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Original article

Usefulness of ablation of complex fractionated atrial electrograms using nifekalant in persistent atrial fibrillation

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ABSTRACT

Background: Additional ablation of complex fractionated atrial electrograms (CFAE) after pulmonary vein isolation (PVI) has been shown to improve the success of ablation of persistent atrial fibrillation (AF). However, extensive ablation is often necessary to eliminate all CFAE or to terminate AF. We assessed the usefulness of the administration of an antiarrhythmic drug (AAD) before CFAE ablation.

Methods and results: One-hundred and ten patients with persistent AF first underwent PVI, roof and floor linear ablation (box isolation). One hundred patients who remained in AF after box isolation were then randomized to either receive (AAD group, $n = 50$) or not receive (no-AAD group, $n = 50$) intravenous nifekalant (0.3 mg/kg) followed by a CFAE ablation. In the AAD group, nifekalant terminated AF in 19 (38%) patients and ablation of localized CFAE was performed in 31 patients who remained in AF after nifekalant, and terminated AF in 11 (35%) patients. In the no-AAD group, ablation of CFAE terminated AF in 13 (26%) patients. The AAD group had a significantly lesser number of radio frequency applications at CFAE sites (18 ± 12 versus 36 ± 10, $p < 0.0001$) and shorter procedure time (162 ± 34 versus 197 ± 29 min, $p < 0.0001$) compared with the no-AAD group. However, there was no significant difference in success rate at 12 months after a single ablation procedure between the two groups (AAD group, 74% versus no-AAD group, 76%).

Conclusions: An approach to ablation using nifekalant may be useful in localizing areas of CFAE, reducing the number of applications at CFAE sites and procedure time. Ablation of only CFAE localized with nifekalant may be sufficient for clinical outcome.

Introduction

Pulmonary vein (PV) isolation is effective for treating paroxysmal atrial fibrillation (AF) [1,2], however, not enough for cure of persistent AF [3]. To improve the clinical outcome in patients with persistent AF, extensive ablation, including multiple linear lesions and/or ablation of complex fractionated atrial electrograms (CFAE), has been adopted [4–11]. CFAE are sometimes recorded over diffuse areas and numerous ablation applications are often necessary to eliminate all CFAE or to terminate AF. Although the most robust endpoint may be termination of AF, this generally requires a very long procedure time [7]. Furthermore, extensive ablation is associated with procedural complications, proarrhythmia [6], and stroke risk, and may compromise atrial mechanical function [12]. An optimal strategy may identify sites of CFAE targeted with ablation and result in AF termination with an acceptable clinical outcome. It is possible that the administration of an antiarrhythmic drug (AAD) may help accomplish this. However, AAD might eliminate not only bystander CFAE but also culprit CFAE, and it is unclear whether ablation of only CFAE localized with AAD is sufficient for a desirable outcome. Therefore, we assessed the usefulness of the administration of AAD before performing CFAE ablation.

Methods

The trial was designed as a prospective, randomized, nonblinded study. All patients referred to the Fukuoka Sanno Hospital for ablation of AF were screened. Exclusion criteria included paroxysmal AF or atrial flutter. Eligible patients were randomized in a 1:1 fashion after PV isolation, roof and floor linear ablation (i.e. box isolation) to either the AAD or no-AAD group. The patients who showed termination of AF during or just after box isolation were excluded before randomization.

Patient characteristics

The study population consisted of 110 consecutive patients with persistent ($n = 47$) and longstanding persistent AF ($n = 63$) who

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Table 1
Baseline characteristics.

Characteristic	AAD group ($n=50$)	No-AAD group ($n=50$)
Age (years)	56 ± 10	57 ± 11
Male sex (%)	88	90
Pers. AF/long AF	19/31	18/32
AF duration (month)	31 ± 34	30 ± 32
LA diameter (mm)	46 ± 6	45 ± 4
LA volume (ml)	73 ± 18	71 ± 20
LV ejection fraction (%)	60 ± 7	61 ± 7

AAD, antiarrhythmic drug; Pers. AF/long AF, persistent/longstanding persistent atrial fibrillation; LA, left atrial; LV, left ventricular.

were referred for catheter ablation guided by NavX system (NavX, with CFE Software, St. Jude Medical, Minnetonka, MN, USA). Persistent AF was defined as AF that was sustained for more than 7 days but which required pharmacologic or electrical cardioversion. Longstanding persistent AF was defined as continuous AF that had lasted for more than one year. A mean of 2 ± 1 antiarrhythmic drugs had been administered, but failed to maintain a normal sinus rhythm. None of the patients had been treated with amiodarone within the 6 months preceding the procedure. No structural heart disease was present in 43 patients. Hypertension was present in 52 patients and coronary artery disease was documented in 7. Ten patients who showed AF termination during or just after box isolation were excluded before randomization. One hundred patients who remained in AF after box isolation were then randomly assigned to receive (AAD group, $n=50$) or not receive (no-AAD group, $n=50$) intravenous nifekalant (0.3 mg/kg). There were no significant differences in the patient characteristics or substrate properties between the two groups (Table 1).

Electrophysiological study

Written informed consent was obtained from all patients. The patients received oral anticoagulants for at least 2 months before ablation. Transoesophageal echocardiography was performed to exclude any left atrial (LA) thrombi before ablation. Antiarrhythmic drugs were discontinued five half-lives before ablation. A 5-Fr quadripolar electrode catheter (St. Jude Medical) was placed in the right atrial appendage, and a 6-Fr octopolar electrode catheter (Japan Lifeline, Tokyo, Japan) was placed in the coronary sinus. Triple transseptal punctures were performed, and three 8-Fr SL0 sheaths (St. Jude Medical) were advanced into the LA. During the procedure, heparinization was continued to maintain an activated clotting time of 300–400 s. The surface electrocardiograms (ECG) and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system for offline analysis (LabSystem™ PRO, Bard Electrophysiology, Lowell, MA, USA). The intracardiac electrograms were filtered from 30 to 500 Hz and measured at a sweep rate of 200 mm/s. Atrial pacing was performed using a programmed stimulator (SEC-3102, Nihon Kohden, Tokyo, Japan).

Two decapolar ring catheters (Lasso, Biosense-Webster, Diamond Bar, CA, USA) were inserted into the LA and used for the mapping of PVs. A deflectable, 7-Fr ablation catheter (Cool path duo, St. Jude Medical) was also inserted into the LA for mapping and ablation. A 3D geometry of the LA was created using the NavX system.

Box isolation

Ablation was performed during AF with an irrigated-tip 4-mm ablation catheter (Cool path duo, St. Jude Medical).

Radio frequency energy was delivered at a power of 30–40 W. The temperature was limited to 40 °C. The luminal oesophageal temperature was monitored with a catheter in the oesophagus close to the tip of the ablation catheter. During ablation at the posterior LA close to the oesophagus, ablation was performed at a maximum power of 20 W and a temperature of 40 °C. If the oesophageal temperature was higher than 40 °C, radio frequency applications were interrupted. Radio frequency energy was delivered for 30 s at each point.

Continuous lesions at the anterior portions of the ipsilateral superior and inferior PVs were initially created under guidance of a Lasso catheter and the NavX system. Ablation was started at the superior wall and continued around the anterior and inferior venous perimeter. At the posterior portions of the PVs, ablation was sequentially targeted to antral segments with the earliest activity until PV isolation was achieved.

Ablation of the LA roof was then performed by creating a contiguous line of ablation lesions to join the superior PVs. Finally, ablation of the LA floor was performed by creating a contiguous line of ablation lesions that joined the inferior PVs to isolate the posterior LA. The entrance block of a box lesion during AF was confirmed by the elimination of PV potentials and posterior LA using a circular mapping catheter.

Mapping of CFAE

After box isolation, CFAE mapping was performed using a 4-mm-tip ablation catheter during AF by point-to-point contact mapping. Regarding the mapping sites for analysis, these were nearly equally distributed in the LA, and the sampling sites were collected from each of the subanatomical regions of the LA except the box region, i.e. the anterior LA, septal LA, anterior roof, inferior LA, lateral LA, around the mitral annulus, and the LA appendage region. In each region, at least 20 points were determined. The points in each region were similar in number and were nearly equally distributed. The NavX mapping parameters were set to "CFE-mean", which is an interval-analysis algorithm that produces a colour map that is representative of the CFAE distribution. The CFAEs were characterized by cycle-length values obtained from each site using a recording duration of 6 s. This duration was determined based on Lin's [13] report that the assessment of fractionated electrograms required a recording duration of $\geq$5 s at each site to obtain a consistent fractionation. The parameters of the automatic algorithm for CFAEs have been described previously. According to the criteria proposed by Nademanee et al. [5], CFAEs were defined as fractionated electrograms composed of two or more deflections with a mean cycle length $\leq$ 120 ms. Non-CFAEs were defined as having a mean cycle length of >120 ms.

Ablation of CFAE

In the no-AAD group, after complete CFAE mapping, ablation of CFAE was then performed. In the AAD group, nifekalant (0.3 mg/kg) was administered for over 5 min. After nifekalant, the CFAE map was created again in the patients who remained in AF. The mean AF cycle length at the coronary sinus, the maximal CFAE (shortest cycle length), the mean degree of CFAE, and the proportion of CFAEs in the LA (% of LA with a mean cycle length <120 ms) were compared before and after drug administration. After re-mapping, ablation of CFAE localized by nifekalant was then performed. In both groups, the endpoint of CFAE ablation was the elimination of all identifiable target electrograms or termination of AF. If AF converted to atrial tachycardia or flutter during ablation, mapping and ablation were performed to terminate the atrial tachycardia or flutter. If the patient remained in AF despite the elimination of all visible CFAE, electrical cardioversion was performed to restore sinus rhythm. During sinus rhythm, exit block of the box lesion was confirmed. Gaps along the ablation lines were detected and closed using high