



Pulmonary Venous Flow Velocity Ratios During Systole and Diastole Assessed by Doppler Echocardiography Predict Recurrent Atrial Fibrillation after Catheter Ablation

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Abstract

Background: Atrial fibrillation (AF) poses risks for stroke and heart failure. We often use catheter ablation (CA) to treat AF. However, recurrence is troublesome in CA. High left atrial pressure and reduced compliance can predict AF recurrence after CA. We explore transthoracic echocardiography (TTE) parameters such as E/e' ratio and pulmonary vein flow (PVF) for predicting recurrent AF after CA.

Methods: We evaluated PVF using the apical four-chamber view by transthoracic echocardiography in 115 adults undergoing CA for AF at our institution. We confirmed recurrent AF by electrocardiography in 35 patients (65+/-11 years, 25 men) during the follow-up period.

Results: Patients with recurrent AF, in comparison with ones without recurrent AF, had a higher diastolic blood flow velocity of PVF (PVd) (56.2 vs. 49.4, p= 0.025) and a smaller systolic blood flow velocity of PVF (PVs) **to** PVd ratio (S/D) (0.97 vs. 1.14, p = 0.048). In Cox hazard analysis, S/D was the only independent predictor of recurrent AF. Recurrent AF was less frequent in the group with an S/D value less than 0.71(the cutoff value of S/D) than that with an S/D value of 0.71 or greater (p=0.002).

Conclusion: Decreased left atrial function independently predicts recurrent AF risk by PVF. We used standard Doppler echocardiography for measuring our study's PVF velocity, which requires neither high-end cardiac-specific echo equipment nor expensive analytic software. The strength of echocardiography is that measuring is easy and reproducing excellent, which suggests that our procedure can provide an indicator that can quickly predict recurrent AF.

Keywords: Recurrent atrial fibrillation; Atrial function; Doppler echocardiography; Pulmonary venous flow; Catheter ablation; transthoracic echocardiography

Introduction

Atrial Fibrillation (AF) is a heart disease that can lead to a serious complication such as stroke or heart failure. We have widely adopted Catheter Ablation (CA) for treating AF. Several factors influence the success of AF ablation. Preventing recurrent AF is challenging for us. A high left atrial pressure involved in reduced left atrial compliance was reported as an independent predictor of recurrent AF after CA [1]. This finding is significant and could help improve predicting AF recurrence. There are methods to estimate left atrial pressure using Transthoracic Echocardiography (TTE), such as estimation from the E/e' ratio (an index of left ventricular diastolic function) and Pulmonary Vein Flow (PVF) velocities. However, no reports investigate the TTE-derived E/e' ratio and PVF as factors for AF recurrence after AF-CA. We aimed to determine the echocardiographic parameters attributing AF recurrence after AF-CA to the left atrial pressure.

Methods

Study design

The study protocol was approved by Clinical Research Judging Committee of Shizuoka General Hospital (SGHIRB#2022052). Patients included in this study were 115 consecutive patients who underwent CA for AF at the Department of Cardiology of Shizuoka General Hospital between April 2015 and March 2020, with a left ventricular Ejection Fraction (EF) of at least 50% and measurable PVF. This study was conducted retrospectively based on anonymized data from actual clinical practice.

Follow up

We started follow-up on the day of the initial CA during the enrollment period at Shizuoka General Hospital. The attending hospital's outpatient cardiology clinic followed up with each patient in the ablation group and periodically performed follow-up examinations for monitoring AF and deciding on medical therapy at 1, 3, 6, and 12 months. The 24-hour Holter recordings were conducted 3 and 12 months after ablation. We resolved any AF episodes > 30 seconds in duration documented on standard ECG recordings or 24-hour Holter recordings as recurrence.

Echocardiographic evaluation

We performed the examinations according to the recommendations of the American Society of Echocardiography [2,3], using the Vivid7 cardiovascular ultrasound system (GE Healthcare, Horten, Norway) in combination with a 5.0-2.2 MHz Doppler transducer and IE33 and Epiq cardiovascular ultrasound system (GE Healthcare, Horten, Norway) (Royal Philips, Amsterdam, Nederland) with 5.0-2.2 MHz Doppler transducers. Using the biplane disk summation method, we computed 2D echocardiographic LV Ejection Fraction (LVEF) from four- and two-chamber views from the apex. Left atrial volume was calculated using the biplane disk summation method, taking a right-angle apical view (apical 4-chamber view and 2-chamber view) to determine the area and length of the left atrium (from the center of the plane of the mitral annulus to the posterior wall). Mitral flow velocities were recorded using pulsed wave Doppler and sample volumes were placed at the apical tip of the mitral valve and viewed from a three-chamber view of the apical-long. We measured peak E-wave velocity, deceleration time, and peak A-wave velocity from the mitral inflow velocity curve. We obtained Tissue Doppler-derived peak LV relaxation velocities from the mitral annulus's lateral and septal horns during the cardiac cycle's early diastole. We recorded pulmonary vein flow velocities using pulsed wave Doppler, placing sample volumes at the orifices of the pulmonary vein at the left atrium and viewed from a four-chamber view of the apical-long. We measured Peak S-wave (PVs) and Peak D-wave (PVd) velocity from the pulmonary vein velocity curve. We defined the ratio of the measured S wave to the D wave as S/D. Echocardiography measured left ventricular End-Diastolic Volume (EDV), left ventricular End-Systolic Volume (ESV), left ventricular Ejection Fraction (EF), and Left Atrial Volume Index (LAVI) using the biplane disk summation method. We measured E/A, E/e', and PVF using the pulsed Doppler technique and determined the ratio of the measured S wave to the D wave from PVF. We examined all measurements according to the American Society of Echocardiography guidelines.

Statistical analysis

We expressed continuous variables as the mean SD or median, interquartile range, and categorical variables as the number and percentage of patients. S/D cutoff values were calculated by the Receiver Operating characteristic Curve (ROC) and further analyzed by Decision Tree Analysis (DCA). We analyzed the recurrent AF risk by the Kaplan-Meier method and compared the differences by log-rank test. We used the Cox proportional hazards model to estimate recurrent AF risks by the variable's presence or absence. We analyzed recurrent AF by multivariate Cox model under adjusting age, gender, baseline variables with P values <0.2 in univariate analysis, and factors considered significant from previous studies. We performed all statistical analyses using R with EZR, a modified version of R commander designed to add statistical functions frequently used in biostatistics [4].

Results

Table 1 shows patient characteristics. The study included 83 males and 32 females with a mean age of 66.1 ± 10.2 years; 69 (60.0%) had paroxysmal AF before CA. 44 (38.3%) had sustained AF. Their rhythm during TTE was in sinus rhythm at 94.7%. Of the 115 patients, 104 (90.4%) underwent a single AF ablation, and the remaining 11 (9.56%) experienced two or more CAs. One hundred fifteen consecutive patients were recruited and followed up for a median of 682.0 days (367.0-1809.5 days), during which 35 patients had Recurrent AF (RAF). Table 2 shows TTE during follow-up; LAVI was 42.37 ± 14.6 ml/m2 and LVEF was $61.6 \pm 4.74\%$.

	Total	Non-recurrent AF	Recurrent AF	
	n=115	n=80	n=35	p-value
Age, year	66.09 (10.23)	66.09 (10.23) 66.44 (9.94) 65.29 (10.97)		0.581
Male, (%)	83 (72.2)	58 (72.5)	25 (71.4)	0.906
AF duration, day	760.37 (1228.80)	691.70 (1186.93)	917.31 (1323.97)	0.367
Paroxmal AF	69 (61.1)	48 (60.8)	21 (61.8)	0.919
Time to event, day	1149.9 (1157.0)	1327.0 (1206.3)	745.2 (930.0)	0.0125
FRCA, (%)	105 (91.3)	73 (91.2)	32 (91.4)	0.975
Two or more CAs, (%)	11 (9.56)	6 (7.5)	5 (14.3)	0.262
Height, cm	164.24 (8.39)	163.78 (8.00)	165.31 (9.23)	0.367
Weight, kg	63.83 (12.73)	62.77 (12.57)	66.26 (12.94)	0.178
BSA, m ²	1.69 (0.19)	1.68 (0.19)	1.73 (0.20)	0.181
AP	15 (13.0)	13 (16.2)	2 (5.7)	0.145
HL	23 (20.0)	14 (17.5)	9 (25.7)	0.319
СКД	10 (8.7)	9 (11.2)	1 (2.9)	0.107
DM	21 (18.3)	12 (15.0)	9 (25.7)	0.181
HT	56 (48.7)	35 (43.8)	21 (60.0)	0.108
LVEF, %	61.61 (4.74)	61.31 (4.52)	62.29 (5.22)	0.313
LAVI, ml/m ²	42.37 (14.55)	41.15 (13.82)	45.14 (15.95)	0.177
BNP, pg/ml	64.50 [5.00, 640.00]	60.50 [5.00, 640.00]	72.50 [14.00, 333.00]	0.312
LVEDV, ml	86.45 (25.85)	86.25 (24.82)	86.91 (28.44)	0.9
LVESV, ml	33.60 (12.22)	33.64 (11.42)	33.51 (14.07)	0.961
LVEF, %	61.61 (4.74)	61.31 (4.52)	62.29 (5.22)	0.313
LAVI, ml/m ²	42.37 (14.55)	41.15 (13.82)	45.14 (15.95)	0.177
Mitral peak E wave, cm/s	71.34 (20.96)	69.41 (21.77)	75.74 (18.52)	0.137
Mitral peak A wave, cm/s	57.87 (16.79)	58.42 (15.43)	56.52 (19.91)	0.585
E/A	1.36 (0.67)	1.29 (0.65)	1.52 (0.70)	0.1
Deceleration time of E, msec	61.61 (4.74)	200.95 (60.42)	205.97 (57.36)	0.678
PVS, cm/s	52.24 (16.44)	53.85 (16.38)	48.56 (16.21)	0.113
PVD, cm/s	51.49 (14.97)	49.42 (12.37)	56.21 (19.04)	0.025

Table 1: Baseline characteristics of Recurrent AF and Non-Recurrent AF.

PVA, cm/s	28.42 (10.79)	28.66 (11.60)	27.89 (8.94)	0.754
S/D, ratio	1.09 (0.42)	1.14 (0.38)	0.97 (0.48)	0.048
Medial E/E'	11.56 (4.23)	11.12 (4.16)	12.54 (4.29)	0.099
Latral E/E'	8.93 (3.91)	8.81 (4.19)	9.20 (3.24)	0.632
Mean E/E'	10.25 (3.89)	9.97 (3.99)	10.87 (3.62)	0.256
TR peak velocity, cm/s	2.39 (0.34)	2.39 (0.34)	2.39 (0.34)	0.992

AF: atrial fibrillation; FRCA: Radiofrequency catheter ablation; BSA: body surface area; AP: angina pectoris; HL: hyperlipemia; DM: Diabetes Mellitus; HT: hypertention; LVEF: left ventricular ejection fraction; LAVI: left atrial volume index; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF; left ventricular ejection fraction; wave; LAVI: left atrial volume index; PVD: pulmonary vein peak S; PVD: pulmonary vein peak D wave; divided by PVD; PVA: pulmonary vein peak A wave; S/D; PVS; TR: tricuspid regurgitation

Variables	Univariate analysis			multivariate analysis		
	HR	95% Cl	p-value	HR	95% Cl	p-value
Age, year	0.98	0.95-1.02	0.3	0.98	0.94-1.02	0.21
Male	1.08	0.52-2.28	0.83	1.57	0.66-3.71	0.29
BSA, m ²	7.12	1.12-45.28	0.038			
AF duration, day	1	1.00-1.00	0.74			
Paroxmal AF	0.98	0.49-1.97	0.96	0.71	0.32-1.54	0.56
AP	0.32	0.08-1.34	0.12			
HL	1.22	0.57-2.62	0.61			
DM	1.45	0.68-3.11	0.34			
HT	1.5	0.76-2.96	0.24	1.51	0.68-3.33	0.29
E/A>=1.6	1.72	0.84-3.49	0.135	1.6	0.60-4.29	0.14
LAVI≧34 ml/m ²	1.42	0.64-3.16	0.38	0.94	0.38-2.32	0.69
meanE/E'>14	1.83	0.83-4.04	0.14	2.08	0.87-4.97	0.17
S/D<0.71*	2.83	1.44-5.58	0.0026	2.84	1.25-6.45	0.0023
TR peak velocity>2.8 m/s	0.97	0.3-3.19	0.96			
BNP, pg/ml	1	1.00-1.00	0.98			

 Table 2: Univariate and multivariate cox proportional hazards model of recurrent AF after the catheter ablation.

AF: atrial fibrillation; BSA: body surface area; AP: angina pectoris; HL: hyperlipemia; DM: Diabetes Mellitus; HT: hypertension; LAVI: left atrial volume index; S/D; PVS divided by PVD; TR: tricuspid regurgitation. *The area under the curve of S/D ratio<0.71 is 0.637 (95% CI: 0.5155-0.7585).

Decision tree analysis

We performed a decision tree analysis using S/D, E/A, and LAVI extracted as significant factors (p<0.2) in a logistic regression analysis with AF recurrence or not as the outcome variable. The S/D conducted the first

branching by the G2 index. When the first branching was performed with S/D = 0.71, the group with S/D < 0.71 had 22 patients, who included 14 with recurrence and eight without recurrence (recurrence rate 63.6%); the group with $S/D \ge 0.71$ had 93 patients, who included 21 with recurrence and 81 without recurrence (recurrence rate 22.6%). When the second branching was performed with E/A, all 11 patients in the $E/A \ge 1.6$ group had no recurrence; in the E/A < 1.6 group of 82 patients, 21 had recurrence and 61 no recurrence (recurrence rate 25.6% in this group). When the third branching was performed with E/A, 5 of 6 patients in the E/A < 1.6 group had a recurrence (recurrence rate 16.7%). Of sixteen patients in the $E/A \ge 1.6$ group, 13 had a recurrence, and three had no recurrence (recurrence rate 18.8%). LAVI was not significant. A scatter plot shows the results of the decision tree analysis, and Figure 1 shows the relationship between E/A and S/D.



S/D 0.71 obtained from the decision tree analysis.

The Cox proportional hazards modeling

The cut-off value of S/D obtained from univariate logistic regression analysis was 0.71 (AUC: 0.64, 95% CI: 0.56-0.76), which coincided with the branching value of the S/D=0.71 obtained from decision tree analysis. The factors associated with RAF included Angina Pectoris (AP), sex, Hypertension (HT), age, BSA, E/A>1.6 (from

decision tree analysis), LAVI \geq 34 ml/m², mean E/E' \geq 14, and S/D<0.71, extracted from the analysis using the univariate Cox proportional hazards model. The multivariate Cox proportional hazards model included gender, HT, pAF or cAF, age, E/A>1.6, LAVI>34 ml/m², mean E/E' \geq 14, and S/D<0.71, and S/D was the only significant factor (HD 2.84 (1.25-6.45)) (Table 2). Figure 2 shows Kaplan-Meier curves of recurrence rates between S/D. The group with S/D<0.71 had a significantly increased rate of RAF after ABL compared to the group with S/D \geq 0.71 (P=0.002).



Kaplan-Meier survival curve analysis demonstrated that low S/D during follow-up (log rank, p=0.00165) is a prognostic factor for recurrent AF. The solid line indicates the group with S/D ≥ 0.71, and the dashed line indicates the group with S/D < 0.71. AF, atrial fibrillation; S/D, PVS divided by PVD. Censoring indicates end of examination or end of follow-up.</p>

Discussion

Our study demonstrated the significant relationship between pulmonary venous blood flow velocity and atrial fibrillation by echocardiography after AF CA. The main results of this study were as follows:

> PVD and S/D were significantly lower in the recurrence group after CA.

- > AF recurred significantly and frequently when S/D<0.71 and $E/A \ge 1.6$.
- > The recurrence rate was 0% when $S/D \ge 0.71$ and $E/A \le 1.6$.
- The Cox proportional hazards model showed that the only significant factor, a decrease in S/D below 0.71, significantly increased the recurrence of AF.

Predictors for success after AF-CA (predictors associated with maintaining sinus rhythm)

Predictors of recurrent AF included long-term persistent AF, enlarged left atrium, aging, hypertension, sleep apnea and obesity, and stiff Left Atrium syndrome (LA fibrosis), identified in numerous previous studies [5]. Among these variables, echocardiography can measure the LA volume or size. Although there were earlier reports on pulmonary venous blood flow velocity, most studies used Transesophageal Echocardiography (TEE) and focused on maintaining sinus rhythm after electrical cardioversion [6]. TEE has the advantage of more precise imaging but the disadvantage of being invasive and not easy to perform. On the other hand, the ability to repeatedly and noninvasively evaluate predictive factors using TTE, as we did in our study, greatly benefits the patient. In other words, early consideration of second and subsequent CA and optimal antiarrhythmic drug therapy in anticipating recurrence may contribute to planning to treat patients with atrial fibrillation.

LA stiffness and PVF

The left atrial function consists of three phases: (1) reservoir, (2) conduit, and (3) contraction. The S wave of pulmonary venous blood velocity corresponds to the reservoir, the D wave to the conduit, and the A wave to the contraction. Junbeom et al. [7] reported that PVD recorded by TEE predicts high left atrial pressure, which indicates recurrent AF. They also showed that high left atrial pressure is associated with increased LA stiffness and poor rhythm outcomes in patients undergoing AF catheter ablation. Most previous studies predicted recurrent AF from echocardiographic findings (TTE or TEE) performed before CA [1,8].

In contrast, we predicted recurrent AF from TTE findings during the follow-up period after AF CA. In our study, PVD was also a significant predictor of recurrent AF after AF CA in univariate analysis. In addition, we found that calculating S/D reflected better left atrial function. In a previous study, AF patients had significantly reduced PVS and only observable PVD, indicating reduced left atrial function [9]. Schotten et al. [10] also reported on atrial function and electrical remodeling after AF duration and defibrillation, with the longer the disease duration after restoring to sinus rhythm, the longer it takes for atrial function and electrical remodeling to recover. The cases with the left ventricular systolic dysfunction have reduced PVS, which implicates reduced LA compliance due to elevated LA pressure, and S/D <1 indicates high LA pressure [11]. PVD is also closely related to LA compliance, and a marked decrease in PVS is called a stiff LA syndrome. On the other hand, the mechanisms involved in impaired atrial contractility after defibrillation are unknown, suggesting that structural remodeling occurs before or after electrical remodeling. This structural remodeling may impair atrial contractility and promote recurrent AF [12].

Clinical implication

Although increased left atrial volume and elevated BNP levels are indicators of structural remodeling, these factors were not significant predictors of recurrent AF in our study [13-15]. It is one of the reasons that the subjects in this study were non-valvular AF patients with preserved EF. In the case of non-valvular AF, a longer duration of AF should affect left atrial volume and BNP values, whereas in the case of shorter period or paroxysmal AF, the left atrial strain values, able to capture minor changes in left atrial function, and our high

E/A and low S/D values may contribute to predicting recurrent AF [15-17]. The two-dimensional strain has recently been regarded as a valuable predictor of recurrent AF [17]. Several reports have identified reduced strain at different LA sites (e.g., LA lateral wall or LA base) as an essential predictor of AF recurrence [18-20]. The fact that LA strain is closely related to left atrial function is the basis for these reports [21]. We also support the usefulness of strain for assessing left atrial function and predicting recurrent AF. However, we believe strain analysis has the disadvantage of limited versatility, needing clear images, a high frame rate, special equipment and software, and so on. Regarding versatility, standard Doppler echocardiography enables us to measure pulmonary venous blood flow velocity in this study. It requires neither specialized high-end cardiac echo equipment nor expensive analysis software. Easy measurement and high reproducibility are the advantages of TTE, which suggests that our procedure can help predict recurrent AF quickly and conveniently anywhere.

Study limitation

The majority of patients in this study had lone atrial fibrillation. In addition, most of the patients in the study were unlikely to develop heart failure, and most were in NYHA class I or II and had no overt heart failure. Our new application is influenced by the rhythm at the time of the TTE. In tachycardia, PVS and PVD are fused, making evaluation difficult. In atrial fibrillation, E/A cannot be evaluated and the accuracy of PVF in predicting recurrence based on E/A is reduced.

Conclusion

We found significant AF recurrence in patients with PVF S/D < 0.71 and E/A \ge 1.6. The PVF S/D and E/A are conventional parameters of left atrial function that are versatile and reproducible. The benefits for patients undergoing repeatable and noninvasive TTE are immeasurable, and we believe our procedure can contribute significantly to planned treatment, such as early consideration of treatment options and optimal antiarrhythmic drug therapy.

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