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Serum level of transforming growth factor beta 1 is associated with left atrial voltage in patients with chronic atrial fibrillation

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ABSTRACT

Background: Atrial tissue fibrosis can cause electrical or structural remodeling in patients with atrial fibrillation. Transforming growth factor beta 1(TGF-β1) signaling acts as a central role in fibroblast activation. In this report, we aimed to investigate the relationship between serum level of TGF-β1 and mean left atrial voltage in patients with chronic atrial fibrillation (CAF).

Methods: A total of 16 consecutive adult patients with CAF who underwent catheter ablation were enrolled. Blood samples for measurement of TGF-β1 were collected from periphery veins and coronary sinus before pulmonary vein isolation. The measurement was performed with a commercially available ELISA kit. Cardiac indices were measured using echocardiography. The left atrial electroanatomic mapping was performed after pulmonary vein isolation.

Results: Serum level of TGF-β1 in peripheral blood was higher than that in coronary sinus ($p < 0.001$). TGF-β1 serum level in coronary sinus negatively correlated with mean left atrial voltage ($r = -0.650$, $p = 0.012$), While periphery TGF-β1 level tended to be negatively correlated with mean left atrial voltage($r = -0.492$, $p = 0.053$). Patients who treated with angiotensin II receptor antagonists had lower coronary sinus TGF-β1 serum level than those who did not treated with angiotensin II receptor antagonists ($p = 0.046$).

Conclusion: Level of TGF-β1 in peripheral serum is higher than that in coronary sinus, and serum level of TGF-β1 in coronary sinus is negatively associated with mean left atrial voltage in patients with CAF, angiotensin II receptor antagonists could affect TGF-β1 serum level.

1. Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia that occurs in individuals with a variety of cardiovascular diseases or without any other evidence of systemic diseases [1]. It affects 5% of the population older than 65 years and the prevalence increases as the population age arises [2]. Despite of more and more research on the mechanisms of AF, the exact cause and pathogenesis of AF remains unclear [3–5]. Two principal forms of remodeling have been described in animal models of AF: electrical remodeling, which affects cellular electrical properties, and structural remodeling, which alters atrial tissue architecture [6]. Structural remodeling can be caused by interstitial fibrosis.

Atrial fibrosis, a detrimental process that causes imbalance in extracellular matrix deposition and degradation, has been implicated as a substrate for AF. However, the precise mechanisms of structural remodeling and the relationship between atrial fibrosis and atrial fibrillation were largely unknown. Recent experimental and clinical studies have provided valuable insights on the mechanisms of atrial fibrosis at molecular and cellular level. A variety of signaling systems, particularly involving angiotensin II and transforming growth factor-β1 (TGF-β1), seem to be centrally involved in the promotion of fibrosis [7]. Angiotensin II promotes aldosterone secretion to increases mRNA levels of TGF-β1, and converts TGF-β1 into its active form. Aminopeptidase A converts angiotensin II into angiotensin III, which also increases TGF-βl expression [8,9]. TGF-β1 is a subtype of TGF-β. TGF-β signaling was implicated in the pathogenesis of fibrotic diseases by regulating the expression of other proteins involved in executing the fibrotic cascade [10]. Using

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human atrial myocardial tissue, Kupfahl et al. noted that angiotensin II might up-regulate the expression of TGF-β1, and TGF-β1 signaling affects collagen production [11]. Extracellular matrix changes can separate cardiomyocyte bundles, which can diminish electrical coupling and slow electrical conduction [12,13]. It is believed that localized atrial fibrosis may complex atrial electrograms and decrease voltage, while diffuse and profound fibrosis can make the local tissue scarred. These fibrosis related with electrophysiologic changes can be represented by electroanatomic bipolar voltage mapping [14–19].

Overall, TGF-β is a critical regulator of extracellular matrix production, and extracellular matrix changes could be reflected by electroanatomical alternations. Therefore, it is potential for further comprehensive research on whether electroanatomical alternations have correlation with serum TGF-β1 level. The aim of this study is to investigate the relationship between mean left atrial voltage and serum level of TGF-β1 in patients with chronic atrial fibrillation (CAF).

2. Methods

2.1. Participants

We retrospectively analyzed a total of 16 consecutive adult patients with drug refractory CAF who underwent catheter ablation for AF using 3D mapping system (NavX, St. Jude Medical Inc., St. Paul, MN, USA) were enrolled at a single university medical center from June 2012 to May 2013. The definition of CAF was based on the Holter monitoring electrocardiogram, requiring the characters that there was the rhythm of AF instead of sinus rhythm by every time checking. Patients were excluded if they were likely to be elevated serum TGF-β1 level: patients with history of myocardial infarction or elevated level of troponin, angina pectoris, thyroid disease, vascular heart disease, hypertrophic cardiomyopathy, chronic kidney disease, chronic lung disease, chronic liver disease, autoimmune disease, any acute rheumatologic or infectious disease, any trauma or surgery. Congenital heart disease was also excluded from this study. All patients provided written informed consent to the study protocol, which was approved by the Human Research Ethics Committee of the first affiliated Hospital of Nanjing Medical University.

2.2. Fibrosis factor of TGF-β1

After local anesthesia, patient underwent placement of intravenous sheaths in three periphery and subclavian vein. A coronary sinus catheter was placed for electrophysiology study through subclavian vein. When the catheter and sheaths had been placed but before interatrial septum piercing, blood was withdrawn from both the coronary sinus and one of the periphery veins. The first 10 cc of blood was discarded, and the second 10 cc were obtained for TGF-β1 measurement. All blood samples were centrifuged at 2000 g for 10 min, serums were extracted and stored at −80 °C. Blood withdrawn from coronary sinus was confirmed by three steps: intracardiac catheter consistent with coronary sinus placement, the fluoroscopic image of the catheter in standard right and left anterior oblique, and the gross darker appearance of blood than withdrawn from the periphery veins. Measurement of serum TGF-β1 level was performed with a commercially available immunoassay/ELISA.

2.3. Electroanatomic mapping

All AF patients underwent transesophageal echocardiography on the day of the study to exclude left atrium (LA) thrombus. After catheter placement, three-dimensional (3D) geometries of LA and pulmonary veins were created separately using the A-Focus catheter coupled with EnSite-NavX. For all patients, high density mapping were achieved after circumferential pulmonary vein isolation and electric cardioversion were required to restore sinus rhythm (Fig. 1). Only mapping points outside of the pulmonary veins were used for analysis [20]. Local voltage was defined as the amplitude from the peak-positive to the peak-negative deflection of the local bipolar electrogram. The average bipolar mapping sites in the LA were 237 ± 72 points for each patient respectively, and the mean peak-to-peak voltage throughout the entire LA was calculated.

2.4. Statistical analysis

All the data were described by mean ± standard deviation. The correlation between various parameters and LA voltage properties were evaluated with Pearson's correlation coefficients. For comparison between groups, the data were analyzed by independent *t*-test. As the distribution of variables were highly skewed, TGF-β1 level and each segments of the voltage value were log-transformed to normalize their distribution before statistical analysis. All analyses were performed by SPSS software (version 13.0, SPSS Inc., Chicago, Illinois). The *P*-value reported was two-sided and the value of less than 0.05 was considered statistically significant.

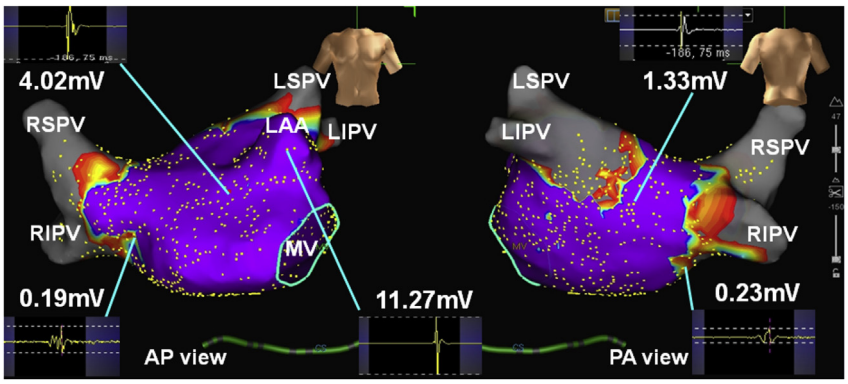

Fig. 1. The example of high density mapping achieved after circumferential pulmonary vein isolation and electric cardioversion to restore sinus rhythm.
LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; MV = mitral valve.

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