

Impact of Sleep-Disordered Breathing on Early and Late Recurrence of Atrial Fibrillation Following Catheter Ablation

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ABSTRACT

Background : Sleep-disordered breathing (SDB) is a well-known risk factor associated with atrial fibrillation (AF). The purpose of this study was to investigate the relationship between SDB and the clinical outcome of catheter ablation in patients with AF.

Methods : A total of 191 consecutive AF patients underwent catheter ablation were included. Prior to the procedure, overnight peripheral oxygen saturation was recorded by pulse oximetry diagnose the presence/absence of SDB. Early recurrence of AF (ERAF) and late recurrence of AF (LRAF) were defined as AF which occurred within three days following the procedure, and AF after a 90-day blanking period, respectively.

Results : SDB was diagnosed in 16.8% (32/191) of all patients. ERAF and LRAF were observed in 37.1% (71/191) and 20.9% (40/191) of patients, respectively. SDB was more frequently observed in patients with ERAF than in those without it (29.6% (21/71) vs. 9.2% (11/120), $P < 0.001$), while SDB was observed at similar levels in patients with and without LRAF (20.0% (8/40) vs. 15.9% (24/151), $P = 0.70$).

Conclusion : Although SDB was significantly associated with the occurrence of ERAF, it had no impact on LRAF following the catheter ablation of AF, which may be due to the different mechanisms of AF recurrence between the early and late clinical phases. (Jikeikai Med J 2018 ; 65 : 29-36)

Key words : Atrial Fibrillation, Catheter Ablation, Early Recurrence, Late Recurrence, Sleep-disordered breathing

INTRODUCTION

Although radiofrequency (RF) catheter ablation targeting the pulmonary veins (PVs) is an established method for curing atrial fibrillation (AF)^{1,2}, issues remain concerning the recurrence of AF after the ablation procedure, which is observed in 30%-70% of treated patients^{3,4}. The recurrence of AF after ablation can be classified into two groups ac-

ording to the phase of occurrence : the early recurrence of AF (ERAF) and the late recurrence of AF (LRAF)⁵. It is also well known that the prevalence of AF is higher in patients with sleep-disordered breathing (SDB) than in those without it⁶, and several reports have described that SDB is an independent predictor of ablation outcome^{7,8}. The purpose of this study was to investigate the relation between SDB and the phase of AF recurrence (ERAF or LRAF) fol-

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lowing catheter ablation in patients with AF.

METHODS

1. Study subjects

This study included 191 consecutive AF patients who underwent catheter ablation for drug-resistant AF (105 with paroxysmal AF and 86 with persistent AF). Antiarrhythmic drugs were discontinued for at least five half-lives prior to ablation and no patients had been treated with amiodarone in the present study. Transesophageal echocardiography or multidetector computed tomography was performed prior to the procedure in all patients in order to evaluate the anatomy of the left atrium (LA) and rule out LA thrombus. In this study, "paroxysmal AF" was defined as AF that spontaneously terminated within seven days, and "persistent AF" was defined as AF that lasted for more than seven days according to the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 Guidelines⁹. All patients provided their written informed consent before the procedure. The study protocol was approved by the ethics committee of The Jikei University School of Medicine.

2. Assessment of sleep-disordered breathing

All patients were admitted to the hospital the day before the procedure, the peripheral oxygen saturation was monitored with a pulse oximeter (Pulsox-300i; Konica Minolta Sensing Inc., Osaka, Japan) the night before. The oxygen desaturation index (ODI) was calculated as the total number of 4% desaturations per hour during sleep. SDB was defined as 4% ODI >10 in the present study, as previously described¹⁰⁻¹². Although polysomnography is considered as the gold standard for the diagnosis of sleep apnea, ODI measured by pulse oximetry has been shown to correlate well with apnea hypopnea index calculated by polysomnography. Therefore, we evaluated the presence of SDB by investigation of ODI¹³.

3. Catheter ablation procedure of AF

After informed consent was obtained from all patients, an electrophysiological study and catheter ablation were performed, as previously described¹⁴. The procedures were performed under conscious sedation via the administration of flunitrazepam and propofol. These sedative agents were

administered at the beginning of the procedure, and no patient required intratracheal intubation in this study population. For respiratory management, a nasal cannula or adaptive servo-ventilation (ASV) (AutoSet CSTM, ResMed, San Diego, CA, USA) or both were used for oxygen delivery. No jaw elevation device was used in this study population.

All four PVs were isolated at their antrum with the guidance of double circular 20-polar mapping catheters (Lasso[®], Biosense Webster, Diamond Bar, CA, USA, and/or Inquiry OptimaTM, St. Jude Medical, St. Paul, MN, USA). The RF energy was delivered by using an irrigated 3.5-mm-tip ablation catheter (Cool PathTM Duo, St. Jude Medical, or ThermoCool NavistarTM, Biosense Webster) with a power limit of 25-30 W and with a maximal temperature limit of 45°C for 30 to 60 seconds at each site. The endpoint of PV isolation was the establishment of a bidirectional conduction block between the LA and PV. After the PV potentials on the circular mapping catheters were eliminated, the absence of conduction from the PV to the LA was confirmed by circumferential pacing inside the PV with a ring catheter during sinus rhythm¹⁴. In patients with persistent AF, electrogram-based ablation or linear ablation or both were added to modify the AF substrate. Electrogram-based ablation was performed at all sites displaying complex fractionated atrial electrograms (CFAE)¹⁵. The linear ablation in the LA consisted of the roof and mitral isthmus line. The conduction block of the roof and mitral isthmus lines was confirmed using a pacing technique, as previously described¹⁶.

If non-PV firing foci were revealed, which were revealed either during the baseline state or provocation, additional RF ablations were performed to eliminate these foci if necessary.

4. Patient follow-up after AF ablation

After ablation procedure, all patients were hospitalized and underwent continuous in-hospital electrocardiographic monitoring for 3 days. In addition, patients with ERAF occurring within 3 days after ablation were more likely to be free of late recurrence at 6 months compared to those with ERAF occurred between 4 to 30 days¹⁷. The authors attributed ERAF within 3 days to the transient inflammation after ablation. The patients underwent periodic follow-up at the outpatient department. The outcome of AF ablation was evaluated by the patient's symptoms, electrocardiography

at periodical follow-ups, and periodically conducted 24-hour ambulatory monitoring (at 1, 3, 6, 9, and 12 months after the procedure and annual intervals thereafter). A cardiac event recorder was used to define the cause of symptoms suggestive of tachycardia. The AF (lasting more than 60 seconds) was classified as ERAF if it occurred within three days after ablation and as LRAF if it occurred after a 90-day blanking period¹⁷.

5. Statistical analysis

Continuous variables are expressed as the mean \pm standard deviation. Statistical significance was assessed with the unpaired Student's *t*-test. Categorical variables, expressed as numbers or percentages, were analyzed with the Chi-square test, unless the expected values in any cells were less than five, in which case Fisher's exact test was used. To analyze independent predictive factors of clinical success, univariate factors presenting $P < 0.1$ were analyzed with the Cox proportional hazard regression model (multivariable analysis). All tests were two-tailed and $P < 0.05$ was considered to be statistically significant. The cumulative event rates (AF recurrence) were calculated according to the Kaplan-Meier method. Statistical analysis was performed using SPSS software program, version 23 (IBM Corporation, Armonk, NY, USA).

RESULTS

1. Patient characteristics and SDB

The patients were 173 men and 18 women with a mean age of 55.7 ± 8.7 years. The mean duration of AF history (since diagnosis) was 5.8 ± 5.2 years. The mean LA diame-

ter was 41.2 ± 5.5 mm and left ventricular ejection fraction was $63.7 \pm 6.7\%$. The diagnosis of SDB was made before the ablation procedure for in 16.8% (32 of 191) of patients. Patients with SDB, when compared with patients without SDB, were older (60.6 ± 7.8 years vs. 54.7 ± 8.5 years, $P < 0.001$), had a higher body mass index (BMI) (26.2 ± 3.3 vs. 24.5 ± 2.8 , $P < 0.001$), and had a longer duration of AF (8.8 ± 7.4 vs. 5.2 ± 4.4 years, $P < 0.001$; Table 1).

2. Ablation procedure results

The total procedure time and total duration of RF energy delivery was 220.1 ± 56.4 and the total duration of RF energy delivery was 41.7 ± 19.3 minutes. Of the 688 target PVs, all PVs were successfully isolated from the LA. Among 86 patients with persistent AF, electrogram-based ablation and linear ablation were performed in 36 and 64 patients, respectively. Among 36 patients who underwent electrogram-based ablation, persistent AF was terminated during ablation in 14 (38.9%). In patients who underwent linear ablation in the LA, roof lines were established in 92.2% (59 of 64 patients) and mitral isthmus block lines were established in 87.5% (56 of 64 patients). There were no significant differences in the ablation strategies between the patients with ERAF or LRAF and those without (Table 2 and 3). Complications occurred in five (2.6%) patients, including cardiac tamponade in three patients and pneumothorax in two patients.

3. Clinical outcome of AF ablation and SDB

After the initial ablation procedure, ERAF was observed in 37.1% (71 of 191) of patients. In patients with ERAF, the duration of AF was significantly longer (7.3 ± 5.7

Table 1. Comparison of characteristics between patients with and without sleep-disordered breathing

	SDB (+) (n=32)	SDB (-) (n=159)	P value
Age (y/o)	60.6 \pm 7.8	54.7 \pm 8.5	<0.001
Male (%)	27 (84.3)	146 (91.8)	0.33
Paroxysmal AF (%)	17 (53.1)	88 (55.3)	0.97
Duration of AF (years)	8.8 \pm 7.4	5.2 \pm 4.4	<0.001
LAD (mm)	41.0 \pm 5.4	42.0 \pm 5.4	0.82
LVEF (%)	63.7 \pm 9.3	63.7 \pm 6.2	0.99
BMI (kg/m ²)	26.2 \pm 3.3	24.5 \pm 2.8	<0.001

Abbreviations : SDB, sleep-disordered breathing ; AF, atrial fibrillation ; LAD, left atrial dimension ; BMI, body mass index ; LVEF, left ventricular ejection fraction

Table 2. Comparison of clinical variables between patients with and without ERAF

	ERAF (+) (n=71)	ERAF (-) (n=120)	P value
Age (y/o)	56.5 ± 8.5	53.6 ± 8.8	0.30
Male (%)	64 (90.1)	109 (90.8)	0.92
Paroxysmal AF (%)	33 (46.5)	72 (60.0)	0.10
Duration of AF (years)	7.3 ± 5.7	4.9 ± 4.6	0.002
LAD (mm)	41.3 ± 5.8	40.9 ± 5.5	0.90
LVEF (%)	64.1 ± 7.6	64.7 ± 6.9	0.77
BMI (kg/m ²)	24.4 ± 3.3	24.4 ± 2.8	0.93
4% ODI	7.2 ± 7.0	4.9 ± 4.2	<0.001
SDB (%)	21 (29.6)	11 (9.2)	<0.001
Roof line (%)	29 (40.8)	35 (29.2)	0.22
MI line (%)	29 (40.8)	35 (29.2)	0.22
CFAE ablation (%)	17 (23.9)	19 (15.8)	0.45
Non-PV foci (%)	6 (8.4)	13 (10.8)	0.78

Abbreviations : AF, atrial fibrillation ; LAD, left atrial dimension ; BMI, body mass index ; LVEF, left ventricular ejection fraction ; BNP, brain natriuretic peptide ; ODI, oxygen desaturation index ; SDB, sleep-disordered breathing ; CFAE, complex fractionated atrial electrogram ; MI, mitral isthmus ; PV, pulmonary vein

Table 3. Comparison of clinical variables between patients with and without LRAF

	LRAF (+) (n = 40)	LRAF (-) (n = 151)	P value
Age (y/o)	55.9 ± 8.6	55.3 ± 9.5	0.76
Male (%)	34 (85)	139 (92.1)	0.29
Paroxysmal AF (%)	23 (57.5)	82 (54.3)	0.86
Duration of AF (years)	7.7 ± 7.5	5.3 ± 4.2	0.01
LAD (mm)	39.5 ± 5.3	40.0 ± 6.3	0.60
LVEF (%)	64.9 ± 5.7	63.3 ± 7.0	0.19
BMI (kg/m ²)	24.1 ± 2.9	24.0 ± 3.0	0.41
4% ODI	5.7 ± 5.6	6.0 ± 5.6	0.78
SDB (%)	8 (20.0)	24 (15.9)	0.70
Roof line (%)	9 (22.5)	55 (36.4)	0.29
MI line (%)	9 (22.5)	55 (36.4)	0.29
CFAE ablation (%)	8 (20.0)	28 (18.5)	0.99
Non-PV foci (%)	3 (7.5)	16 (10.6)	0.78

Abbreviations : AF, atrial fibrillation ; LAD, left atrial dimension ; BMI, body mass index ; LVEF, left ventricular ejection fraction ; ODI, oxygen desaturation index ; SDB, sleep-disordered breathing ; CFAE, complex fractionated atrial electrogram ; MI, mitral isthmus, PV, pulmonary vein

years vs. 4.9 ± 4.6 years, $P = 0.002$) and the mean 4% ODI was significantly higher (7.2 ± 7.0 vs. 4.9 ± 4.2, $P < 0.001$) than in patients without ERAF (Table 2). Additionally, SDB was more frequently observed in patients with ERAF than in patients without ERAF (29.6%, 21 of 71 patients vs. 9.2%, 11 of 120 patients, $P < 0.001$). According to multi-variable analysis, the presence of SDB of (odds ratio 3.23,

95% confidence interval 1.40–7.46, $P = 0.025$) and AF history (odds ratio 1.08, 95% confidence interval 1.01–1.15, $P = 0.006$) were independent predictors of ERAF following the single ablation procedure (Table 4).

After the initial catheter ablation of AF, LRAF was observed in 20.9% (40 of 191) of patients. Patient with LRAF and those without showed similar baseline data, except for

Table 4. Multivariate analysis assessing predictors of ERAF following AF ablation

Variable	Odds ratio	95% CI	P value
SDB	3.23	1.40 to 7.46	0.025
Duration of AF (years)	1.08	1.01 to 1.15	0.006

Abbreviations : AF, atrial fibrillation ; SDB, sleep-disordered breathing

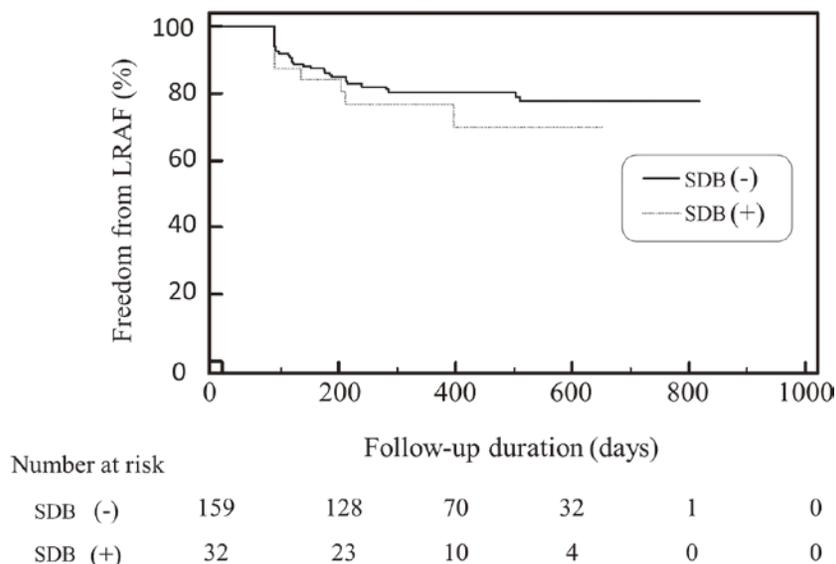


Fig. 1. A comparison of patients who had the late recurrence of atrial fibrillation (LRAF) patients with and without sleep-disordered breathing (SDB). There were no significant differences in the clinical success rates of single AF ablation between patients with and without SDB.

the longer AF history in patients with LRAF (7.7 ± 7.5 years vs. 5.3 ± 4.2 years, $P = 0.01$; Table 3). In contrast to the ERAF, the LRAF, when present or absent, did not cause a significant difference in the mean 4% ODI (5.7 ± 5.6 vs. 6.0 ± 5.6 ; $P = 0.78$) or the presence of SDB (20.0%, 8 of 40 patients vs. 15.9%, 24 of 151 patients; $P = 0.70$). During a median time of 328 days (mean 387.3 ± 213.8 days), Kaplan-Meier analysis showed that clinical outcomes (LRAF) of catheter ablation of AF were equivalent between patients with SDB and patients without SDB ($P = 0.42$; Fig. 1).

DISCUSSION

1. Main findings

The present study has given detailed insight into the relationship between SDB and the recurrence of AF after catheter ablation. Of patients who underwent catheter ablation of AF, 16.8% (32 of 191 patients) were found to have

SDB. In addition, SDB was more frequently observed in patients with ERAF than in patients without ERAF and was an independent predictor of ERAF following catheter ablation. Although the presence of SDB was an independent predictor of ERAF following catheter ablation of AF, the incidence of LRAF was similar in both groups.

2. The prevalence of SDB in patients with AF

In this study, SDB was suspected to be present in 16.8% of patients who underwent AF ablation, which is a lower percentage than in previous studies^{7,18}. One possible reason for difference in the prevalence of SDB is that SDB is observed more frequently in patients with obesity than in patients without obesity^{19,20}. The mean BMI was lower in the present study (24.4 kg/m^2) than in previous studies (29 to 35 kg/m^2)^{21,22}, which might partly explain the lower prevalence of SDB in the present study. Another possible reason for the prevalence of SDB differing is that it increases as patients become older²³. The subjects of the present study

having a lower mean age (55.7 years) than in previous studies (60 to 65 years) would lead to a lower SDB prevalence^{18,24}.

3. The recurrence of AF after ablation and SDB

In the present study, SDB was related to ERAF, which occurred within three days after catheter ablation of AF. A review of the recurrence of atrial tachyarrhythmias after catheter ablation, using definitions of the post-ablation procedure blanking period ranging from 72 hours to three months, found that the rate of early recurrence ranges from 6.7% to 65%²⁵. In the present study, the incidence of ERAF (37.1%) was similar to rates in these previous reports. The possible mechanisms of ERAF are a combination of an inflammatory response to thermal injury, a modification of the autonomic nervous system, and direct mechanical injury leading to changes in atrial myocardial conduction and refactoriness^{25,26}. On the other hand, SDB is known to influence structural changes of the heart due to tissue inflammation, hypoxemia, hypercapnia, and exaggerated negative intrathoracic pressure^{6,27,28}. Thus, ERAF, which is possibly caused by these atrial tissue changes with ablation, might occur more frequently in patients with SDB than in those without it.

Previous studies have been suggested that SDB is correlated with the development of AF and its recurrence after catheter ablation^{6,27,29}. However, in the present study SDB was associated with ERAF but not with LRAF (true AF recurrence). The mechanism of LRAF after catheter ablation has been shown to involve the electrical reconnection of isolated PVs, recovered conduction of LA linear ablation lesion, and non-PV foci^{30,31}, which are not involved in the mechanism of AF development in patients with SDB (hypoxemia, hypercapnia, and tissue inflammation). Furthermore, SDB does not increase AF recurrence after catheter ablation of AF and successful PV isolation is an independent predictor of recurrence of AF³². The main mechanism of LRAF after catheter ablation had been demonstrated to be the reconnection of PVs. Thus, the outcome of AF ablation is affected less by SDB than by the reconnection of PVs^{31,32}. Although SDB itself causes AF to progress and might be a mechanism for AF recurrence after catheter ablation, AF recurs when isolated PVs reconnect in the majority of patients with SDB³². To the best of our knowledge, the present study is the first to demonstrate that associations differ

between AF recurrence and SDB according to when AF recurs.

LIMITATIONS

The present study had several limitations. First, the recurrence rate in the present study was potentially better than recent registry because our judgement of the clinical outcome of the AF ablation on the basis of symptoms, serial electrocardiograms, and 24-hour ambulatory monitoring might have caused asymptomatic AF recurrence to be underestimated. Second, because only a small number of patients were evaluated at a single institution, the study might have a participant selection bias. Therefore, further studies with a larger number of patients should be performed to provide a more detailed analysis.

CONCLUSIONS

Although the presence of SDB was significantly related to ERAF after the catheter ablation of AF, it had no impact on LRAF and suggests different mechanisms of AF recurrence.

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