CLINICAL INVESTIGATIONS

Left ventricular stiffness estimated by diastolic wall strain is associated with paroxysmal atrial fibrillation in structurally normal hearts

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Background: Left ventricular (LV) diastolic dysfunction depends on an impaired relaxation and stiffness. Abnormal LV relaxation contributes to the development of atrial fibrillation (AF), but the role of LV stiffness in AF remains unclear.

Hypothesis: Diastolic wall strain (DWS), a load-independent, noninvasive direct measure of LV stiffness, correlates with prevalent AF.

Methods: This study included 328 consecutive subjects with structurally normal hearts: 164 paroxysmal AF patients and 164 age- and sex-matched (1:1) controls. We calculated the DWS from the M-mode echocardiographic measurements of the LV posterior wall thickness at end-systole and end-diastole during sinus rhythm.

Results: The DWS was lower in the AF patients (0.35 ± 0.07) than in the controls (0.41 ± 0.06 ; $P < 0.001$). After adjusting for the risk factors of AF using a conditional logistic regression analysis, a history of hypertension, plasma brain-type natriuretic peptide level, and DWS were independently associated with AF prevalence, whereas body mass index, LV mass index, left atrial volume, and any conventional indices of the diastolic function were not. A low DWS (<0.380) was the strongest indicator of AF (odds ratio: 6.22, 95% confidence interval: 3.08–14.2, $P < 0.001$).

Conclusions: Increased LV stiffness estimated by DWS was a strong determinant of the prevalence of AF. LV stiffness may play a role in the pathogenesis of paroxysmal AF in structurally normal hearts.

KEYWORDS

Atrial fibrillation, Diastolic dysfunction, Stiffness, Diastolic wall strain

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia that substantially increases morbidity and mortality.¹ AF occurs in patients with structural heart diseases in which electrophysiological alterations in the diseased atrial tissue promote the genesis of AF. On the other hand, AF also occurs in structurally normal hearts, although its pathological mechanism remains incompletely defined. An understanding of the predisposing factors for AF is of great importance, because early identification of individuals who are at risk for AF would allow its prevention and targeted intervention.

A prior study showed that the incidence of AF was associated with left ventricular (LV) diastolic dysfunction evaluated by transthoracic echocardiography.² The conventional echocardiographic indices for estimating LV diastolic function, such as isovolumetric relaxation time, E/A ratio, mitral annular velocity (E'), and deceleration time of LV early filling velocity (DCT), mainly reflect LV myocardial relaxation and are influenced by loading conditions.³ However, LV diastolic function is determined not only by LV myocardial relaxation (ie, active relaxation property), but also by the passive LV filling property that is described as LV stiffness. Direct estimation of LV stiffness usually requires invasive pressure-volume measurements,

and the role of LV stiffness in the development of AF is still unknown.

Recently, a novel echocardiographic index, diastolic wall strain (DWS), has been reported as a noninvasive direct measure of LV stiffness.⁴ DWS is based on the linear elastic theory, in which impaired diastolic thinning of the LV posterior wall reflects the resistance to deformation during diastole (ie, increased LV stiffness) in the presence of a preserved LV systolic function. The DWS correlated well with LV stiffness invasively measured in an animal model. Furthermore, it has been shown that DWS is independent of loading conditions.⁴ The purpose of this study was to evaluate the relationship between AF and LV stiffness assessed by DWS.

2 | METHODS

2.1 | Study Subjects

Consecutive patients who underwent transthoracic echocardiography in Nippon Medical School Chiba Hokusoh Hospital between January 2013 and October 2015 were considered for inclusion in this study. The study was approved by the institutional review board. The medical records were reviewed to assess patient characteristics. Patients with structural heart diseases, left ventricular ejection fraction (LVEF) <50%, a history of heart failure, ischemic heart diseases, intraventricular conduction defects, thyroid dysfunction, and an insufficient echocardiographic quality for measuring DWS were excluded. A total of 164 patients with ≥ 1 documented episode of paroxysmal AF by a 12-lead surface electrocardiogram or 24-hour Holter monitoring were included in this study (AF group). Because both the echocardiographic measurements and AF prevalence greatly depend on patient age and sex,^{3,5,6} we selected 164 age- and sex-matched (1:1) patients who had no history of AF as controls (non-AF group). The definitions of hypertension (HT), diabetes mellitus (DM), strokes, and vascular disease were based as CHA₂DS₂-VASc scoring.⁷ The creatinine clearance was calculated using the Cockcroft-Gault formula.

2.2 | Echocardiographic Measurements

All echocardiographic data were obtained during sinus rhythm in both groups. Measurements of interventricular septal thickness and posterior wall thickness (PWT) and calculation of LV mass, left atrial (LA) volume,

and LVEF were performed according to the recommendation of the American Society of Echocardiography.⁶ Left ventricular mass index (LVMI) and left atrial volume index (LAVI) were defined as the ratio of the LV mass and LA volume to the body surface area, respectively. The mitral peak E and A velocities and DCT 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. Diastolic dysfunction was classified into 3 levels (abnormal relaxation: E/A <0.75 or DCT >240 ms; pseudo-normal LV filling: E/A 0.75–1.50, DCT 151–240 ms, and LA volume ≥ 28 mL/m²; restrictive diastolic filling: E/A >1.5 or DCT ≤ 150 ms), as defined previously.²

The DWS was calculated using the following formula: $DWS = (PWT \text{ at end-systole} - PWT \text{ at end-diastole}) / PWT \text{ at end-systole}$ (Figure 1).⁴ DWS was measured by 2 doctors with a single-blind method. The mean $\pm$ SD of the intraobserver and interobserver variability of DWS were 0.013 ± 0.012 and 0.019 ± 0.011 , respectively ($n = 30$).

2.3 | Statistical Analysis

Continuous variables were expressed as mean $\pm$ SD. The differences between the 2 groups were assessed using the Mann-Whitney *U* test. Categorical variables were compared by Fisher exact test. Relationships between 2 variables were examined using the Spearman rank correlation test. The Kruskal-Wallis test, followed by a post-hoc testing with a Mann-Whitney *U* test and Bonferroni correction, was used for multiple comparisons. A conditional logistic regression analysis was used to adjust for the clinical and echocardiographic variables potentially affecting the prevalence of paroxysmal AF. When the distribution of the variables in the measurements was skewed, regression analyses were performed after a logarithmic transformation. All tests were 2-tailed, and $P < 0.05$ indicated statistical significance.

3 | RESULTS

3.1 | Patient Characteristics

The clinical characteristics of the study patients are presented in Table 1. The prevalence of HT and the CHA₂DS₂ score were higher in the AF group than in the non-AF group. In addition to age and sex

FIGURE 1 Measurements and calculation of DWS. Representative echocardiographic recordings in the non-AF and AF groups are shown. The M-mode parasternal long-axis view is used to measure the LV PWT at end-systole (PWTs) and end-diastole (PWTd). The DWS is calculated by the formula $(PWTs - PWTd) / PWTs$. Abbreviations: AF, atrial fibrillation; DWS, diastolic wall strain; LV, left ventricular; PWT, posterior wall thickness.

TABLE 1 Clinical characteristics

Variables	Overall, n = 328	Non-AF, n = 164	AF, n = 164	P Value
Age, y	65 ± 9	65 ± 9	65 ± 9	0.654
Male sex	202 (62)	101 (62)	101 (62)	1.000
BMI, kg/m ²	23 ± 3	23 ± 4	24 ± 3	0.085
HT	167 (51)	68 (42)	99 (60)	0.001
DM	73 (22)	41 (25)	32 (20)	0.288
CHADS ₂ score	1.0 ± 1.0	0.8 ± 0.9	1.1 ± 1.0	0.003
CHA ₂ DS ₂ -VASc score	2.0 ± 1.4	1.9 ± 1.4	2.1 ± 1.4	0.180
CrCl, mL/min	79 ± 25	81 ± 24	78 ± 26	0.193
HbA _{1c} , %	6.1 ± 0.8	6.1 ± 0.9	6.1 ± 0.6	0.973
TC, mg/dL	193 ± 37	192 ± 38	195 ± 37	0.520
HDL-C, mg/dL	56 ± 15	56 ± 16	56 ± 14	0.841
LDL-C, mg/dL	113 ± 30	114 ± 30	111 ± 31	0.293
BNP, pg/mL	53 ± 64	35 ± 30	70 ± 82	<0.001
Medications				
RAASI	125 (38)	52 (32)	73 (45)	0.011
β-Blocker	82 (25)	21 (13)	61 (37)	<0.001
CCB	118 (36)	51 (31)	67 (41)	0.084
Diuretic	42 (7)	8 (5)	16 (10)	0.136
Statin	91 (27)	53 (32)	38 (23)	0.084

Abbreviations: BMI, body mass index; BNP, plasma brain-type natriuretic peptide; CCB, calcium channel blocker; CHADS₂, congestive HF, HT, age ≥75 y, DM, prior stroke/TIA/TE; CHA₂DS₂-VASc, congestive HF, HT, age ≥75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (women); CrCl, creatinine clearance; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; RAASI, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; TC, total cholesterol.

Data are presented as n (%) or mean ± SD.

matched by the study design, there were no differences in body mass index (BMI), prevalence of DM, renal function, or lipid profiles between the 2 groups. The plasma brain-type natriuretic peptide (BNP) levels were higher in the AF group than in the non-AF group. Renin-angiotensin-aldosterone system inhibitors (RAASI) and β-blockers were prescribed to more patients in the AF group than in the non-AF group because the AF group patients had a higher prevalence of HT, and β-blockers were prescribed for a rate-control treatment of AF.

3.2 | Echocardiographic Measurements

The echocardiographic data are shown in Table 2. The LVMI was higher in the AF group than in the non-AF group. Patients in the AF group had a larger LAVI than did the non-AF group patients. Patients in both groups had a similar LV systolic function assessed by LVEF. When the Doppler echocardiographic indices representing LV diastolic function were compared, the E/A and E/E' ratios were higher, and the DCT was shorter, in patients in the AF group than in non-AF group patients. The AF group patients had more severe diastolic dysfunction defined by the conventional grading method when compared with the non-AF group patients (more pseudo-normal LV filling and less abnormal relaxation in the AF group, but no difference in

TABLE 2 Echocardiographic measurements

Variables	Overall, N = 328	Non-AF, n = 164	AF, n = 164	P Value
IVS, mm	9.3 ± 1.5	9.2 ± 1.6	9.4 ± 1.5	0.064
PWT, mm	8.2 ± 1.6	8.0 ± 1.7	8.3 ± 1.4	0.082
LVEDD, mm	48 ± 6	48 ± 6	49 ± 5	0.166
LVESD, mm	30 ± 4	30 ± 4	30 ± 4	0.310
LVMI, g/m ²	91 ± 20	87 ± 19	94 ± 21	0.003
LAVI, mL/m ²	25 ± 9	22 ± 8	27 ± 10	<0.001
LVEF, %	67 ± 6	67 ± 6	68 ± 6	0.577
E velocity, cm/s	70 ± 19	69 ± 18	71 ± 21	0.164
A velocity, cm/s	76 ± 19	78 ± 19	74 ± 20	0.064
E/A ratio	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.4	0.018
E' velocity, cm/s	6.9 ± 4.2	6.8 ± 1.9	7.0 ± 5.6	0.489
E/E' ratio	11.2 ± 3.4	10.8 ± 3.2	11.6 ± 3.5	0.022
DCT, msec	222 ± 56	231 ± 58	212 ± 52	0.003
Diastolic dysfunction				
Abnormal relaxation	137 (42)	82 (50)	55 (34)	0.004
Pseudo-normal LV filling	47 (14)	15 (9)	32 (20)	0.011
Restrictive diastolic filling	41 (13)	15 (9)	26 (16)	0.094
DWS	0.38 ± 0.07	0.41 ± 0.06	0.35 ± 0.07	<0.001

Abbreviations: A, peak late diastolic transmitral flow velocity; AF, atrial fibrillation; DCT, deceleration time; DWS, diastolic wall strain; E, peak early diastolic transmitral flow velocity; E', peak early diastolic mitral annular velocity; IVS, interventricular septum; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PWT, posterior wall thickness; SD, standard deviation.

Data are presented as n (%) or mean ± SD.

restrictive diastolic filling between the groups). Finally, the LV stiffness estimated by the DWS was lower in the AF group patients than in the non-AF group patients.

DWS was not correlated with age, LAVI, or conventional Doppler echocardiographic indices of diastolic function including the E/A and E/E' ratios and DCT (all *P* = not significant); whereas DWS was inversely correlated with LVMI (*r* = −0.139; *P* = 0.011). Because DWS has been shown to decrease in patients with HT,^{4,8} and the AF group included more HT patients, we separately measured DWS by the presence or absence of HT in each group (Figure 2). DWS was significantly lower in the AF group patients than in the non-AF group patients, regardless of a history of HT.

3.3 | Contributing Variables for the Prevalence of Paroxysmal AF

A conditional logistic regression analysis was conducted to determine the variables contributing to the prevalence of paroxysmal AF by adjusting for BMI, history of HT, plasma BNP levels, LVMI, LAVI, LVEF, E/E' ratio, presence or absence of each level of diastolic function, and DWS (Table 3). The analyses identified that a history of HT, higher plasma BNP levels, and a lower DWS were independently associated with the prevalence of paroxysmal AF, whereas the BMI,

FIGURE 2 Comparisons of the DWS among patients with paroxysmal AF with and without HT. Note that the DWS was lower in the AF patients irrespective of the presence of HT. Each box displays the median, 75th percentile, and 25th percentile values; the horizontal bars indicate the 10th and 90th percentiles. Abbreviations: AF, atrial fibrillation; DWS, diastolic wall strain; HT, hypertension.

TABLE 3 Conditional logistic regression analysis for the prevalence of paroxysmal AF

Variables	OR (95% CI)	P Value
BMI	0.97 (0.86-1.09)	0.589
HTN	1.98 (1.00-3.90)	0.049
Log BNP	2.68 (1.64-4.38)	<0.001
LVMI	1.02 (0.99-1.04)	0.097
LAVI	1.03 (0.98-1.08)	0.221
LVEF	0.99 (0.94-1.06)	0.837
Log E/e'	0.89 (0.25-3.13)	0.850
Abnormal relaxation	0.48 (0.22-1.05)	0.065
Pseudo-normal LV filling	0.56 (0.18-1.79)	0.331
Restrictive diastolic filling	0.84 (0.30-2.34)	0.738
DWS <0.380	6.62 (3.08-14.2)	<0.001

Abbreviations: AF, atrial fibrillation; BMI, body mass index; BNP, brain-type natriuretic peptide; CI, confidence interval; DWS, diastolic wall strain; E, peak early diastolic transmitral flow velocity; E', peak early diastolic mitral annular velocity; HTN, hypertension; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; OR, odds ratio.

LVMI, LAVI, LVEF, and conventional echocardiographic indices of the diastolic function were not. A low DWS (< median [0.380]) was the strongest indicator of AF prevalence. DWS remained an independent indicator of AF prevalence when DWS was entered in the same model as a continuous variable (odds ratio: 1.22, 95% confidence interval: 1.14-1.31 per 0.01 decrease, $P < 0.001$).

4 | DISCUSSION

LV diastolic dysfunction is not uncommon in the general population and is associated with the incidence of heart failure and increased mortality.⁹ The pathophysiology of LV diastolic dysfunction is complex, but it can be simply described as an impaired LV relaxation and/or increased LV stiffness.³ A recent study reported that an early stage of diastolic dysfunction could start with an increase in the LV stiffness even before the abnormal LV relaxation becomes apparent.¹⁰ Both an impaired LV relaxation and increased LV stiffness augment the LV filling pressures at rest or with exercise. An increased LV filling pressure raises the LA wall stress, leading to atrial structural and electrical remodeling that promotes AF.

In this matched case-control study, we found that LV stiffness assessed by DWS was independently associated with the prevalence of AF in structurally normal hearts, but the conventional echocardiographic indices of LV diastolic function were not. Tsang et al² reported that the scheme of grading the diastolic dysfunction using transmitral Doppler flow profile was an important predictor of AF incidence in the elderly population. The Framingham Heart Study demonstrated that echocardiographic measurements, including LA size, LV systolic function, and LV wall thickness, were independent predictors of AF.¹¹ Although patients in the AF group had higher grades of diastolic dysfunction defined by that scheme and a larger LA volume, these were no longer independent indicators of AF prevalence after adjustments for other potential variables related to AF. This may be attributable to the difference in the study population, in which we studied only patients with a structurally normal heart and normal LV systolic function, whereas previous studies also included patients with coronary artery disease and congestive heart failure.^{2,11}

It is known that the E' velocity measured by tissue Doppler velocities at the mitral annulus is a more sensitive parameter for abnormal LV relaxation, and the E/E' ratio can be an estimate of the LV filling pressure.³ Although the E/E' ratio was higher in the AF group patients compared with the non-AF group patients, it was also not an independent indicator of AF prevalence after adjusting for the risk factors of AF. One limitation of estimating the LV filling pressure by the E/E' ratio is that the E' velocity is positively related to the preload, and the E/E' ratio may not provide a reliable estimate of the LV filling pressure, especially in normal subjects like our study population.³ Alternatively, the E/E' ratio might have been an independent indicator if it had been measured during exercise, because a low DWS was reported to be associated with an increased post-exercise E/E' ratio in elderly patients without any obvious myocardial ischemia.¹²

HT and LV hypertrophy are known to be risk factors for AF.¹³ In this study, the AF patients had a higher prevalence of HT and LVMI when compared with the age- and sex-matched control patients without a history of AF. Actually, a history of HT was an independent indicator for the prevalence of AF. It has been shown that subjects with HT and LV hypertrophy had lower DWS than normal subjects.^{4,8} We found an inverse correlation between the DWS and LVMI, which was consistent with previous studies.^{10,14} Thus, an increased LV stiffness seems to mediate the association between HT and AF. Nevertheless, the DWS was lower in the AF patients

independent of the presence of HT or LV hypertrophy, indicating that the inherent properties of LV stiffness contributed to the prevalence of AF.

We also identified that high plasma BNP levels were related to the prevalence of AF, even after accounting for other AF risk factors. The association between plasma BNP levels and AF was consistent with a prior study in which a high plasma BNP level predicted the risk of AF in the general population.¹⁵ The independent value of plasma BNP levels for predicting AF in patients with a structurally normal heart might be attributable to a subclinical cardiovascular pathology or a consequence of the intermittent strain during clinical and/or subclinical AF.

In our study, the average value of DWS in the non-AF group was 0.41. Similar values were reported in the normal control group in the previous studies.^{4,14} Although the normal value for DWS has not yet been established, consistent results among the different studies and a low intra- and interobserver variability confirmed the reliability of DWS, providing that the quality of the echocardiographic recording was sufficient.

4.1 | Study Limitations

This study is a retrospective case-control study, and a causal relationship between DWS and AF remains inconclusive. However, our results show a strong relationship between low DWS and prevalent AF, and thus further investigation is warranted. Additional prospective studies following a large cohort of patients with various values of DWS will be required to establish the role of DWS in the development of AF.

There is evidence that the risk of AF in HT patients is dependent on the degree of blood pressure control.¹⁶ We could not obtain any specific information about control of blood pressure in each patient. This might have influenced the effect of HT as a contributing variable for the prevalence of AF.

5 | CONCLUSION

An increased LV stiffness estimated by DWS was strongly associated with prevalence of AF in structurally normal hearts. LV stiffness may play an important role in the pathogenesis of paroxysmal AF.

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Conflicts of interest

The authors declare no potential conflicts of interest.

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