Journal of Cardiology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Impact of the extent of low-voltage zone on outcomes after voltage-based catheter ablation for persistent atrial fibrillation

Takanori Yamaguchi (MD)[a,b,*], Takeshi Tsuchiya (MD, PhD)[b], Akira Fukui (MD, PhD)[c], Yuki Kawano (MD)[a], Toyokazu Otsubo (MD)[b], Yuya Takahashi (MD)[b], Kei Hirota (MD)[b], Kenta Murotani (PhD)[d], Kenichi Eshima (MD, PhD)[a], Naohiko Takahashi (MD, PhD)[c]

[a] Department of Cardiology, Saga-ken Medical Centre Koseikan, Saga, Japan
[b] EP Expert Doctors-Team Tsuchiya, Kumamoto, Japan
[c] Department of Cardiology and Clinical Examination, Faculty of Medicine, Oita University, Yufu, Japan
[d] Division of Biostatics, Clinical Research Center, Aichi Medical University, Nagakute, Japan

ARTICLE INFO

Article history:
Received 15 March 2018
Received in revised form 5 April 2018
Accepted 20 April 2018
Available online xxx

Keywords:
Atrial fibrillation
Catheter ablation
Fibrosis
Low-voltage zone
Voltage-based ablation

ABSTRACT

Background: Low-voltage zones (LVZs), as measured by electroanatomic mapping, are thought to be associated with fibrosis. We reported the efficacy of atrial fibrillation (AF) ablation aiming to homogenize left atrial (LA) LVZ. The purpose of this study was to evaluate the impact of LVZ extension outcomes after LVZ homogenization in patients with nonparoxysmal AF.

Methods: This prospective observational cohort study included 172 patients with nonparoxysmal AF undergoing their initial ablation. LVZ was defined as an area with bipolar electrograms <0.5 mV during sinus rhythm. LVZ extent was calculated as the percentage of LA surface area, and subsequently, LVZ was categorized into stages I (<5%), II (≥5% to <20%), III (≥20% to <30%), and IV (≥30%). Patients with LVZs underwent LVZ ablation aimed at homogenization of ≥80% of LVZs following pulmonary vein isolation. The primary endpoint was atrial tachyarrhythmia recurrence-free survival after a single procedure at 18 months off antiarrhythmic drugs. The association of %LVZ with recurrence-free survival was examined using Cox proportional hazard models.

Results: The survival rates were 76%, 74%, 57%, and 28% in patients with stages I, II, III, and IV LVZ, respectively. The difference was significant between stages I and IV (log-rank, $p < 0.001$), while not significant between stages I vs. II and I vs. III ($p = 0.843$, $p = 0.073$, respectively). Cox proportional hazard model revealed that %LVZ was an independent predictor of recurrence-free survival (hazard ratio, 1.025 per 1% increase, $p < 0.001$; unadjusted model). The results were similar after demographic and clinical covariate adjustments and after excluding 12 patients who did not achieve homogenization of ≥80% of LVZ.

Conclusions: The extent of LVZ is an independent predictor for recurrence even after LVZ homogenization.

Introduction

Pulmonary vein isolation (PVI) is an effective approach for the treatment of paroxysmal atrial fibrillation (PAF); however, the outcomes of PVI alone for persistent AF (PeAF) are unsatisfactory [1–4]. To improve the outcomes, substrate modification has been performed. However, PVI and conventional substrate modification, including empiric linear ablation in the left atrium (LA) and complex fractionated atrial electrogram ablation, showed no benefit over PVI alone in patients with PeAF [2].

Development and progression of atrial fibrosis, which plays an important role in AF maintenance [5–7] is the hallmark of structural remodeling in AF. Atrial fibrosis can be detected, localized, and quantified by a non-invasive imaging method based on delayed-enhancement magnetic resonance imaging (DE-MRI) [8]. Another method to estimate fibrotic tissue is electroanatomic voltage mapping [9,10]. The extent of fibrosis estimated by both DE-MRI [8] and electroanatomic voltage mapping during sinus rhythm (SR) [9,10] is associated with poor outcomes after PVI.

* Corresponding author at: Department of Cardiology, Saga-ken Medical Centre Koseikan, 400 Nakabaru, Kase-machi, Saga 840-8571, Japan.
E-mail address: takano-yamaguchi@nifty.com (T. Yamaguchi).

https://doi.org/10.1016/j.jjcc.2018.04.010
0914-5087/

Recently, we reported the efficacy of voltage-based substrate modification aiming at homogenization of low-voltage zone (LVZ) in addition to PVI for PeAF [11]. Other investigators have also developed LA voltage-based substrate modification including LVZ homogenization and/or linear ablation across LVZ [12–14] or box isolation of fibrotic areas (BIFA) [15]. In these studies, the regional and individual extents of LVZs are ablated in addition to PVI, whereas only PVI is performed in patients without LVZs. Schreiber et al. [16] recently reported that the efficacy of BIFA was limited in patients with severe fibrotic atrial cardiomyopathy (FACM). However, knowledge regarding the impact of the extent of LVZ on the outcomes after LVZ homogenization is still lacking. This study aimed to assess the hypothesis that the extent of LVZ is an independent predictor for atrial tachyarrhythmia recurrence even after catheter ablation for PeAF aimed at homogenization of the LVZ.

Methods

Study design and patient population

This prospective, three-center, observational cohort study enrolled 172 consecutive patients with nonparoxysmal AF who underwent LA voltage-based AF ablation between April 2014 and July 2016. The study excluded patients with prior AF ablation, those with LA diameter in the parasternal long-axis view >60 mm, those with severe valvular heart disease, and those who failed SR restoration by external biphasic direct-current (DC) cardioversion. PeAF and long-standing PeAF were defined according to the HRS/EHRA/ECAS expert consensus statement [17]. All patients had symptomatic, drug-refractory AF. Written informed consent was obtained from all patients, and the study was approved by the institutional committee on human research. The primary endpoint was freedom from documented atrial tachyarrhythmia after a single procedure without antiarrhythmic drugs (AADs) at 18 months. Secondary endpoints were major complications associated with AF ablation defined according to the expert consensus statement [17] and occurrence of stiff LA syndrome [18]. LA volume was evaluated using 64-slice computed tomography, and assessed by measuring LA body volume, LA appendage (LAA), and all pulmonary veins (PVs) from the LA ostium to the first bifurcations [11]. AADs, except amiodarone, were discontinued for at least five half-lives before ablation.

Voltage mapping and ablation procedure

Electrophysiological studies and ablation procedures were performed under deep sedation or general anesthesia [19]. A temperature-monitoring probe (SensiTherm™; St. Jude Medical, St. Paul, MN, USA) was inserted into the esophagus. Voltage mapping approach and ablation procedure details have been described in our previous study [11]. Briefly, after obtaining LA geometry using EnSite NavX™ (St. Jude Medical), high-density bipolar voltage mapping of LA was performed during SR using a 20-pole circular mapping catheter with a 1-mm electrode length and 2-mm interelectrode spacing (Reflexion HD™; St. Jude Medical). Voltage mapping was performed during SR. For patients with AF rhythm, external biphasic DC cardioversion up to 270 J was performed to restore SR before or after PVI. LVZ was defined as an area with a bipolar peak-to-peak voltage amplitude of <0.5 mV [6,7,9–16] and covering >5% of the LA surface area [10]. The total LVZ area was calculated as the percentage of LA surface area excluding the PV antral region, LAA orifice, and mitral valve, and LVZ was subsequently categorized as stages I (minimum LVZ, <5%), II (mild, ≥5% to <20%), III (moderate, ≥20% to <30%), and IV (extensive, ≥30%) according to the Utah fibrosis classification [8]. LA was divided into six segments (anterior wall, septal wall, roof, posterior wall, inferior wall, and lateral wall) to describe LVZ distribution [11].

PVI was performed in all patients with a continuous lesion around the antral region using an open-irrigation 4-mm tip electrode catheter (Cool Flex™; St. Jude Medical) through a deflectable sheath (Agilis™; St. Jude Medical). The endpoint of PVI was the entrance block from the LA to the PV and exit block from the PV to the LA using circular mapping catheters. For stage I patients, no substrate modification was performed, whereas for stages II–IV, LVZ homogenization was performed. LVZ was sometimes identified at sites very close to the esophagus, His bundle, and LAA. LVZ ablation in these locations may cause complications including esophageal injury, atrioventricular block, and electrical LAA isolation. Therefore, the endpoint of homogenization was set at ≥80% of total LVZ.

LVZ homogenization was performed on up to 40% of the LA surface. Patients with LVZ of ≥40% of the LA surface underwent isolation of LVZ [15] and/or linear ablation across LVZ [12] to prevent stiff LA syndrome [18]. Strategic linear lesions were created to connect the LVZ ablation area to anatomical obstacles, such as the mitral annulus, to prevent secondary atrial tachycardia (AT) because of a narrow residual isthmus (<2 cm) [11]. Finally, superior vena cava (SVC) isolation and cavotricuspid isthmus linear ablation were performed at the physician's discretion.

Follow-up

Follow-up was performed at 1, 3, 6, 12, and 18 months using 12-lead electrocardiogram. Additionally, 24-h Holter monitoring was performed at 3 and 12 months and 7-day Holter monitoring at 6 and 18 months. Any detectable atrial tachyarrhythmia lasting >30 s beyond a 3-month blanking period after the procedure was considered as recurrence [17]. When recurrence was suspected according to symptoms or self-pulse check findings, 7–30-day event recorder monitoring was performed. AADs were discontinued between 6 and 12 months. All patients underwent transthoracic echocardiography at 6 months, and new-onset pulmonary hypertension was evaluated. Dyspnea symptoms suggestive of stiff LA syndrome were also monitored [18].

Statistical analysis

Statistical analysis was performed using JMP software, version 11.0 (SAS, Cary, NC, USA). Normally and non-normally distributed data expressed as the mean ± standard deviation and median with interquartile range (IQR) were compared using the unpaired *t*-test and Wilcoxon rank-sum test, respectively. Categorical data were compared using the chi-square test or Fisher's exact test, as appropriate. A *p*-value of <0.05 was considered statistically significant. An atrial tachyarrhythmia-recurrence free survival curve was estimated using the Kaplan–Meier method, and stage I was compared with stages II, III, and IV using the log-rank test with Bonferroni correction.

Recurrence-free survival was related to the individual demographic and clinical covariates using univariate Cox proportional hazard regression models [8]. Cox regression analyses were also performed to assess the relationship between the time to recurrence and LVZ extent (%). Models were created without covariate adjustment (model 1) and after adjusting for the following sets of demographic and clinical covariates: age and sex (model 2); age, sex, and AF type (model 3); age, AF type, and LA volume/body surface area (BSA, model 4); and AF type, LA volume/BSA, and CHA_2DS_2-VAS_C score ≥4 (model 5). The inclusion of these covariates was based on existing knowledge about the risk factors for recurrence [17]. Subanalysis was performed to assess the

Please cite this article in press as: Yamaguchi T, et al. Impact of the extent of low-voltage zone on outcomes after voltage-based catheter ablation for persistent atrial fibrillation. J Cardiol (2018), https://doi.org/10.1016/j.jjcc.2018.04.010