Case Report
Ischemic stroke resulting from isolated left atrial fibrosis independent of atrial fibrillation: a case report with review of the literature

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Abstract: Objective: To investigate the underlying mechanism of unexplained ischemic stroke in a 29-year-old male patient without atrial fibrillation (AF). Methods: Clinical data including surface 12 leads electrocardiogram (ECG), 24 hours Holter recording, cranial MRI and transthoracic echocardiography (TTE) were analyzed, meanwhile, electrophysiology study (EPs) was performed by means of detailed voltage mapping of left and right atrium. Results: Surface ECG manifested embryonic P wave in 12 leads, multiple Holter recordings revealed arrhythmia of atrial premature contractions (APCs) and short run of atrial tachycardia (AT) without AF, voltage mapping demonstrated diffuse and massive low-voltage areas within left atrium, however, right atrium presented normal voltage mapping, which suggested isolated left atrial fibrosis or standstill contributing to the occurrence of ischemic stroke. The patient received anticoagulation with dabigatran and no stroke recurred during 3 years of follow-up. Conclusion: Mechanical dysfunction of left atrium could lead to ischemic stroke even in the absence of AF, and patient with left atrial standstill need long term anticoagulation.

Keywords: Atrial fibrillation, ischemic stroke, atrial fibrosis, anticoagulation

Introduction
Atrial fibrillation is one of the most common arrhythmias in clinical practice, which could result in ischemic stroke and heart failure. The ischemic stroke risk of AF patients is 5 times greater than those with sinus rhythm [1]. CHA₂DS₂-VASc score had been proved as a reliable method for risk stratification and recommended as guideline for directing anticoagulation therapy in non-valvular AF patients by many cardiovascular societies [2]. However, sometimes CHA₂DS₂-VASc score is not an absolute gold standard for predicting future risk of ischemic stroke, especially for low or intermediate risk patients [3], which implied that some other factors may contribute to the pathogenesis of ischemic stroke.

Case report
A 29-year-old male patient was referred to our hospital with unexplained ischemic stroke for 5 months, who suffered sudden onset of right limbs weakness, speech difficulties with temporal blindness in Jan 2016. MRI scan confirmed left cerebral infarction with cortex involvement, and the characteristics of MRI imaging and clinical manifestation supported the cardioembolic stroke. In the past 6 years, he complained of paroxysmal palpitation and multiple 24-hour ambulatory ECG recordings just revealed APCs and short runs of AT without AF. He denied history of hypertension, diabetes mellitus, hyperthyroidism, cardiomyopathy and alcohol abuse. In particular, the patient experienced intermittent fever during childhood without definite etiology.

12 leads surface ECG revealed sinus rhythm with small or embryonic P wave in limb and precordial leads (Figure 1). Holter recording (Figure 2) showed frequent APCs and 20 episodes of short runs of AT without AF, positive P wave of APCs in lead V1 suggesting left atrial origin. Transthoracic echocardiography (TTE) revealed left atrium enlargement (42 mm, anteroposterior diameter) with normal left ventricular func-
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There was no thrombus and spontaneous contrast phenomenon detected by transesophageal echocardiography (TTE), meanwhile, there was no atherosclerosis plaque in carotid artery observed by echo. No significant findings were revealed by laboratory test, including negative of extractable nuclear antigen (ENA), antinuclear antibody, β2-glycoprotein and anticardiolipin antibody. Homocysteine was in normal range (15.4 umol/L). MRI scan showed left occipital lobe infarction with cortex involvement (Figure 3).

After obtaining informed consent, intracardiac electrocardiogram were recorded using an electrophysiology system (Prucka CardioLabTM General Electric Health Care system). One decapolar mapping catheter (Biosense Webster, Diamond Bar, CA) was positioned in the coronary sinus (CS) through the right jugular vein access using the standard Brockenbrough technique [4], atrial transseptal puncture was performed under fluoroscopic guidance, L1-type Swartz sheath (St Jude Medical, Minneapolis, MN) was transseptally introduced into left atrium via right femoral vein, and intravenous unfractionated heparin 5000u was administrated immediately after atrial transseptal puncture. Selective pulmonary vein venography was performed to identify all PV ostia; one decapolar circular mapping catheter (Lasso Biosense Webster) was advanced to reconstruct LA geometry and perform voltage mapping. Low voltage and normal voltage were defined as potential less than 0.1 mv and greater than 0.5 mv respectively. The mapping result revealed that there was massive and extensive area of low-voltage within LA including left atrial appendage, and mapping catheter in coronary sinus could simultaneously record distinctive atrial potential, which suggested epicardial atrium of LA may not be affected by fibrosis (Figure 4A, 4B); only the septal portion connecting with right atrium and small spots of roof adjacent to left super pulmonary vein (LSPV) remained intact voltage (Figure 4C), however, right atrium was not affected and manifested as normal voltage (Figure 5A-C). The EP findings supported the diagnosis of isolated left atrial standstill, which was the underlying mechanism of embryonic P wave of surface ECG. Even most of endocardial LA exhibited low voltage, and the decapolar mapping catheter in the CS still recorded distinct atrial potential, which suggested LA epicardial may have some intact myocardium.

It was believed that isolated left atrial standstill could play an important role in thrombus formation due to its mechanical dysfunction, consequently, the patient received long-term anticoagulation therapy shifting from warfarin to dabigatran with the dosage of 150 mg twice daily. During 2 years’ follow-up, no thromboembolic events recurred.

Discussion

Cardioembolic stroke is the highest risk of mortality and poor functional outcome in all subtypes of ischemic stroke; in clinical practice,
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Figure 2. Short run of atrial tachycardia. Holter recording revealed short run of atrial tachycardia (black arrow indicated the minimal P wave of atrial tachycardia in lead V₁, the upright P wave suggested left atrium origin).

nearly 30% ischemic stroke has not been identified the cause and known as cryptogenic stroke or ESUS (embolic stroke of undetermined source) [5]. The MRI characteristics of this subtype stroke was affecting the territory of major branches or distal end vessels of the cerebral artery tree [6]. The cerebral MRI scan of the patient in this report manifested same features and firstly diagnosed as cryptogenic stroke. There are several mechanisms responsible for cryptogenic stroke, including occult paroxysmal atrial fibrillation, patent foramen ovale, hypercoagulability, and substenotic atherosclerosis [7]. However, a series of clinical examination had ruled out these possibilities.

Many clinical studies have strongly supported the close relationship between AF and ischemic stroke [8], and some researches demonstrated that long-term ECG monitoring could increase
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Figure 3. Cranial MRI scan. Left occipital lobe infarction (black arrow showed gray area) with cortex involvement.

detection of AF after cryptogenic stroke [9]. However, ASSERT and TRENDS study did not prove constant temporal association between AF and stroke [10, 11], and only 25% patients have AF episodes in the 30 days prior to embolic events, which suggested that AF may not be the direct etiology of stroke in most patients. In our study, several 24-hour ECG recordings of this patient had not detected AF, which further confirmed this hypothesis.

Recent data suggest that the pathological atrial substrate, or atrial cardiopathy, that underlies AF, rather than atrial fibrillation itself, may be an important cause of unexplained strokes [12]. Cardiac emboli may occur temporally dis-associated from episodes of AF, while biomarkers of left atrial structural and electrophysiological abnormalities have been associated with stroke risk, even in the absence of AF. In our case, the specific characteristic of ECG was embryonic P wave which suggested diseased atrium, and the intracardiac mapping finally demonstrated isolated left atrial standstill attributed to the pathogenesis of abnormal P wave. Recently, Bayés syndrome [13] was introduced into clinical practice, which manifested as prolonged P wave duration > 120 ms with biphasic morphology in the inferior leads, and closely associated with cardioembolic stroke due to left atrial electromechanical dysfunction. Benito [14] had proved severe atrial fibrosis in patients with Bayés syndrome. Therefore, embryonic or prolonged P wave could be used as a non-invasive marker of fibrosis. It was suggested that relying on surface ECG to detect AF could underestimate atrial disease or dysfunction and perhaps the attributed embolic risk, and some data demonstrated electromechanical dissociation between surface ECG and echocardiographic left atrial function. One study [15] showed that 6 out of 24 patients with a history of AF and recent stroke undergoing transesophageal echocardiogram (TEE) had a LAA flow pattern of typical AF despite in sinus rhythm at the time of TEE.

Recent study [16, 17] showed that certain genetic mutation linked with AF was closely associated with ischemic stroke even before the evidence of AF. For example, single-nucleotide polymorphism (rs2200733 and rs10033464) is associated with increased risk of AF and ischemic stroke, especially those thought to be cardioembolic, even in those without detected AF.

The term fibrotic atrial cardiomyopathy was originally proposed by Kottkamp [18] to describe a specific, primary form of atrium pathology, characterized by extensive fibrosis as the substrate of AF and thromboembolism. The absolute risk of stroke with AF is variable and derives from biological factors and comorbidities that promote thrombogenic substrate of AF, and atrial fibrosis could be the independent risk factor of stroke in the absence of AF. It is hypothesized that AF and thromboembolism may result from the same substrate: atrial fibrosis. In this case report, the patient had not been detected with AF by several Holter recordings. Even he suffered occult AF, the CHA\textsubscript{2}DS\textsubscript{2}-VAS\textsubscript{C} score was only 0 which suggested no indication for anticoagulation therapy based upon current guideline. CHA\textsubscript{2}DS\textsubscript{2}-VAS\textsubscript{C} is a prediction model quantifying individual stroke risk, however, our case indicated that this method was not reliable for stroke classification in moderate risk young patients with atrial fibrosis.

Atrial fibrosis could be assessed by delayed-enhancement MRI. Some study had shown that patients who had experienced a prior stroke had a significantly higher percentage of LA fibrosis than those without stroke, and the incidence rate of stroke was positively correlated with stage of left atrial fibrosis [19]. Some study revealed that the severity of LA fibrosis was associated with LAA flow pattern, and sponta-
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Figure 4. Voltage mapping of left atrium (LA). A: Decapolar circular catheter could only record minimal potentials (white arrow indicating intracardiac potential) in the roof of LA, mapping catheter in coronary sinus could simultaneously record normal atrial potential (yellow arrow). B: In PA projection, voltage mapping indicated extensive low voltage area (red color area represented local voltage less than 0.1 mv indicating scar or fibrosis, green color indicated voltage between 0.1-0.5 mv indicating partial fibrosis, purple color area represented local voltage greater than 0.5 mv indicating normal tissue). C: In AP projection, only the septal portion connecting with right atrium and small spots of roof adjacent to LSPV exhibited intact voltage. PA: Posteroanterior; AP: Anteroposterior. LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein.
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**Figure 5.** Voltage mapping of right atrium (RA). A: Decapolar circular catheter could record normal potentials (white arrow) in RA. B: In LAO projection, mapping indicated normal voltage in RA (purple color area represented local voltage greater than 0.5 mv) except SVC (red color indicated the position of superior vena cava) and IVC. C: The combination of LA and RA voltage mapping in LAO projection. SVC: superior vena cava; IVC: inferior vena cava. LAO: left anterior oblique.
neous contrast and LAA thrombus were linked with more pronounced LA fibrosis on TEE examination [20]. These findings confirmed that LA fibrosis could be a variable of structural atrial remodeling and a useful tool for clinicians to use in conjunction with the CHA\_DS\_VAS\_index for anticoagulation risk stratification, and LA substrate analysis could be used in addition to standard clinical variables.

Lee [21] reported that a young male patient suffered cerebral infarction with left atrium standstill without evidence of AF, which was similar to our case. Atrial standstill was characterized by the absence of electrical and mechanical activity, and this patient manifested as single left atrium involvement and normal right atrium known as partial atrial standstill. The underlying mechanism of left atrial standstill could be related to specific atrial inflammation linked with recurrent fever during his childhood.

Left atrial fibrosis could be an independent risk factor for cardioembolic stroke in the absence of AF. Patients with severe left atrial fibrosis should be anticoagulated despite of atrial fibrillation.

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Disclosure of conflict of interest

None.

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