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Atrial Fibrillation, Atrial Cardiopathy and Cryptogenic Strokes

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Introduction

Cryptogenic stroke (CS) refers to the cerebral infarcts for which no definite cause is identified after adequate diagnostic evaluation [1]. It accounts for 10-15% of all strokes. Most of the cryptogenic strokes are embolic-appearing non-lacunar infarcts based on the radiographic pattern [2]. Recognition of this feature triggered the introduction of the concept of Embolic Stroke of Undetermined Source (ESUS), representing the embolic stroke in the absence of intracranial or extracranial stenosis of 50% or more, known cardioembolic source or other determined stroke mechanisms [3].

Paroxysmal atrial fibrillation (AF) has been recognized as an important cause of CS, especially in older patients. However, paroxysmal AF is transient in nature and difficult to detect in many cases. Studies with prolonged cardiac monitoring, by either implantable cardiac monitor (ICM) or 30-day cardiac event monitor (CEM), have significantly increased the rate of AF detection in CS patients [4,5]. Several premorbid factors have been identified to predict AF detection, and associated with increased risk of ischemic stroke [6-12]. Many of these factors are biomarkers of atrial cardiopathy.

Atrial cardiopathy is often considered as a functional or structural disorder of the left atrium (LA). Although there are no specific criteria or thresholds indicative of atrial cardiopathy as yet, it may be provisionally diagnosed by the presence of one of the biomarkers of left atrial dysfunction such as enlarged LA size or volume, prolonged atrial conduction time, P wave dispersion on the electrocardiogram (ECG), and elevation in serum biomarkers [13-15]. These markers are also strong predictors of AF in CS patients. However, it is unclear whether atrial cardiopathy and AF act alone or causatively in stroke recurrence, and whether anticoagulation is warranted in atrial cardiopathy without AF detection in secondary stroke prevention. Therefore, understanding the interplay among AF, atrial cardiopathy and CS has important therapeutic implications.

Predictors for AF Detection in CS Patients

In a recent study [16], we enrolled 389 CS patients between February 2014 and September 2017 who received implantable cardiac monitors (ICMs). AF episodes were detected in 102 patients (26.2%), and the median time to AF detection was 133 days, while 287 patients (73.8%) demonstrated no AF episodes after monitoring of at least 12 months, with median follow-up of 542 days. A variety of parameters including patient demographics, stroke characteristics, and pre-defined risk factors were compared between patients with and without AF detection. We found that only age and LA diameter were significant predictors of AF detection. The risk of AF detection increased by 110% with each additional decade since age of 55 [odds ratio (OR) 2.10, 95% CI 1.64-2.68, p<0.0001], and by 90% with each additional 5 mm increase of LA diameter (OR 1.91, 95% CI 1.33-2.74, p=0.0004).

Consistent with our study, Poli et al. also reported enlarged LA diameter as independent predictor of AF in CS patients [7]. Besides LA size, several other factors were identified as AF predictors in CS patients, including PR interval [6], LA volume index [9,17], total atrial conduction time [18], and P-wave terminal force in lead V1 (PTFV1) [10-12]. All these factors are essentially indicators for atrial cardiopathy [13-15].

To further investigate the role of atrial cardiopathy in AF prediction in CS patient, we extended our study to examine biomarkers of atrial cardiopathy within our cohort. Since our last publication, we continued the ICM follow-up in those "no AF" patients until October 2020.

During the interval time, while 11 patients were found to have AF and were all started on oral anticoagulation, 189 patients successfully completed at least 2 years of recording without AF detection, including 129 patients (68.3%) with recordings more than 3 years and 151 patients (79.9%) more than 1000 days.

We compared several biomarkers related to LA function in electrocardiogram and echocardiogram between AF and no AF groups, including PR interval, LA diameter, LA diameter index, LA volume, LA volume index and left ventricle (LV) E/e' ratio (Table 1). The AF group was the combination of 102 AF patients from our previous publication and the new 11 AF patients found during the interval time. As shown in Table 1, parameters such as PR interval, LA diameter, LA diameter index, LA volume as well as LA volume index, were all significantly greater in AF patients than those without AF detection. Only average LV E/e' ratio was not statistically significant between two groups (p=0.0736); however, AF group tended to have higher LV e/e' ratio, indicating an over-strained LA due to the LV diastolic dysfunction [19].

One of the strengths of the current study was to only include those patients without AF detection after prolonged ICM recording (all more than 2 years and about 2/3 more than 3 years) to minimize any possible contamination of AF patients. However, there were several limitations of the updated analysis. First, there were significant number of missing values in both groups. In this retrospective study, echocardiogram reporting was not standardized, causing smaller sample size in several datasets. Second, the study did not involve several other parameters that are also important for atrial cardiopathy assessment, including PTFV1, P-wave area, and B-type natriuretic peptide (BNP). Transthoracic echocardiogram (TTE) was used in our study for measuring LA size. TTE is superior to transesophageal (TEE) in quantification of LA size because the distance between the probe and the target allows for complete capture of the atrial borders [20]. In addition, the reference values for LA size by TEE have not been established [20]. In contrast, TEE offers superior resolution of the posterior structures including LA, mitral valve, and LA appendage (LAA). Atrial cardiopathy parameters in TEE, such as LAA flow velocity and LA spontaneous echo contrast, were not studied in the current report.

Nonetheless, our new analysis further supports the notion that left atrial cardiopathy is a key predictor of occult AF in CS patients. We again confirmed our previous study [16] as well as others [7] that LA diameter is a predictor for AF detection in CS patients. Furthermore, the new data are consistent with previous literature that PR interval and LA volume index are also positive predictors for AF detection in this population [6,9,17]. However, in disagreement with a previous publication [9], we found LA diameter index is also a predictor for AF. Taken together, our study emphasizes the importance of LA dysfunction and atrial cardiopathy in the prediction of AF among CS patients.

Recurrent Strokes after CS

In our recent publication of 389 CS patients mentioned above [16], a total of 25 recurrent strokes occurred in 17 patients with AF detected, while 48 recurrent strokes occurred in 36 patients without AF. Median length of follow-up was 843 and 904 days, respectively. No significant difference was found between the two subsets of cohorts in terms of patient demographics, stroke risk factors, time to first stroke, or infarct topography. Most recurrent strokes continued to exhibit embolic pattern radiologically. Specifically, in patients found to have AF, 9 recurrent strokes occurred before AF detection in 7 patients and 16 recurrent strokes occurred after AF detection in 11 patients. Interestingly, in patients whose recurrent strokes occurred after AF detection, the median time to AF detection was much shorter (90 *vs.* 251 days), and the median time to first stroke recurrence was much

	AF (n=113)	**no AF (n=189)**	***p* value#**
PR interval (ms)	175.9 ± 45.3/4.3 (n=112)	165.8 ± 24.9/1.9 (n=179)	0.0151*
LA diameter (mm)	37.9 ± 7.0/0.7 (n=105)	35.0 ± 5.9/0.4 (n=172)	0.0002*
LA diameter index (mm/m^2)	1.95 ± 0.62/0.06 (n=100)	1.76 ± 0.35/0.03 (n=164)	0.0019*
LA volume (ml)	60.9 ± 21.8/2.6 (n=69)	46.4 ± 15.2/1.4 (n=123)	<0.0001*
LA volume index (ml/m^2)	29.4 ± 10.7/1.34 (n=64)	24.1 ± 8.1/0.74 (n=121)	0.0002*
LV e/e' average	11.5 ± 4.2/0.53 (n=65)	10.3 ± 4.3/0.38 (n=131)	0.0736
Data are presented as Mean ± SD/SEM. LA, left atrium; LV, left ventricle; #Statistical analysis was performed with independent t-test; *Statistical significance			

Table 1: Comparison of LA function in CS patients with and without AF detection.

longer (422 *vs.* 76 days) than in those whose strokes recurred before AF detection, indicating the importance of early detection of AF and early initiation of anticoagulation in this population.

A recent subgroup analysis from NAVIGATE ESUS trial showed that 309 of 7231 patients suffered recurrent strokes during median follow-up of 11 months. Of the 270 classifiable strokes, 71% were embolic (58% ESUS and 13% cardioembolism), consistent with our findings that most recurrent strokes continue to present with embolic feature [21]. It was also found that in these ESUS patients with recurrent strokes, LA diameter was significantly larger (4.1 *vs.* 3.7 cm) in patients (n=27) with AF detected during follow-up period than those (n=282) without AF recorded [21]. In addition, among 361 ESUS patients with LA diameter >4.6cm in this trial, 3 patients in Rivaroxaban group versus 11 patients in Aspirin group suffered recurrent strokes (1.7% *vs.* 6.5%, p=0.02) during the follow-up period, supporting the role of anticoagulation in secondary stroke prevention for patients with atrial cardiopathy [22]. Similarly, greater LA volume index was also associated with recurrent strokes in patients after ESUS, presumably due to the higher likelihood of AF detection [9].

However, it is unclear whether atrial cardiopathy could act alone or only serve as a surrogate of AF in developing strokes. On one hand, almost all indicators for atrial cardiopathy have been shown to be strongly associated with and serve as important risk factors for occult AF [13,14], including echocardiographic markers (LA enlargement, spontaneous echocardiographic contrast, and reduced LAA flow velocity), electrocardiogram markers (PSVT, increased PTFV1, prolonged PR interval), MRI marker (atrial fibrosis), and serum biomarker (BNP). Evidence indeed show that AF is both a cause and a consequence of atrial cardiopathy [13]. While on the other hand, lack of direct evidence of a causal association including a temporal relationship between AF and thromboembolic events in most patients with AF argues that AF is simply a marker of atrial cardiopathy, and the latter may be the real underlying cause of stroke in these patients [14,15]. Moreover, electromechanical dissociation between surface EKG and echocardiographic LA dysfunction during sinus rhythm underestimates atrial dysfunction as the attributed embolic risk [14,15]. A study of 41 patients with AF after cardioversion showed that about one-third of the patients had non-sinus contraction of LAA while in normal sinus rhythm on the surface EKG [23]. In another study of 24 patients with a history of paroxysmal AF and recent stroke, 25% of the patients had a LAA flow pattern characteristic for AF on TEE despite being in sinus rhythm at the time of exam [24]. Taken together, these data suggest that electrical AF does not provide the sole mechanism of embolic events in patients with evidence of atrial dysfunction and that other mechanisms such as atrial enlargement, fibrosis, or inflammation associated with atrial cardiopathy may explain the embolic stroke even in the absence of AF [13-15].

To investigate whether atrial cardiopathy may lead to recurrent strokes without AF detection in CS patients, we followed our "no AF" cohort (n=159) for prolonged period (average 1473 days) and recorded their recurrent strokes (Table 2). We compared the parameters of LA function in the absence or presence of recurrent strokes in this cohort. 31 patients suffered recurrent strokes with 8 of them having had more than one recurrent stroke. Indexes of LA function including PR interval, LA diameter, LA diameter index, LA volume, LA volume index as well

	No. recurrent strokes (n=158)	**Recurrent strokes (n=31)**	***p* value[#]**
Recurrent strokes		43	
Patients with > 1 recurrent stroke		8	
Age (years)	64.74 ± 11.63/0.93	66.52 ± 10.00/1.80	0.4284
Male sex (%)	77 (48.7%)	13 (41.9%)	0.4802
Length of follow-up (days)	1491.11 ± 404.08/32.15	1383.61 ± 444.60/79.85	0.1845
PR interval (ms)	167.06 ± 25.94/2.13 (n=149)	159.53 ± 18.21/3.33 (n=30)	0.1318
LA diameter (mm)	34.91 ± 6.03/0.51 (n=142)	35.23 ± 5.23/0.96 (n=30)	0.7827
LA diameter index (mm/m^2)	1.75 ± 0.35/0.03 (n=137)	1.81 ± 0.36/0.07 (n=29)	0.4198
LA volume (ml)	45.18 ± 14.23/1.41 (n=102)	52.11 ± 18.78/4.10 (n=21)	0.0574
LA volume index (ml/m^2)	23.58 ± 7.12/0.71 (n=100)	26.51 ± 11.69/2.55 (n=21)	0.2800
LV e/e' average	9.94 ± 3.76/0.36 (n=109)	12.06 ± 6.16/1.31 (n=22)	0.1320
Data are presented as Mean ± SD/SEM; LA; Left Atrium; LV: Left Ventricle; [#]Statistical analysis was performed with independent t-test			

Table 2: Comparison of LA function in AF-free CS patients with and without recurrent strokes.

as LV E/e' were comparable between patients with and without recurrent strokes, although larger LA volume had insignificant tendency favoring recurrent strokes (Table 2). Our result indicates that left atrial dysfunction failed to show its association with recurrent strokes in CS patients in the absence of AF.

Our current study is by far the longest stroke follow-up after CS to our knowledge (nearly 4 years in average). However, it is inconclusive given its limitations. Similar to above discussion, the missing values on echocardiographic reporting and small sample size in recurrent strokes made this analysis underpowered. Additionally, only limited biomarkers for atrial cardiopathy were included in the analysis. Further study on a broader range of biomarkers for LA dysfunction should be considered.

Conclusion

Occult AF remains a most compelling cause of CS. Markers for LA dysfunction are not only strong predictors for AF detection but are also closely associated with recurrent strokes after CS. The exact roles that AF and atrial cardiopathy play in the developing stroke is still unclear. As atrial cardiopathy and AF are tightly intertwined between each other, it is difficult to tease out whether left atrial cardiopathy in the absence of AF can trigger left atrial thromboembolism or it simply serves as surrogate for occult AF that is ultimately responsible for the stroke, although there is evidence favoring both sides of the argument. Currently, there is an ongoing biomarker-driven randomized phase 3 clinical trial of apixaban versus aspirin in patients who have evidence of atrial cardiopathy and ESUS (ARCADIA). We eagerly await ARCADIA trial result to further decipher associations amongst AF, atrial cardiopathy and CS.

Disclosures

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