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Original article

Relationship between vitamin D level and left atrial fibrosis in patients with lone paroxysmal atrial fibrillation undergoing cryoballoon-based catheter ablation

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ABSTRACT

Background: Left atrial (LA) fibrosis is known as the hallmark for arrhythmogenic substrate in atrial fibrillation (AF). Quantification of LA fibrosis by using delayed-enhanced magnetic resonance imaging (DE-MRI) in AF patients is a pioneering noninvasive technique. Vitamin D (vitD) negatively regulates the renin–angiotensin system, binds to vitD receptors on cardiac myocytes, and has antioxidant properties that may ameliorate the inflammation and proarrhythmic substrate formation. However, its role in LA fibrosis is unclear. We aimed to investigate the association of serum 25(OH)D level with the extent of LA fibrosis by using DE-MRI and also predictors for AF recurrence after cryoablation was assessed in patients with paroxysmal AF.

Methods: A total of 48 patients with lone paroxysmal AF (41.7% female; age: 48.5 ± 8.4 years) who underwent DE-MRI at 1.5 T and initial cryoballoon-based catheter ablation along with 48 healthy control subjects were enrolled. Fibrosis degree was categorized according to Utah class defined in the DECAAF study.

Results: Serum 25(OH)D levels were significantly lower in AF group compared to control group (25.8 ± 7.6 ng/ml vs. 31.0 ± 9.5 ng/ml, $p = 0.004$). Serum 25(OH)D levels were associated with moderate–severe LA fibrosis independent of other measures (OR: 0.72, 95% CI: 0.54–0.97, $p = 0.028$). At a mean 16.5 ± 2.6 months follow-up, late recurrence was observed in 10 (20.8%) patients. In multivariable Cox regression analysis, LA volume index (HR: 1.42, 95% CI: 1.01–2.01, $p = 0.045$) and the extent of LA fibrosis (HR: 1.14, 95% CI: 1.01–1.28, $p = 0.034$) were found as independently associated with late AF recurrence during follow-up.

Conclusion: Lower levels of serum 25(OH)D are significantly associated with more extensive LA fibrosis in patients with lone paroxysmal AF and may be implicated in the pathophysiology of AF recurrence after cryoablation. Further large-scale studies are needed to elucidate the exact role of vitD deficiency and replacement on LA fibrosis.

Introduction

The exact pathogenesis of atrial fibrillation (AF) has not been clarified. AF develops and persists as a complex interaction between triggers and atrial substrate, which are essential components for disease process [1]. As a surrogate of atrial substrate, atrial fibrosis is associated with electrical, contractile, and structural remodeling of atrial tissue. Enhanced oxidative stress, inflammation and activation of renin–angiotensin system (RAS) are shown to be involved in the pathogenesis of atrial fibrosis [2,3]. Currently, catheter ablation techniques primarily aim to eliminate triggers such as pulmonary veins for patients with paroxysmal AF [4]. However, a significant amount of patients fail to remain in sinus rhythm during follow-up [5,6]. Thus, the role of atrial substrate should be considered among these patients [7]. Cardiac magnetic resonance imaging with delayed enhancement technique (DE-MRI) has emerged as an effective method to noninvasively

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assess and quantify the extent of left atrial (LA) fibrosis for selection of appropriate patients before catheter ablation [8].

Besides its essential role in healthy bone metabolism, vitamin D (VitD) is also important for physiological functioning of various extraskeletal tissues and organs including heart [9]. Serum 25-hydroxyvitamin D [25(OH)D] level is usually measured as a circulating indicator of VitD status [10]. It has been proposed that vitD exhibits antioxidant properties, and regulates RAS and inflammatory pathways [11,12]. Furthermore, vitD receptors are also found in myocytes and fibroblasts in the heart, which mediate cardiac remodeling [13]. Given the associations of vitD status with several AF risk factors and the potential link between vitD, RAS, and inflammation, low vitD levels may be involved in occurrence of atrial fibrosis and AF. However, previous studies regarding the association of serum vitD level with the risk of AF revealed conflictory data [14–16]. Also, to the best of our knowledge, there was no study in the literature evaluating the association of serum vitD level with the severity of LA fibrosis and success of cryoballoon-based catheter ablation among patients with lone paroxymal AF.

Therefore, in this study, we aimed to assess the relationship between serum vitD level and quantity of LA fibrosis using DE-MRI. Also, the prognostic value of serum vitD level was evaluated after catheter ablation for paroxysmal AF.

Methods

Study population

In this prospective study, a total of 53 symptomatic lone paroxysmal AF patients who underwent preablation DE-MRI and subsequent initial first-generation cryoballoon-based catheter ablation at our University Hospital between October 2010 and August 2011 were enrolled. Of these patients, catheter ablation was postponed in one patient because of the development of cardiac tamponade during transseptal puncture. Four patients were excluded due to poor-image quality MRI characterized as blurring due to patient motion and significant gating artifacts. Thus, a total of 48 patients with AF were eligible for the final analysis. Additionally, a total of 48 healthy subjects who were admitted to our outpatient clinic for check-up and had no cardiovascular or any other organ system disease were randomly enrolled as a control group.

Subjects who were aged $\geq$60 years, had persistent or permanent AF, structural heart disease, moderate–severe valvular disease, thrombus in LA, uncontrolled thyroid or parathyroid disease, and individuals using calcium or vitD supplementation or therapies that interfere with vitD metabolism, coronary artery disease, stroke, hypertension, diabetes mellitus, chronic liver or kidney disease, systemic/local inflammatory or infectious disease, contraindication for anticoagulation, pregnancy, malignancy, gastrointestinal dysfunction (inflammatory bowel disease and malabsorption), LA anteroposterior diameter $>$55 mm, previous history of catheter ablation, and history of claustrophobia (for MRI) were excluded from the study.

Severity of clinical symptoms was recorded according to European Heart Rhythm Association (EHRA) score [17]. Lone AF was defined in patients who were $<$60 years old, without structural heart disease based on patient history, physical examination, and imaging methods including chest X-ray and echocardiography, and no history of coronary artery disease, diabetes mellitus, or hypertension [18]. Paroxysmal AF is defined as self-terminating episode, usually within 48 h, and may continue for up to 7 days [17].

Demographic and clinical information was recorded on the day of echocardiographic evaluation. Body weight (kg) and height (m) were determined, and body mass index (BMI; kg/m^2) was calculated. Alcohol intake is defined as having up to 1 drink per day for women and up to 2 drinks per day for men, in which heavy drinkers and abusers were excluded. Additionally, in order to properly demonstrate other factors that may have an impact on vitD status, all subjects were enquired about age, weight, height, clothing style, physical activity (by using subject responses in regard to hours spent on exercise, at work or leisure time), current smoking habits, and sunlight exposure (by calculating the average time spent in the sun per day) by a questionnaire.

Preablation evaluation

All AF patients underwent preablation transthoracic and transesophageal echocardiographic examination and cardiac MRI as a study protocol. All echocardiographic measurements were calculated according to the criteria proposed by the American Society of Echocardiography [19]. Echocardiographic examination was performed by using a VIVID 5 Dimension Cardiovascular Ultrasound System (Vingmed-General Electric, Horten, Norway) with a 3.5 MHz transducer.

Informed consent was taken from each patient before enrollment. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by local ethics committee.

Laboratory tests

Venous blood samples were obtained without venostasis by the venipuncture of the large antecubital veins of the patients at least 24 h before cryoablation. Serum was stored at -80 °C. The 25-OH-D concentration was measured with direct enzyme-linked immunosorbent assay (ImmunDiagnostiK, Bensheim, Germany), and intraassay and interassay coefficient of variations were $\leq$3.8% and $\leq$4.1%, respectively. The concentration of intact-parathyroid hormone (iPTH) was determined by use of immunoradiometric assay Immulite 2000 (Siemens Healthcare Diagnostics Products, Erlangen, Germany) with a reference range of 9.5–75 pg/ml. The average intra- and interassay CV [coefficient of variation] for iPTH were $\leq$4.2% and $\leq$3.5%, respectively.

Cardiac magnetic resonance imaging

Scanning and quantification of LA fibrosis was performed using similar techniques that have been previously described by the Utah group [8]. All the patients were in normal sinus rhythm during DE-MRI acquisition. Studies were performed by a General Electric 1.5-T High Definition scanner 2.0 $\pm$ 0.8 days prior to ablation (Signa Excite HD; GE Medical Systems, Waukesha, WI, USA) using an 8-channel phased-array receiver coil. In all patients, there was only one DE-MRI study performed at our center prior to cryoablation. A contrast-enhanced three-dimensional (3D) fast low-angle shot (FLASH) MR angiography sequence and a cine true-fast imaging with steady-state precession (FISP) sequence were used to define the anatomy of the LA and the PVs. The scan was acquired $\sim$18 (range: 17–20) min after contrast agent injection [0.15 mmol/kg i.v., meglumin gadoterad (Dotarem, Guerbet, Aulnay, France)] using a 3D inversion recovery, respiration navigated, electrocardiogram (ECG)-gated, gradient echo pulse sequence. Typical acquisition parameters were as follows: free breathing using navigator gating; a transverse imaging volume with voxel size 1.25 mm $\times$ 1.25 mm $\times$ 4 mm, which was then reconstructed to 0.625 mm $\times$ 0.625 mm $\times$ 2 mm; repetition time (TR)/echo time (TE) = 4.8/2.3 ms; parallel imaging using the generalized autocalibrating partially parallel acquisitions (GRAPPA) technique with reduction factor R = 2 and 32 reference lines; field of view (FOV): 300–340 mm; flip angle: 20°; matrix size:

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