VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2016, Vol. 23, No. 4, 429–436
DOI: 10.5603/CJ.a2016.0028

ISSN 1897–5593

Factors associated with stroke in patients with paroxysmal atrial fibrillation beyond $CHADS_2$ score

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Abstract

Background: *This study was conducted to investigate factors associated with stroke in patients with paroxysmal atrial fibrillation (PAF) beyond $CHADS_2$ score in terms of left ventricular (LV) diastolic function or left atrial (LA) function.*

Methods: *One hundred and sixty-one patients with PAF and age less than 75 (mean age 61 ± ± 10; 69 male) who underwent transthoracic echocardiography were investigated. Patients were divided into two groups according to the stroke status (group 1 — no stroke vs. group 2 — presence of stroke). Baseline echocardiographic parameters and LA segmental (4 segments: basal septal, lateral, inferior, and anterior) strain rate (SR) during normal sinus rhythm were analyzed.*

Results: *CHAD score (except S_2) was similar between the two groups (0.6 ± 0.7 vs. 0.9 ± 0.7, p = 0.125). Patients with stroke had slightly lower body mass index (24.5 ± 2.7 vs. 23.4 ± ± 2.4, p = 0.052). Echocardiographic parameters did not show any differences in both systolic and diastolic functions between the two groups, however elevated E/E' ratio was noted (9.5 ± ± 3.8 vs. 11.6 ± 3.9, p = 0.010) due to higher E velocity (63.5 ± 15.9 vs. 70.9 ± 16.0 cm/s, p = 0.046). In the analysis of LA SR, there are no differences of SR among the 4 segments. However, standard deviations (SD) of time to peak SR (SD of tA-SR) of the 4 segments were higher in patients with stroke (10.9 ± 9.9 vs. 22.1 ± 18.1 ms, p = 0.009) which indicates dyssynchronous contraction of LA. In multivariate analysis, SD of tA-SR (OR 1.074, CI 1.024–1.128, p = 0.004) and elevated E/E' (OR 1.189, CI 1.006–1.406, p = 0.048) were independently associated with stroke in patients with PAF.*

Conclusions: *Elevated E velocity, E/E' and SD of tA-SR were associated with occurrence of stroke in patients with PAF even with similar CHAD scores. Increased SD of tA-SR and E/E' were independently associated with stroke in patients with PAF.* (Cardiol J 2016; 23, 4: 429–436)

Key words: paroxysmal atrial fibrillation, stroke, left atrium, strain rate

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Received: 13.04.2016 Accepted: 23.05.2016

Introduction

Atrial fibrillation (AF) is the most common arrhythmia occurring in 4% of the population aged 60 or above [1, 2]. Problems associated with AF are not limited to heart failure (HF) but also include an increased risk of thromboembolic events [3]. Therefore, $CHADS_2$ or CHA_2DS_2-VASc score is recommended for the assessment of thromboembolic risk and treatment [3, 4]. When considering the mechanisms for AF [3], overlooking the left atrium (LA) in part of the assessment of thromboembolism (TE) might be associated with remaining risk of TE in patients with relatively low risk of TE measured by $CHADS_2$ or CHA_2DS_2-VASc score. The LA serves multiple functions, acting as a reservoir during ventricular systole, as a conduit during early diastole, as an active contractile chamber that augments left ventricular (LV) filling in late diastole and as a suction source that refills itself in early systole [5]. In terms of atrial function, atrial size is regarded as a surrogate marker of function, with larger atria thought to represent a dysfunctional LA [6, 7]. Several other parameters may be useful including the peak velocity of the A wave and its velocity time integral obtained from transmitral Doppler flow [8, 9], atrial fraction [9, 10], and atrial ejection force [10, 11]. In addition, A' velocity using tissue Doppler imaging (TDI) for assessing global atrial function [12, 13] and segmental atrial function can be evaluated using color Doppler tissue imaging (CDTI) [12], as well as strain and strain rate (SR) imaging [14, 15]. Among them, atrial strain and SR using CDTI has been used to assess LA synchronicity in patients with AF [16, 17]. In addition, atrial synchrony and global strain in patients with paroxysmal AF (PAF) and its impact of pulmonary vein isolation by 3-dimensional strain echocardiograph and Kobayashi et al. [18] found that impaired LA function in patients with PAF and LA structural reverse remodeling occurred much earlier after pulmonary vein isolation than the reversal of LA dyssynchrony. Patients with PAF are relatively younger, have a shorter AF history, less frequently experience valvular disease, HF, and diabetes mellitus than patients with sustained AF. Yet, the risk of TE does not differ between chronic or persistent AF [19].

Therefore, we aimed to investigate the factors associated with stroke in patients with PAF beyond $CHADS_2$ score in terms of LA function and mechanics in South Korea.

Methods

Study design and participants

We conducted an observational cross-sectional study. In this study, we enrolled 161 patients with PAF who underwent echocardiography during normal sinus rhythm and normal LV systolic function at Kangnam Sacred Heart Hospital between January 2010 and January 2016 (59 ± 10 years, 113 [72%] men). The primary endpoint of this study was the occurrence of ischemic stroke. Patients aged 75 or above, or with persistent long-standing, and permanent AF, concomitant significant arrhythmia, AF associated with systemic diseases such as hyperthyroidism, hypoxemia, infection, etc., significant valvular diseases, pericardial diseases, myocardial diseases, or decreased LV systolic function (ejection fraction [EF] less than 50%) or pre-existing stroke at the time of diagnosis of PAF, or hemorrhagic stroke were excluded from the study. Enrolled patients were divided into two groups according to the occurrence of stroke after diagnosis of PAF: group 1: 138 patients without stroke vs. group 2: 79 patients with stroke. The participants underwent transthoracic echocardiography and CDTI of the LA with zooming for strain and SR. We also collected baseline demographic and anthropometric data.

The study was approved by the Bioethical Committee of our University.

Transthoracic echocardiography

Transthoracic echocardiography was performed using standard techniques with a 2.5-MHz transducer. The standard 2-dimensional and Doppler echocardiography was performed using a commercially available echocardiographic machine (Vivid 7R GE Medical System, Horten, Norway). LV internal diameter (LVID), interventricular septal thickness (IVS), and ventricular inferolateral wall thickness (= posterior wall thickness, PWT) were measured at end-diastole according to the standards established by the American Society of Echocardiography [20]. LVEF was determined by the biplane Simpson's method. Maximal LA volume was calculated using the prolate ellipsoid model and indexed to the body surface area (LA volume index [LAVI]). LV mass (LVM) was calculated using the linear method: $LVM = 0.8 \cdot 1 : 04 \cdot [(IVS + LVID + PWT)^3 - LVID^3] + 0.6$ g. Thereafter, the LVM index was obtained using the following formula: LV mass/body surface area (BSA). LA volume was

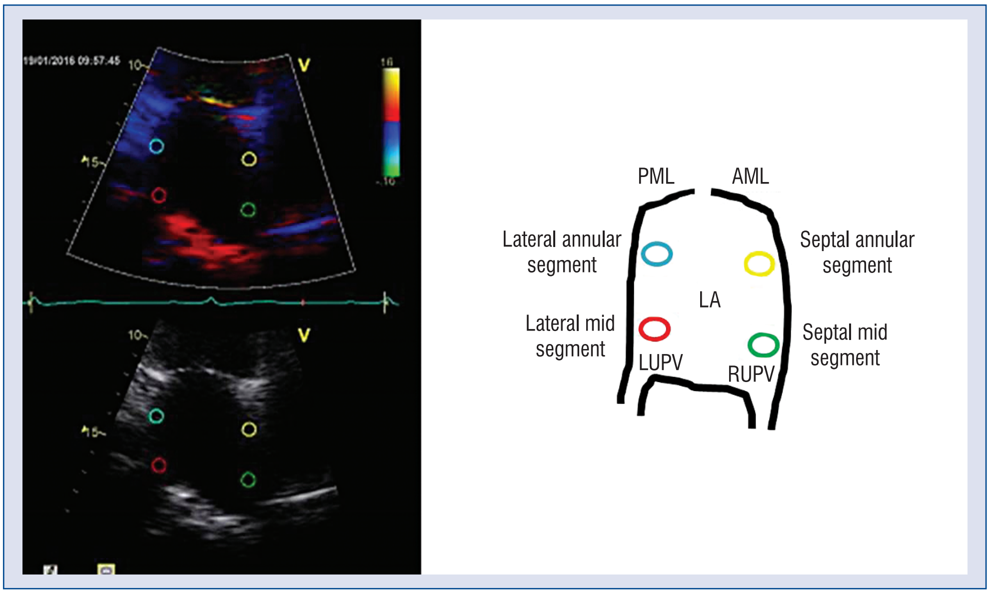

Figure 1. Left atrial walls, a narrow (10 mm × 2 mm) sample volume is selected and placed in the middle of the septal and lateral walls of the atrium and in the annuls of the septal and lateral segments in apical 4-chamber view in zooming of left atrium (LA); AML — anterior mitral leaflet; PML — posterior mitral leaflet; RUPV and LUPV — right and left pulmonary vein.

measured by biplane method of disks and LAVI was calculated by LA volume indexed to BSA.

Conventional and tissue measurements

Mitral flow velocities were recorded in the apical 4-chamber view. Mitral inflow measurements included the E/A ratio and the peak early (E) and peak late (A) flow velocities. The tissue Doppler of the mitral annulus movement was also obtained from the apical 4-chamber view. A 1.5-mm sample volume was placed sequentially at the lateral and septal annular sites. Analysis was performed for early diastolic (E') and late diastolic (A') peak tissue velocities. As a non-invasive parameter for LV stiffness, the LV filling index (E/E') was calculated using the ratio of transmitral flow velocity to annular velocity. Adequate mitral and TDI signals were recorded in all patients [21].

Left atrium strain and strain rate

Images were obtained using a narrow sector (frame rate > 110 fps) and attempts were made to align the atrial wall parallel to the Doppler beam [22]. Because of the thin atrial walls, a narrow (10 mm × 2 mm) sample volume was selected and placed in the middle of the septal and lateral walls of the atrium and in the annulus of the septal and lateral segments in apical 4-chamber view in zooming of LA (Fig. 1). The image was tracked frame by frame, ensuring in each frame that the sample volume was moved to its original location in the middle of the segment using dedicated software available on an offline measuring station (EchoPac PC, GE-Vingmed, Horten, Norway). Figure 2 shows images of atrial SR (A — synchronous LA, B — dyssynchronous LA). The vertical red line denotes aortic valve closure (AVC). The horizontal shift arrow denotes the time from AVC to peak A-SR (tA-SR).

Statistical analysis

Continuous variables were analyzed using Student's t-test and dichotomous variables were analyzed using the χ^2 test. In addition, multivariate analysis (logistic and linear regression, SPSS for Macintosh, version 23, SPSS, Inc., Chicago, Ill, USA) was performed. All variables that had a p value ≤ 0.05 were considered statistically significant.

Results

Baseline demographic characteristics and echocardiographic parameters

Table 1 shows baseline demographic characteristics of the patient population. In our study, 23 (14%) patients with PAF had a stroke with similar $CHADS_2$ score (except S_2) (0.6 ± 0.7 vs.

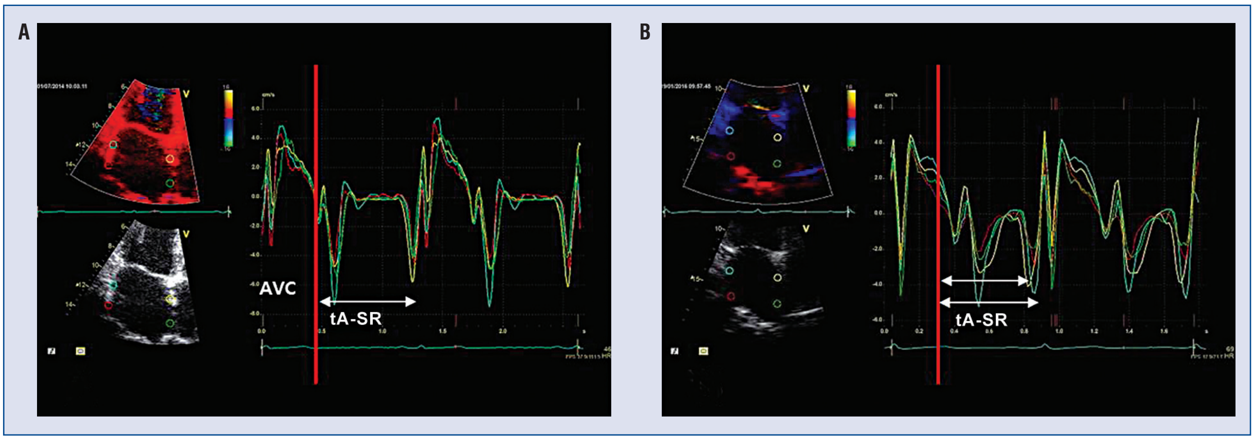

Figure 2. Color tissue Doppler image of left atrium (LA) in a patient without stroke (**A**) and a patient with stroke (**B**); AVC — aortic valve closure; tA-SR — time from AVC to peak A-SR.

Table 1. Baseline demographic characteristics.

Variables	Group 1 (n = 138)	Group 2 (n = 23)	P
Age [years]	59 ± 10	62 ± 9	0.137
Women	44 (32%)	4 (18%)	0.219
Body mass index [kg/m^2]	24.5 ± 2.7	23.4 ± 2.4	0.052
C-SBP [mm Hg]	130 ± 22	139 ± 22	0.330
C-DBP	76 ± 10	78 ± 10	0.656
B-SBP	124 ± 18	136 ± 29	0.167
B-DBP	74 ± 16	72 ± 13	0.618
Pulse rate [bpm]	69 ± 13	71 ± 16	0.608
CHAD score	0.6 ± 0.7	0.9 ± 0.7	0.125
Current medications:			
Aspirin	43 (31%)	7 (30%)	1.000
Clopidogrel	9 (7%)	1 (6%)	1.000
Oral anticoagulation	3 (2%)	3 (13%)	0.038
ACEI or ARBs	40 (29%)	9 (39%)	0.336
Beta-blockers	21 (15%)	2 (9%)	0.534
Calcium channel blockers	37 (27%)	10 (44%)	0.136
Statins	35 (25%)	7 (32%)	0.486

C — central; B — brachial; SBP — systolic blood pressure; DBP — diastolic blood pressure; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker

0.9 ± 0.7, p = 0.125). Patients with stroke had a slightly lower body mass index (24.5 ± 2.7 vs. 23.4 ± 2.4, p = 0.052). Otherwise, blood pressure was similar in both groups.

Table 2 shows echocardiographic parameters of the patient population. Cardiac size was similar in both groups, especially LA size represented as LAVI measured by biplane Simpson's method even smaller in patients with stroke (LAVI: 26.5 ± 9.2 vs. 25.3 ± 8.9 mL/m^2, p = 0.534); there was no difference in terms of LV systolic function. However, patients with stroke had more elevated E/E' (9.5 ± ± 3.8 vs. 11.6 ± 3.9, p = 0.010) due to higher E velocity (63.5 ± 15.9 vs. 70.6 ± 19.0 cm/s, p = 0.046).

Analysis of LA strain rate

Strain rate of the 4 segments of LA did not differ between the two groups, as shown in Table 3. However, standard deviation (SD) of time to peak atrial SR was significantly increased in pa-

Table 2. Baseline echocardiographic findings.

Variables	Group 1	Group 2	P
Indexed LA volume [mL/m^2]	26.5 ± 9.2	25.3 ± 8.9	0.534
LV mass index [g/m^2]	91.0 ± 24.4	97.2 ± 25.0	0213
Diastolic IVSWT [mm]	9.4 ± 1.6	9.3 ± 2.1	0.936
Systolic IVSWT [mm]	12.9 ± 2.0	12.8 ± 2.5	0.187
Diastolic LVPWT [mm]	8.8 ± 1.5	9.3 ± 1.8	0.185
Systolic LVPWT [mm]	12.7 ± 1.9	13.4 ± 2.5	0.099
LV end-diastolic dimension [mm]	50.3 ± 3.9	49.7 ± 4.7	0.642
LV end-systolic dimension [mm]	32.7 ± 3.7	32.1 ± 4.1	0.504
LV ejection fraction [%]	64.1 ± 6.3	66.1 ± 5.4	0.610
Peak E wave velocity [cm/s]	63.5 ± 15.9	70.6 ± 19.0	0.046
Peak A wave velocity [cm/s]	68.5 ± 19.0	72.7 ± 20.2	0.321
E/A ratio	1.0 ± 0.5	1.1 ± 0.5	0.312
Deceleration time [ms]	198.6 ± 41.8	184.6 ± 34.9	0.124
Septal peak E' velocity [cm/s]	7.1 ± 2.3	6.6 ± 2.3	0.298
Septal peak A' velocity [cm/s]	8.8 ± 2.3	8.2 ± 2.4	0.227
Septal E'/A' ratio	1.0 ± 1.1	0.8 ± 0.4	0.606
Septal E/E' ratio	9.5 ± 3.8	11.6 ± 3.9	0.010
Septal peak S' velocity [cm/s]	7.4 ± 1.5	7.2 ± 1.8	0.479
Estimated RVSP [mm Hg]	29.6 ± 6.0	29.5 ± 8.0	0.910

LA — left atrial; IVSWT — interventricular septal wall thickness; LVPWT — left ventricular posterior wall thickness; LV — left ventricular; RVSP — right ventricular systolic pressure

Table 3. Analysis of left atrial strain.

Variables	Group 1	Group 2	P
Basal septal E-SR [S^{-1}]	–3.9 ± 2.3	–2.9 ± 2.4	0.066
Basal septal A-SR [S^{-1}]	–4.5 ± 2.3	–4.1 ± 3.0	0.579
Septal tA-SR [ms]	754 ± 218	703 ± 209	0.313
Basal lateral E-SR [S^{-1}]	–5.2 ± 3.2	–3.3 ± 2.1	0.009
Basal lateral A-SR [S^{-1}]	–5.1 ± 2.6	–4.8 ± 3.9	0.710
Lateral tA-SR [ms]	766 ± 218	724 ± 204	0.404
Basal inferior E-SR [S^{-1}]	–3.5 ± 2.3	–2.0 ± 1.6	0.001
Basal inferior A-SR [S^{-1}]	–3.8 ± 2.2	–3.1 ± 2.7	0.218
Inferior tA-SR [ms]	763 ± 217	724 ± 209	0.443
Basal anterio E-SR [S^{-1}]	–3.1 ± 2.0	–2.5 ± 2.1	0.175
Basal anterior A-SR [S^{-1}]	–3.2 ± 1.8	–2.7 ± 1.7	0.267
Anterior tA-SR [ms]	760 ± 217	709 ± 208	0.288
SD of tA-SR [ms]	10.9 ± 9.9	22.1 ± 18.1	0.009

A-SR — peak atrial strain rate in late diastole; tA-SR — duration from aortic valve closure to peak atrial strain rate; E-SR — peak early diastolic strain rate; SD — standard deviation

tients with stroke (10.9 ± 9.9 vs. 22.1 ± 18.1 ms, p = 0.009), which represents dyssynchronous LA contraction during LV diastole. Figure 2 shows the difference in TDI of the LA in a patient without stroke (Fig. 2A) and with stroke (Fig. 2B). Figure 2A shows synchronous atrial contraction and Figure 2B shows dyssynchronous atrial contraction during diastole.

Table 4. Factors associated with stroke.

Variables	Odds ratio	95% confidence interval	P
Univariate analysis			
E	1.026	1.000-1.054	0.051
E/E'	1.157	1.029-1.031	0.015
SD of tA-SR [ms]	1.071	1.025-1.119	0.002
Multivariate analysis			
E	1.029	0.991-1.068	0.132
E/E'	1.189	1.006-1.406	0.048
SD of tA-SR [ms]	1.074	1.023-1.128	0.004

tA-SR — duration from aortic valve closure to peak atrial strain rate; SD — standard deviation

Factors associated with stroke in patients with PAF

In an univariate analysis, elevated E velocity of mitral inflow, elevated E/E' ratio, and increased SD of time to peak atrial contraction during diastole were associated with occurrence of stroke in patients with PAF. Among them, increased SD of time to peak atrial contraction (OR 1.074, CI 1.024–1.128, p = 0.004) and elevated E/E' ratio (OR 1.189, CI 1.006–1.406, p = 0.048) were independently associated with occurrence of stroke in patients with PAF in multivariate analysis (Table 4).

Discussion

This study aimed to find echocardiographic or other factors associated with occurrence of stroke in patients with PAF and low $CHADS_2$ score. Therefore, we selected patients aged 74 or less without congestive HF. We found that 23 (14%) sample patients with PAF had a stroke in this study, despite similar $CHADS_2$ score when compared to patients without stroke. Elevated E velocity of mitral inflow, elevated E/E' ratio, and increased SD of time to peak atrial contraction during diastole were associated with occurrence of stroke. Among them, increased SD of time to peak atrial contraction and elevated E/E' ratio were independently associated with occurrence of stroke in patients with PAF.

There were no significant differences in demographic factors between the two groups. Due to the fact that we enrolled subjects who had a relatively low risk of TE, the study subjects had low $CHADS_2$ score (except stroke) regardless of the presence of stroke.

In terms of echocardiographic parameters, LA size presented as LAVI was similar between the two groups, even slightly smaller in patients with stroke. It is well known that increased LA size is associated with occurrence of AF [23, 24], and LA enlargement is associated with poor prognosis and cardiovascular events, such as cerebral infarction and HF, as well as adverse overall outcomes [25, 26]. However, LA size was not associated with the occurrence of stroke in patients with PAF and they had low risk for TE, according to our study. E/E' ratio was elevated in patients with stroke due to elevated E velocity of mitral inflow in our study, but the values were within normal limits without clinical significance. However, when considering LA function, as opposed to size, there was a significant difference between the two groups. Atrial size is also regarded as a surrogate marker of function, with larger atria thought to represent a dysfunctional LA [6, 7]. However, our study suggests that patients who do not have mitral valve disease or other systemic diseases show normal LA size, even though they had a documented PAF. In addition, LA size was not associated with the occurrence of stroke. Among several parameters assessing LA function, atrial strain and SR using CDTI has been used to assess LA synchronicity in patients with AF [16, 17]. Dell'Era et al. [16] reported a change of atrial asynchrony and function before and after electrical cardioversion for persistent AF and predictive value of data of LA mechanics before cardioversion for recurrence of AF. Likewise, there was a significant difference in LA synchronicity between the two groups in our study. Patients who had a stroke showed increased SD of time to peak atrial contraction during diastole, suggesting LA dyssynchrony. Kuppahally et al. [17] explained that LA wall fibrosis measured by delayed-enhancement magnetic resonance imaging is inversely related to LA strain and SR, and that these are related to the AF burden. Furthermore, they suggested that echocardiographic assessment of LA structural and functional remodeling is quick and feasible, and may be helpful in predicting outcomes in AF [17].

Limitations of the study

This study had several limitations. First of all, current guideline recommends CHA_2DS_2-VASc score to discriminate a very low risk of TE in patients with AF, not $CHADS_2$ score [4]. Checking for aortic plaque or peripheral vascular disease is not always possible as some patients refuse further evaluation. For this reason, $CHADS_2$ score is still widely used in daily clinical practice. Secondly, we did not perform cardiac magnetic resonance imaging as Kuppahally et al. [17], therefore we could not clarify the mechanism of LA dyssynchronicity. Thirdly, the sample size was small, thus further study is recommended. In addition, we only measured LA function in one apical view, more detailed analysis could be useful in future studies. Lastly, we did not perform transesophageal echocardiography (TEE) in all patients who had stroke to assess whether the LA was the source of stroke. This was because many patients refused TEE. Therefore, correlation between the TEE and LA dyssynchronicity would be necessary in further studies.

Clinical implications

Although this study had several limitations, it did show that both $CHADS_2$ score and LA size were not good predictors for occurrence of stroke in patients with PAF and low risk TE. LA function measured by atrial strain and SR using CDTI revealed that dyssynchronous LA was associated with stroke. Therefore, we recommend routine analysis of LA strain and SR using CDTI and calculation of synchronicity in patients with PAF. If dyssynchronous LA was detected, further evaluations to estimate CHA_2DS_2-VASc score and/or a more aggressive oral anti-coagulation therapy could be considered for those patients.

Conclusions

Fourteen percent of the sample patients with PAF had stroke in this study, although they had similar $CHADS_2$ score compared to patients without stroke. Elevated E velocity of mitral inflow, elevated E/E' ratio, and increased SD of time to peak atrial contraction during diastole were associated with the occurrence of stroke. Among them, increased SD of time to peak atrial contraction suggesting dyssynchronous LA was independently associated with occurrence of stroke in patients with PAF.

Conflict of interest: None declared

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