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Left Atrial Mechanics Assessed Early during Hospitalization for Cryptogenic Stroke Are Associated with Occult Atrial Fibrillation: A Speckle-Tracking Strain Echocardiography Study

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Background: Occult atrial fibrillation (AF) is an important contributor to cryptogenic stroke, yet remains difficult to unmask at presentation. This study investigated the predictive value of left atrial (LA) mechanics by strain echocardiography during stroke hospitalization for the presence of AF as detected on early 30-day monitoring and routine clinical follow-up.

Methods: Left atrial mechanics were studied by strain echocardiography in a retrospective cohort of 191 patients with cryptogenic stroke and 30-day mobile cardiac outpatient telemetry poststroke to diagnose AF. After this, AF was diagnosed via routine clinical follow-up. The independent and incremental value of measures of LA size and mechanics (i.e., strain and strain rate in the reservoir, conduit, and booster pump phase) to predict AF on top of clinical characteristics was assessed.

Results: Of 191 patients, 15% ($n = 28$) developed AF, of which 10 were observed during 30-day mobile cardiac outpatient telemetry and 18 were observed at a median follow-up of 25 (interquartile range, 10-43) months. Median time from embolic stroke to strain echocardiography was 1 day (interquartile range, 1-2 days). Left atrial mechanics were significantly worse in AF ($P < .05$ for all), despite largely similar baseline cardiovascular risk profile. Booster pump strain rate was the strongest predictor for AF, independent of age, LA volume index, E/e′, and reservoir strain (odds ratio = 2.88 per SD increase; 95% confidence interval, 1.29-6.41; $P = .010$). Adding LA strain reservoir strain and booster pump function significantly enhanced a multivariate model to predict AF. Freedom from AF was significantly lower in subjects with a booster pump strain rate (at stroke presentation) worse than –0.67 sec^{-1}, as derived from receiver operator curve analysis ($P < .001$).

Conclusions: Left atrial mechanics and particularly the LA booster pump function assessed early during hospitalization for cryptogenic stroke can identify patients at greater likelihood of future diagnosis of AF. These findings could in part relate to LA mechanical stunning after spontaneous cardioversion, which—when identified by early strain echocardiography—can inform further risk stratification and decision-making. (J Am Soc Echocardiogr 2020;■:■-■.)

Keywords: Atrial fibrillation, Strain echocardiography, Left atrium, Cryptogenic stroke

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Abbreviations

2D = Two-dimensional

AF = Atrial fibrillation

LA = Left atrium, atrial

LAVI = Left atrial volume index

PALS = Peak atrial longitudinal reservoir strain

ROC = Receiver operating curve

TOAST = A trial of ORG 10172 in acute stroke treatment

Ischemic brain infarction accounts for 87% of all strokes, with an estimated global prevalence of 67.6 million.[1] In approximately 15%–30% of ischemic strokes,[2,3] neurological imaging is consistent with embolism, although the source of embolism remains undetermined after diagnostic workup. These cases are referred to as cryptogenic stroke[4] and they represent an etiologically heterogeneous group with an annual stroke recurrence rate of up to 5%.[5] Left atrial (LA) myopathy and/or occult atrial fibrillation (AF), two growing epidemics,[6] are considered important contributors to thromboembolism in at least 30% of cryptogenic strokes.[7] Hence, there is a critical need to identify a subgroup of cryptogenic stroke cases with a high yield for long-term rhythm monitoring and potential benefit from anticoagulation therapy. Left atrial strain imaging has emerged as a tool to detect subtle (often subclinical) abnormalities in LA mechanics (i.e., LA reservoir and booster pump function) and, therefore, might be extremely valuable in this subgroup of cryptogenic stroke cases.

Accordingly, the purpose of this study was to assess the predictive value of LA mechanics by speckle-tracking strain echocardiography for the detection of occult AF in cryptogenic stroke and evaluate their incremental value to clinical features and conventional echocardiographic parameters.

MATERIAL AND METHODS

Study Population

The study cohort was retrospectively identified from the institutional clinical and echocardiographic database of stroke patients admitted between 2005 and 2016 at Massachusetts General Hospital. Eligible patients were 40 years of age or older, who were diagnosed with ischemic stroke based on clinical examination by the attending neurologist and findings on computed tomography or brain magnetic resonance imaging, who underwent inpatient 48-hour rhythm monitoring and transthoracic echocardiogram, and, importantly, who had received a mobile cardiac outpatient telemetry device after index hospitalization. Stroke was considered cryptogenic by the hospital's stroke team in absence of (1) major-risk cardioembolic sources, (2) ≥50% luminal stenosis in the extracranial or intracranial arteries supplying the infarcted area, and (3) an unrevealing diagnostic stroke workup otherwise, resulting in a trial of ORG 10172 in acute stroke treatment (TOAST) classification of 5 or stroke of undetermined etiology.[4]

Additional exclusion criteria were as follows: (1) history of AF/atrial flutter or their occurrence during 48-hour inpatient cardiac monitoring, (2) mitral valve stenosis, (3) left ventricular ejection fraction <35% or left ventricular apical aneurysm, (4) indication for chronic anticoagulation, (5) recent myocardial infarction or coronary artery bypass grafting less than 1 month prior to stroke, and (6) inability to perform LA strain imaging. The presence of a patent foramen ovale was not an exclusion criterion unless it was clinically interpreted as causative, which then classified the stroke as TOAST 4 (other determined source).

The time of index stroke marked the time point of entry in the analysis. Clinical data were collected for each participant at the time of index stroke and used to compute clinical scores (CHA_2DS_2VASC score, National Institute of Health Stroke Scale). The study was approved by the hospital's Institutional Review Board (Partners IRB), and the need for a written informed consent was waived given the retrospective analysis of clinically acquired data.

Image Acquisition and Analysis

Transthoracic echocardiographic examinations were performed during index hospitalization by qualified sonographers, following a standard imaging protocol using a commercially available system (Philips Medical Systems, EPIQ 7 or IE33, Andover, MA) equipped with a S5-1 or X5-1 phased-array transducer and stored for offline analysis. Conventional echocardiographic parameters were measured according to the American Society of Echocardiography recommendations,[8] using a commercially available software package (Siemens Syngo Dynamics, Malvern, PA). E/e′ was calculated as the ratio of the transmitral Doppler E-wave velocity (E), divided by the composite mean of the lateral and medial early diastolic mitral annular velocity (e′). Left atrial volume was measured using the modified Simpson rule and indexed to body surface area to calculate LA volume index (LAVI) by a single experienced echocardiographer (D.Y.S.). All echocardiographic measurements were performed blinded for the outcome of AF during mobile cardiac outpatient telemetry or clinical follow-up.

LA Speckle-Tracking Analysis

Left atrial speckle-tracking analysis was performed offline on a non-foreshortened apical four-chamber view using a third-party vendor-independent software package (two-dimensional [2D] cardiac performance analysis, TomTec imaging systems GmbH), according to the Task force recommendations.[9] Ventricular end diastole was used as the zero reference point (i.e., R-R gated speckle-tracking was conducted). After the observer manually traced the endocardial LA border in the four-chamber view in end diastole, the software automatically tracked the endocardial borders throughout the subsequent frames of the selected beat. Adequate tracking of the region of interest on the contour was verified and if necessary adjusted to ensure reliable speckle correlation. The mean frame rate was 62 Hz.

Peak atrial longitudinal strain (PALS) was determined as the peak positive strain value (i.e., lengthening) during late ventricular systole on the averaged longitudinal strain curve. Additionally, the (positive) reservoir strain rate in late ventricular systole, (negative) conduit strain rate in early diastole, and (negative) booster pump strain rate were determined from the averaged LA longitudinal strain rate curve (Figure 1). Left atrial maximum opposing wall delay (i.e., a measure of intra-atrial dyssynchrony) was calculated as the difference in time to peak longitudinal strain between the interatrial septum and free lateral wall of the LA.[10]

Left atrial strain analysis was performed offline by the first author, blinded to other study-related parameters.

Clinical Follow-up and Diagnosis of AF

Generally at stroke admission, permissive hypertension was applied in our institution, as per American Heart Association/American Stroke Association guidelines.[11] Abruptly lowering blood pressure

HIGHLIGHTS

- Occult AF contributes to the pathogenesis of cryptogenic stroke in up to 30%.
- LA strain echocardiography can identify stroke patients at high risk of AF.
- Impaired booster pump strain rate is a strong and independent predictor of AF.
- Impaired LA mechanics warrant extended rhythm follow-up.

was avoided in these patients due to the risk of worsening cerebral ischemia.[12]

After index hospitalization, all patients were followed up for the primary endpoint of AF with a 30-day mobile cardiac outpatient telemetry system (First-Call, Andover, MA), which automatically captured arrhythmic events, even in the absence of symptoms. Each event was automatically transmitted to the monitoring center without patient interference via a built-in wireless cellular connection and assessed by a certified monitoring technician. Rhythm follow-up after 30 days was performed at the discretion of the treating physician and retrospectively obtained from the electronic health record system (Epic System Corporation, Verona, WI). Atrial fibrillation was defined as an irregular supraventricular rhythm with variable R-R interval and absence of P waves on resting electrocardiogram or ≥30 seconds during rhythm monitoring.[13] Importantly, episodes of irregular supraventricular rhythm of <30 seconds on mobile cardiac outpatient telemetry were not considered diagnostic for AF.

Statistical Analysis

Categorical data were expressed as absolute numbers and percentages and compared with the χ^2 test (or Fisher's exact test if a cell number was <5). Continuous variables were described as mean ± SD if normally distributed or median (interquartile ranges) otherwise. Normality was assessed by the Shapiro-Wilk statistic. Continuous variables were compared with the independent Student's *t* test or Mann-Whitney *U* test, as appropriate. Univariate and multivariate regression analyses were performed to assess the (independent) predictive value of LA strain-derived parameters for detection of AF, among clinical risk scores and conventional echocardiographic parameters, both in a binary manner (binary logistic regression) and in a time-to-event analysis (Cox proportional hazards regression). Collinearity diagnostics were performed to warrant stability of the multivariate model. These analyses were reiterated in a subgroup with age <65 years and CHA_2DS_2VASC-score < 3. Next a competing risk Fine and Gray's analysis with AF as the primary outcome and all-cause death as competing risk was compared with the initial Cox regression model.

Additionally, the predictive performance of LA strain-derived parameters, compared with LAVI, was computed by receiver operating characteristic (ROC) curve analysis. A discriminatory cutoff was derived from this analysis and used to dichotomize the population. Freedom from AF was estimated by the Kaplan-Meier method based on these cutoff values and compared with the corresponding log-rank test. Finally, the incremental value of LA strain-derived indices over clinical and conventional echocardiographic parameters to predict AF in cryptogenic stroke was evaluated by the likelihood ratio test and the change in global χ^2 value between each multivariate model.

Statistical significance was always set at a two-tailed probability level of <.05. Statistics were performed using SPSS version 22 (IBM, Chicago, IL), except for the competing risk analysis and nested Cox regression, which were performed in STATA version 12.1 (StataCorp LLC, College Station, TX).

RESULTS

Patient Characteristics

Among 259 patients with ischemic stroke, 68 (26%) were excluded. The reasons for exclusion are summarized in Supplemental Figure 1, among which a total of 37 patients were excluded by the stroke team, as their stroke was explained by a different etiology (TOAST classification ≠ 5). Left atrial speckle-tracking was inadequate in 9.5% (n = 21) of patients who were subsequently excluded from further analysis. This group of excluded patients (n = 21) was comparable to the studied cohort (n = 191) in terms of cardiovascular risk factors and left ventricular ejection fraction.

Baseline characteristics of the final study population (n = 191) are summarized in Table 1. During 30-day mobile cardiac outpatient telemetry, a total of 10 (5%) patients were diagnosed with AF. In addition, a total of 18 (9%) patients were diagnosed with AF after a median clinical follow-up of 25 (10-43) months. Patients with cryptogenic stroke and subsequent AF (n = 28, 15%) were slightly older than patients without AF (65 ± 14 vs 70 ± 11 years, P = .037). However, cardiovascular risk factors and CHA_2DS_2-VASC score were comparable between the two groups (P = NS for all). Indices of left ventricular size and systolic function were similar for both subgroups (P = NS).

LA Mechanics

The median time between stroke presentation and echocardiography was 1 day (interquartile range, 1-2). Median LAVI was 32.2 mL/m^2 and significantly larger in patients with cryptogenic stroke who developed AF after index stroke (Table 2, P = .001). Indices of LA reservoir (PALS and reservoir strain rate) and booster pump function (medial A′ and booster pump strain rate) were significantly lower in AF (P < .001 for all). Left atrial maximum opposing wall delay was significantly worse in patients who developed AF (P = .007). These differences were found despite no difference in time interval between stroke admission and echocardiography recordings for both subgroups (P = .509).

Predictors of AF after Cryptogenic Stroke

The association between clinical risk factors, echocardiographic parameters, and AF was evaluated using univariate and multivariate binary logistic and Cox regression analysis (respectively, Tables 3 and 4). Factors associated with AF in univariate analysis (P < .10) were age, LAVI, medial A′, and E/e′, as well as indices of LA reservoir (PALS and reservoir strain rate) and booster pump function (booster pump strain rate). PALS was independently associated with AF in cryptogenic stroke, even after adjustment for age, E/e′, LAVI, and opposing wall delay (odds ratio [OR] = 0.35 per SD increase; 95% confidence interval [CI], 0.18-0.70; P = .003; Table 3). Similarly, maximum opposing LA wall delay was an independent multivariate predictor for AF (OR = 1.64 per SD increase; 95% CI, 1.06-2.54; P = .027; Table 3). However, in the subsequent step of the multivariate model including booster pump strain rate, the latter remained the strongest independent predictor for AF (OR = 2.88 per SD increase; 95% CI, 1.29-6.41; P = .010; Table 3).

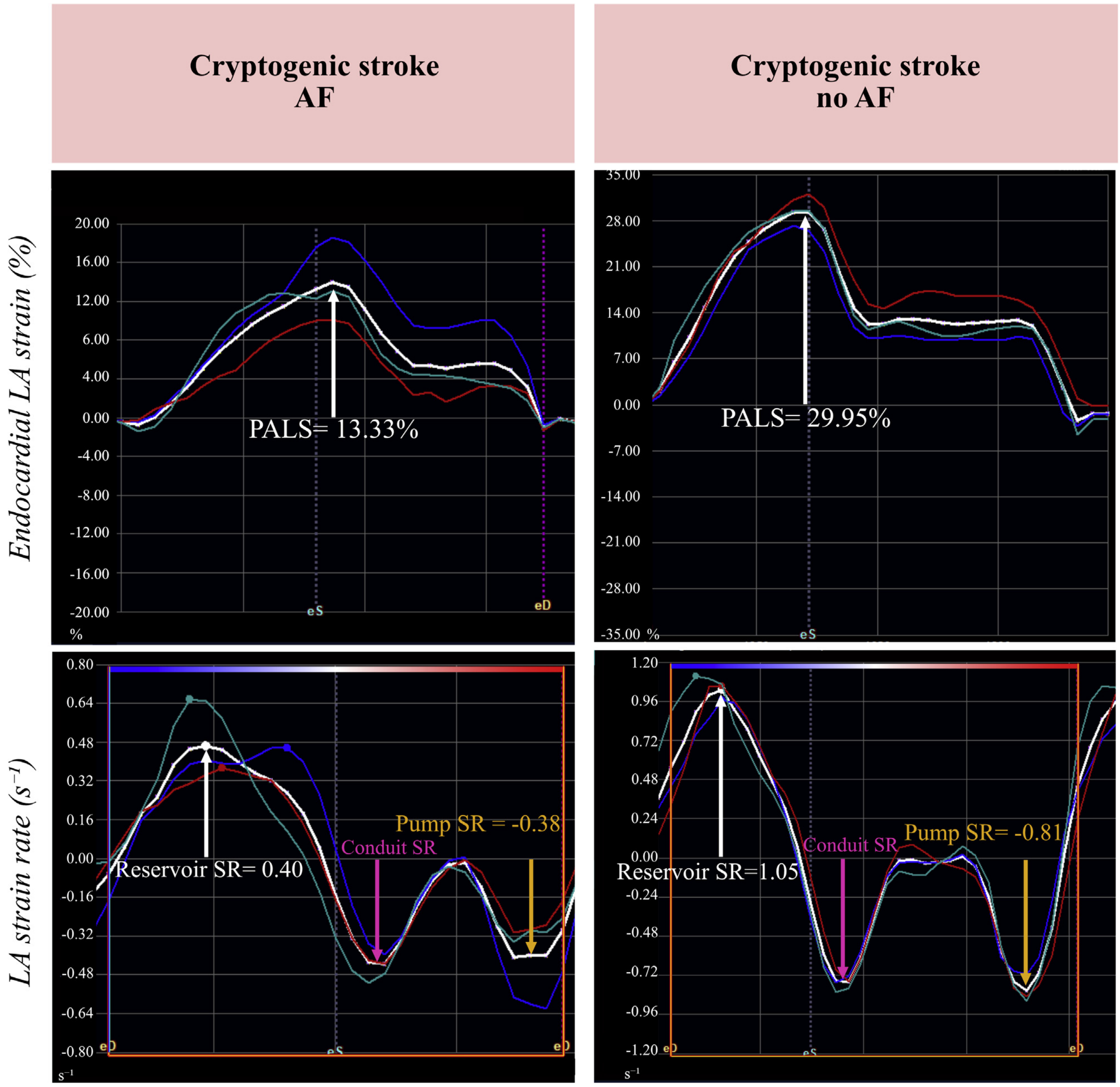

Figure 1 Left atrial strain imaging in cryptogenic stroke with and without detected AF. The threefold action of the LA was assessed using speckle-tracking-derived strain and strain rate. PALS and reservoir strain rate were significantly lower in cryptogenic stroke with detected AF (*white arrows*). Atrial contractility was significantly worse, as indicated by a higher booster pump strain rate value in the latter subgroup (*yellow arrow*). Please note the difference in scale between AF and no AF, with markedly lower values in the patient that was diagnosed with AF during follow-up. The *white curve* represents the averaged strain (rate) curve, whereas the *green, blue, and red curves* represent strain (rate) in the lateral wall, interatrial septum, and roof, respectively. *SR*, Strain rate.

In multivariate Cox regression analysis (accounting for the time to first detected AF after index stroke), booster pump strain rate was independently associated with time to first AF (hazard ratio = 2.88 per SD increase; 95% CI, 1.28-6.49; P = .011; Table 4). Moreover, booster pump strain rate remained the only independent predictor for time to first AF (P = .016), even with all-cause mortality as a competing risk (Supplemental Table 1).

Of note, pump strain rate remained a significant univariate predictor for AF in the subgroup with age <65 years and CHA_2DS_2VASC < 3 (n = 77).

Discriminatory Cutoff

Figure 2 and Table 5 render the results of ROC curve analysis for LA mechanics and LAVI. PALS and booster pump strain rate were echocardiographic predictors for AF, with an area under the curve of 0.74 and 0.77, respectively (P < .001 for both). A threshold PALS value of 20.4% identified future AF in cryptogenic stroke with a sensitivity of 75% and specificity of 69%. Similarly, a value of −0.67 sec^{-1} for booster pump strain rate yielded a 73% sensitivity and 65% specificity for AF detection after cryptogenic stroke. Using these cutoffs, freedom from AF in time-to-event analysis was significantly lower

Table 1 Baseline patient characteristics

	All patients (N = 191)	AF (n = 28)	No AF (n = 163)	P value
Demographics				
Age, years	65 ± 14	70 ± 11	64 ± 14	.037
Gender, female, n (%)	90 (47)	16 (57)	74 (45)	.250
Race, Caucasian, n (%)	147 (77)	27 (96)	120 (74)	.008
BSA, m^2	1.91 ± 0.27	1.93 ± 0.28	1.91 ± 0.27	.780
Comorbidities				
Hypertension, n (%)	116 (61)	16 (57)	100 (61)	.674
Diabetes mellitus, n (%)	35 (18)	6 (21)	29 (18)	.646
Dyslipidemia, n (%)	75 (39)	13 (46)	62 (38)	.401
Smoking history, n (%)	32 (17)	4 (14)	28 (17)	1.000
CHA_2DS_2-VASC, absolute	3 (2-4)	3 (2-4)	3 (2-4)	.253
Stroke presentation				
NIHSS, absolute	3 (1-6)	3 (1-5)	3 (1-6)	.884
Cortical infarct (%)	111 (58)	11 (39)	100 (61)	.029
Bilateral infarct (%)	27 (14)	5 (18)	22 (13)	.541
Supra + infratentorial infarct (%)	15 (8)	3 (11)	12 (7)	.542
LV parameters				
LVEF, %	67 (63-72)	66 (63-70)	68 (63-73)	.274
IVSd, mm	11 (10-13)	11 (10-13)	11 (10-12)	.312
LVIDd, mm	43 (40-48)	45 (40-47)	43 (40-48)	.617
PWTd, mm	10 (9-11)	10 (9-13)	10 (9-11)	.223
Days up to TTE	1 (1-2)	2 (1-2)	1 (1-2)	.509

BSA, Body surface area; *IVSd*, interventricular septum thickness in diastole; *LV*, left ventricle, *LVEF*, left ventricular ejection fraction; *LVIDd*, left ventricular internal diameter in diastole; *NIHSS*, National Institute of Health Stroke Scale; *PWTd* Posterior wall thickness in diastole.
Data are presented as mean ± SD, n (5%), or median (interquartile range).

Table 2 Baseline LA and LV diastolic function indices in cryptogenic stroke with and without subsequent AF detection

Variables	All patients (N = 191)	AF (n = 28)	No AF (n = 163)	P value
LAVI, mL/m^2	32.2 (25.1-42.2)	43.6 (30.9-49.7)	31.2 (24.5-39.7)	.001
LA emptying fraction, %	54.3 (46.7-60.8)	46.9 (37.6-58.6)	55.2 (48.3-62.1)	.004
PALS, %	22.3 (19.0-28.1)	17.4 (15.7-22.3)	23.2 (19.4-28.3)	<.001
SR reservoir, sec^{-1}	0.83 (0.69-0.99)	0.68 (0.56-0.82)	0.86 (0.72-1.0)	<.001
SR conduit, sec^{-1}	−0.56 (−0.75-0.40)	−0.43 (−0.58-036)	−0.60 (−0.77-0.44)	.003
SR pump, sec^{-1}	−0.72 (−0.88-0.57)	−0.55 (−0.69-0.39)	−0.74 (−0.92-0.59)	<.001
Opposing wall delay, msec	33 (0-67)	67 (33-100)	33 (0-67)	.007
E, cm/sec	70 (57-84)	75.5 (70-102)	67 (56-81)	<.001
A, cm/sec	81 (64-94)	80 (61-94)	81 (64-93)	.821
EA ratio, absolute	0.88 (0.72-1.11)	1.04 (0.87-1.36)	0.86 (0.69-1.08)	.006
E/e′, absolute	9.69 (7.35-12.97)	12.40 (9.87-15.00)	9.38 (7.13-12.00)	.001
A′ medial, cm/sec	90 (80-110)	90 (70-105)	90 (80-110)	.174

LV, Left ventricle; *SR*, strain rate.
Data are presented as median (interquartile range).

Table 3 Predictors for AF in cryptogenic stroke

Variable	Univariate OR (95% CI)	Univariate *P* value	Multivariate (step 1) OR (95% CI)	Multivariate (step 1) *P* value	Multivariate (step 2) OR (95% CI)	Multivariate (step 2) *P* value
Age	1.03 (1.00-1.07)	.039	0.99 (0.95-1.03)	.561		
Female sex	1.60 (0.71-3.60)	.253				
Dyslipidemia	1.41 (0.63-3.16)	.402				
Hypertension	0.84 (0.37-1.89)	.674				
Diabetes mellitus	1.26 (0.47-3.38)	.646				
CHA_2DS_2VASC, per 1 increase	1.20 (0.88-1.63)	.262				
LVEF, per SD increase	0.83 (0.56-1.22)	.340				
E/e′, per unit increase	1.08 (1.02-1.15)	.011	1.02 (0.93-1.13)	.650		
LAVI, per SD increase	1.98 (1.33-2.97)	.001	1.37 (0.81-2.32)	.238		
A′ medial, per SD increase	0.71 (0.47-1.06)	.094		*		*
PALS, per SD increase	0.33 (0.18-0.59)	<.001	0.35 (0.18-0.70)	.003	0.61 (0.31-1.21)	.160
SR reservoir, per SD increase	0.34 (0.19-0.59)	<.001		*		*
SR pump, per SD increase	4.23 (2.09-8.54)	<.001		Step 2	2.88 (1.29-6.41)	.010
Opposing wall delay, per SD increase	1.75 (1.20-2.53)	.003	1.64 (1.06-2.54)	.027	1.59 (1.04-2.44)	.034

LVEF, Left ventricular ejection fraction; *SR*, strain rate.
Covariates are presented with OR (95% CI) and corresponding *P* value. Covariates with $P < .10$ in univariate analysis were entered in a multivariate binary logistic regression model. Booster pump strain rate was introduced in step 2 (right-sided panel).
*A′, and reservoir strain rate were excluded due to collinearity.

Table 4 Univariate and multivariate Cox proportional hazard regression for time to AF

Variable	Univariate HR (95% CI)	Univariate *P* value	Multivariate HR (95% CI)	Multivariate *P* value
Age, per 1 year increase	1.03 (1.00-1.06)	.029	0.99 (0.96-1.03)	.688
Female sex	1.53 (0.72-3.23)	.268		
Dyslipidemia	1.31 (0.62-2.76)	.476		
Hypertension	0.82 (0.39-1.74)	.611		
Diabetes mellitus	1.28 (0.52-3.18)	.590		
CHA_2DS_2VASC, per 1 increase	1.21 (0.91-1.62)	.188		
LVEF, per SD increase	0.86 (0.61-1.22)	.409		
E/e′, per unit increase	1.06 (1.02-1.10)	.002	0.97 (0.91-1.05)	.455
LAVI, per SD increase	1.65 (1.27-2.15)	<.001	1.23 (0.77-1.98)	.389
A′ medial, per SD increase	0.70 (0.48-1.03)	.068		*
PALS, per SD increase	0.38 (0.24-0.61)	<.001	0.63 (0.31-1.30)	.214
SR reservoir, per SD increase	0.39 (0.25-0.63)	<.001		*
SR pump, per SD increase	3.89 (2.11-7.20)	<.001	2.88 (1.28-6.49)	.011
Opposing wall delay, per SD increase	1.52 (1.13-2.04)	.006	1.29 (0.92-1.83)	.145

LVEF, Left ventricular ejection fraction; *SR*, strain rate.
Covariates are presented with hazards ratios (HR), 95% CI, and corresponding *P* value. Covariates with $P < .10$ in univariate analysis were entered in the multivariate model regression model.
*A′ and reservoir SR were excluded due to collinearity.

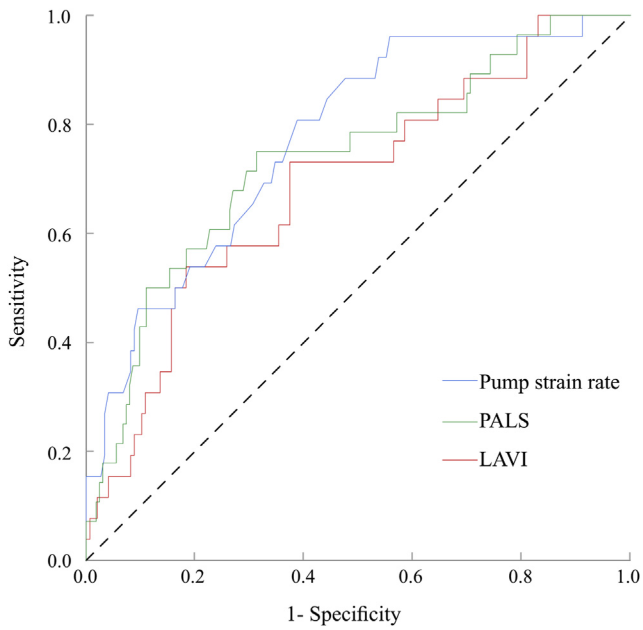

Figure 2 ROC curve analysis for LA mechanics to predict AF. Overlaying ROC analysis indicating a large AUC for PALS and booster pump strain rate, versus LAVI. *AUC*, Area under the curve; *SR Pump*, booster pump strain rate.

in subjects with cryptogenic stroke with PALS < 20.4% ($P < .001$) or booster pump strain rate > -0.67 sec^{-1} ($P = .001$).

Incremental Value of LA Strain for AF Detection in Cryptogenic Stroke

The incremental predictive value of PALS, LA opposing wall delay, and booster pump strain rate over existing indices is illustrated in Figure 3, after applying a sequential nested Cox regression algorithm. A predictive model based on conventional clinical parameters and LAVI alone was significantly refined by adding PALS and opposing wall delay (likelihood $\chi^2 = 22.84$, $P = .004$) and subsequently significantly improved by booster pump strain rate (likelihood $\chi^2 = 30.24$, $P = .007$).

Reproducibility

Reproducibility of all LA strain measurements was tested blinded in a random sample of 15 patients, included in the retrospective cohort. The intraclass correlation coefficients for intra- and interobserver variability are presented in Table 6 and show overall good agreement. Intraobserver variability was assessed by the first author at a later stage. Interobserver variability was verified by the second author, blinded to other measurements. Scatter plots showing the overall range in LA indices for cryptogenic stroke with and without subsequent AF are presented in Supplemental Figure 2. Supplemental Figure 3 displays Bland-Altman plots regarding the interobserver and intraobserver variability for measurements of PALS and booster pump strain rate.

DISCUSSION

This study evaluated LA mechanics by echocardiography immediately after cryptogenic stroke in order to unmask diagnosis of AF. The key findings are (1) LA mechanics are significantly impaired in patients with cryptogenic stroke who subsequently develop AF versus patients without AF; (2) LA booster pump function (as measured by booster pump strain rate) is the strongest predictor for AF, independent of E/e′, LAVI, and PALS; (3) adding LA mechanics post-stroke to a predictive model for AF based on clinical variables and LAVI significantly increases the predictive value.

LA Mechanics in Cryptogenic Stroke

Left atrial remodeling is an important underlying substrate in AF and stroke, two major health problems with potentially disabling consequences that frequently coexist.[14] Left atrial strain imaging has emerged as a new biomarker[15-17] to detect subtle abnormalities in LA reservoir or contractile function and therefore may improve the risk stratification for stroke in AF[18-20]—or vice versa—may unmask occult AF in cryptogenic stroke. An additional advantage is its lower sensitivity to changes in loading conditions, as compared with volumetric or tissue Doppler–derived imaging.[15,21]

Several studies have shown an association between PALS and post-stroke AF, even after controlling for LA size[22,23] and clinical risk scores.[22] Furthermore, Pathan *et al.*[24] elegantly demonstrated the incremental value of LA strain above current risk-prediction models for predicting AF in cryptogenic stroke, which is in line with the findings of our study. These findings suggest that quantifying subclinical LA dysfunction could be helpful in determining patients who are at a higher risk of future AF and by extension at a higher likelihood that the recent stroke was related to AF. However, the abovementioned studies are limited by a variable (or nonreported) time delay between the index stroke and echocardiography and by heterogeneous ambulatory rhythm monitoring, that is, mainly detecting future symptomatic rather than occult AF.

Our present study adds to these prior findings by reporting the predictive value of LA strain in cryptogenic stroke patients with dedicated 30-day mobile cardiac outpatient telemetry for occult (asymptomatic) AF (Tables 3 and 4). Furthermore, the short interval between stroke presentation and echocardiography (median 1 day) is a particular strength of this study that might explain the novel finding of significantly impaired booster pump strain rate (atrial

Table 5 ROC analysis of conventional and strain-derived echocardiographic parameters to predict AF

Variable	AUC	*P* value	95% CI	Cutoff	Sensitivity, %	Specificity, %
LAVI, mL/m^2	0.69	.001	0.58-0.80	38.6	58	74
PALS, %	0.74	<.001	0.63-0.84	20.4	75	69
SR pump, sec^{-1}	0.77	<.001	0.68-0.87	−0.67	73	65

AUC, area under the curve; *SR*, strain rate.

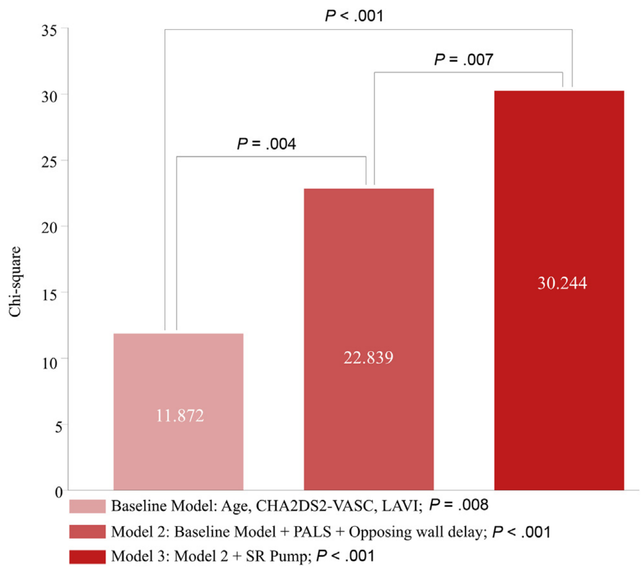

Figure 3 Incremental value of LA mechanics. Incremental value of LA strain indices over clinical parameters and LAVI for AF prediction. *SR Pump*, booster pump strain rate.

Table 6 Intra- and interobserver variability for LA strain measurements

Variable	ICC interobserver variability	ICC intraobserver variability
PALS	0.98	0.97
SR reservoir	0.96	0.97
SR pump	0.91	0.91

ICC, intraclass correlation coefficient; *SR*, strain rate.

contractile function) in cryptogenic stroke with AF. Moreover, in both a time-to-event and binary regression analysis this booster pump function was the strongest predictor for AF, independent of E/e′, LAVI, and PALS. The addition of booster pump strain rate significantly enhanced a multivariate predictive model including the conventionally used PALS. These results remained valid after adjusting for death as competing risk.

Atrial Stunning and Thromboembolic Risk in Cryptogenic Stroke

Atrial "mechanical stunning" after conversion of AF to sinus rhythm—whether spontaneous or provoked—is well known and underscores the relevance of anticoagulating patients in the first weeks after elective cardioversion. Spontaneous resumption of sinus rhythm after acute (60 minutes) pacing-induced AF in normal canine hearts resulted in a markedly depressed contractile function of the LA and LA appendage.[25] Contractile dysfunction was more profound and lasted longer in the LA appendage. Similar findings were obtained in humans, following electrical and pharmacologic cardioversion of atrial arrhythmias.[26-31] The net effect of "stunning" is stasis of blood flow, as demonstrated by worsening or new LA spontaneous echocardiographic contrast[26-28,32] or even de novo thrombi[33,34] in the postcardioversion recovery period. Of note, atrial stunning was found after all modes of cardioversion,[35] suggesting it is a function of the underlying arrhythmia and possible atrial myopathy rather than the effect of electrical energy.

In our present study in cryptogenic stroke, LA mechanics at a median of 1 day after stroke presentation were significantly depressed in patients who were ultimately diagnosed with AF over time. While this primarily reflects intrinsic LA pathology and/or fibrosis predisposing for AF (supported by lower PALS), there could be a factor of postconversion LA stunning that plays a role in the observed LA mechanics if occult AF was the cause of stroke. Our study, however, cannot address such association. Nevertheless, markers of LA stunning (a′, booster pump strain rate) were significantly lower in patients with AF versus patients without AF, with the booster pump strain rate being the strongest independent predictor of AF in this cohort, more than PALS. This concept of "atrial stunning" has been observed in other studies[31,36] using deformation imaging immediately after electrical cardioversion of persistent AF, with significant recuperation of LA mechanics over time. Of note, a univariate association between booster pump strain rate and AF was maintained in the subgroup of young patients (<65 years) with fewer cardiovascular risk factors, yet confirmation in a larger cohort of young patients could further endorse the clinical value of LA strain imaging in cryptogenic stroke.

Clinical Implications

This study confirms the incremental predictive ability of LA strain to unmask occult AF in cryptogenic stroke. Left atrial reservoir strain (as a marker of LA disease and underlying substrate predisposing for AF) and booster pump function (as a marker of atrial stunning) may be used in cryptogenic stroke to identify patients who may benefit from long-term rhythm monitoring and/or up-front anticoagulation therapy.

The U.S. national incremental costs of AF are estimated to range from $6.0 billion (AF-related costs only) up to $26.0 billion (AF-related costs, other cardiovascular and noncardiovascular costs).[37] Incorporating LA mechanics into diagnostic algorithms for AF detection could beneficially alleviate stress on public health costs. Future studies are needed to evaluate the cost-effectiveness of imaging-guided cardiac rhythm monitoring strategies after cryptogenic ischemic stroke, particularly in an era of an increasingly older population with higher rates of cardiovascular risk factors and pretest probability of occult AF.

Limitations

Although the median time to AF detection was 41 days in CRYSTAL-AF,[38] outpatient rhythm follow-up in this study was restricted to 30 days as per prevailing guidelines at the time.[39] Rhythm follow-up after 30 days was based on routine clinical follow-up, which could potentially underestimate the AF incidence after cryptogenic stroke and by consequence underestimate the association between LA mechanics and AF. However, AF detection rates by mobile cardiac outpatient telemetry were in line with previous literature.[40-44] Left atrial strain computation requires optimal image quality to ensure reliable speckle correlation and was not quantifiable in 21 (9.5%) patients. Furthermore, intervendor variability should be taken into account when interpreting the strain cutoffs presented in this study. The cutoff values for PALS and booster pump strain rate require external validation in a prospective stroke cohort. Due to the retrospective design of this study, no adjustments were made for possible confounders such as alcohol[45] and sleep apnea[46-48] that contribute to LA myopathy and stroke. Finally, the retrospective time period (2005–16) lends itself to issues with changing imaging technology (echo and brain magnetic resonance imaging/computed tomography), definitions, and diagnostic practices.

CONCLUSION

Left atrial strain imaging immediately after cryptogenic stroke adds significant predictive value for future occurrence of AF. Impaired booster pump strain rate is a strong and independent predictor of AF, which might reflect a component of atrial stunning and could warrant extended rhythm follow-up. Further prospective studies that incorporate LA strain indices into management algorithms in patients presenting with cryptogenic stroke are needed.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2020.09.009.

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics—2019 update: a report from the American Heart Association. Circulation 2019;139:56-528.
2. Ornello R, Degan D, Tiseo C, Di Carmine C, Perciballi L, Pistoia F, et al. Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes a systematic review and meta-analysis. Stroke 2018;49:814-9.
3. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurol 2015;14:903-13.
4. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke definitions for use in a multicenter clinical trial. Stroke 1993;24:35-41.
5. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 2004;62:569-73.
6. Alkhouli M, Friedman PA. Ischemic stroke risk in patients with nonvalvular atrial fibrillation JACC review topic of the week. J Am Coll Cardiol 2019;74:3050-65.
7. Ntaios G. Embolic stroke of undetermined source: JACC review topic of the week. J Am Coll Cardiol 2020;75:333-40.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.e14.
9. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2018;19:591-600.
10. Martens P, Deferm S, Bertrand PB, Verbrugge FH, Ramaekers J, Verhaert D, et al. The detrimental effect of RA pacing on LA function and clinical outcome in cardiac resynchronization therapy. JACC Cardiovasc Imaging 2019;4:895-906.
11. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:344-418.
12. Bath PM, Appleton JP, Krishnan K, Sprigg N. Blood pressure in acute stroke: to treat or not to treat: that is still the question. Stroke 2018;49:1784-90.
13. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962.
14. Delgado V, Di Biase L, Leung M, Romero J, Tops LF, Casadei B, et al. Structure and function of the left atrium and left atrial appendage: AF and stroke implications. J Am Coll Cardiol 2017;70:3157-72.
15. Thomas L, Muraru D, Popescu BA, Sitges M, Rosca M, Pedrizzetti G, et al. Evaluation of left atrial size and function: relevance for clinical practice. J Am Soc Echocardiogr 2020;33:934-52.
16. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol 2014;63:493-505.
17. Hoit BD. Assessment of left atrial function by echocardiography: novel insights. Curr Cardiol Rep 2018;20:96.
18. Shih JY, Tsai WC, Huang YY, Liu YW, Lin CC, Huang YS, et al. Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. J Am Soc Echocardiogr 2011;24:513-9.
19. Obokata M, Negishi K, Kurosawa K, Tateno R, Tange S, Arai M, et al. Left atrial strain provides incremental value for embolism risk stratification over CHA2DS2-VASc score and indicates prognostic impact in patients with atrial fibrillation. J Am Soc Echocardiogr 2014;27:709-14.
20. Inoue YY, Alissa A, Khurram IM, Fukumoto K, Habibi M, Venkatesh BA, et al. Quantitative tissue-tracking cardiac magnetic resonance (CMR) of left atrial deformation and the risk of stroke in patients with atrial fibrillation. J Am Heart Assoc 2015;4:e001844.
21. Genovese D, Singh A, Volpato V, Kruse E, Weinert L, Yamat M, et al. Load dependency of left atrial strain in normal subjects. J Am Soc Echocardiogr 2018;31:1221-8.
22. Kim D, Shim CY, Cho IJ, Kim YD, Nam HS, Chang HJ, et al. Incremental value of left atrial global longitudinal strain for prediction of post stroke atrial fibrillation in patients with acute ischemic stroke. J Cardiovasc Ultrasound 2016;24:20-7.
23. Pagola J, González-Alujas T, Flores A, Muchada M, Rodriguez-Luna D, Seró L, et al. Left atria strain is a surrogate marker for detection of atrial fibrillation in cryptogenic strokes. Stroke 2014;45:164-6.
24. Pathan F, Sivaraj E, Negishi K, Rafiudeen R, Pathan S, D'Elia N, et al. Use of atrial strain to predict atrial fibrillation after cerebral ischemia. JACC Cardiovasc Imaging 2018;11:1557-65.
25. Louie EK, Liu D, Reynertson SI, Loeb HS, McKiernan TL, Scanlon PJ, et al. "Stunning" of the left atrium after spontaneous conversion of atrial fibrillation to sinus rhythm: demonstration by transesophageal Doppler techniques in a canine model. J Am Coll Cardiol 1998;32:2081-6.
26. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for "atrial stunning" as a mechanism of thromboembolic complications. J Am Coll Cardiol 1994;23:307-16.
27. Grimm RA, Stewart WJ, Maloney JD, Cohen GI, Pearce GL, Salcedo EE, et al. Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterization by simultaneous transesophageal echocardiography. J Am Coll Cardiol 1993;22:1359-66.
28. Weiss R, Marcovitz P, Knight BP, Bahu M, Souza JJ, Zivin A, et al. Acute changes in spontaneous echo contrast and atrial function after cardioversion of persistent atrial flutter. Am J Cardiol 1998;82:1052-5.
29. Sanders P, Morton JB, Kistler PM, Vohra JK, Kalman JM, Sparks PB. Reversal of atrial mechanical dysfunction after cardioversion of atrial

fibrillation: implications for the mechanisms of tachycardia-mediated atrial cardiomyopathy. Circulation 2003;108:1976-84.
30. Wozakowska-Kapłon B, Opolski G. Concomitant recovery of atrial mechanical and endocrine function after cardioversion in patients with persistent atrial fibrillation. J Am Coll Cardiol 2003;41:1716-20.
31. Thomas L, Mckay T, Byth K, Marwick TH. Abnormalities of left atrial function after cardioversion: an atrial strain rate study. Heart 2007;93:89-95.
32. Falcone RA, Morady F, Armstrong WF. Transesophageal echocardiographic evaluation of left atrial appendage function and spontaneous contrast formation after chemical or electrical cardioversion of atrial fibrillation. Am J Cardiol 1996;78:435-9.
33. Black IW, Fatkin D, Sagar KB, Khandheria BK, Leung DY, Galloway JM, et al. Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation: a multicenter study. Circulation 1994;89:2509-13.
34. Stoddard MF, Dawkins PR, Prince CR, Longaker RA. Transesophageal echocardiographic guidance of cardioversion in patients with atrial fibrillation. Am Heart J 1995;129:1204-15.
35. Khan IA. Atrial stunning: basics and clinical considerations. Int J Cardiol 2003;92:113-28.
36. Kaya EB, Tokgözoğlu L, Aytemir K, Kocabaş U, Tülümen E, Deveci OS, et al. Atrial myocardial deformation properties are temporarily reduced after cardioversion for atrial fibrillation and correlate well with left atrial appendage function. Eur J Echocardiogr 2008;9:472-7.
37. Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. Circ Cardiovasc Qual Outcomes 2011;4:313-20.
38. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478-86.
39. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-236.
40. Tayal AH, Tian M, Kelly KM, Jones SC, Wright DG, Singh D, et al. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. Neurology 2008;71:1696-701.
41. Flint AC, Banki NM, Ren X, Rao VA, Go AS. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the stroke and monitoring for PAF in real time (SMART) registry. Stroke 2012;43:2788-90.
42. Kamel H, Navi BB, Elijovich L, Josephson SA, Yee AH, Fung G, et al. Pilot randomized trial of outpatient cardiac monitoring after cryptogenic stroke. Stroke 2013;44:528-30.
43. Khan M, Miller DJ, Schultz LR. Indecision in the clinical practice of anticoagulation for brief atrial arrhythmias after cryptogenic stroke. J Stroke Cerebrovasc Dis 2013;22:500-3.
44. Favilla CG, Ingala E, Jara J, Fessler E, Cucchiara B, Messé SR, et al. Predictors of finding occult atrial fibrillation after cryptogenic stroke. Stroke 2015;46:1210-5.
45. Kadlecová P, Andel R, Mikulík R, Handing EP, Pedersen NL. Alcohol consumption at midlife and risk of stroke during 43 years of follow-up cohort and twin analyses. Stroke 2015;46:627-33.
46. Munoz R, Duran-Cantolla J, Martínez-Vila E, Gallego J, Rubio R, Aizpuru F, et al. Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke 2006;37:2317-21.
47. Catalan-Serra P, Campos-Rodriguez F, Reyes-Nuñez N, Selma-Ferrer MJ, Navarro-Soriano C, Ballester-Canelles M, et al. Increased incidence of stroke, but not coronary heart disease, in elderly patients with sleep apnea: role of continuous positive airway pressure treatment. Stroke 2019;50: 491-4.
48. McDermott M, Brown DL. Sleep apnea and stroke. Curr Opin Neurol 2020;33:4-9.