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Original article

Left ventricular diastolic dysfunction is associated with atrial remodeling and risk or presence of stroke in patients with paroxysmal atrial fibrillation

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ABSTRACT

Background: Although the degree of electroanatomical remodeling of the left atrium (LA) is influenced by left ventricular (LV) diastolic function, clinical implications of estimated LV filling pressure (E/Em) are limited in patients with atrial fibrillation (AF). We hypothesized that increased E/Em is related to an advanced LA remodeling, a high CHA_2DS_2-VASc score, and the presence of stroke or transient ischemic attack (TIA) in patients with paroxysmal AF.

Methods: We included 1098 patients with paroxysmal AF (male 74.5%, 57.6 ± 11.3 years old) who underwent AF catheter ablation. We compared E/Em to clinical parameters, echocardiography, and three-dimensional-computed tomography findings.

Results: The E/Em > 15 group ($n = 98$) was older ($p < 0.001$) and had more females ($p < 0.001$), greater LA volume index ($p < 0.001$), higher CHA_2DS_2-VASc score ($p < 0.001$), and stroke/TIA prevalence ($p = 0.001$) than groups with an E/Em of 8–15 ($n = 676$) or <8 ($n = 324$). An E/Em was independently associated with the presence of stroke/TIA (OR 1.638, 95% CI 1.050–2.554, $p = 0.030$) after adjusting for age, sex, body surface area, LA volume index, and LA appendage volume index.

Conclusions: In patients with paroxysmal AF, the elevated LV filling pressure estimated by E/Em is independently associated with the presence of stroke or TIA.

Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) is frequently correlated with atrial fibrillation (AF) [1]. The onset of AF triggers HFpEF in patients with subclinical left ventricular (LV) diastolic dysfunction and may predispose to a poorer prognosis in patients with heart failure [2,3]. There has been a growing interest in understanding a mechanical linkage between diastolic dysfunction and AF with particular attention to the complex interaction between the left atrium (LA) and the LV during diastole [4]. The ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annular velocity (Em) has been used to assess LV filling pressure, and an E/Em > 15 usually indicates pulmonary capillary wedge pressure > 20 mmHg [5]. The correlation of E/Em with pulmonary capillary wedge pressure has been found in patients with AF as well as in sinus rhythm [5–8]. Moreover, the prognostic significance of LV filling pressure estimated by E/Em is well recognized in different clinical settings and populations including heart failure and non-valvular AF [9,10]. We recently reported that LA appendage (LAA) function is closely related to E/Em and the degree of electroanatomical remodeling of LA in patients with paroxysmal AF [11,12]. Although Kosiuk et al. [13] reported a relationship between LV diastolic dysfunction and risk of stroke in 124 patients with AF as a brief report, no other study showed systemic analyses for the relationship between LV diastolic function and risk of stroke in a larger number of patients with AF. Therefore, we hypothesized that LV filling pressure estimated by E/Em is associated with advanced LA remodeling and the risk of events of stroke in patients with paroxysmal AF. The purpose of this study was to evaluate the relationships among E/Em, LA remodeling, CHA_2DS_2-VASc score, and the presence of stroke or transient ischemic attack (TIA) in patients with paroxysmal AF.

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Methods

Patient selection

The study protocol adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System. The study enrolled 1098 consecutive patients (74.5% of who were male, 57.6 ± 11.3 years old) who underwent pre-procedural transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), and radiofrequency catheter ablation (RFCA) for symptomatic drug-refractory paroxysmal AF. The exclusion criteria for RFCA were as follows: (1) persistent or permanent AF; (2) any mitral valve disease, including mild-degree disease; (3) AF with rheumatic valvular disease; (4) associated structural heart disease other than left ventricular hypertrophy; and (5) prior AF ablation. All patients provided proper written informed consent. A total of 1098 patients were selected for the study, and then were categorized into three groups based on their E/Em measured with TTE and Doppler study. We compared the patient groups of E/Em > 15 (n = 98), E/Em 8–15 (n = 676), and E/Em < 8 (n = 324) according to the recommendation of the European Society of Cardiology [14]. The prevalence of stroke was defined as a history of focal neurologic deficit with acute onset and lasting for more than 24 hours with positive results on neuroimaging studies, and TIA was defined as sudden-onset focal neurologic symptoms or signs that resolved within 24 hours [15].

Echocardiographic and computed tomographic evaluation of the heart

TTE was conducted using commercially available devices (iE33, Philips Medical System, Andover, MA, USA; Vivid 7 or Vivid E9, GE Vingmed Ultrasound, Horten, Norway), and standard M-mode, 2-dimensional, and Doppler images were acquired in the parasternal and apical views. The 2-dimensional images were acquired to calculate the following characteristics: LV end-diastolic dimension, LV end-systolic dimension, posterior wall thickness at end diastole, interventricular septal wall thickness at end diastole, and LV ejection fraction. LV mass and LV mass index were calculated using American Society of Echocardiography (ASE)-recommended formula, area length method [16]. The value of early mitral inflow peak velocity (E) was taken by placing sample volume at the opening level of the mitral valve leaflet tips based on the pulse wave Doppler method. Tissue Doppler-derived early diastolic mitral annular velocity (Em) was collected from the septal corner of the mitral annulus in the apical four-chamber view. TEE was performed to measure pulmonary vein flow velocity as well as LAA emptying flow velocity. 3-dimensional spiral computed tomography (64 Channel, Light Speed Volume Ct, Philips, Brilliance 63, Amsterdam, Netherlands) was performed on all patients.

Electrophysiological mapping and radiofrequency catheter ablation

Intracardiac electrograms were recorded using the Prucka Cardio Lab^{TM} electrophysiology system (General Electric Medical Systems Inc., Milwaukee, WI, USA). A 3D electroanatomical map (NavX, St. Jude Medical Inc., Minnetonka, MN, USA) was generated by merging NavX system-generated 3D geometry of the LA and pulmonary veins with corresponding 3D spiral CT images. Using a multi-polar ring catheter (Lasso, Johnson & Johnson Inc, Diamond Bar, CA, USA), a 3D LA voltage map was generated from contact bipolar electrograms of 350–500 points on the LA endocardium during high RA pacing (pacing cycle length 500 ms). The bipolar electrograms were filtered at 32–300 Hz. Color-coded voltage maps were generated by recording bipolar electrograms and measuring peak-to-peak voltage as previously described [17]. However, when frequently re-initiating AF required more than 3 electrical cardioversions, the LA voltage map was not constructed. In the end, 759 of the 1098 patients had a complete set of LA and LAA voltage data.

Data analyses

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) software for Windows (version 20.0). Continuous variables were expressed as the mean ± standard deviation (SD) and compared using Student's t-tests and ANOVAs followed by post hoc analyses using Bonferroni's method. Categorical variables were reported as frequencies (percentage) and compared using Chi-square tests or Fisher's exact tests. To confirm the association between E/Em ratio and the presence of stroke/TIA and/or CHA_2DS_2-VASc score >2 after controlling potential confounding variables, we used multiple logistic regression analyses. A p-value <0.05 was regarded as statistically significant.

Results

E/Em and the degree of LA remodeling

Table 1 summarizes the clinical characteristics in each grade of E/Em. The patients in the E/Em > 15 group had an older age ($p < 0.001$), a higher proportion of females ($p < 0.001$), a lower body surface area ($p < 0.001$), and a higher CHA_2DS_2-VASc score ($p < 0.001$). They were also more likely to have congestive heart failure ($p < 0.001$), hypertension ($p < 0.001$), diabetes mellitus ($p = 0.004$), and a history of stroke or TIA ($p < 0.001$) than those with a low E/Em. Remarkably, nearly 20% of patients with E/Em > 15 reported a history of stroke/TIA. When the E/Em > 15, E/Em 8–15, and E/Em <8 groups were compared to each other using post hoc analyses, the patients with level of E/Em > 15 had greater LA volume index ($p < 0.001$), LA dimension ($p < 0.001$), and LV mass index ($p < 0.001$), and lower LAA emptying flow velocity ($p < 0.001$) than other groups. Fig. 1 displays the exemplary LA electroanatomical voltage maps and LAA emptying flow velocity depending on the E/Em.

E/Em and presence of stroke/TIA

Fig. 2 shows the relationships of LA volume index ($p < 0.001$), LV mass index ($p < 0.001$), LAA emptying flow velocity ($p < 0.001$), LAA volume index ($p < 0.001$), and E/Em ($p < 0.001$) depending on CHA_2DS_2-VASc scores. Table 2 presents the logistic regression analyses for clinical and electroanatomical variables associated with the presence of stroke/TIA. In the univariate logistic regression analyses, the presence of stroke/TIA was associated with old age ($p < 0.001$), lesser body surface area ($p = 0.020$), higher E/Em ($p < 0.001$), as well as greater LA volume index ($p < 0.001$) and LAA volume index ($p = 0.002$), and lower LAA emptying flow velocity ($p < 0.001$). In the multivariate logistic regression analyses, an E/Em was independently associated with the presence of stroke/TIA (OR 1.638, 95% CI 1.050–2.554, $p = 0.030$) after adjusting for age, sex, body surface area, LA volume index, and LAA volume index. We performed the logistic regression analyses for clinical and anatomical variables associated with CHA_2DS_2-VASc scores (>2, n = 269; 1–2, n = 509; and 0, n = 320), and compared 114 patients with a history of stroke/TIA and 984 patients without one in supplementary tables.

Discussion

This is the first systemic analysis for the relationship of LV diastolic function with LA remodeling, and risk or presence of

Table 1
Clinical, electroanatomical, and echocardiographic parameters depending on E/Em.

	All subjects ($n=1098$)	E/Em > 15 ($n=98$)	E/Em 8–15 ($n=676$)	E/Em ≤ 8 ($n=324$)	p-value
Age (years)	57.64 ± 11.33	64.83 ± 9.31*,†	59.17 ± 10.69‡	52.30 ± 11.05	**<0.001**
Female gender (%)	280 (25.5)	50 (51.0)	189 (28.0)	41 (12.7)	**<0.001**
Body mass index (kg/m^2)	24.70 ± 2.85	24.81 ± 2.73	24.86 ± 2.88‡	24.33 ± 2.79	**0.021**
Body surface area (m^2)	1.80 ± 0.18	1.70 ± 0.16*,†	1.80 ± 0.18‡	1.85 ± 0.17	**<0.001**
AF duration (months)	40.92 ± 54.58	37.50 ± 30.30	44.51 ± 58.35	36.79 ± 54.27	**0.840**
CHA_2DS_2-VASc score	1.59 ± 1.55	2.77 ± 1.83*,†	1.74 ± 1.55‡	0.92 ± 1.12	**<0.001**
CHF (%)	50 (4.6)	16 (16.3)	25 (3.7)	9 (2.8)	**<0.001**
Hypertension (%)	499 (45.4)	62 (63.3)	334 (49.4)	103 (31.8)	**<0.001**
Age >75 (%)	68 (6.2)	12 (12.2)	50 (7.4)	6 (1.9)	**<0.001**
Diabetes mellitus (%)	134 (12.2)	21 (21.4)	84 (12.4)	29 (9.0)	**0.004**
Stroke/TIA (%)	114 (10.4)	18 (18.4)	78 (11.5)	18 (5.6)	**<0.001**
Vascular disease (%)	162 (14.8)	25 (25.5)	108 (16.0)	29 (9.0)	**<0.001**
Medications					
ACEI/ARB (%)	357 (32.5)	48 (49.0)	237 (35.1)	72 (22.2)	**<0.001**
β-Blocker (%)	345 (31.4)	40 (40.8)	207 (30.7)	98 (30.2)	0.111
Statin (%)	301 (27.4)	37 (37.8)	205 (30.4)	59 (18.2)	**<0.001**
AAD (%)	59 (5.4%)	8 (8.2%)	38 (5.6%)	13 (4.0%)	0.251
3D-CT & voltage map					
LA volume index(mL/m^2)	73.19 ± 20.77	86.85 ± 24.87*,†	73.46 ± 20.89‡	68.38 ± 16.89	**<0.001**
LAA volume index (mL/m2)	6.34 ± 2.95	6.55 ± 2.83	6.47 ± 3.08	5.99 ± 2.68	0.082
Mean LA voltage (mV)	1.35 ± 0.65	1.23 ± 0.65	1.34 ± 0.64	1.39 ± 0.67	0.195
LAA voltage (mV)	2.51 ± 1.56	2.11 ± 1.28	2.58 ± 1.58	2.50 ± 1.55	0.068
TTE					
LA dimension (mm)	39.71 ± 5.57	43.00 ± 5.61*,†	40.16 ± 5.50‡	37.80 ± 5.06	**<0.001**
LV mass index, (g/m^2)	92.42 ± 21.13	105.81 ± 26.46*,†	93.78 ± 20.62‡	85.64 ± 17.67	**<0.001**
LVEF (%)	63.88 ± 8.00	63.80 ± 11.43	64.09 ± 8.13	63.45 ± 6.29	0.494
E velocity (m/s)	0.73 ± 0.67	0.85 ± 0.22†	0.77 ± 0.79‡	0.61 ± 0.47	**<0.001**
DT (ms)	190.98 ± 43.49	197.53 ± 52.26	189.83 ± 42.53	191.30 ± 42.40	0.276
Em velocity (cm/s)	7.41 ± 2.36	4.61 ± 1.34*,†	6.99 ± 1.83‡	9.17 ± 2.38	**<0.001**
Sm velocity (cm/s)	6.75 ± 1.56	5.75 ± 1.34*,†	6.59 ± 1.50‡	7.37 ± 1.51	**<0.001**
E/Em	10.40 ± 5.03	–	–	–	–
Sinus rhythm during TTE	791 (72.0%)	79 (80.6%)	472 (69.8%)	240 (74.1%)	0.053
A velocity (m/s)	0.58 ± 0.19	0.67 ± 0.24*,†	0.61 ± 0.19‡	0.47 ± 0.13	**<0.001**
E/A ratio	1.28 ± 0.64	1.36 ± 0.55	1.25 ± 0.68	1.32 ± 0.55	0.196
TEE					
LAA-FV (cm/s)	57.14 ± 20.70	44.88 ± 20.33*,†	56.90 ± 20.64‡	62.05 ± 19.10	**<0.001**
PV-FV systolic/diastolic	1.28 ± 0.50	1.20 ± 0.57	1.26 ± 0.49	1.33 ± 0.50	0.152

p-values <0.05 were marked as bold.
AAD, antiarrhythmic drug; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type II receptor blocker; A velocity, late diastolic mitral inflow peak velocity during atrial contraction; CHF, congestive heart failure; E velocity, early diastolic mitral inflow peak velocity; Em velocity, early diastolic mitral annulus (septal area) peak velocity; EF, ejection fraction; DT, deceleration time: time from peak E velocity to decline to baseline; LA, left atrium; LAA, LA appendage; LAA-FV, LA appendage flow velocity; LV, left ventricle; Sm velocity, mitral annular septal area peak systolic velocity; TEE, trans-esophageal echocardiography; TIA, transient ischemic attack; TTE, trans-thoracic echocardiography; PV-FV systolic/diastolic, systolic/diastolic ratio of pulmonary vein flow velocity.
* $p<0.05$, E/Em > 15 vs. E/Em 8–15 by post hoc analyses using Bonferroni's method.
† $p<0.05$, E/Em > 15 vs. E/Em ≤ 8 by post hoc analyses using Bonferroni's method.
‡ $p<0.05$, E/Em 8–15 vs. E/Em ≤ 8 by post hoc analyses using Bonferroni's method.

stroke in over 1000 patients with relatively homogeneous patients with paroxysmal AF. The present study demonstrates that high LV filling pressure estimated by E/Em is related to the structural remodeling of LA and LAA emptying flow velocity, and is independently associated with the presence of stroke/TIA in patients with paroxysmal AF. These findings suggest that the reason for the increased thromboembolic risk in patients with AF is not the simple immobilization of LAA, but a combination of mechanisms and interrelationships between multiple risk factors of stroke, LV filling pressure, LA remodeling, and LAA function. Therefore, systemic understanding of AF and more comprehensive approaches are required for the prevention of ischemic stroke in patients with AF.

The association between high LV filling pressure and history of ischemic stroke in AF

AF is characterized by the loss of mechanical atrial function due to asynchronous LA contraction, inability to augment LV filling, and highly variable cycle lengths. All these factors complicate diastolic function assessment in AF. Although the conventional Doppler echocardiographic assessment of transmitral flow and pulmonary vein flow indices can be utilized in analyzing the LV diastolic filling pattern, it cannot be applied readily in the absence of atrial waveform during AF [6,18]. However, the relationship between E/Em and LV filling pressure has been validated in patients with AF [2,6]. Our present study showed that E/Em was significantly associated with atrial remodeling and a history of stroke or TIA in over 1000 patients with paroxysmal AF. This relationship may be explained with the deleterious effect of raised LV filling pressure on LA pressure and volume overload as well as that of stretching-induced atrial fibrotic changes on the reduction of LA compliance and function [19]. In a sub-analysis of patients with a CHA_2DS_2-VASc score ≤2, an E/Em was not associated with the presence of stroke or TIA (OR 1.236, 95% CI 0.584–2.616, $p = 0.579$). Therefore, the risk of stroke in patients with AF needs to be understood in terms of long-term systemic changes associated with hemodynamic stress and advanced remodeling, especially in patients with higher stroke risk.

LV diastolic dysfunction, LA remodeling and comorbidities

Consistent with our study, many studies have reported the associations of LV diastolic dysfunction with hypertension, arterial stiffness, or diabetes [20,21]. These risk factors, all of which are included in CHA2DS2-VASc score, can cause LA remodeling and

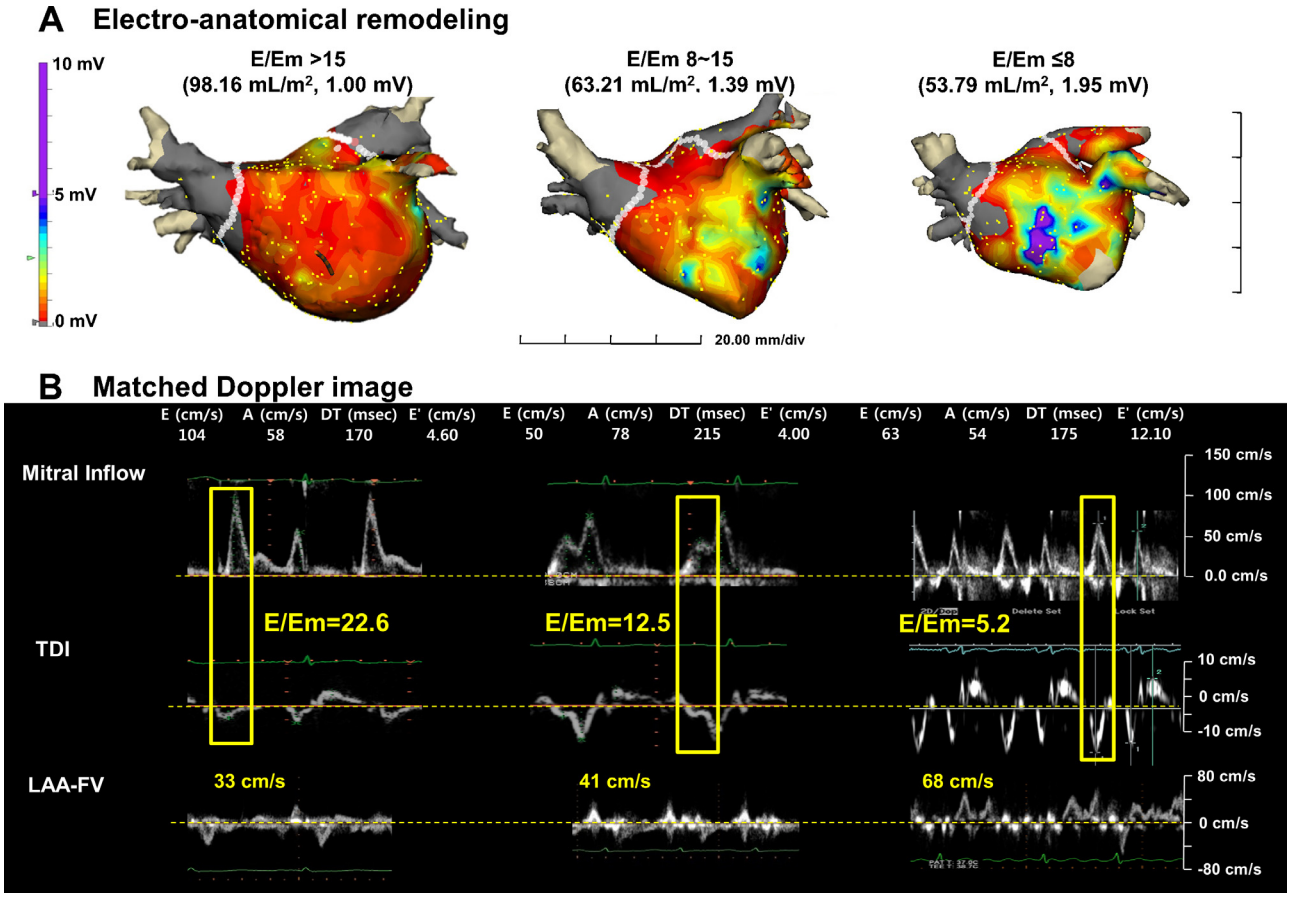

Fig. 1. (A) Anterior views of color-coded left atrial voltage maps (reconstructed three-dimensional spiral computed tomography image) depending on the degree of E/Em. (B) Doppler images matching the electro-anatomical maps. A velocity, late diastolic mitral inflow peak velocity during atrial contraction; E velocity, early diastolic mitral inflow peak velocity; Em (E′) velocity, early diastolic mitral annulus (septal area) peak velocity; DT (deceleration time), time from peak E velocity to decline to baseline; LAA-FV, left atrial appendage flow velocity; TDI, Tissue Doppler Imaging (septal area).

fibrosis [22], thus it remains to be elucidated whether LV diastolic dysfunction has a significant cause-and-effect relationship with stroke events or whether the two are simply associated, and whether an improvement in LV diastolic dysfunction and LA reverse remodeling reduces stroke risk or not. Moreover, LV diastolic dysfunction could have adverse effects on clinical outcome after catheter ablation for AF [23]. Therefore, prospective clinical studies for stroke incidence in relation to the improvement

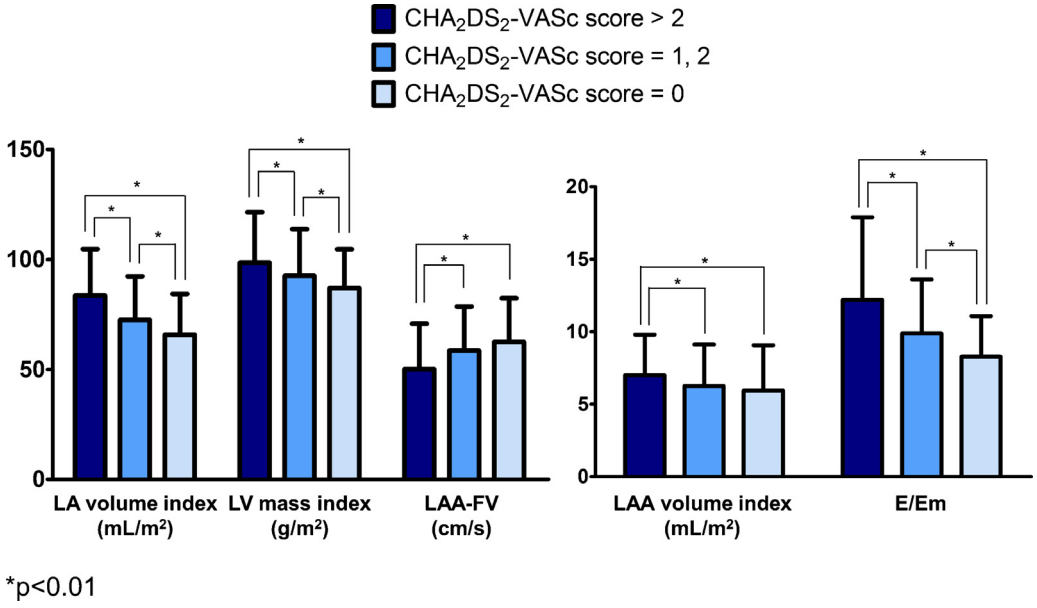

Fig. 2. A comparison of echo-Doppler parameters between groups of different CHA_2DS_2-VASc scores. *p-values were calculated by post hoc analyses using Bonferroni's method. LAA-FV, left atrial appendage flow velocity; LA, left atrial; LV, left ventricular.

Table 2
Univariate and multivariate logistic regression analyses for the presence of stroke/TIA.

Stroke/TIA	Univariate analyses		
	OR	95% CI	*p*-value
Age (years)	1.056	1.035–1.077	**<0.001**
Female	1.275	0.832–1.953	0.264
Body surface area (m^2)	0.266	0.087–0.810	**0.020**
Body mass index (kg/m^2)	0.962	0.898–1.032	0.278
3D-CT			
LA volume index (mL/m^2)	1.023	1.012–1.034	**<0.001**
LAA volume index (mL/m^2)	1.112	1.039–1.190	**0.002**
TTE			
LA dimension (mm)	1.079	1.043–1.117	**<0.001**
LV mass index, (g/m^2)	1.006	0.997–1.016	0.180
LVEF (%)	0.980	0.959–1.003	0.082
E velocity (m/s)	1.013	0.767–1.336	0.929
Em velocity (cm/s)	0.899	0.825–0.980	**0.015**
Sm velocity (cm/s)	0.741	0.647–0.849	**<0.001**
E/Em	1.968	1.404–2.759	**<0.001**
TEE			
LAA-FV (cm/s)	0.968	0.957–0.980	**<0.001**
PV-FV Systolic/diastolic	0.782	0.468–1.306	0.348

Stroke/TIA	Multivariate analyses		
	OR	95% CI	*p*-value
Model 1			
E/Em	1.535	1.063–2.216	**0.022**
Model 2			
E/Em	1.594	1.027–2.476	**0.038**
Model 3			
E/Em	1.638	1.050–2.554	**0.030**
Model 4			
E/Em	1.427	0.860–2.367	0.169

p-values <0.05 were marked as bold.
E/Em was analyzed as categorical variable (E/Em > 15, E/Em 8–15, and E/Em < 8).
Model 1; Adjusted for age, sex, and body surface area.
Model 2; Adjusted for independent variables in model 1 and LA volume index.
Model 3; Adjusted for independent variables in model 2 and LAA volume index.
Model 4; Adjusted for independent variables in model 3, Sm velocity, and LAA-FV.
E velocity, early diastolic mitral inflow peak velocity; Em velocity, early diastolic mitral annulus (septal area) peak velocity; EF, ejection fraction; LA, left atrium; LAA, LA appendage; LAA-FV, LA appendage flow velocity; LV, left ventricle; Sm velocity, mitral annular septal area peak systolic velocity; TEE, trans-esophageal echocardiography; TIA, transient ischemic attack; TTE, trans-thoracic echocardiography; PV-FV systolic/diastolic, systolic/diastolic ratio of pulmonary vein flow velocity.

in LV diastolic function after rhythm control could be helpful for understanding the mechanism of stroke in patients with AF.

Limitations

Given that this study was a single center cohort study that included a highly selected group of paroxysmal AF patients referred for catheter ablation, the findings cannot be generalized to all types of AF within the general population. It remains to be elucidated whether elevated LV filling pressure has a significant cause-and-effect relationship with stroke events. A study with prospective design is warranted to determine whether a change in E/Em reduces the incidence of stroke.

Conclusion

LV filling pressure estimated by E/Em is related to the structural remodeling of LA and LAA emptying flow velocity, and independently associated with high risk of stroke represented by high CHA_2DS_2-VASc score and the presence of stroke/TIA in patients with paroxysmal AF.

Disclosures

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2015.10.008.

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