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Original article

Diastolic wall strain predicts progression from paroxysmal to persistent or permanent atrial fibrillation in structurally normal hearts

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ABSTRACT

Background: Atrial fibrillation (AF) is characterized by a progression from paroxysmal to persistent or permanent AF. Recent studies have shown that AF progression is related to a worse morbidity and mortality, and poorer outcomes of radiofrequency catheter ablation (RFCA). We previously showed that left ventricular (LV) compliance assessed by diastolic wall strain (DWS) was a strong determinant of prevalent AF.

Methods and results: We studied 306 paroxysmal AF patients with structurally normal hearts. The DWS was non-invasively measured with echocardiography. During a follow-up of 35 ± 19 months, AF progression occurred in 60 of 172 (35%) patients treated with medications only (medication group), and 3 of 134 (2%) who underwent RFCA (RFCA group) ($p < 0.001$). In the medication group, patients with a DWS <0.38 had a higher incidence of AF progression than those without (log-rank $p < 0.001$), while the AF progression rate was low irrespective of the DWS in the RFCA group. In a multivariate analysis, the DWS and left atrium volume index (LAVI) were independent predictors of AF progression in the medication group (hazard ratio, 1.13 per 0.01 decrease; 95% CI: 1.08–1.18; $p < 0.001$, and 1.04 per 1 mm increase; 95% CI: 1.01–1.08; $p = 0.012$, respectively). In the medication group, AF progression occurred in only 5 of 61 (8%) patients with a DWS ≥0.38, whereas 27 of 40 (68%) with a DWS <0.38 and LAVI >34 mL/m^2 progressed to persistent or permanent AF.

Conclusions: The LV compliance estimated by the DWS was independently associated with AF progression. The DWS would be useful to stratify patients at risk of AF progression who could benefit from an earlier RFCA intervention.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of thromboembolisms, heart failure, and death [1]. AF is a progressive disease, characterized by a gradual shift from paroxysmal AF (PAF) to persistent or permanent AF (PerAF) over time. Although the risk of thromboembolisms had been believed to be independent of the AF type (PAF or PerAF), recent evidence has documented that PerAF patients have a higher risk of thromboembolic events and worse survival compared with PAF patients even under appropriate anticoagulation therapy [2]. Also, in the recent data from the Japanese AF registry, the risk of hospitalization for heart failure was observed to be transiently elevated during the progression period from PAF to PerAF [3]. Thus, preventing the progression from PAF to PerAF should have important clinical implications.

In the past decades, radiofrequency catheter ablation (RFCA) has become an established therapy for symptomatic AF. It has been shown that RFCA also reduces the progression from PAF to PerAF [4]. However, RFCA of PerAF is less successful than that of PAF in maintaining sinus rhythm [5] and suppressing AF progression [6]. Hence, earlier intervention might be preferable in PAF patients with a high likelihood of progression, and a better risk stratification for AF progression should be required.

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An echocardiographic index, the diastolic wall strain (DWS), has been reported as a non-invasive direct measure of the left ventricular (LV) compliance [7]. Our previous study showed that the LV compliance evaluated by the DWS was a strong determinant of the prevalence of AF [8]. Decreased LV compliance increases the filling pressures in the LV and atrial wall stress, leading to atrial structural and electrical remodeling that would promote AF persistence. In the present study, we examined the role of LV compliance in the progression from PAF to PerAF, and the usefulness of the DWS for the risk stratification of AF progression in PAF patients with structurally normal hearts, with or without RFCA intervention.

Methods

Study subjects

Consecutive patients with PAF confirmed by a 12-lead electrocardiogram (ECG) or 24-hour Holter monitoring, who underwent transthoracic echocardiography at Nippon Medical School Chiba Hokusoh Hospital between May 2004 and February 2016, were screened for this study. The study was approved by the institutional review board. Patients were excluded from the study if any of the following were present: (1) LV ejection fraction <50%, (2) LV wall motion abnormality, (3) ischemic heart disease, (4) non-ischemic cardiomyopathy, (5) valvular heart disease, (6) congenital heart disease, (7) intraventricular conduction defect, (8) thyroid dysfunction, (9) history of prior RFCA procedures, (10) insufficient echocardiographic quality for measuring the DWS, or (11) presence of AF during the echocardiography. Hypertensive patients with LV hypertrophy only were included in this study.

A total of 306 patients were studied. We determined the $CHADS_2$ and CHA_2DS_2-VASc scores, which assess the thromboembolic risk in patients with AF [9]. We also determined the HATCH score, which was previously proposed to assess the clinical risk for AF progression, calculated by assigning 1 point each for hypertension, an age ≥75 years, and chronic obstructive pulmonary disease (COPD), and 2 points each for a transient ischemic attack or stroke and heart failure [10]. The definitions of hypertension, diabetes mellitus, strokes, vascular disease, and COPD were based on that previously reported [9,10]. The creatinine clearance was calculated using the Cockcroft-Gault formula.

Echocardiographic measurements

All echocardiographic data were acquired during sinus rhythm. Measurements of the myocardial wall thickness, cardiac chambers, LV ejection fraction, and calculation of the LV mass were performed in line with the recommendations of the American Society of Echocardiography (ASE) [11]. The left atrial (LA) volume index and LV mass index were defined as the ratio of the LA volume and LV mass to the body surface area, respectively. The mitral peak E and A velocities and deceleration time were measured using pulsed wave Doppler recordings of the transmitral flow sampled at the mitral valve tips. The e' velocity was measured at the septal and lateral mitral annulus with the tissue Doppler signals, and the E/e' ratio was calculated. According to the recent ASE recommendations for the evaluation of LV diastolic function [12], diastolic dysfunction was diagnosed if ≥2 of the following variables were fulfilled: (1) average E/e' ratio >14, (2) septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s, (3) peak tricuspid regurgitation velocity >2.8 m/s, and (4) LA volume index >34 ml/m^2. Furthermore, the diastolic dysfunction was classified into three grades using the reported algorithm for the estimation of the LV filling pressures and grading the LV diastolic dysfunction [12]. If the LV diastolic function was normal, the diastolic dysfunction was classified as grade 0. The DWS was evaluated in the M-mode parasternal long-axis view and calculated using the following formula: DWS = (LV posterior wall thickness at end-systole − LV posterior wall thickness at end-diastole)/LV posterior wall thickness at end-systole (Fig. 1) [7].

RFCA procedures

RFCA was performed according to the Japanese Circulation Society 2006/2011 guidelines for non-pharmacotherapy of cardiac arrhythmias or 2012 guidelines for indications of catheter ablation and/or patient preference [13]. Using an electroanatomical

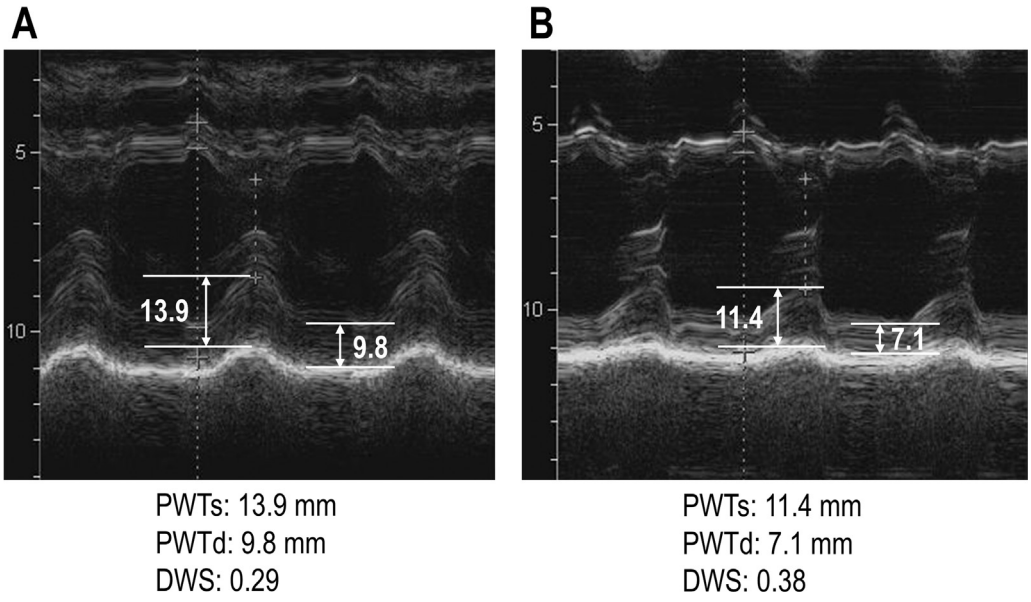

Fig. 1. Representative examples of the diastolic wall strain (DWS) measurements in patients with (A) and without (B) atrial fibrillation progression in the medication group. The M-mode parasternal long-axis view is used to measure the left ventricular posterior wall thickness at end-systole (PWTs) and end-diastole (PWTd). The DWS is simply calculated by the formula (PWTs − PWTd)/PWTs.

mapping system (CARTO, Biosense Webster, Irvine, CA, USA, or EnSite NavX, St. Jude Medical, Inc., St. Paul, MN, USA), contiguous RFCA lesions were created at the level of the LA antrum encircling the right and left pulmonary veins with an open irrigation catheter until the electrical isolation of all pulmonary vein potentials was achieved. A steerable sheath (Agilis, St. Jude. Medical, Inc.) was used for the ablation catheter in all procedures. If a myocardial extension of the superior vena cava (SVC) of >30 mm or AF-triggering ectopic beats were observed in the SVC, an electrical isolation of the SVC was also performed [14]. In the case of an AF recurrence, we performed repeat RFCA procedures where re-isolation was made if pulmonary vein and/or SVC electrical reconnections were documented.

Follow-up

All patients were seen for follow-up every 2–3 months, and the patient symptoms and a 12-lead ECG were obtained at each hospital visit. A 24-hour Holter monitoring was performed if necessary to confirm the persistence of AF. As stated in the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for the management of patients with AF, PerAF was defined as continuous AF lasting longer than 7 days [15]. Progression from PAF to PerAF was defined as the ECG documentation of AF on ≥3 consecutive ECGs, and a 24-hour Holter monitoring separated by a minimum of 1 week.

Statistical analysis

Continuous variables are presented as the mean ± SD and categorical variables as the observed number of patients (percentage). The Mann–Whitney *U* test and Fisher's exact test were used for the comparison of continuous and categorical variables between two groups, respectively. The relationship between DWS and the diastolic dysfunction grade was evaluated by a Jonckheere–Terpstra trend test. The cumulative progression-free survival (i.e. without progression to PerAF) was estimated using the Kaplan–Meier method. The log-rank test was used to compare the AF progression-free survival curves. The hazard ratios of AF progression were calculated using a Cox proportional hazard model, in which all variables showing a statistically significant relationship with AF progression in a univariate model and clinical variables potentially affecting AF progression (age, sex, and HATCH score) were included in a multivariate model. A receiver operating characteristic curve (ROC) analysis was used to determine the predictive accuracy of independent predictors of AF progression. A value of $p < 0.05$ was considered statistically significant.

Results

Among the 306 PAF patients studied, 172 were treated with medications only (medication group), and 134 also underwent RFCA (RFCA group). During a mean follow-up of 35 ± 19 months, progression from PAF to PerAF occurred in 60 (35%) patients in the medication group [92 (54%) patients were treated with antiarrhythmic drugs]. In contrast, only 3 (2%) PAF patients progressed to PerAF in the RFCA group ($p < 0.001$), in which a repeat RFCA was performed in 41 (31%) patients. The incidence of AF progression was 12% and 0.7% per year in the medication and RFCA groups, respectively. Table 1 shows the baseline patient characteristics with and without AF progression in each group. In the medication group, the patients who developed AF progression had a higher prevalence of a prior stroke or transient ischemic attack, but similar $CHADS_2$, CHA_2DS_2-VASc, and HATCH scores, when compared with the patients without AF progression. The level of the brain natriuretic peptide, renal function, and use of medications including antiarrhythmic drugs, β-blockers, and renin-angiotensin system inhibitors did not significantly differ between the patients with and without AF progression. Echocardiographic data showed that the patients with AF progression had a larger LA volume index, LV mass index, and marginally larger LV end-systolic volume and lower LV ejection fraction. The diastolic dysfunction grade assessed by the recommended algorithm using the conventional echocardiographic indices was higher in the patients with AF progression than in those without. In the RFCA group, the clinical characteristics were similar irrespective of AF progression, except for a higher HATCH score in the patients with AF progression. In contrast to the medication group, all echocardiographic data were comparable between the patients with and without AF progression in the RFCA group.

DWS

We assessed the observer variation in the DWS with a single-blind method from 30 randomly selected patients, and the mean ± SD of the intraobserver and interobserver variability was 0.013 ± 0.012 and 0.019 ± 0.011, respectively. Since the DWS is an index of the LV compliance, which is one of the determinants of LV diastolic function, we examined the relationship between the DWS and diastolic dysfunction grade defined by the conventional echocardiographic indices. Although there seemed to be a tendency for the DWS to decrease with a higher diastolic dysfunction grade, the trend was not statistically significant (Fig. 2). In the medication group, the DWS was lower in the patients who developed AF progression than in those who did not (0.31 ± 0.04 versus 0.38 ± 0.04, $p < 0.001$). In the RFCA group, the DWS did not differ between the patients with and without AF progression (0.31 ± 0.05 versus 0.36 ± 0.05, $p = 0.125$).

Predictors of AF progression

In the medication group, the univariate analysis showed that the LA volume index, diastolic dysfunction grade, and DWS were significantly associated with AF progression, while the age, sex, body mass index (BMI), medications including antiarrhythmic drugs, and the other echocardiographic parameters were not (Table 2). The association of the HATCH score with AF progression did not reach a statistically significant level ($p = 0.079$). In the multivariate analysis, the DWS and LA volume index remained significant as risk factors for AF progression, but the diastolic dysfunction grade was no longer a significant predictor of AF progression (Table 2). On the other hand, no variables predicted AF progression in the RFCA group.

We previously reported that a DWS <0.38 was a strong indicator of prevalent AF in structurally normal hearts [8]. Fig. 3 shows the incidence of AF progression according to the DWS in each group. In the medication group, the patients with a DWS <0.38 had a worse progression-free survival compared to those with a DWS ≥0.38 (log-rank $p < 0.001$). On the other hand, the DWS did not significantly affect the progression-free survival in the RFCA group (log-rank $p = 0.189$).

Predictive accuracy of the criteria for AF progression in the medication group

In the medication group, we examined the accuracy of the DWS and LA volume index criteria for predicting AF progression. The area under the ROC curves for the DWS and LA volume index were 0.90 (95% CI 0.84–0.95) and 0.65 (95% CI 0.56–0.74), respectively ($p < 0.001$, Fig. 4). The sensitivity, specificity, positive predictive value, and negative predictive value of the DWS, LA volume index, and combined criteria (DWS plus LA volume index) are shown in

Table 1
Baseline characteristics.

Variables	Medication group ($n=172$)			RFCA group ($n=134$)		
	No AF progression ($n=112$)	AF progression ($n=60$)	p-Value	No AF progression ($n=131$)	AF progression ($n=3$)	p-Value
Age (years)	68 ± 9	67 ± 8	0.417	63 ± 10	62 ± 2	0.537
Female, n (%)	45 (40)	19 (32)	0.322	41 (31)	0 (0)	0.553
Body mass index, kg/m^2	23 ± 3	24 ± 3	0.297	24 ± 3	23 ± 2	0.798
Hypertension, n (%)	68 (61)	35 (58)	0.870	71 (54)	2 (67)	1.000
Diabetes mellitus, n (%)	20 (18)	13 (22)	0.549	20 (15)	1 (33)	0.403
Heart failure, n (%)	0 (0)	0 (0)	NA	0 (0)	1 (33)	0.022
History of a stroke or TIA, n (%)	5 (5)	9 (15)	0.021	10 (8)	1 (33)	0.228
COPD, n (%)	2 (2)	1 (2)	1.000	3 (2)	0 (0)	1.000
$CHADS_2$ score	1.1 ± 0.9	1.3 ± 1.0	0.325	1.0 ± 1.0	1.7 ± 0.6	0.116
0, n (%)	28 (25)	14 (23)		48 (37)	0 (0)	
1, n (%)	56 (50)	26 (44)		50 (38)	1 (33)	
≥2, n (%)	26 (25)	20 (33)		33 (25)	2 (67)	
CHA_2DS_2-VASc score	2.2 ± 1.3	2.3 ± 1.5	0.995	1.8 ± 1.3	2.3 ± 1.5	0.481
0, n (%)	12 (11)	6 (10)		22 (17)	0 (0)	
1, n (%)	17 (15)	17 (28)		37 (28)	1 (33)	
≥2, n (%)	83 (74)	37 (62)		72 (55)	2 (67)	
HATCH score	0.9 ± 0.8	1.0 ± 0.9	0.250	0.8 ± 0.8	2.0 ± 1.0	0.031
0, n (%)	36 (32)	17 (28)		51 (39)	0 (0)	
1, n (%)	60 (54)	29 (48)		61 (47)	1 (33)	
≥2, n (%)	16 (14)	14 (24)		19 (14)	2 (67)	
Creatinine clearance, mL/min	73 ± 22	77 ± 25	0.373	86 ± 28	81 ± 20	0.816
BNP, pg/mL	63 ± 63	67 ± 55	0.663	52 ± 54	41 ± 8	0.916
Baseline medications						
Class I AAD, n (%)	49 (44)	21 (35)	0.329	38 (29)	1 (33)	1.000
Class III AAD, n (%)	2 (2)	3 (5)	0.344	2 (2)	0 (0)	1.000
β-Blockers, n (%)	78 (70)	43 (72)	0.862	67 (51)	2 (67)	1.000
CCB, n (%)	44 (39)	29 (48)	0.262	48 (37)	2 (67)	0.555
ACEI or ARB, n (%)	46 (41)	27 (45)	0.631	43 (33)	1 (33)	1.000
Diuretics, n (%)	9 (8)	9 (15)	0.193	11 (8)	1 (33)	0.247
Statins, n (%)	29 (26)	17 (28)	0.722	29 (22)	1 (33)	0.536
Echocardiographic parameters						
LAVI, mL/m^2	29 ± 10	34 ± 12	0.001	28 ± 10	25 ± 8	0.851
LV mass index, g/m^2	99 ± 26	109 ± 28	0.008	95 ± 23	104 ± 16	0.340
LV end-diastolic dimension, mm	49 ± 5	50 ± 6	0.124	50 ± 6	46 ± 2	0.190
LV end-systolic dimension, mm	30 ± 4	32 ± 5	0.038	31 ± 5	30 ± 4	0.695
LV ejection fraction, %	67 ± 6	65 ± 7	0.032	67 ± 7	65 ± 7	0.568
E-wave deceleration time, ms	218 ± 48	226 ± 68	0.974	218 ± 52	220 ± 73	0.869
e', cm/s	6.4 ± 1.7	6.9 ± 2.4	0.097	7.4 ± 6.2	5.0 ± 0.5	0.497
E/e' ratio	12 ± 4	12 ± 4	0.182	11 ± 4	13 ± 2	0.198
Diastolic dysfunction grade	0.5 ± 0.7	0.8 ± 0.9	0.037	0.4 ± 0.6	0 ± 0	0.314
0, n (%)	72 (64)	31 (52)		97 (74)	3 (100)	
1, n (%)	30 (27)	15 (25)		22 (17)	0 (0)	
2, n (%)	9 (8)	11 (18)		12 (9)	0 (0)	
3, n (%)	1 (1)	3 (5)		0 (0)	0 (0)	

Continuous variables are presented as mean ± SD.
AAD, antiarrhythmic drugs; ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BNP, brain natriutretic peptide; CCB; calcium channel blockers; COPD, chronic obstructive pulmonary disease; E, peak early diastolic transmitral flow velocity; e', peak early diastolic mitral annular velocity; LAVI, left atrial volume index; LV, left ventricular; TIA, transient ischemic attack.

Table 3. Of the 172 patients in the medication group, 61 (36%) had a DWS of ≥0.38. AF progression occurred only in 5 of 61 (8%) patients with a DWS ≥0.38. The positive predictive value of the presence of LA enlargement (i.e. LA volume index >34 mL/m^2 by the ASE recommendation) alone was limited in the medication group (47%, 95% CI 34–61%). However, in the patients with a DWS <0.38 and LA enlargement had a higher positive predictive value for AF progression (68%, 95% CI 51–81%), and 27 of 40 (68%) PAF patients with a DWS <0.38 and LA enlargement progressed to PerAF.

Discussion

After an initial diagnosis of AF, self-terminating PAF often, but not always, progresses to sustained PerAF, which is related to a significant morbidity and mortality [2,3,10]. In general AF populations who are treated with medication, the annual incidence of AF progression ranges from 10% to 20%, resulting in a high incidence of progression in the long-term follow-up (from 50% to 77% after 12 years) [4]. Although our PAF cohort did not include patients with cardiomyopathy, ischemic, or valvular heart disease, which are known to be associated with AF progression [16,17], the AF progression rate in our study (12% per year) was comparable to the previous studies [4]. Progression to PerAF was not suppressed by the use of antiarrhythmic drugs or renin–angiotensin system inhibitors that might affect the natural course of PAF patients [18,19]. RFCA greatly suppressed the progression to PerAF in our PAF cohort (0.7% per year), which was consistent with the previous studies [4]. However, it has been shown that the efficacy of RFCA is reduced once PAF progresses to PerAF [6]; hence, it is of clinical importance to determine PAF patients at a higher risk for AF progression who might benefit from earlier intervention with RFCA.

Previous cohort studies found several clinical predictors of the progression of PAF to PerAF in medically-treated populations. In the Canadian Registry of Atrial Fibrillation study, the age, significant aortic stenosis or mitral regurgitation, LA dilatation, and cardiomyopathy were the independent predictors of AF progression [17]. The Euro Heart Survey study showed that heart

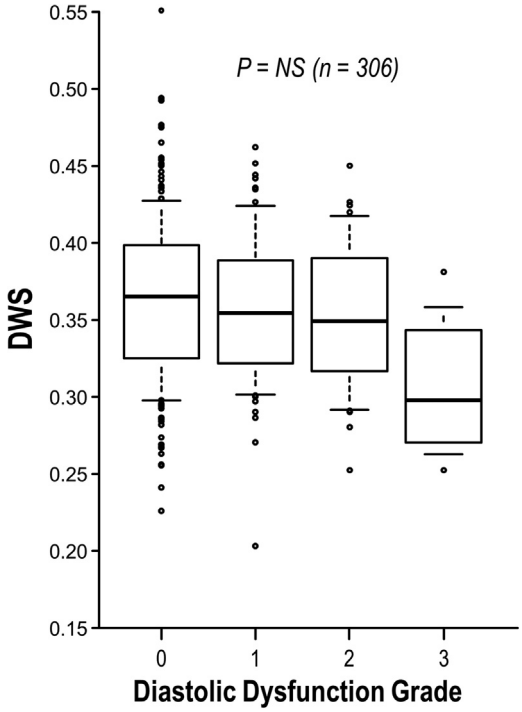

Fig. 2. The relationship between diastolic wall strain (DWS) and the diastolic dysfunction grade defined by the American Society of Echocardiography recommendation algorithm [12]. Each box displays the median, 75th percentile, and 25th percentile values; the horizontal bars indicate the 10th and 90th percentiles. The median of the DWS seems to be lower in the higher diastolic dysfunction grade, but this trend was not statistically significant.

failure, an age >75 years, previous transient ischemic attacks or strokes, COPD, and hypertension were independently associated with AF progression, and they developed the HATCH score using those parameters to estimate the risk of AF progression [10]. In the present study, the HATCH score was not independently associated with AF progression. This may be explained by the difference in the study population. In the Euro Heart Survey study, 32% of the patients had coronary artery disease, 19% had valvular heart disease, and 11% had COPD [10]. In contrast, our cohort excluded patients with ischemic or valvular heart disease, and only 0.6% of our patients had COPD. Thus, our study included healthier patients, and the HATCH score may have limitations in the prediction of AF progression in low-risk PAF patients as in our study cohort. Previous studies found that age alone was an independent predictor of AF progression, in which the hazard ratio was 1.27–1.40 for every 10-year increase of age [16,17]. In our study, age was not a predictor of AF progression, possibly because of the difference in the study population and insufficient length of the follow-up period (≈3 years). Obesity has also been shown to be a risk factor of AF progression, in which a greater BMI has a higher likelihood of AF progression [20]. The BMI did not predict AF progression in our study, but our result did not seem to contradict the previous study, because the mean BMI in our patients was low, which fell into the lowest-risk category of AF progression [20].

Although we studied the population with normal LV function, some had a low value of DWS. Previous studies showed that the mean or median values of DWS ranged from 0.40 to 0.44 in normal subjects, 0.38–0.39 in patients with LV hypertrophy, 0.29–0.33 in patients with heart failure with preserved ejection fraction, and 0.24–0.27 in patients with heart failure with reduced ejection fraction [7,8,21–23]. Thus, a DWS seems to decrease progressively as the heart disease becomes more advanced. The DWS <0.38 implies a relatively mild impairment of LV compliance, and our results indicated that mild enhancement of LV stiffness would promote AF progression even in patients with normal LV function. Since the negative predictive value of a DWS <0.38 was high (92%), the DWS could be useful in determining patients at low risk for AF progression. The LA volume index was also an independent predictor of AF progression, but the LA enlargement alone had a limited accuracy for the prediction of AF progression. However, LA enlargement could be a good indicator of AF progression in patients with a DWS <0.38. Thus, the combined use of the DWS and LA volume index would help determine patients at high risk for AF progression.

We could not identify any other echocardiographic parameters that were independent risk factors for AF progression, including the diastolic dysfunction grade. Diastolic dysfunction encompasses impaired relaxation and decreased compliance. Abnormal LV relaxation leads to a reduction in LA emptying with a higher LA pressure during early-diastole, while decreased LV compliance elevates the LV filling and LA pressures during mid- to late-diastole. In the presence of impaired LV compliance during

Table 2
Unadjusted and adjusted hazard ratios for atrial fibrillation progression in the medication group.

Variables	Univariate model			Multivariate model		
	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Age	1.00	0.97–1.04	0.862	0.99	0.95–1.03	0.607
Female	0.86	0.49–1.49	0.582	0.64	0.34–1.22	0.175
Body mass index	1.06	0.98–1.13	0.141			
Hypertension	0.94	0.56–1.59	0.829			
$CHADS_2$ score	1.25	0.96–1.62	0.104			
CHA_2DS_2-VASc score	1.07	0.89–1.30	0.467			
HATCH score	1.33	0.97–1.84	0.079	1.02	0.70–1.50	0.905
AAD	0.90	0.54–1.50	0.689			
β-Blockers	0.94	0.53–1.66	0.830			
ACEI or ARB	1.28	0.77–2.14	0.343			
LAVI	1.04	1.02–1.06	<0.001	1.04	1.01–1.08	0.012
LV mass index	1.01	1.00–1.02	0.084			
LV end-systolic dimension	1.04	0.98–1.10	0.185			
LV ejection fraction	0.98	0.94–1.02	0.286			
e′	1.09	0.96–1.25	0.195			
Diastolic dysfunction grade	1.51	1.12–2.04	0.007	0.92	0.61–1.38	0.672
DWS (per 0.01 decrease)	1.13	1.08–1.18	<0.001	1.13	1.08–1.18	<0.001

AAD, antiarrhythmic drugs; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CI, confidence interval; DWS, diastolic wall strain; *e′*, peak early diastolic mitral annular velocity; LAVI, left atrial volume index; LV, left ventricular.

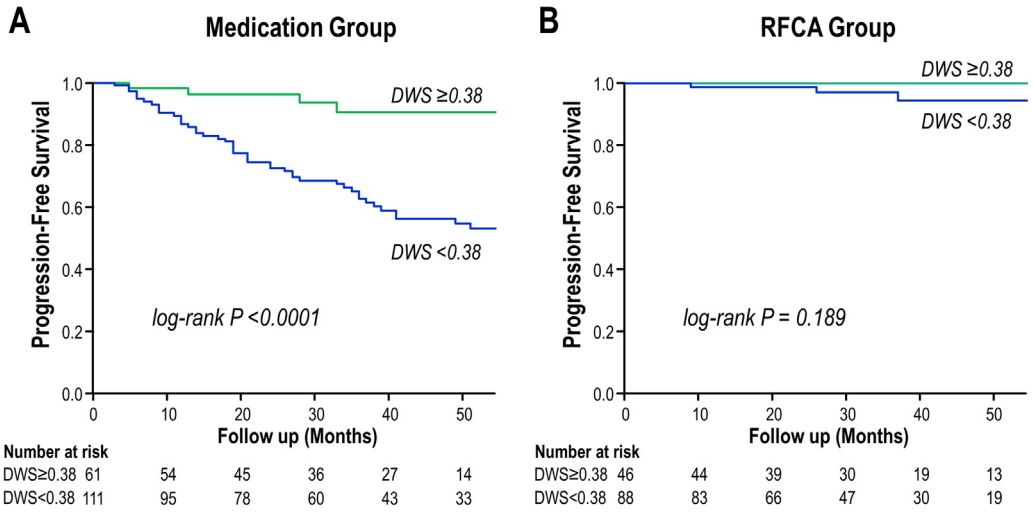

Fig. 3. Kaplan–Meier atrial fibrillation progression-free survival curves stratified by a diastolic wall strain (DWS) of 0.38 in the medication group (A) and radiofrequency catheter ablation (RFCA) group (B). The green lines represent the survival curves in patients with a DWS ≥0.38 and the blue lines those in patients with a DWS <0.38.

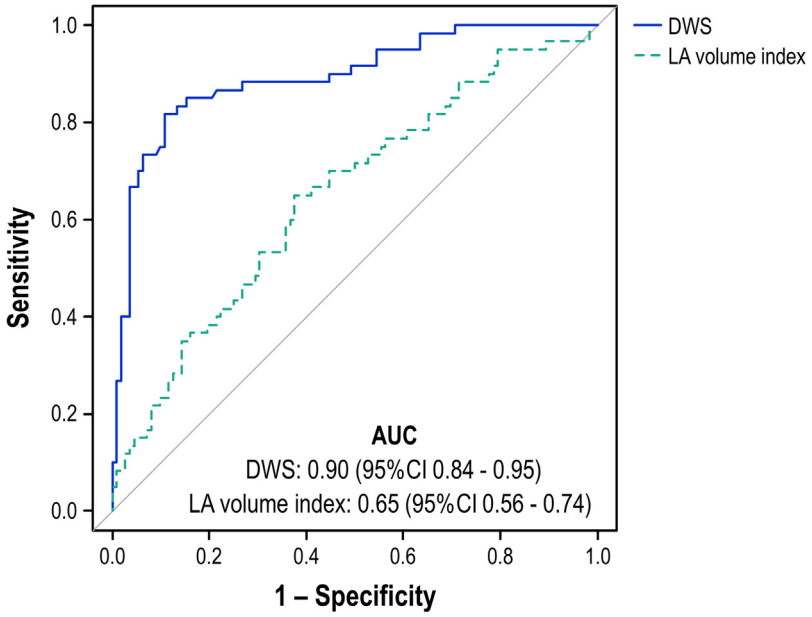

Fig. 4. The area under the receiver operating characteristic curve (AUC) for predicting atrial fibrillation progression with the diastolic wall strain (DWS) and left atrial (LA) volume index in the medication group.

Table 3
Sensitivity, specificity, and predictive values of the DWS and left atrial volume for predicting AF progression in the medication group.

Criteria for predicting AF progression	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
DWS <0.38	92	50	50	92
LAVI >34 mL/m^2	45	73	47	71
DWS <0.38 *plus* LAVI >34 mL/m^2	45	88	68	75

AF, atrial fibrillation; DWS, diastolic wall strain; LAVI, left atrial volume index.

late-diastole, the atrial wall stress would be further enhanced by atrial contraction. The increased atrial wall stress induces atrial structural and electrical remodeling that would promote the persistence of AF. The diastolic dysfunction grade is defined using the conventional echocardiographic indices including the *E*/*A* ratio, peak *E* and *e′* velocity, all of which mainly reflect LV relaxation [12]. In contrast, the DWS is a measure of the LV compliance [7]. Despite a tendency for the DWS to have become lower with a higher diastolic dysfunction grade, their relationship was not statistically significant. This confirms that the conventional echocardiographic parameters primarily indicate LV relaxation, but they are limited in the estimation of the LV compliance. Our results indicated that LV compliance, rather than LV relaxation, may play a greater role in the progression from PAF to PerAF. A

recent study showed that in addition to the LA size, the LA global strain measured by two-dimensional speckle-tracking echocardiography independently predicted AF progression [24]. The LA global strain represents functional and structural remodeling of the LA that is a key feature in the perpetuation of AF. The LA global strain or other 3-dimensional LA measurements [25] were not measured in our study, and their additional values to predict AF progression remains to be clarified. Nevertheless, the DWS was a good indicator of AF progression despite being a simple index that is measurable even with a former-generation ultrasound system.

One might think that a low DWS also reflects irreversible LA and LV remodeling and predicts a poor outcome of RFCA. In fact, patients with a low DWS and heart failure with preserved ejection fraction had a higher rate of death [22]. However, a recent study demonstrated that RFCA of AF was effective independently of the type of heart failure [26]. Our results showed that RFCA greatly reduced the rate of progression from PAF to PerAF regardless of the value of the DWS. Thus, patients with a low DWS and LA enlargement would benefit from earlier RFCA and be good candidates for RFCA. Alternatively, RFCA could be deferred in patients with a high DWS. The DWS might help stratify patients at risk for AF progression in structurally normal hearts.

Limitations

First, this was a retrospective cohort study. A further prospective study is still needed to firmly establish the usefulness of the DWS in predicting AF progression in patients with PAF. Further, the cut-off values of the DWS and utility of the DWS to guide the treatment strategies need to be evaluated in future prospective studies. Second, we included only patients who were in sinus rhythm at the time of the echocardiographic measurements. Because the DWS is independent of the cycle length and loading conditions [7], the values of the DWS measured during AF may be comparable to those during sinus rhythm. Nevertheless, the DWS needs to be estimated during sinus rhythm until the accuracy of the DWS during AF is validated. Third, we did not have any data on the AF burden that showed it was associated with AF progression [27]. This raises the possibility that the low DWS cohort might have had a higher AF burden, since we previously showed that a low DWS was associated with a high prevalence of AF [8]. Finally, the DWS is based on a linear elastic theory in the presence of a preserved LV systolic function, and may not reflect the global LV compliance since it is measured regionally on the LV posterior wall [7]. We excluded patients with ischemic or structural heart disease because they may have had an impaired LV systolic function and significant regional variability in the LV compliance. Further studies are needed to clarify the role of DWS in patients with ischemic or structural heart disease.

Conclusions

A decreased LV compliance assessed by DWS was an independent predictor of AF progression in PAF patients with structurally normal hearts. The DWS could be useful to stratify PAF patients at risk for AF progression who could benefit from earlier RFCA intervention.

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Conflict of interest

None declared.

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