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Association between Inter-atrial Septum Motion and Persistent Atrial Fibrillation Recurrence after Catheter Ablation

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Background : Recently, several echocardiographic parameters have been proposed as predictors of the recurrence of persistent atrial fibrillation (psAF) after catheter ablation (CA). This study aimed to evaluate whether a decrease in inter-atrial septum (IAS) motion was associated with recurrence of psAF after CA.
Methods : A total of 103 consecutive patients who underwent CA for psAF were retrospectively reviewed. IAS motion was measured 48-72 hours before CA using transesophageal echocardiography. The primary outcome was AF recurrence beyond 3 months post-ablation. The follow-up period was 12 months after CA.
Results : PsAF recurrence after CA occurred in 29 (28.2 %) patients. The median value of IAS motion was 4.1 mm (interquartile range 2.4, 5.4), and the decline in IAS motion was an independent predictor of AF recurrence in a multivariate analysis of various models. Kaplan-Meier analysis showed that AF recurrence was significantly higher in the low IAS motion group (IAS motion $<$ 4.2, n = 47) than in the high IAS motion group (IAS motion $\geq$ 4.2, n = 52) (log-rank test, p = 0.001). A negative correlation was observed between IAS motion and left atrial volume (LAV), and conversely, a positive correlation was found between IAS motion and left atrial appendage flow velocity. The low IAS motion group had a higher left atrial pressure (LAP) than the high IAS motion group.
Conclusions : PsAF recurrence after CA was associated with reduced IAS motion. Decreased IAS motion could be an important finding suggestive of left atrial remodeling as well as LAV enlargement and increasing LAP. *Shinshu Med J 69 : 189—201, 2021*

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Key words : atrial fibrillation, catheter ablation, inter-atrial septum, transesophageal echocardiography, left atrial pressure

I Introduction

The effectiveness of pulmonary vein isolation (PVI) for atrial fibrillation (AF) has recently been established[1)2)]. Furthermore, with the advent of three-dimensional mapping and balloon ablation (BA), the success rate of PVI has also increased in patients with persistent AF (psAF). Superior vena cava (SVC) isolation[3)], creating block lines to the cavo-tricuspid isthmus (CTI), and complete isolation of the left atrial wall (box isolation) are other options for catheter ablation (CA) for psAF[4)5)]. However, AF may recur even after an acutely successful CA[6)]. In particular, psAF, in which remodeling of the left atrium is progressing, occurs more frequently after CA than paroxysmal

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AF[7]. In addition, several other factors have been associated with AF recurrence[8)-11)]. Electrical and structural remodeling of the left atrium is also thought to be involved[10].

In general, prior transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) to assess cardiac function and morphology are important for safely performing CA. Recently, several echocardiographic parameters have been proposed as predictors of recurrence of psAF after CA[12]. Left atrial diameter (LAD) and left atrial volume (LAV) can be easily measured by TTE, and LAD and LAV enlargements may act as predictors of AF recurrence after CA[13,14]. TEE is required to ensure the absence of left atrial thrombi prior to CA[15,16], and also provides a wide range of information. Determining the thickness of the inter-atrial septum (IAS), the location of the fossa ovalis, and the presence of an atrial septal defect (ASD) or patent foramen ovale (PFO) is essential for successful IAS puncture before PVI. The IAS is often observed to move with the heartbeat during TEE[17,18]. This movement may be affected by various factors, and Masai et al. have reported that a decline in this movement is correlated with an increase in left atrial pressure (LAP)[18]. The elevation of LAP occurs as the LAD expands and the LAV increases and the stretching stress may be a cause AF[19,20]. However, the direct relationship between IAS motion and psAF recurrence after CA is still unknown.

In this study, we observed and measured IAS motion on TEE performed before CA for psAF. We aimed to evaluate whether a decrease in IAS motion was associated with recurrence of AF after CA.

Ⅱ Materials and Methods

A Patient population

Patients who underwent their first CA for psAF at Shinshu University Hospital between August 2014 and May 2018 were retrospectively reviewed. The inclusion criterion was symptomatic, drug-refractory psAF. Patients with ASD, PFO, atrial septal aneurysm, moderate or more severe mitral valve disease, any cancer, severe chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease class 2 or more), and those on hemodialysis were excluded. AF duration was defined as the period from the day when AF was first documented to CA. Oral administration of amiodarone was discontinued 1 month before CA, and other anti-arrhythmia drugs (AAD) were discontinued at 1 week before CA. AAD were prescribed at discharge at the discretion of the attending cardiac electrophysiologist. IAS motion was examined in all patients before CA, as described below. The study protocol was approved by the ethics committee of Shinshu University Hospital (Apr 9, 2020, No.4705). Informed consent was obtained from as many patients as possible, which was limited by the retrospective study design. However, the information pertaining to this study was published on the homepage of our institution, and all study participants had the opportunity to refuse participation.

B Echocardiographic parameters and measurement of IAS motion

All patients underwent TTE and TEE during the AF rhythm at 48 to 72 hours before CA. TTE was performed using an iE 33 (Philips Medical Systems, Andover, MA) and X5-1 transducer probe (frequency 1-5 MHz). TEE was performed using iE 33 with an 8-2t transducer probe (frequency 1-5 MHz). All evaluations were performed in a physiological laboratory.

Left ventricular ejection fraction (LVEF), LAD, LAV, LAV index (LAVI) and the peak transmitral velocity/peak lateral mitral annular velocity (lateral E/e') ratio were measured by TTE. LVEF was measured using Simpson's method. LAV was determined according to the end-systolic maximum LAV before mitral valve opening on the 4-chamber and 2-chamber views using the biplane disc summation method. LAVI was determined by dividing the LAV by the body surface area according to the DuBois equation[21]. The lateral E/e' ratio was measured in accordance with the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging[22]. All values were calculated using the average of 5 heartbeats.

Left atrial appendage (LAA) flow velocity and IAS motion were measured using TEE. LAA flow velocity was measured at the LAA outlet using the pulse Doppler method. The flow velocity was selected as the maximum value among 5 heartbeats.

Patients who were in sinus rhythm during measurement of IAS motion were excluded from the study in order to focus on patients with true psAF. Accordingly, IAS motion was measured during AF rhythm in all patients. The IAS motion was defined as follows, with some modifications to the measurement method in the previous study[18] : (1) Using a two-dimensional system, the IAS was visualized in the mid-esophageal bicaval view (90°-120°). At this time, patients with ASD, PFO, or atrial septal aneurysm were excluded from this study. (2) An M-mode echocardiogram was drawn with the cursor passing through the central portion of the IAS on the 2D echocardiogram. (3) The amplitude of IAS motion was measured using the M-mode. (4) The IAS motion was defined as the distance from the most anterior position to the most posterior position over 5 cardiac cycles **(Fig. 1)** due to the large variation in the amplitude for each heartbeat during AF. All echocardiographic measurements were performed by two independent reviewers who were blinded to the ablation methods and the clinical outcomes. The variation between reviewers was small, with an inter-class correlation coefficient for the average IAS motion of 0.951 (95 % confidence interval [CI] : 0.944-0.975, $p < 0.001$; **Fig. 2**). Due to the low variance among the reviewers, the quantitative data from one reviewer was used for all figures and tables. Including the analyses performed by the other reviewers did not affect the statistical significance or the overall magnitude of the observed changes.

C　CA procedure and measurement of LAP

PVI was performed by radiofrequency CA (RFCA) using an irrigated catheter with contact force (ThermoCool ; Biosense Webster, CA). A three-dimensional mapping system was used to simulate the geometry of the left atrium and pulmonary veins. CTI block

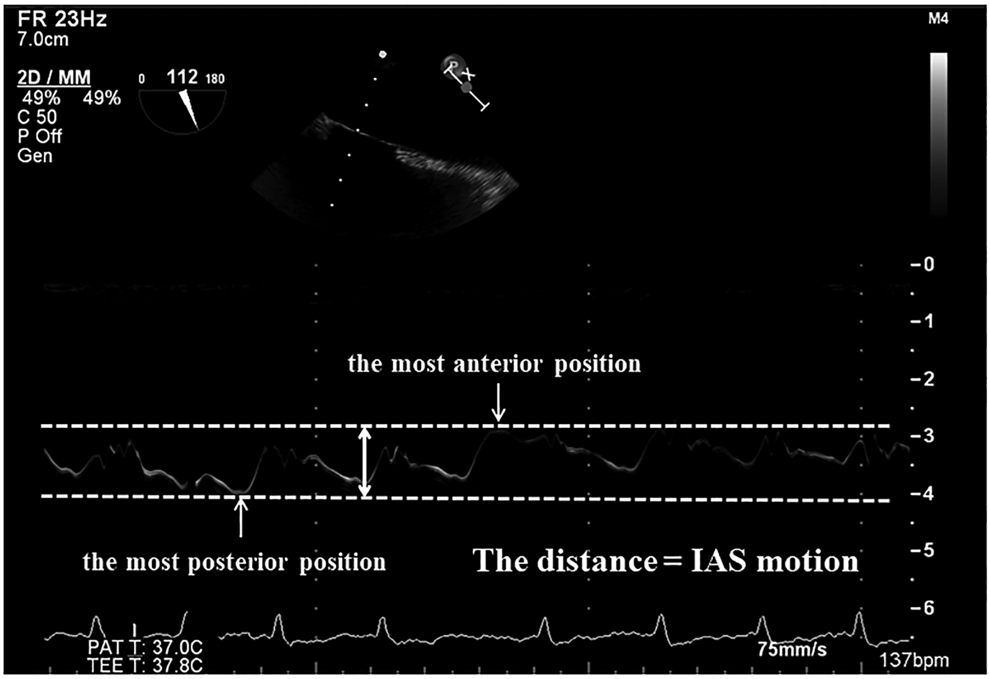

Fig. 1　Measurement of IAS motion

IAS motion was observed in the mid-esophageal bicaval view (90°-120°) with transesophageal echocardiography. An M-mode echocardiogram was drawn with the cursor passing through the central part of the IAS of the 2D echocardiogram. At this time, the IAS motion was depicted as the IAS amplitude. IAS motion was defined as the distance from the most anterior to the most posterior position during 5 cardiac cycles.
IAS, inter-atrial septum.

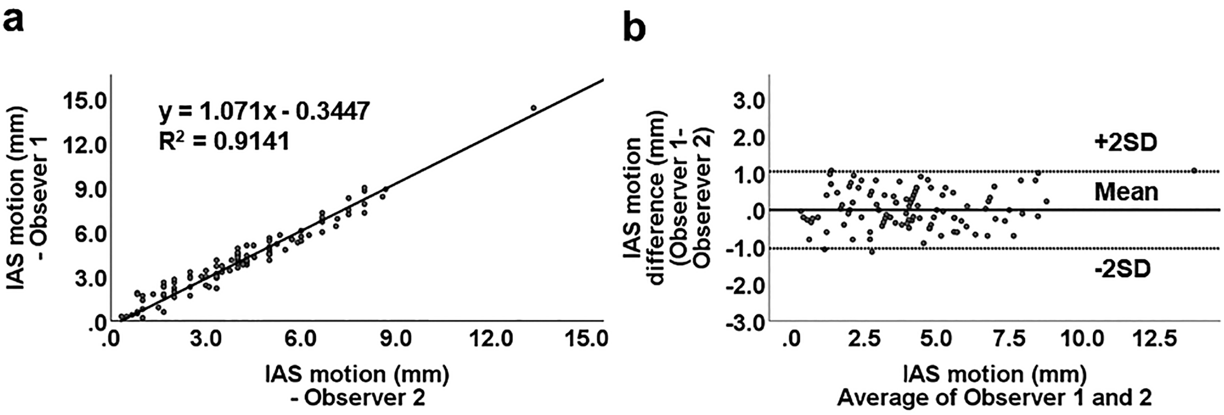

Fig. 2 Inter-observer variance of IAS motion

(a) Regression plot for determination of IAS motion by two echocardiographic observers blinded to the ablation methods and clinical outcome. There is a high correlation coefficient ($r = 0.951$; $p < 0.001$) with a slope close to 1.0. (b) Bland and Altman analysis showed no difference in IAS motion between the two observers. The solid horizontal line represents the mean difference between the two observers, and the dashed horizontal line represents the 95 % limits of agreement.
IAS, inter-atrial septum ; SD, standard deviation.

line ablation was performed if common atrial flutter was observed before or during CA. SVC isolation was performed if patients did not have sinus node dysfunction. Complete left atrial posterior wall isolation, complex fractionated atrial electrogram ablation and linear ablation of the mitral isthmus were not performed.

The patient was sedated with dexmedetomidine and thiopental, and respiratory management was performed using adaptive servoventilation (ASV). During the CA procedure, defibrillation was performed from the intra-cardiac electrode to restore sinus rhythm immediately before IAS puncture. After IAS puncture, a long sheath was inserted into the left atrium and the LAP under sinus rhythm was measured. Maximum LAP, minimum LAP and mean LAP were recorded using CardioLab (General Electric Medical Systems Inc., Milwaukee, WI).

The procedural endpoints were defined as follows : the entrance and exit blocks between each pulmonary vein and the left atrium were confirmed, no induction of sustained AF or atrial tachycardia by rapid atrial pacing and 10 μg isoproterenol infusion after PVI, and no documented dormant conduction between the pulmonary vein and the left atrium, induced by adenosine triphosphate. All patients received oral anticoagulation for at least 4 weeks before CA, which was subsequently continued for at least 12 months.

D Follow-up and endpoint

All patients were monitored regularly for 12 months after CA. Data from 12-lead electrocardiography (ECG) or Holter monitoring were obtained at follow-up visits every 3 months, or when the patient came to the hospital complaining of palpitations. AF recurrence was defined as AF or atrial tachycardia lasting more than 30 seconds, as confirmed by 12-lead ECG or Holter monitoring after CA. The three-month period immediately following the CA was excluded as a blanking period.

E Statistics

Normally distributed quantitative variables according to the Shapiro-Wilk test were presented as the mean ±standard deviation (SD), while non-normally distributed variables were presented as the median of the interquartile range (IQR). Quantitative variables were compared using either Student's t-test or the Mann-Whitney test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant. Multiple logistic regression analysis using the stepwise method was used to identify predictors of AF recurrence. Receiver-operating characteristic (ROC) curve analysis was performed to assess the optimal cut-off value of IAS motion for predicting AF recurrence. The

Kaplan-Meier method was employed to estimate the cumulative event rates of AF recurrence. Spearman's rank correlation coefficient was calculated to determine the relationship between IAS motion and other echocardiographic parameters and LAP. All analyses were performed using SPSS statistical software, version 24.0 (IBM Corp., Armonk, NY).

Ⅲ Results

A Patient characteristics and IAS motion

A total of 103 patients were enrolled in this study. AF recurrence after CA occurred in 29 patients (28.2 %) during the follow-up period. The median value of IAS motion was 4.1 mm (IQR, 2.4, 5.4). **Table 1** summarizes the baseline characteristics. The cohort was divided into two groups (high IAS motion group; IAS motion ≥ 4.2 mm, n = 47 and low IAS motion group; IAS motion < 4.2 mm, n = 56) based on the ROC curve analysis described later. Although the CHA2DS2-Vasc score was significantly higher in the low IAS motion group, the presence of factors related to the CHA2DS2-Vasc score such as age, female sex, and diabetes mellitus, did not differ between the two groups. The brain natriuretic peptide and C-reactive protein levels were significantly higher in the low IAS motion group. LAV and LAVI was significantly larger in the low IAS motion group, but LAD showed no significant difference. The differences in lateral E/e' and LAA flow velocity were statistically significant. Amiodarone, beta-blockers and calcium antagonists were used during the perioperative period, but the rates of their use did not differ between the two groups. There were no significant differences between the two groups in the number of patients undergoing PVI alone or those undergoing additional SVC isolation and/or CTI block line. Mean arterial pressure, maximum LAP, and mean LAP were higher in the low IAS motion group while there was no difference in minimum LAP values.

B Association between IAS motion and AF recurrence

Logistic regression analysis was performed to determine the factors related to psAF recurrence **(Table 2)**. High body mass index (BMI), large LAV, decreased IAS motion, increased maximum LAP, and increased mean LAP were significantly associated with AF recurrence. Low lateral E/e' and increased LAVI tended to be higher in the patients that developed AF recurrence. There was no relationship between AF recurrence after CA and the type of antiarrhythmic drugs prescribed at discharge or the ablation methods. A multivariate analysis performed using various models adjusted for BMI, LAV, systolic LAP, and mean LAP showed that decreased IAS motion was independently associated with AF recurrence after CA. ROC curve analysis for IAS motion's ability to predict AF recurrence was performed and compared with that of LAV **(Fig. 3)**. This analysis showed that the optimal cut-off value for IAS motion was 4.2 mm (area under the curve [AUC]: 0.75, 95 % CI 0.64-0.85, $p = 0.001$), with a specificity and sensitivity of 89.3 % and 56.1 %, respectively. The AUC for IAS motion exceeded that for LAV (0.75 vs. 0.66). **Fig. 4** shows the AF recurrence-free curve for the high and low IAS motion groups. During follow-up, the high IAS motion group had fewer AF recurrences than the low IAS motion group ($p = 0.001$, log rank test).

C Relationship between IAS motion and other echocardiographic parameters and LAP

A comparison of IAS motion and parameters obtained by TTE and TEE was performed as shown in **Fig. 5**. IAS motion was not correlated with LAD (correlation coefficient; $r = -0.11$, $p = 0.26$), but showed a negative correlation with LAV and lateral E/e' ($r = -0.26$, $p = 0.01$; and $r = -0.24$, $p = 0.014$, respectively). Conversely, a positive correlation was found between LAA flow velocity and IAS motion ($r = 0.30$, $p = 0.002$).

In addition, the relationship between IAS motion and LAP measured during CA was also examined. In patients with reduced IAS motion, the mean LAP was increased; that is, IAS motion was negatively correlated with systolic LAP and mean LAP ($r = -0.31$, $p = 0.016$; and $r = -0.39$, $p = 0.002$, respectively). The mean LAP in the low and high IAS motion groups were 12 mmHg (IQR, 9, 14) and 9 mmHg (IQR, 5, 11), respectively, showing a significant intergroup difference **(Fig. 6)**.

Table 1　Baseline characteristics

	All patients (n＝103)	IAS motion≧4.2 mm (n＝47)	IAS motion＜4.2 mm (n＝56)	p-value
Age (years)	64 (58, 69)	61 (48, 69)	65 (61, 69)	0.066
Female sex	15 (14.6)	7 (14.9)	8 (14.3)	1.00
Body mass index (kg/m^2)	24.7±3.4	24.1±3.8	25.3±3.1	0.20
Hypertension	55 (53.4)	20 (42.6)	35 (62.5)	0.053
Congestive heart failure	14 (13.6)	6 (12.8)	8 (14.3)	1.00
Diabetes mellitus	19 (18.4)	5 (10.6)	14 (25.0)	1.00
Previous cerebral infarction	10 (9.7)	2 (6.9)	8 (10.8)	0.21
Coronary artery disease	6 (5.8)	3 (6.4)	3 (5.4)	0.83
Peripheral artery disease	2 (1.9)	1 (1.8)	1 (2.1)	1.00
CHA_2DS_2-Vasc score	1 (1, 2)	1 (0, 2)	2 (1, 3)	0.005
AF Duration (month)	36 (12, 72)	24 (12, 60)	36 (12, 72)	0.76
BNP (pg/ml)	99.7 (54.6, 181)	69.4 (34.3, 142)	115 (66.1, 203)	0.012
eGFR (ml/min/1.73m^2)	66.0 (57.0, 72.0)	64.0 (59.0, 73.0)	66.5 (54.3, 71.5)	0.98
C-reactive protein (mg/dl)	0.05 (0.03, 0.10)	0.04 (0.02, 0.07)	0.06 (0.04, 0.13)	0.012
Left atrial diameter (mm)	42.0 (38.0, 45.0)	39.5 (36.0, 44.5)	42.5 (39.3, 45.3)	0.099
Left atrial volume (ml)	75.0 (52.1, 94.0)	60.1 (47.0, 80.0)	81.0 (59.7, 101)	0.001
Left atrial volume index (ml/m^2)	40.7 (29.1, 51.2)	31.3 (28.2, 47.8)	44.1 (32.6, 53.3)	0.002
LVEF (%)	62.1±11.9	60.9±9.1	63.1±13.0	0.41
Lateral E/e'	7.20 (5.70, 8.67)	6.30 (5.20, 7.55)	7.60 (6.43, 10.6)	0.001
LAA flow velocity (cm/s)	35.7 (24.3, 56.9)	43.6 (30.0, 68.5)	31.0 (21.5, 41.0)	0.006
IAS motion (mm)	4.1 (2.4, 5.4)	5.5 (4.6, 7.0)	2.6 (1.7, 3.6)	＜0.001
Ineffective AAD before CA				
Amiodarone	16 (15.5)	8 (17.0)	8 (14.3)	0.79
Beta- blocker	51 (49.5)	23 (48.9)	28 (50.0)	1.00
Calcium antagonist	48 (46.6)	18 (38.3)	30 (53.6)	0.17
ACE-I/ARB	45 (43.7)	17 (36.2)	28 (50.0)	0.17
AAD at discharge				
Amiodarone	14 (13.6)	5 (10.6)	9 (16.1)	0.57
Beta-blocker	60 (58.3)	25 (53.2)	35 (62.5)	0.42
Calcium antagonist	40 (38.8)	14 (29.8)	26 (46.4)	0.11
ACE-I/ARB	44 (42.7)	16 (34.0)	28 (50.0)	0.11
Ablation method				
PVI only	35 (34.0)	17 (36.2)	18 (32.2)	0.67
PVI＋SVCI	42 (40.8)	17 (36.2)	25 (44.6)	0.43
PVI＋CTI block line	8 (7.8)	4 (8.5)	4 (7.1)	0.80
PVI＋SVCI＋CTI block line	18 (17.5)	9 (19.1)	9 (16.1)	0.68
Procedure findings				
Mean arterial pressure (mmHg)	90 (80, 101)	81 (75, 95)	92 (87, 101)	0.017
Heart rate (bpm)	62 (55, 71)	58 (51, 66)	64 (59, 73)	0.082
Maximum LAP (mmHg)	18 (15, 24)	17 (13, 21)	19 (17, 24)	0.045
Minimum LAP (mmHg)	3 (1, 5)	2 (0, 4)	4 (2, 5)	0.089
Mean LAP (mmHg)	10 (8, 13)	9 (5, 11)	12 (9, 14)	0.010

IAS, interatrial septum ; AF, atrial fibrillation ; BNP, brain natriuretic peptide ; eGFR, estimated glomerular filtration rate ; LVEF, left ventricular ejection fraction ; E/e', early diastolic left ventricular filling velocity / peak early diastolic mitral annulus velocity ; LAA, left atrial appendage ; AAD, anti-arrhythmia drug ; ACE-I, angiotensin converting enzyme-inhibitor ; ARB, angiotensin II receptor blocker ; PVI, pulmonary vein isolation ; SVCI, superior vena cava isolation ; CTI, cavo tricuspid isthmus ; LAP, left atrial pressure.

Table 2　Logistic regression analysis

	Univariate		Multivariate					
			Model 1		Model 2		Model 3	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value	OR (95 % CI)	p-value	OR (95 % CI)	p-value
Age	1.03 (0.98-1.08)	0.21						
Female sex	1.33 (0.41-4.30)	0.63						
BMI	1.14 (1.00-1.31)	0.045	1.13 (0.97-1.31)	0.12				
Hypertension	1.10 (0.47-2.56)	0.83						
Congestive heart failure	1.52 (0.39-5.88)	0.55						
Diabetic mellitus	1.12 (0.37-3.45)	0.84						
Previous cerebral infarction	1.64 (0.33-8.33)	0.55						
CHA_2DS_2-Vasc score	1.32 (0.91-1.89)	0.15						
AF Duration	1.03 (0.94-1.13)	0.56						
BNP	1.00 (1.00-1.00)	0.59						
eGFR	1.03 (0.99-1.07)	0.12						
Left atrial diameter	1.37 (0.71-2.67)	0.35						
Left atrial volume	1.02 (1.00-1.04)	0.020	1.01 (1.00-1.03)	0.17	1.02 (0.99-1.05)	0.21	1.02 (0.99-1.05)	0.16
Left atrial volume Index	1.03 (1.00-1.06)	0.061						
LVEF	1.03 (0.99-1.07)	0.13						
Lateral E/e'	0.82 (0.68-1.00)	0.053						
LAA flow velocity	0.99 (0.97-1.01)	0.24						
IAS motion	0.69 (0.55-0.88)	0.003	0.66 (0.49-0.88)	0.005	0.57 (0.36-0.88)	0.012	0.58 (0.37-0.91)	0.017
AAD at discharge								
Amiodarone	0.47 (0.15-1.47)	0.20						
Beta-blocker	0.84 (0.35-2.00)	0.69						
Calcium antagonist	1.16 (0.48-2.78)	0.74						
ACE-I/ARB	0.76 (0.32-1.83)	0.54						
Ablation method								
PVI only	1.57 (0.64-3.80)	0.32						
PVI + SVCI	0.57 (0.24-1.36)	0.20						
PVI + CTI block line	0.53 (0.18-1.36)	0.25						
PVI + SVCI + CTI block line	0.83 (0.14-4.73)	0.83						
Systolic LAP	1.12 (1.02-1.22)	0.017			1.09 (0.97-1.22)	0.15		
Diastolic LAP	1.16 (0.96-1.41)	0.13						
Mean LAP	1.16 (1.01-1.33)	0.038					1.15 (0.96-1.37)	0.13

OR, Odds ratio ; CI, confidence interval ; BMI, Body mass index ; AF, atrial fibrillation ; BNP, brain natriuretic peptide ; eGFR, estimated glomerular filtration rate ; LVEF, left ventricular ejection fraction ; E/e', early diastolic left ventricular filling velocity / peak early diastolic mitral annulus velocity ; LAA, left atrial appendage ; IAS, interatrial septum ; AAD, anti-arrhythmia drug ; ACE-I, angiotensin converting enzyme-inhibitor ; ARB, angiotensin II receptor blocker ; PVI, pulmonary vein isolation ; SVCI, superior vena cava isolation ; CTI, cavo tricuspid isthmus ; LAP, left atrial pressure.

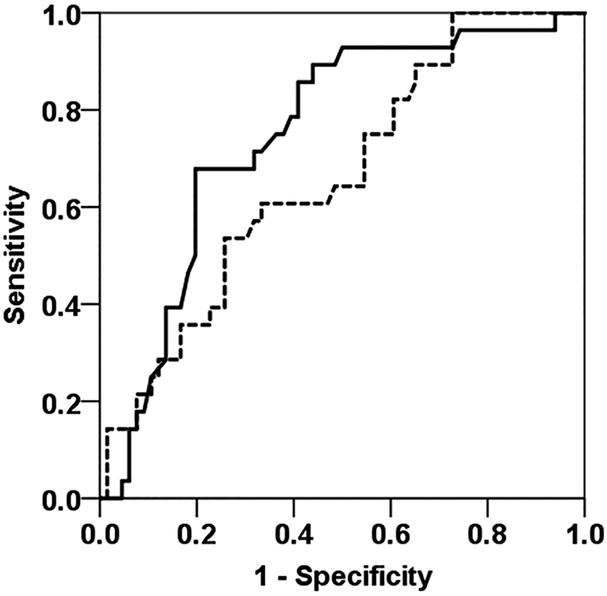

Fig. 3 ROC curve analysis for IAS motion and LAV
The optimal cut-off value for IAS motion was 4.2 mm (the specificity and sensitivity were 89.3 % and 56.1 %, respectively). The area under the curve (AUC) of IAS motion was 0.75 (95 % CI 0.64-0.85, p = 0.001). The AUC for IAS motion exceeded that for LAV (0.75 vs. 0.66).
ROC, receiver-operating characteristic ; IAS, inter-atrial septum ; LAV, left atrial volume.

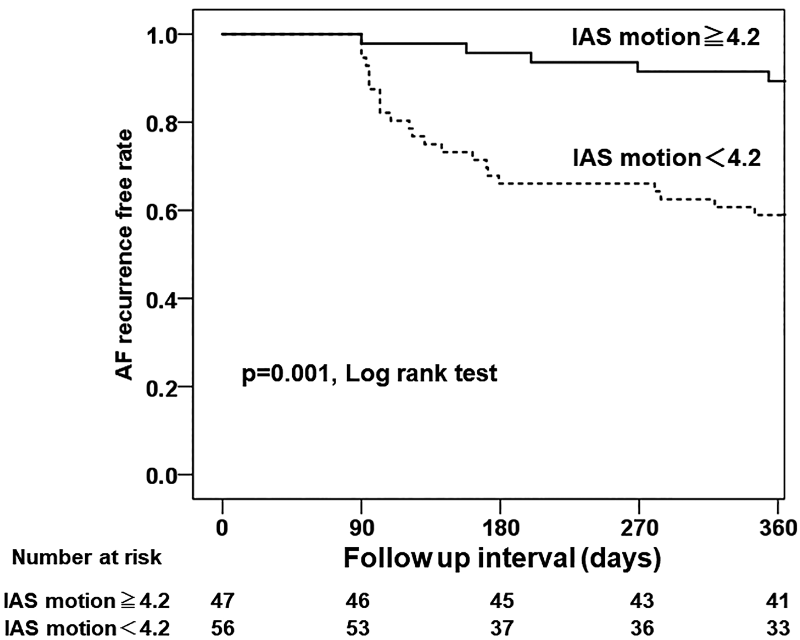

Fig. 4 Kaplan-Meier analysis for the probability of AF recurrence after CA according to IAS motion
The solid line represents the high IAS motion group, and the dashed line represents the low IAS motion group.
AF, atrial fibrillation ; CA, catheter ablation ; IAS, inter-atrial septum.

Ⅳ Discussion

This study showed that a decline in IAS motion was independently associated with AF recurrence after CA. In addition, IAS motion was significantly correlated with other echocardiographic parameters, such as LAV and E/e', which are associated with AF recurrence. Moreover, patients with decreased IAS motion also had a higher LAP measured during CA than those with preserved IAS motion. Our results suggest that the decrease in IAS motion reflected the increase in LAP, which might increase the risk of AF recurrence following CA.

The IAS is a membrane-like structure that separates the left and right atria. TTE and TEE studies have confirmed the amplitude movement of the IAS

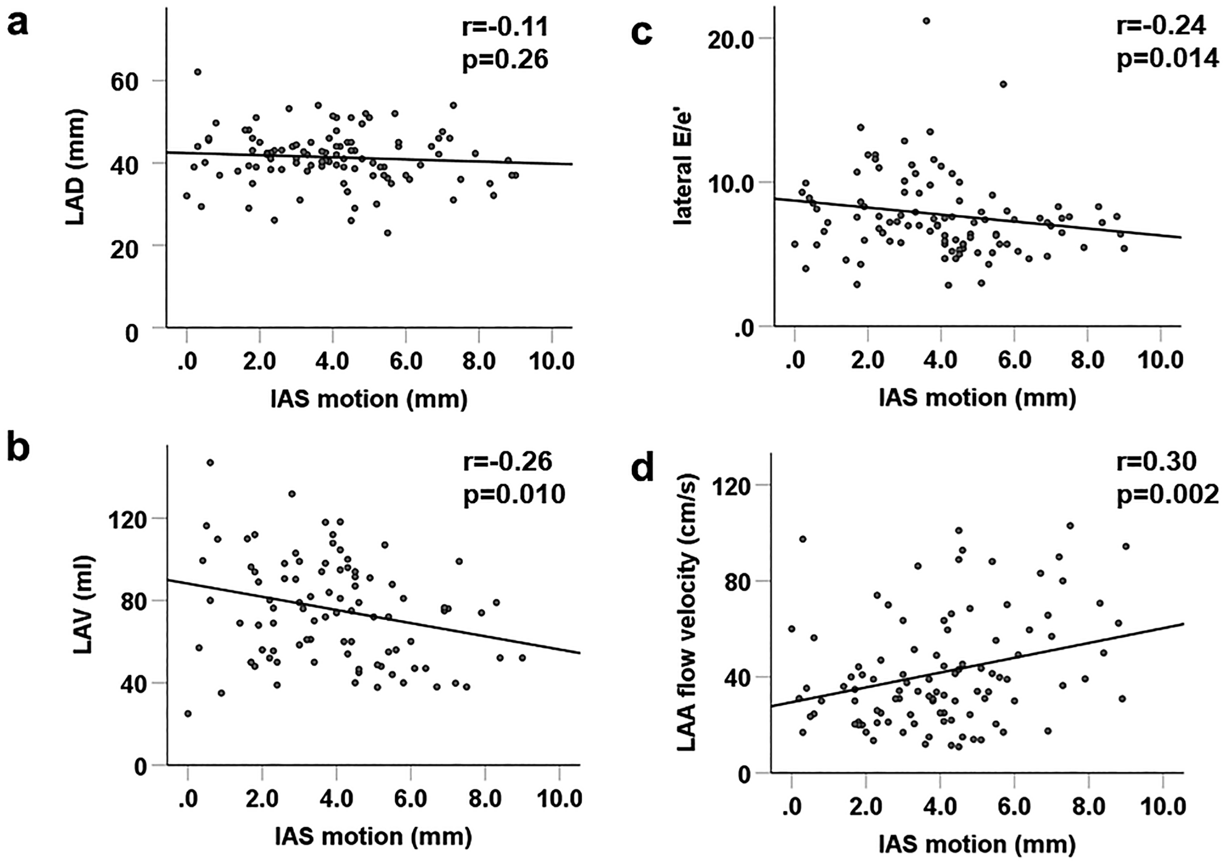

Fig. 5 Associations between IAS motion and other echocardiographic parameters

(a) IAS motion and LAD. (b) IAS motion and LAV. (c) IAS motion and lateral E/e'. (d) IAS motion and LAA velocity flow. IAS motion had a negative correlation with LAV and lateral E/e' ($r=-0.26$, $p=0.01$; and $r=-0.24$, $p=0.014$, respectively), and a positive correlation with LAA flow velocity ($r=0.30$, $p=0.002$).

IAS, inter-atrial septum ; E/e', early diastolic left ventricular filling velocity / peak early diastolic mitral annulus velocity ; LAA, left atrial appendage ; LAD, left atrial diameter ; LAV, left atrial volume.

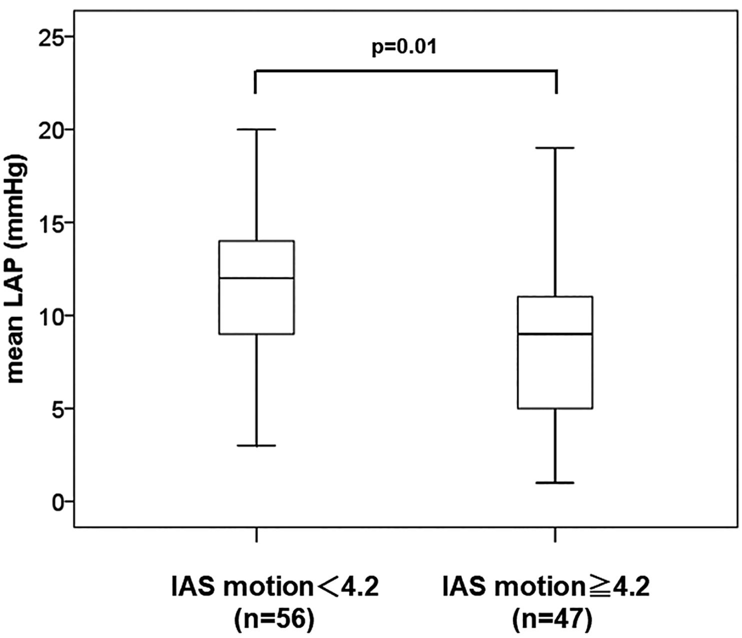

Fig. 6 Comparison of mean LAP according to IAS motion

The mean LAP was significantly higher in the low IAS motion group than in the high IAS motion group (12 mmHg vs. 9 mmHg, respectively). Horizontal lines represent the median, boxed areas are the interquartile range, and vertical whiskers represent the 10 %-90 % range.

IAS, inter-atrial septum ; LAP, left atrial pressure.

during the cardiac cycle[23]. Previously, Tei et al. suggested that there was a decrease in IAS activity in patients with atrial overload[17]. IAS motion has been reported to be influenced by various factors and might reflect the compliance and pressure of the left atrium[6]. The normal values for IAS motion are not clear ; Masai et al. have reported that IAS motion in patients with AF rhythm was 7.6 mm to 12.2 mm, and motion$<$10 mm as low IAS motion[18]. This study defined IAS motion$<$4.2 mm as a decrease in IAS motion. This threshold was supported by an ROC curve analysis for prediction of AF recurrence. In addition, the Bland and Altman analysis showed little difference in the values of IAS motion between the two echocardiographic reviewers, suggesting that the IAS motion measurement had high inter-rater reliability.

Several reports have described the association between echocardiographic parameters, including expansion of LAD and LAV[13)24)], and recurrence of AF after CA[12]. LAA flow velocity has been evaluated as a surrogate marker of left atrial function. Previous studies have reported a higher rate of AF recurrence after CA in patients with reduced LAA flow velocity[25)26)]. Studies have also shown that increased E/e' reflects decreased left ventricular diastolic function and increased LAP[27)28)]. These parameters may indirectly reflect left atrial structural remodeling and LAP elevation. In this study, IAS motion was negatively correlated with LAD, LAV, and E/e', and positively correlated with LAA flow velocity. These findings suggest that progression of left atrial structural remodeling and an increase in LAP might indicate a decrease in IAS motion.

LAP measured invasively via IAS puncture has been reported as an independent predictor of AF recurrence after PVI[29]. Park et al. found that elevated LAP was closely associated with electro-anatomical remodeling of the left atrium and was an independent predictor of AF recurrence after CA[30]. Moreover, LAP measured during trans-septal puncture has also been shown to be an independent predictor of AF recurrence after cryoablation with second-generation cryoballoons[19]. In this study, LAP measurements were performed during CA in sedated patients and could have been affected if the patient had sleep apnea syndrome ; however, the use of ASV may mean that this is not an issue. Patients with reduced IAS motion have reportedly higher LAP[18]. Even in our study, the average LAP values were significantly increased in patients with reduced IAS motion. Thus, the decrease in IAS motion may be an indicator of LAP elevation.

Cases of psAF with LAV enlargement and LAP increase are often accompanied by such electrical remodeling as spreading of the low voltage area (LVA) of the left atrium[30)-32)]. Since left atrial LVA can be the arrhythmogenic substrate and circuit of atrial tachycardia, its expansion may lead to AF recurrence after CA. To summarize, the following mechanism can be considered : (1) Persistence of AF. (2) Enlargement of LAV. (3) Increase in LAP. (4) Progress of structural and electrical remodeling of left atrium. (5) Increased possibility of AF recurrence.

Since an enlargement of LAV and increase in LAP were observed in the group with reduced IAS motion in our study, decreased IAS motion might be considered to reflect the steps (2) and (3).

A　Clinical implications

Estimating the state of left atrial remodeling prior to CA is very important for predicting the likelihood of recurrence, determining the appropriate ablation strategy, and managing patients post-ablation. Although LAD and LAV measured by TTE are useful in estimating left atrial remodeling, we have shown that IAS motion was more useful for predicting AF recurrence. Elevated LAP is another useful indicator of left atrial remodeling, but its measurement must be made invasively during CA. IAS motion, conversely, can be easily measured with TEE before CA. In other words, measuring IAS motion may be useful for prediction of left atrial remodeling before CA.

B　Limitations

This study had several limitations. First, this was a small observational study ; therefore, sampling bias may be present. Validation in prospective trials with larger cohorts is needed. Second, while TEE was essential for measuring IAS motion, it is an invasive procedure and its use is decreasing due to the development of contrast-enhanced computed tomography and the prevalence of direct oral anticoagulants[33]. However, the risk of thrombosis during oral anticoagulant therapy is reported to be about 0.6 %[34], and thrombosis of the left atrium is a contraindication for CA of AF. Therefore TEE is still being performed prior to CA at many institutions. Being able to predict the recurrence of psAF by simple TEE IAS motion assessment would be of great clinical significance. Third, IAS motion and LAP could not be measured simultaneously. If IAS motion were measured by TEE during the CA, the correlation with LAP would have been more apparent. However performing TEE during the CA was difficult. Lastly, several ablation methods were used in this study; nevertheless, in all cases, the same conditions were eventually assessed at the end of the procedure, i.e., AF was not induced by isoproterenol administration and atrial burst pacing after ablation. No significant differences were found between the ablation methods, such as performing additional SVC isolation and/or CTI block lines, and the recurrence rate in this study.

V **Conclusions**

This study showed that AF recurrence after CA was associated with lower IAS motion. Our results indicate that the decrease in IAS motion may represent an important finding suggestive of left atrial remodeling as well as enlargement of LAV and increasing LAP.

References

1) January CT, Wann LS, Alpert JS, et al: 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 130: e199-267, 2014

2) Jaïs P, Cauchemez B, Macle L, et al: Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation 118: 2498-2505, 2008

3) Chang HY, Lo LW, Lin YJ, et al: Long-term outcome of catheter ablation in patients with atrial fibrillation originating from the superior vena cava. J Cardiovasc Electrophysiol 23: 955-961, 2012

4) Saad EB, Slater C: Complete isolation of the left atrial posterior wall (box lesion) to treat longstanding persistent atrial fibrillation. J Atr Fibrillation 7: 1174, 2014

5) Sanders P, Hocini M, Jaïs P, et al: Complete isolation of the pulmonary veins and posterior left atrium in chronic atrial fibrillation. Eur Heart J 28: 1862-1871, 2007

6) Ganesan AN, Shipp NJ, Brooks AG, et al: Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc 2: e004549, 2013

7) Atar D, Berge E, Le Heuzey JY, et al: The association between patterns of atrial fibrillation, anticoagulation, and cardiovascular events. Europace 22: 195-204, 2020

8) Jiang H, Wang W, Wang C, Xie X, Hou Y: Association of pre-ablation level of potential blood markers with atrial fibrillation recurrence after catheter ablation: a meta-analysis. Europace 19: 392-400, 2017

9) Yanagisawa S, Inden Y, Kato H, et al: Decrease in B-type natriuretic peptide levels and successful catheter ablation for atrial fibrillation in patients with heart failure. Pacing Clin Electrophysiol 39: 225-234, 2016

10) Pump A, Di Biase L, Price J, et al: Efficacy of catheter ablation in nonparoxysmal atrial fibrillation patients with severe enlarged left atrium and its impact on left atrial structural remodeling. J Cardiovasc Electrophysiol 24: 1224-1231, 2013

11) Rotter M, Jaïs P, Garrigue S, et al: Clinical predictors of noninducibility of sustained atrial fibrillation after pulmonary vein isolation. J Cardiovasc Electrophysiol 16: 1298-1303, 2005

12) Ejima K, Kato K, Arai K, et al: Impact of atrial remodeling on the outcome of radiofrequency catheter ablation of paroxysmal atrial fibrillation. Circ J 78: 872-877, 2014

13) Njoku A, Kannabhiran M, Arora R, et al : Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation : a meta-analysis. Europace 20 : 33-42, 2018
14) Liao YC, Liao JN, Lo LW, et al : Left atrial size and left ventricular end-systolic dimension predict the progression of paroxysmal atrial fibrillation after catheter ablation. J Cardiovasc Electrophysiol 28 : 23-30, 2017
15) Wu M, Gabriels J, Khan M, et al : Left atrial thrombus and dense spontaneous echocardiographic contrast in patients on continuous direct oral anticoagulant therapy undergoing catheter ablation of atrial fibrillation : Comparison of dabigatran, rivaroxaban, and apixaban. Heart Rhythm 15 : 496-502, 2018
16) Gunawardene MA, Dickow J, Schaeffer BN, et al : Risk stratification of patients with left atrial appendage thrombus prior to catheter ablation of atrial fibrillation : An approach towards an individualized use of transesophageal echocardiography. J Cardiovasc Electrophysiol 28 : 1127-1136, 2017
17) Tei C, Tanaka H, Kashima, et al : Real-time cross-sectional echocardiographic evaluation of the interatrial septum by right atrium-interatrial septum-left atrium direction of ultrasound beam. Circulation 60 : 539-546, 1979
18) Masai K, Kishima H, Takahashi S, et al : Interatrial septal motion as a novel index to predict left atrial pressure. Heart Vessels 33 : 762-769, 2018
19) Evranos B, Kocyigit D, Gurses KM, et al : Increased left atrial pressure predicts recurrence following successful cryoablation for atrial fibrillation with second-generation cryoballoon. J Interv Card Electrophysiol 46 : 145-151, 2016
20) Linhart M, Lewalter T, Mittmann-Braun EL, et al : Left atrial pressure as predictor for recurrence of atrial fibrillation after pulmonary vein isolation. J Interv Card Electrophysiol 38 : 107-114, 2013
21) Ujino K, Barnes ME, Cha SS, et al : Two-dimensional echocardiographic methods for assessment of left atrial volume. Am J Cardiol 98 : 1185-1188, 2006
22) Nagueh SF, Smiseth OA, Appleton CP, et al : Recommendations for the evaluation of left ventricular diastolic function by echocardiography : An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 29 : 277-314, 2016
23) Hołda MK, Krawczyk-Ożóg A, Koziej M, et al : Mid-esophageal bicaval versus short-axis view of interatrial septum in two-dimensional transesophageal echocardiography for diagnosis and measurement of atrial septal pouches. Echocardiography 35 : 827-833, 2018
24) Winkle RA, Jarman JW, Mead RH, et al : Predicting atrial fibrillation ablation outcome : The CAAP-AF score. Heart Rhythm 13 : 2119-2125, 2016
25) Spittler R, Bahlke F, Hoffmann BA, et al : Predictors of successful complex catheter ablation for persistent atrial fibrillation despite failure of targeted procedural arrhythmia termination. J Cardiovasc Electrophysiol 30 : 1026-1035, 2019
26) Hori Y, Nakahara S, Nishiyama N, et al : Impact of low-voltage zones on the left atrial anterior wall on the reduction in the left atrial appendage flow velocity in persistent atrial fibrillation patients. J Interv Card Electrophysiol 56 : 299-306, 2019
27) Lavine SJ, Sivaganam K, Strom JA : Indexing peak rapid filling velocity to both relaxation and filling volume to estimate left ventricular filling pressures. Eur Heart J Cardiovasc Imaging 20 : 646-654, 2019
28) Reddy YNV, Obokata M, Egbe A, et al : Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. Eur J Heart Fail 21 : 891-900, 2019
29) Bergau L, Vollmann D, Luthje L, et al : Measurement of left atrial pressure is a good predictor of freedom from atrial fibrillation. Indian Pacing Electrophysiol J 14 : 181-193, 2014
30) Park J, Joung B, Uhm JS, et al : High left atrial pressures are associated with advanced electroanatomical remodeling of left atrium and independent predictors for clinical recurrence of atrial fibrillation after catheter ablation. Heart Rhythm 11 : 953-960, 2014
31) Ammar-Busch S, Buiatti A, Tatzber A, et al : Predictors of low voltage areas in persistent atrial fibrillation : is it

really a matter of time? J Interv Card Electrophysiol 57 : 345–352, 2020

32) Kumagai Y, Iwayama T, Arimoto T, et al : Biatrial volume, estimated using magnetic resonance imaging, predicts atrial fibrillation recurrence after ablation. Pacing Clin Electrophysiol 41 : 1635–1642, 2018

33) Munir S, Chang JH, Salahudeen SR, et al : Atrial thrombi detection prior to pulmonary vein isolation : diagnostic accuracy of cardiac computed tomography versus transesophageal echocardiography. Cardiol J 22 : 576–582, 2015

34) Göldi T, Krisai P, Knecht S, et al : Prevalence and management of atrial thrombi in patients with atrial fibrillation before pulmonary vein isolation. JACC Clin Electrophysiol 5 : 1406–1414, 2019

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