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Combined Assessment of Left Atrial Volume Parameters for Predicting Recurrence of Atrial Fibrillation Following Pulmonary Vein Isolation in Patients with Paroxysmal Atrial Fibrillation

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Running Head: Combined LA Assessment for PAF

Abstract

Objectives: Our aim was to test the hypothesis that comprehensive simplified left atrial (LA) assessment derived from routine echocardiography may be more useful than assessment of LA volume alone for predicting atrial fibrillation (AF) recurrence after pulmonary vein isolation (PVI).

Methods: We studied 156 patients with paroxysmal AF (PAF) who had undergone PVI. Echocardiography was performed within two days before PVI. Maximum (Max-LAVi) and minimum LA volume index (Min-LAVi) were calculated with the biplane modified Simpson's method, and then normalized to the body surface area. On the basis of previous findings, the pre-defined cutoff value of Max-LAVi for AF recurrence was set at Max-LAVi ≥ 34mL/m^2. ΔLA volume index (ΔLAVi) was also calculated as Max-LAVi minus Min-LAVi. The follow-up period after PVI was 24 months.

Results: AF recurrence was observed in 35 patients. Multivariate logistic regression analysis showed that ΔLAVi (odds ratio [OR]: 1.131; 95% confidence interval [CI]: 1.057-1.221; $p<0.001$) was an independent predictor of AF recurrence. Sequential logistic regression models for predicting AF recurrence revealed that a model based on clinical variables including age, gender and AF duration ($\chi2=1.65$) was improved by the addition of Max-LAVi ≥ 34mL/m^2 ($\chi2=13.8$; $p<0.001$), and further improved by the addition of ΔLAVi ($\chi2=18.2$; $p=0.036$). Of note is that only 1.02 ± 0.10 minutes per patient was needed to obtain a comprehensive LA assessment that included Max-LAVi, Min-LAVi, and ΔLAVi.

Conclusion: This easy-to-use comprehensive simplified LA approach from routine echocardiography may well have clinical implications for better management of PAF patients.

Key words; atrial fibrillation; echocardiography; left atrium

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia observed in clinical practice and is associated with several important adverse clinical outcomes, including impairment of quality of life, embolism events, heart failure (HF), and death[1-5]. Pulmonary vein isolation (PVI) has become a common treatment for patients with symptomatic, drug-resistant AF to restore normal sinus rhythm and significantly improve symptoms and quality of life. Since the success rate of PVI, defined as no AF relapse, of up to 70% for patients with paroxysmal AF (PAF) and around 50% for those with persistent AF[6], AF recurrence is common and a significant number of patients require repeated procedures[7]. Multiple factors have been identified to account for AF recurrence after PVI, such as age, AF duration, left ventricular (LV) function, left atrial (LA) size, and comorbidities such as hypertension, diabetes mellitus, obesity, and obstructive sleep apnea. Of these factors, LA size, which contributes to structural remodeling and therefore to atrial fibrosis, has been found to be strongly associated with AF recurrence after PVI[8-10]. In addition, LA volume is reportedly a robust predictor for recurrence of AF after PVI[2,11-14], because using LA dilation and LA dimension may be problematic since the former can be asymmetric and the latter tends to underestimate~~s~~ and therefore not reflect actual LA size. Recently, several studies have indicated that LA strain as assessed by means of two-dimensional (2-D) speckle-tracking echocardiography, has a higher predictive value for AF recurrence after PVI than LA size obtained from conventional echocardiography[15-19]. This is because LA strain can reflect LA reservoir, conduit and booster pump functions, and it correlates with the extent of LA fibrosis. Although its usefulness is quite obvious, assessment by means of LA speckle-tracking strain imaging is not yet a routine echocardiographic examination, and simple additive predictive parameters for AF recurrence after PVI in addition to LA volume from routine echocardiography may be needed for better management of AF patients referred for PVI. The purpose of our study was therefore to test the hypothesis that comprehensive simplified LA assessment based on routine transthoracic echocardiography may be more useful than assessment of LA volume alone for predicting AF recurrence after PVI.

METHODS

Study Population

This study was a retrospective analysis of 156 PAF patients who had undergone PVI and came to Kobe University Hospital between June 2013 and March 2016. PAF was defined as self-terminating within 7 days after onset as confirmed by means of routine electrocardiograms (ECG) or Holter ECG. Patients were excluded from enrolment in the study if they met any of the following criteria: (1) LVEF < 50%; (2) previous history of open-heart surgery; (3) serious renal dysfunction defined as glomerular filtration rate < 30 ml/min/1.73 m^2; (4) uncontrolled hypertension > 180/100 mmHg; (5) more than moderate valvular heart disease. This study was approved by the local ethics committee of our institution (No. 180085).

Echocardiographic Examination

All echocardiographic studies were performed with commercially available echocardiographic systems equipped with a 3.5-MHz transducer within two days before PVI (Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway). All patients were in sinus rhythm during echocardiography. Digital routine grayscale 2-D cine loops and tissue Doppler cine loops were obtained from three consecutive beats with end-expiratory apnea from standard apical and parasternal views. Sector width was optimized to allow for complete myocardial visualization while frame rate was maximized regardless of heart rate. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging[20].

Assessment of LA Volume and Function

Maximum (Max-LAVi) and minimum LA volume index (Min-LAVi) were calculated with the biplane modified Simpson's method from apical four- and two-chamber views, and then normalized to the body surface area. In addition, ΔLA volume index (ΔLAVi; ΔLAVi=[Max-LAVi minus Min-LAVi]), LA emptying fraction (LAEF; LAEF=[Max-LAV minus Min-LAV]/Max-LAV×100), and LA expansion index (LAEI; LAEI=[Max-LAV minus Min-LAV]/Min-LAV×100) were also calculated[14 21]. On the basis of previous findings, the pre-defined cutoff of Max-LAVi for recurrence of AF was set at a Max-LAVi ≥ 34 mL/m^2 [2].

Definition of Recurrence of AF

All patients who underwent PVI were followed at the out-patient arrhythmia clinic of our hospital every month for at least 24 months after the procedure: an ECG was obtained every month and additional Holter recordings were obtained when the patient's symptoms suggested occurrence of AF. Recurrence of AF was defined as any episode of AF lasting > 30s after PVI and was confirmed by means of ECG or Holter ECG. The follow-up period after PVI was 24 months.

Statistical Analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data, and as the median and interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages.

The parameters of subgroups were compared by means of Student *t* test or Mann-Whitney U test as appropriate, while proportional differences were evaluated by using Fisher's exact test or the χ^2 test as appropriate. The initial univariate regression analysis to identify univariate predictors of AF recurrence was followed by a multivariate regression model using stepwise selection, with the p levels for entry from the model set at <0.05. Sequential logistic models were performed to determine the incremental benefit of using ΔLAVi for predicting of AF recurrence over clinical variables including age, gender and AF duration, as well as Max-LAVi ≥ 34 mL/m^2. Optimal cutoff values for the association of ΔLAVi with AF recurrence were determined by means of receiver-operator characteristics curve analysis, as well as by calculating the area under the curve (AUC). The intraclass correlation coefficient was used to determine inter- and intra-observer reproducibility for ΔLAVi from 20 randomly selected subjects. For all steps, a p value of < 0.05 was regarded as statistically significant. All analyses were performed with commercially available software (SPSS software version 24.0, SPSS Inc., Chicago, IL).

RESULTS

Patient Characteristics

The baseline clinical and echocardiographic characteristics of the 156 PAF patients are summarized in Table 1. Their mean age was 67 years (57-72), 45 patients (29%) were female, and LVEF was 65.6% (61.4-70.0). The mean AF duration was 12 months (6-60). The intraclass correlation coefficients for inter-observer reproducibility of ΔLAVi was 0.952 (95% CI: 0.843-0.985), while the corresponding coefficients for intra-observer reproducibility was 0.933 (95% CI: 0.801-0.978).

Comparison of Clinical and Echocardiographic Parameters for Patients with and without AF Recurrence

During the follow-up period of at least 24 months, recurrence of AF after PVI was observed in 35 patients (22%) (Table 1). As for clinical characteristics, no significant differences were detected between patients with and without AF recurrence. As for echocardiographic characteristics, however, and as expected, Max-LAVi, Min-LAVi and ΔLAVi of patients with AF recurrence were significantly larger than of those without AF recurrence (46.9 mL/m^2 [33.4-53.4] vs. 31.1 mL/m^2 [24.8-41.2], $p < 0.001$; 26 mL/m^2 [19.7-33.6] vs. 19 mL/m^2 [13-25], $p <0.001$; 17.2 ± 8.1 mL/m^2 vs. 12.7 ± 5.1 mL/m^2, $p = 0.003$, respectively). In addition, patients with AF recurrence showed higher prevalence of Max LAVi ≥ 34mL/m^2 than those without it (74% vs. 43%; $p = 0.001$). Finally, the differences in LAEF and LAEI were not statistically significant.

Predictor of AF Recurrence

Univariate analysis using the logistic regression model showed that Max-LAVi ≥ 34mL/m^2 and ΔLAVi were associated with AF recurrence. OR and 95% CI for each of these variables are given in Table 2. An important finding of the multivariate logistic regression analysis was that ΔLAVi (OR: 1.131; 95% CI 1.057-1.221; $p<0.001$) proved to be an independent predictor of AF recurrence. The incremental advantage of using sequential logistic regression models for the prediction of AF recurrence is demonstrated in Figure 1. A model based on clinical variables including age, gender and duration of AF ($\chi 2 = 1.65$) was improved by addition of Max-LAVi ≥ 34mL/m^2 ($\chi 2 = 13.8$; $p < 0.001$), and further improved by addition of ΔLAVi ($\chi 2 = 18.2$; $p = 0.036$). Of note is that only 1.02 ± 0.10 minutes per patient was needed to obtain a comprehensive simplified assessment of the left atrium that included Max-LAVi, Min-LAVi, and ΔLAVi from routine apical four- and two-chamber views.

Receiver-operator characteristic curve analysis revealed that the optimal cutoff value of ΔLAVi for AF recurrence was 18mL/m^2 with sensitivity of 49%, specificity of 84%, and AUC 0.68 (p=0.002). Among patients with Max-LAVi ≥ 34mL/m^2, those with ΔLAVi < 18mL/m^2 showed a significantly lower prevalence of AF recurrence did those with ΔLAVi ≥ 18mL/m^2 (23% vs. 48%, p=0.028) (Figure 2). Figure 3 shows representative cases of comprehensive simplified assessment of the left atrium from patients with and without AF recurrence.

DISCUSSION

The findings of this study indicate that LA enlargement in PAF patients is strongly associated with AF recurrence after PVI. ΔLAVi, which is a simple parameter obtainable from routine echocardiography without requiring much time, appears to be a valuable factor in addition to LA enlargement for predicting AF recurrence for PAF patients.

Predictor of AF Recurrence

AF is independently associated with a two-fold increase in the risk of all-cause mortality for women and a 1.5-fold increase for men[6]. Death due to stroke can be largely mitigated by anticoagulation, while the current evidence base shows that other cardiovascular deaths, such as HF and sudden death, remain common even in AF patients who have received treatment[22]. Furthermore, AF is also associated with the development of HF with preserved EF[23]. PVI of AF is becoming an effective therapy for selected groups of patients to restore normal sinus rhythm and significantly improve symptoms and quality of life, but its success rate may depend on patient characteristics. PVI has become a common treatment for patients with symptomatic, drug-resistant AF. The success rate of PVI of AF patients is highly variable, and with a range of up to 70% for patients with PAF and of around 50% for those with persistent AF[6]. AF recurrences has thus remained common and a significant number of patients require repeated procedures. Previous reports have shown that LA size is a strong predictor of AF recurrence after PVI[2, 3, 21, 24-27]. LA enlargement, which signifies atrial anatomical remodeling, may also be associated with electrical remodeling. These changes may create an arrhythmogenic substrate that may increase the risk of AF recurrence. LA volume in particular, which serves as an index that encompasses multiplane measurements obtained by means of transthoracic echocardiography, is a well-established parameter for predicting AF recurrence after PVI[2, 3]. Shin et al reported that LAVI of 34 mL/m^2 showed a sensitivity of 70% and a specificity of 91% for predicting AF recurrence in 68 AF patients, and multivariate logistic regression analysis showed that LAVI was the only independent predictor of AF recurrence[2]. It has recently been reported that LA myocardial function is a more powerful predictor than LA size of AF recurrence after PVI[17, 19, 28-30]. LA myocardial function comprises reservoir, conduit, and booster pump functions to maintain adequate LV end-diastolic volume by actively emptying the LA at end-diastole, an activity which can be assessed by means of two-dimensional speckle-tracking imaging of strain or strain rate. In addition, Kojima et al reported that a reduction in the LA reservoir and booster pump functions detected in PAF patients by means of speckle-tracking strain echocardiography occurred even before LA dilatation[31]. The superior prognostic strength of LA speckle-tracking strain findings over those obtained for other echocardiographic parameters such as LA size could be explained by positing the hypothesis that reductions detected by means of LA speckle-tracking strain imaging more effectively reflect severe impairment of LA performance, because LA speckle-tracking strain has been shown to be a noninvasive surrogate marker of LA fibrosis,[32] which may serve as a substrate for slow conduction and intra-atrial reentry[33]. Thus, LA speckle-tracking strain may be useful in clinical settings for selection of AF patients referred for PVI.

In this study, we showed the superior utility of ΔLAVi, which was calculated as the difference between maximum and minimum LA volume index, over that of LAEF or LAEI for predicting AF recurrence for PAF patients. Previous studies demonstrated the usefulness of LAEF or LAEI for predicting AF recurrence after PVI[34-36]. Our study found that LAEF and LAEI of patients with AF recurrence were lower than those of patients without AF recurrence, but the differences between LAEF and LAEI were not statistically significant. In addition, LAEF constitutes part of the LA booster pump function, and LAEI part of the LA reservoir function, but ΔLAVi may also encompass the LA emptying and expansion function. Thus, an increase in ΔLAVi may present earlier than a reduction in LAEF or LAEI, and thus can be a sensitive predictor, like LA speckle-tracking strain, for AF recurrence.

Some investigators reported that the difference between maximum and minimum LA volume in patients with AF recurrence was smaller than that in patients without AF recurrence, and LAEF was also lower in patients with AF recurrence[35, 37], however, Chin et al[38] showed the opposite result as our study. Their LAVI of study population was much larger compared to Chin et al's and our study so that this discrepancy may depend on LAVI of study population. Thus, we speculated that LA remodeling due to AF begins with the enlargement of maximum LA volume, and then happens to enlarge minimum LA volume, leading to lower LAEF.

Clinical Implications

LA strain parameters obtained with speckle-tracking echocardiography could serve as a promising and novel means for predicting AF recurrence after PVI. Although it the utility of these parameters is obvious, obtaining them can be very different from a routine clinical examination. Moreover, there is currently no software designed specifically for LA speckle-tracking strain analyses because such analyses have been performed by using programs that were developed for overall LV analysis, and it is not really clear whether the same software programs are also suitable for LA function. The predictive capability of LA volume has been previously reported, and our present study demonstrated the utility of the combined assessment of LAVI and ΔLAVi, which can be obtained by means of conventional routine echocardiography, for predicting AF recurrence after PVI in PAF patients. In addition, this comprehensive simplified LA assessment proved to be simple and not time-consuming. ΔLAVi appears to be a valuable additive factor to LAVI for predicting AF recurrence in PAF patients, and may well have clinical implications for better management of such patients.

Study Limitations

This study covered a small number of patients in a single-center retrospective study, so that future studies involving larger numbers of patient are required to verify our findings. Study populations in this study included only PAF patients, and non-PAF patients such as persistent or permanent AF were not part of this study. Moreover, the well-known parameters associated with AF recurrence such as age, hypertension or diabetes did not predict AF recurrence in this study. Although its possible reason remains uncertain, a small number of patients may be linked to this finding. Finally, the assessment of LA speckle-tracking strain parameters was not performed in this study. Therefore, the comparison of ΔLAVi and LA speckle-tracking strain parameters for ability of predicting AF recurrence after PVI was not part of study.

Conclusion

ΔLAVi appears to be a valuable additive factor for predicting AF recurrence for PAF patients. This easy-to-use comprehensive simplified LA approach derived from routine echocardiography may well have clinical implications for better management of PAF patients.

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Disclosures:

We have no disclosures.

Author Contributions:

Fumitaka Soga: Concept/design, data analysis/interpretation, drafting article, statistics, and data collection

Hidekazu Tanaka: Concept/design, data analysis/interpretation, drafting article, statistics, and data collection

Yasuhide Mochizuki: Concept/design, data analysis/interpretation, approval of article

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FIGURE LEGENDS

Figure 1: The incremental advantage of using sequential logistic regression models for the prediction of AF recurrence. A model based on clinical variables including age, gender and duration of AF was improved by addition of Max-LAVi ≥ 34mL/m^2, and further improved by addition of ΔLAVi.

Figure 2: Of the patients with Max-LAVi ≥ 34mL/m^2, those with ΔLAVi < 18mL/m^2 showed a significantly lower prevalence of AF recurrence than did those with ΔLAVi ≥ 18mL/m^2.

Figure 3: Representative cases of comprehensive simplified assessment of the left atrium of patients with and without AF recurrence after PVI.

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Table 1

Baseline clinical and echocardiographic characteristics of patients

	All patients (n=156)	Patients **without** AF recurrence (n=121)	Patients **with** AF recurrence (n=35)	p value
Clinical Characteristics				
Age (years)	67 (57-72)	67 (59-72)	61 (54-71)	0.094
Gender (female), n (%)	45 (29)	36 (30)	9 (30)	0.682
BSA (m^2)	1.74 (1.59-1.84)	1.72 (1.57-1.84)	1.80 (1.65-1.88)	0.127
BMI (kg/m^2)	22.7 (21.2-25.0)	22.7 (21.5-24.8)	22.3 (20.2-25.7)	0.549
BNP (pg/mL)	33.6 (18.0-75.8)	35.3 (19.3-80.2)	31.3 (13.1-63.4)	0.158
AF duration (months)	12 (6-60)	14 (6-60)	12 (5-54)	0.813
CHA_2DS_2-VASc score	2 (1-2)	2 (1-2.5)	1 (0-2)	0.062
Systolic blood pressure (mmHg)	138 (124-152)	139 (125-153)	133 (123-147)	0.133
Diastolic blood pressure (mmHg)	81 (74-90)	81 (73-92)	81 (76-86)	0.478
Heart rate (bpm)	54 (45-68)	67 (59-75)	66 (56-76)	0.669
Comorbidities				
Hypertension, n (%)	83 (53)	65 (54)	18 (35)	0.883
DM, n (%)	17 (11)	16 (13)	1 (3)	0.088
DL, n (%)	35 (22)	30 (25)	5 (14)	0.205
Cardiovascular event, n (%)	13 (8)	10 (8)	3 (9)	0.907
Drug				

CCB, n (%)	48 (31)	36 (30)	12 (34)	0.590
ACEI/ARB, n (%)	54 (35)	44 (36)	10 (29)	0.412
β-blocker, n (%)	62 (40)	47 (39)	15 (43)	0.645
Diuretics, n (%)	8 (5)	8 (7)	0 (0)	0.121
Statin, n (%)	31 (20)	26 (21)	5 (14)	0.359
Anti-Arrhythmia Agents, n (%)	66 (42)	49 (40)	17 (49)	0.376
Anti-Coagulation, n (%)	155 (99)	121 (100)	34 (97)	0.062
Echocardiographic Parameters				
Assessment of Left Ventricle				
LVEF (%)	65.6 (61.4-70.0)	65.7 (61.3-70.3)	65.5 (69.4-69.5)	0.719
E (cm/s)	53.3 (45-68)	63.3 (51.7-78)	63.8 (46.2-83.9)	0.901
A (cm/s)	64.0±19.2	65±19	59±20	0.075
E/A	1.00 (0.75-1.37)	0.97 (0.74-1.3)	1.1 (0.74-1.44)	0.338
E/e'	10.4 (8.26-13.5)	10.6 (8.48-13.6)	9.29 (7.87-11.7)	0.090
Assessment of Left Atrium				
Max-LAVi (mL/m^2)	33.7 (25.6-46.7)	31.1(24.8-41.2)	46.9 (33.4-53.4)	<0.001
Max-LAVi ≥ 34 mL/m^2, n (%)	114 (73)	52 (43)	26 (74)	0.001
Min-LAVi (mL/m^2)	20.2 (13.7-28.0)	19 (13-25)	26 (19.7-33.6)	<0.001
ΔLAVi (mL/m^2)	13.7±6.13	12.7±5.1	17.2±8.1	0.003
LAEF (%)	39.0±12.3	39.4±12.2	37.6±12.6	0.436
LAEI (%)	70.0 (42.6-92.3)	71.0 (42.7-94.2)	63.9 (42.1-85.6)	0.404

Data are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).

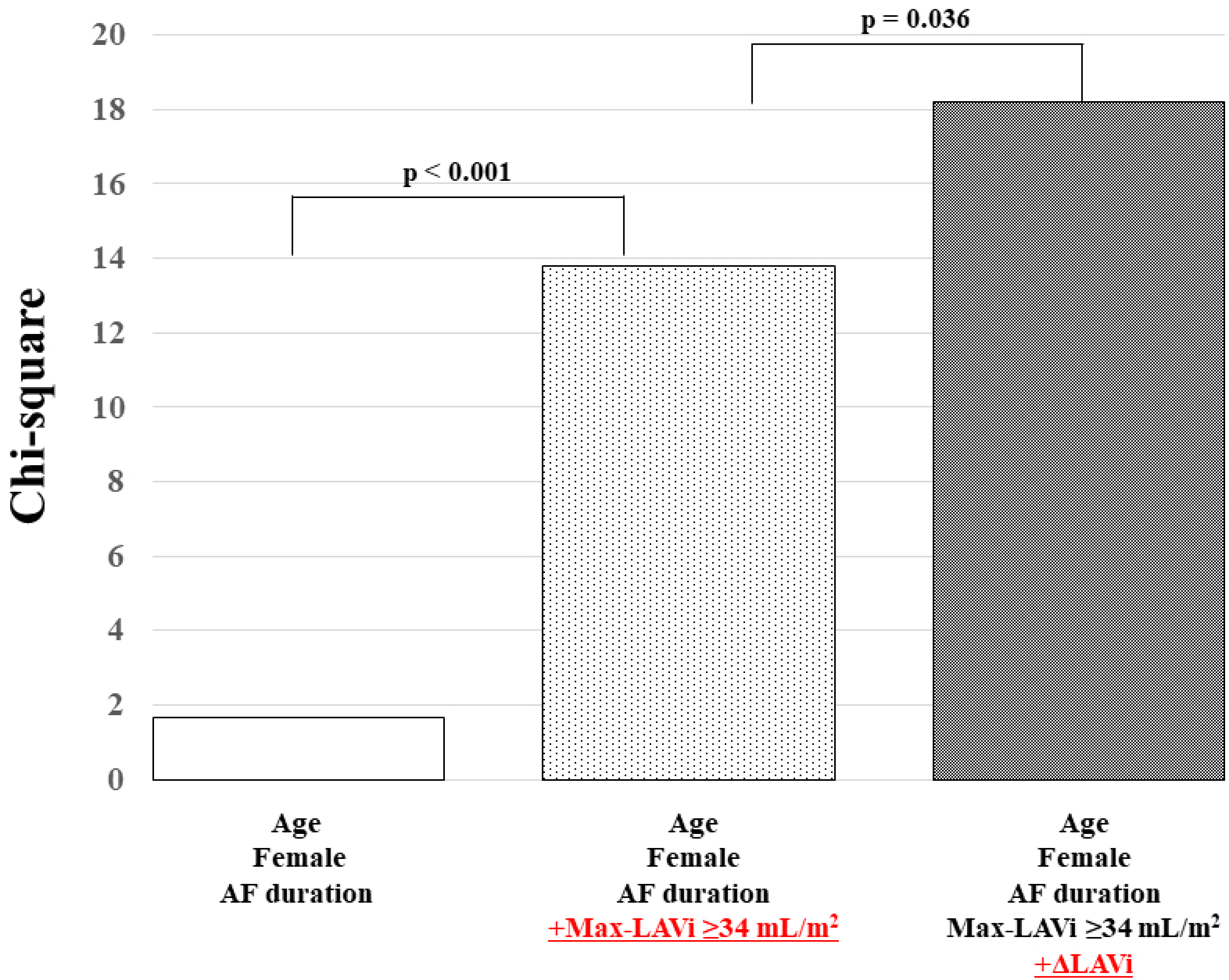
BSA= body surface area; BMI= body mass index; BNP= plasma brain natriuretic peptide; DM= diabetes mellitus; DL= Dyslipidemia; CCB= calcium channel blocker; ACEI= angiotensin-converting enzyme inhibitor; ARB= angiotensin II receptor blocker; LVEF= left ventricular ejection fraction; E= peak early diastolic mitral flow velocity; A= peak late diastolic mitral flow velocity; e'= Spectral pulsed-wave Doppler–derived early diastolic velocity from the septal mitral annulus; LAVi= left atrial volume index; LAEF= left atrial emptying fraction; LAEI= left atrial expansion index.

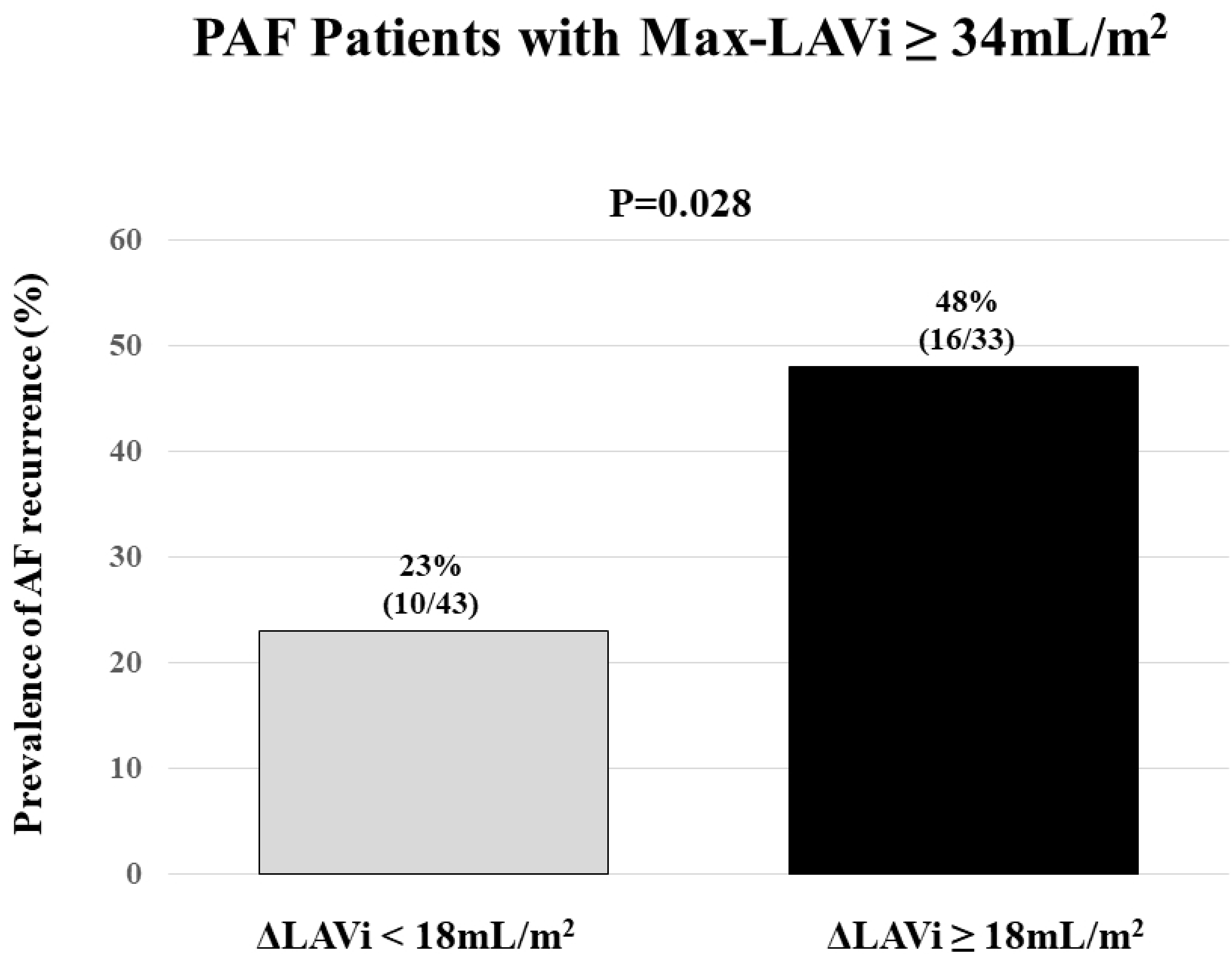
Table 2

Univariate and multivariate logistic regression analysis

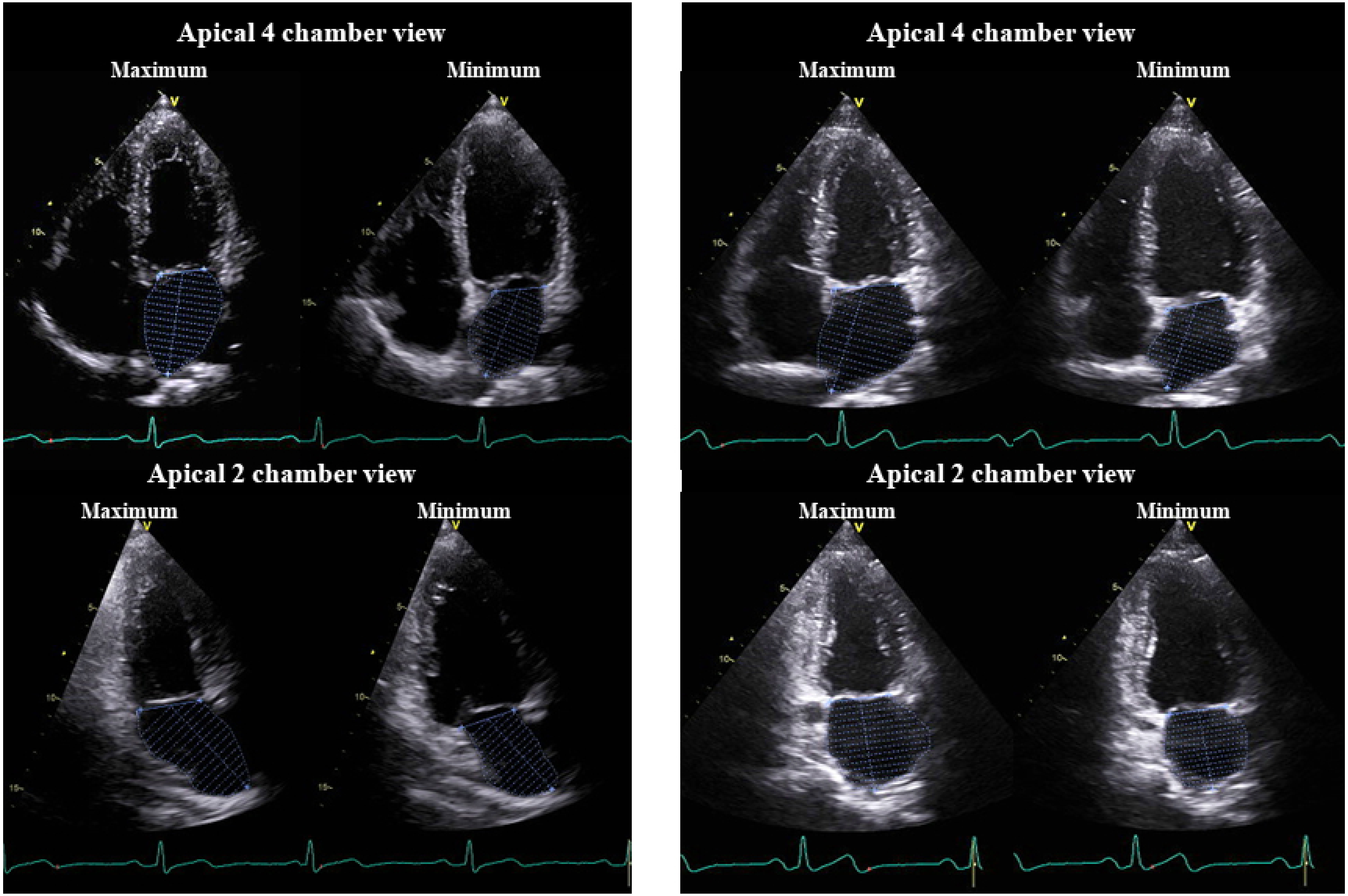
Covariate	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
<u>**Clinical Characteristics**</u>						
Age	0.975	0.946-1.005	0.107			
Gender (female)	0.837	0.357-1.961	0.681			
BSA	0.971	0.523-1.800	0.925			
BMI	0.984	0.877-1.105	0.788			
BNP	0.996	0.990-1.002	0.209			
AF duration	1.001	0.993-1.008	0.874			
Systolic blood pressure	0.984	0.965-1.004	0.116			
Hypertension	0.945	0.446-2.003	0.082			
DM	0.197	0.025-1.538	0.121			
<u>**Echocardiographic Parameters**</u>						
Assessment of Left Ventricle						
LVEF	0.991	0.943-1.040	0.705			
E/e'	0.930	0.844-1.024	0.141			
Assessment of Left Atrium						
Max-LAVi ≥ 34 mL/m^2	3.944	1.706-9.120	<0.001			
ΔLAVi	1.131	1.057-1.211	<0.001	1.131	1.057-1.211	<0.001

CI = confidence interval; OR = odds ratio. Other abbreviations as in Table 1.


p = 0.036
p < 0.001
Chi-square
20
18
16
14
12
10
8
6
4
2
0
Age
Female
AF duration
Age
Female
AF duration
+Max-LAVi ≥34 mL/m2
Age
Female
AF duration
Max-LAVi ≥34 mL/m2
+ΔLAVi


PAF Patients with Max-LAVi ≥ 34mL/m²
P=0.028
Prevalence of AF recurrence (%)
60
50
40
30
20
10
0
23%
(10/43)
48%
(16/33)
ΔLAVi < 18mL/m²
ΔLAVi ≥ 18mL/m²

Patient without AF Recurrence	Patient with AF Recurrence



	Patient without AF Recurrence		Patient with AF Recurrence
Max-LAVi	29.9 mL/m^2	Max-LAVi	50.9 mL/m^2
Min-LAVi	14.6 mL/m^2	Min-LAVi	27.1 mL/m^2
ΔLAVi	15.3 mL/m^2	ΔLAVi	23.8 mL/m^2