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Original article

Good responders to catheter ablation for long-standing persistent atrial fibrillation: Clinical and genetic characteristics

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ABSTRACT

Background: Radiofrequency catheter ablation (RFCA) for long-standing persistent atrial fibrillation (L-PeAF) is challenging and has a relatively high recurrence rate. We explored clinical and genetic characteristics associated with being good responders (no early or clinical recurrence within 12 months in the absence of anti-arrhythmic drugs) to RFCA among patients with L-PeAF.
Methods: Of 1319 patients in the Yonsei AF Ablation Cohort, this study included 141 consecutive patients with L-PeAF (80.9% male, age 57.8 ± 9.7 years) who were followed >12 months after RFCA.
Results: During 25 (19–35) months follow-up, the recurrence rate was 39%, and 38 patients (27%) were categorized as good responders, those had a shorter AF duration ($p = 0.010$), and smaller left atrial (LA) size ($p = 0.033$) than others. The *rs2106216* (16q22/*ZFHX3*) genetic polymorphism was independently associated with being a good responder in multivariate analysis (adjusted OR = 2.70, 95% CI 1.41–5.14, $p = 0.003$), after adjusting for LA size and AF duration. The *rs2106261* had predictive value for clinical recurrence of AF after RFCA among patients with an AF duration 12–65 months (log rank, $p = 0.025$).
Conclusions: Despite a relatively high recurrence rate after RFCA for L-PeAF, patients with a shorter AF duration and smaller LA size showed a more favorable outcome. The *rs2106216* polymorphism (*ZFHX3*) was independently associated with being good responders to RFCA for L-PeAF, especially with AF duration 12–65 months.

Introduction

Radiofrequency catheter ablation (RFCA) is an effective rhythm control strategy for patients with atrial fibrillation (AF), and it has become a standard procedure for anti-arrhythmic drug (AAD) resistant AF in current guidelines for AF management [1]. The main target of AF catheter ablation is the pulmonary vein (PV) antrum, and complete durable circumferential PV isolation (CPVI) is a cornerstone of this procedure [2]. However, RFCA is still challenging in patients with persistent AF (PeAF) or long-standing persistent AF (L-PeAF) [3]. Because of a substantially high recurrence rate, catheter ablation for L-PeAF is considered to be insufficient with CPVI alone [4]. To overcome this limitation, various ablation strategies have been attempted, including additional linear ablation, complex fractionate atrial electrogram (CFAE) guided ablation, right atrial (RA) ablation, non-PV foci ablation, or rotor ablation, etc. Despite the various ablation strategies for L-PeAF, the success rates of single procedures have ranged between 20% and 60% [3]. With 1.3–2.3 times of multiple procedures, long-term AF control rate is 72–79% with or without AAD [5]. Although RFCA for L-PeAF significantly reduces AF burden, this procedure still has limitations, even when performed with current technology at world-class, experienced institutions. Therefore, we sought to identify patient factors predicting favorable success rates, and hypothesized that better patient selection criteria may improve clinical outcomes, reduce unnecessary cardiac tissue damage, or avoid unnecessary ablation procedures and reduce medical costs and procedure-related complications. Recently, there were several reports for the

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relationship between genetic polymorphism and clinical outcome of AF ablation [6–9]. Although there are significant ethnic differences [10], genetic polymorphism can be utilized as an innate biomarker to identify good responders for AF catheter ablation. The purposes of this study were to evaluate long-term clinical outcomes of L-PeAF after linear ablation, and to explore clinical predictors representing atrial remodeling and genetic factors associated with AF recurrence after RFCA for L-PeAF.

Materials and methods

Patient selection and definition of "good responder"

This study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University Health System and registered at Clinicaltrials.gov (registration number: NCT02138625). All patients provided written informed consent. Among the 1319 patients in the Yonsei AF Ablation Cohort, 421 patients had non-paroxysmal AF, and we included 330 consecutive patients with L-PeAF who were enrolled between March 2009 and November 2013. We defined AF duration based on electrocardiographic (ECG) documents, not on the presence of symptoms alone. Each patient underwent RFCA for symptomatic AF that was refractory to pharmacologic management. Exclusion criteria included the following: (1) follow-up duration less than 12 months ($n = 134$), (2) valvular heart disease with a grade higher than 2 ($n = 9$), (3) structural heart disease other than left ventricular hypertrophy ($n = 8$), (4) previous RFCA or cardiac surgery ($n = 11$), or (5) no available genetic data for the six single nucleotide polymorphisms (SNPs) previously documented to be associated with AF in genome-wide association studies (GWAS, $n = 27$). A total of 141 patients with L-PeAF were included in this study. We defined the "good responders" as those patients without an early or clinical recurrence of AF at least for 12 months after RFCA, in the absence of AAD treatment.

Measurement of left atrial size and volume

Both transthoracic and transesophageal echocardiography, and 3D cardiac computed tomography (CT; 64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Amsterdam, Netherlands) were performed in all patients to determine whether they had combined structural heart disease or a left atrial (LA) thrombus. LA size and volume index were measured using transthoracic echocardiography in all patients. The 3D spiral CT images were analyzed on an image processing workstation (Aquarius, Terarecon Inc., Foster City, CA, USA). For the regional volumetric analyses, each LA image was subdivided according to embryological origin as follows: anterior LA, venous LA, and LA appendage.

Electrophysiologic mapping and radiofrequency ablation

All AADs were discontinued for at least five half-lives prior to RFCA, and amiodarone was stopped for more than 4 weeks. Anticoagulation was maintained before the procedure. For patients taking novel oral anticoagulants, we stopped these medications for 24 h before RFCA and switched them to subcutaneous injection of low molecular weight heparin. A 3D electroanatomical map (NavX, St. Jude Medical Inc., Minnetonka, MN, USA; CARTO3, Johnson & Johnson Inc., Diamond Bar, CA, USA) was generated using a circular PV mapping catheter (Lasso; Biosense-Webster Inc., Diamond Bar, CA, USA). NavX or CARTO system-generated 3D geometry of the LA and PVs was merged with the corresponding 3D spiral CT images. RFCA (25–35 W, 47 °C, irrigation flow rate of 20–35 mL/min, 30 s of radiofrequency energy delivery at each ablation point, Stockert generator, Biosense Webster) was performed using an open irrigated-tip catheter (Celsius, Biosense-Webster Inc.; Coolflex, St. Jude Medical Inc., St. Paul, MN, USA), with guidance from the 3D electroanatomic mapping (NavX system, St. Jude Medical Inc.). After CPVI, we added a roof line, a posterior-inferior line, an anterior line, and a cavo-tricuspid isthmus line as a standard lesion set. Additional ablations of the superior vena cava (15.6%), non-PV foci (12.0%), or complex fractionated electrograms (18.4%) were conducted at the operator's decision.

We generated 3D-voltage maps in 96 patients after CPVI by obtaining contact bipolar electrograms from 350 to 500 points on the LA endocardium during atrial pacing with a pacing cycle length of 500 ms. Bipolar electrograms were filtered at 32–300 Hz. Color-coded voltage maps were generated by recording bipolar electrograms and measuring peak-to-peak voltage as previously described [11]. If frequently recurring AF still persisted after 3 attempts of cardioversion, no further efforts were made to generate a LA voltage map.

Post-ablation management and follow-up

Among 141 patients, 35 patients (24.8%) kept anti-arrhythmic medication before AF recurrence because of high chance of recurrence with frequent atrial premature beats or short runs of non-sustained atrial tachycardia, and were not included in good responders. Other patients including good responders were followed in the absence of anti-arrhythmic medications after RFCA. Patients visited the outpatient clinic regularly at 1, 3, 6, and 12 months after the procedure, and every 6 months thereafter or whenever symptoms reoccurred after RFCA. ECG was performed during every visit and 24- or 48-h Holter monitoring and/or event recording was performed at 3 and 6 months, and every 6 months thereafter in accordance with the 2012 HRS/EHRA/ECAS Expert Consensus Statement Guidelines [2]. In addition, whenever patients reported palpitations, Holter or event monitor recordings were obtained and evaluated for the possible recurrence of the arrhythmia. We defined recurrence of AF as any episode of AF or atrial tachycardia lasting for 30 s or longer [12]. Any documentation of AF recurrence after the 3-month blanking period was classified as a clinical recurrence [12].

Genotyping

We evaluated top six SNPs that have previously proven to be associated with AF in a European ancestry database and an Asian population [13–15]: *rs2200733* and *PITX2* (*rs6843082* and *rs17042171*) on chromosome 4q25, *ZFHX3* (*rs7193343* and *rs2106261*) on chromosome 16q22, and *KCNN3* (*rs13376333*) on chromosome 1q21. We used whole blood samples for the DNA extraction and genetic analyses. The forementioned genetic polymorphisms were analyzed using validated TaqMan assays (Applied Biosystems, Life Technologies, Carlsbad, CA, USA). The polymerase chain reaction products were amplified using 0.9 μm each of the forward and reverse primers, 0.2 μm each of the fluoresce in amidite and VIC minor groove binder sequence-specific probes, 3 ng DNA, 5.0 mM $MgCl_2$, and 1× TaqMan Universal PCR Master Mix containing AmpliTaq gold DNA polymerase in a 5.5 μL reaction volume. All SNPs had a call rate of greater than 99%.

For validation study, genomic DNA was extracted from peripheral blood monocytes by standard protocol (QuickGene DNA whole blood kit L, Kurabo, Osaka, Japan) using same patient's blood. Affymetrix Genome-Wide Human SNP Array 6.0 chip (Affymetrix, Inc., Santa Clara, CA, USA) was used to genotype 137 patients according to Affymetrix's protocol. Four patients were not genotyped due to the lack of genomic DNA. There was no

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