA, Quinones MA (1996) Assessment of left ventricular filling pressures by Doppler in the presence of atrial fibrillation. Circulation 94:2138–2145
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W (2006) Recommendations for chamber quantification. Eur J Echocardiogr 7:79–108
16. Tsang TSM, Barnes ME, Gersh BJ, Bailey KR, Seward JB (2002) Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 90:1284–1289
17. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 22:107–133
18. Moller JE, Pellikka PA, Hillis GS, Oh JK (2006) Prognostic importance of diastolic function and filling pressure in patients with acute myocardial infarction. Circulation 114:438–444
19. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH, ESC Committee for Practice Guidelines (2010) Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Europace 12:1360–1420
20. Arias MA, García-Río F, Alonso-Fernández A, Mediano O, Martí I, Villamor J (2005) Obstructive sleep apnoea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation 112:375–383
21. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS (2008) Atrial fibrillation and obesity—results of a meta-analysis. Am Heart J 155:310–315
22. Dimitri H, Ng M, Brooks AG, Kuklik P, Stiles MK, Lau DH, Antic N, Thornton A, Saint DA, McEvoy D, Antic R, Kalman JM, Sanders P (2012) Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. Heart Rhythm 9:321–327
23. Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM (2005) Diastolic dysfunction and left atrial volume: a population-based study. J Am Coll Cardiol 45:87–92
24. Schneider C, Malisius R, Krause K, Lampe F, Bahlmann E, Boczor S, Antz M, Ernst S, Kuck KH (2008) Strain rate imaging for functional quantification of the left atrium: atrial deformation predicts the maintenance of sinus rhythm after catheter ablation of atrial fibrillation. Eur Heart J 29:1397–1409
25. Bazzano LA, Khan Z, Reynolds K, He J (2007) Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. Hypertension 50:417–423
26. Peppard PE, Young T, Palta M, Skatrud J (2000) Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 342:1378–1384
27. Haentjens P, Van Meerhaeghe A, Moscariello A, De Weerdt S, Poppe K, Dupont A, Velkeniers B (2007) The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome. Arch Intern Med 167:757–765
28. Bradley TD, Floras JS (2003) Sleep apnea and heart failure–part II: central sleep apnea. Circulation 107:1822–1826
29. Liu T, Li GP, Li LJ (2005) Atrial dilatation and atrial fibrillation: a vicious circle? Med Hypotheses 65:410–411
30. Arias MA, Baranchk A (2013) Atrial fibrillation and obstructive sleep apnea: something more than a coincidence. Rev Esp Cardiol 66:529–531
31. Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, Colombo PC, Basner RC, Factor P, LeJemtel TH (2008) Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation 117:2270–2278
32. Baranchuk A, Parfrey B, Lim L, Morriello F, Simpson CS, Hopman WM, Redfearn DP, Fitzpatrick M (2011) Interatrial block in patients with obstructive sleep Apnea. Cardiol J 18:171–175
33. Maeno K, Kasai T, Kasagi S, Kawana F, Ishiwata S, Ohno M, Yamaguchi T, Narui K (2013) Relationship between atrial conduction delay and obstructive sleep apnea. Heart Vessels 28:639–645
34. Chao TF, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Chiou CW, Chen SA (2014) Incidence and risk of atrial fibrillation in sleep-disordered breathing without coexistent systemic disease. Circ J 78:2182–2187
35. Baranchuk A, Pang H, Seaborn GEJ, Yazdan-Ashoori P, Redfearn DP, Simpson CS, Michael KA, Fitzpatrick M (2013) Reverse atrial electrical remodelling induced by continuous positive airway pressure in patients with severe obstructive sleep apnea. J Interv Card Electrophysiol 36:247–253
36. Bayir PT, Demirkan B, Bayir O, Duyuler S, Firat H, Güray U, Güray Y, Tatar EÇ (2014) Impact of continuous positive airway pressure therapy on atrial electromechanical delay and P-wave dispersion in patients with obstructive sleep apnea. Ann Noninvasive Electrocardiol. 19:226–233
37. Abe H, Takahashi M, Yaegashi H, Eda S, Tsunemoto H, Kamikozawa M, Koyama J, Yamazaki K, Ikeda U (2010) Efficacy of continuous positive airway pressure on arrhythmias in obstructive sleep apnea patients. Heart Vessels 25:63–69
38. Braga B, Poyares D, Cintra F, Guilleminault C, Cirenza C, Horbach S, Macedo D, Silva R, Tufik S, De Paola AA (2009) Sleep-disordered breathing and chronic atrial fibrillation. Sleep Med 10:212–216
39. Platonov PG, Mitrofanova LB, Orshanskaya V, Ho SY (2011) Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. J Am Coll Cardiol 58:2225–2232
40. Inoue K, Kurotobi T, Kimura R, Toyoshima Y, Itoh N, Masuda M, Higuchi Y, Date M, Koyama Y, Okamura A, Iwakura K, Fujii K (2012) Trigger-based mechanism of the persistence of atrial fibrillation and its impact on the efficacy of catheter ablation. Circ Arrhythm Electrophysiol 5:295–301