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A novel individualized substrate modification approach for the treatment of long-standing persistent atrial fibrillation: Preliminary results

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ABSTRACT

Background: The most effective approach for long-standing persistent atrial fibrillation (LPAF) ablation remained undetermined. Our goal was to explore the heterogeneous left atrial substrate in patients with LPAF and to evaluate the effectiveness of a novel individualized substrate modification (ISM) approach in LPAF ablation.
Methods: One hundred and twenty-four patients with LPAF were randomized to ISM group ($n = 64$) or stepwise ablation (SA) group ($n = 60$). After pulmonary vein isolation, ISM was performed in the ISM group and SA was applied in the SA group. The clinical effectiveness after a single and a repeated procedure was compared.
Results: The total procedural time was significantly shorter in ISM than that in SA. In the ISM group, mild left atrial substrate was observed in 17 (27.4%), moderate in 26 (41.9%) and severe in 19 (30.6%) patients after successful cardioversion of the 62 patients. The intention-to-treat analysis showed that sinus rhythm was maintained in 65.5% of patients in the ISM group and in 45.0% of patients in the SA group after a single procedure, $P = 0.04$. Atrial tachycardia (AT) recurred in 5 of 22 in the ISM group and in 20 of 33 in the SA group, $P = 0.01$. After a repeated procedure, 75% of patients in the ISM group and 63.3% of patients in the SA group were free of further recurrence, $P = 0.16$.
Conclusions: Left atrial substrate varied noticeably in patients with LPAF. The ISM approach was superior to SA approach in terms of procedural time, recurrence rate of AT and clinical effectiveness after a single procedure. However, they yielded comparable outcomes after a repeated procedure.

1. Introduction

Despite the high effectiveness of catheter ablation (CA) for paroxysmal atrial fibrillation (PAF) [1,2], it is less effective for long-standing persistent AF (LPAF), even though the complex stepwise ablation (SA) approach is applied [3–5]. The modest effectiveness of CA in LPAF was attributed to the AF maintaining substrate, and substrate modification was deemed necessary to achieve a favorable outcome [3–5].

LPAF was defined as AF lasting for more than one year [6], which indicated that it might cover the patient population with non-uniform baseline characteristics. Heart commodities, left atrial diameter (LAD), AF duration, and cardiac function might differ markedly in LPAF patients. We then hypothesized that the AF substrate was heterogeneous in LPAF population and that an approach of individualized substrate modification (ISM) was plausible.

The aim of this study was to evaluate the feasibility, safety and effectiveness of the ISM approach in LPAF ablation in comparison with the SA approach. Besides, the heterogeneous left atrial substrate was assessed.

2. Methods

2.1. Study population

Between March 2011 and December 2012, 124 LPAF patients presenting for CA were randomly allocated to ISM group or SA group. The randomization was generated by the computer. Exclusion criteria were as follows: age <18 or >75 years, left atrial diameter >55 mm, presence of left atrial thrombus by transesophageal echocardiography examination, history of CA or surgical ablation, contraindication to oral anticoagulation with warfarin and history of cerebrovascular event. All patients provided written informed consent. The study protocol was approved by the Institutional Ethics Committee. The study design was shown in Fig. 1.

Warfarin anticoagulation with therapeutic international normalized ratio (INR) was applied for one month prior to procedure, which was replaced by low molecular weight heparin (LMWH) 5 days before study. LMWH was paused 12 h prior to ablation. All antiarrhythmic drugs (AADs) except amiodarone were suspended for at least five half-lives. Amiodarone was withdrawn for more than one month prior to ablation.

2.2. Electrophysiological (EP) study and circumferential pulmonary vein isolation (CPVI)

The EP study was performed under conscious fasting state with continuous intravenous injection of fentanyl for analgesia. After two transseptal procedures, One bolus of Heparin 100 u/kg was injected intravenously and followed by 1000 u per hour to maintain an activated clotting time of 300–350 s. One decopolar circular mapping catheter (Lasso,

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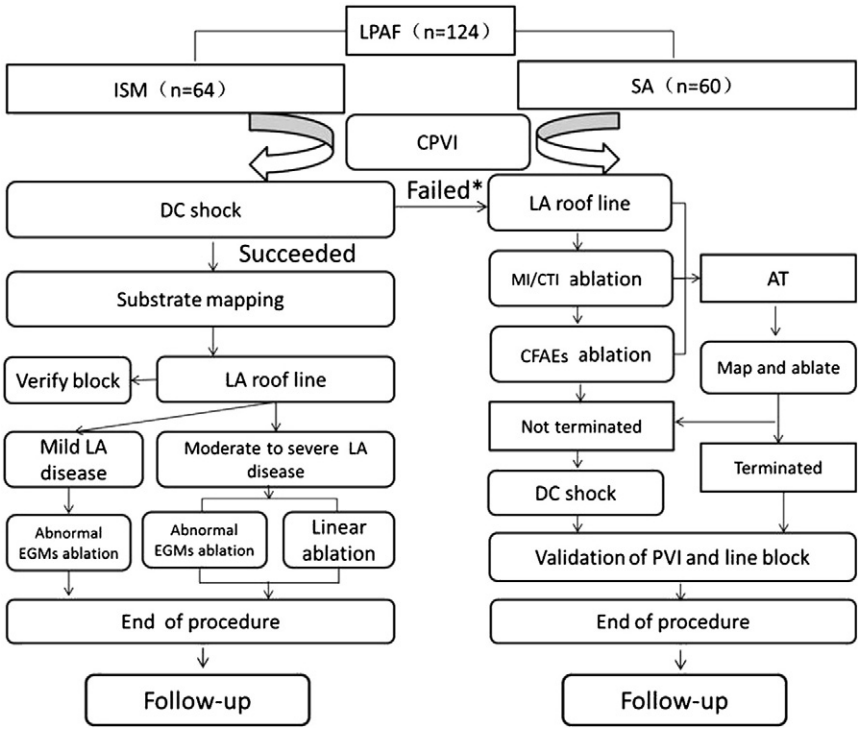

Fig. 1. The overall design of the study. *: note that the subject in ISM was viewed as a recurrence if cardioversion failed after CPVI, but the subject was allowed to undergo SA. LPAF: long-standing persistent atrial fibrillation; ISM: individualized substrate modification; SA: stepwise ablation; LA: left atrium; CPVI: circumferential pulmonary vein isolation; MI: mitral isthmus; CTI: cavo-tricuspid isthmus; CFAEs: complex fractionated atrial electrograms; AT: atrial tachycardia.

Biosense Webster, Diamond Bar, CA, USA) was utilized to record PV potentials. A 3.5 mm saline-irrigated catheter (Thermo-cool NaviStar, Biosense Webster, Diamond Bar, CA, USA) was advanced in the left atrium for mapping and ablation. Biopolar endocardial electrograms were filtered at the range of 30–500 Hz.

The procedure of CPVI was performed in both ISM and SA group guided by CARTO3 system (Biosense Webster, Diamond Bar, CA, USA) and was described in detail elsewhere [7,8]. The endpoint of CPVI was elimination of PV potentials or dissociation of PV potentials with atrial electrical activity.

2.3. Electroanatomic substrate mapping in ISM group

Electroanatomic mapping was performed under stable sinus rhythm (SR) after PV isolation, by means of 360 J of direct current (DC) shock. If AF failed to be cardioverted or recurred immediately after cardioversion, the subject was allowed to undergo stepwise ablation and was viewed as a treatment failure in ISM group. The data would be analyzed on the intention-to-treat basis. The results would also be analyzed according to the treatment actually received.

The ablation catheter was carefully manipulated to acquire 200–400 points in the left atrium (LA). The points were accepted after careful evaluation of tip-tissue contact, based on the four criteria [9]: adequate tactile pressure feedback, stable fluoroscopic catheter movement, desirable catheter icon to LA geometry surface proximity, and constant morphology and voltage of endocardial electrograms. The points acquired inadvertently during premature beats were excluded. LA voltage map was reconstructed and displayed in a color-coded manner. Interpolation fill threshold was 10 mm.

Bipolar voltage was defined as the amplitude from the peak-positive to peak-negative deflection of bipolar electrograms. In LA voltage map, low voltage zone (LVZ) was defined as bipolar voltage < 0.5 mV and displayed in red, normal area as bipolar voltage ≧ 1.0 mV and displayed in purple, and borderline area as bipolar voltage between 0.5 and 1.0 mV and displayed in variegation [10,11] (Fig. 2).

After the contour of LVZ was delineated manually, the LVZ area, total LA area and the proportion of LVZ (LVZ %) were calculated automatically by CARTO 3 system software (Biosense Webster, Diamond Bar, CA, USA) (Fig. 2). LA substrate was graded as *mild* for LVZ% < 10%, *moderate* for LVZ% between 10% and 20% and *severe* for LVZ% ≥ 20%, and it served as the fundamental criterion for designing ablation lesions for ISM.

The endocardial electrograms were classified as single potential, short (<10 ms) split potentials, long (10–50 ms) split potentials, and fractionated potentials [12]. Double and fractionated potentials were defined as abnormal potentials (APs) (Fig. 2).

2.4. Individualized substrate modification in ISM group

LA roof line was the fundamental step for substrate modification prior to individualized substrate ablation in our study. After that, for patients with *mild* substrate, APs within LVZ were ablated and no further linear ablation would be ablated (Fig. 3A). For patients with *moderate* and *severe* substrate, APs within LVZ were ablated and additional linear ablation was applied. Short linear ablation was deployed to connect LVA with anatomic or electrical barrier if the LVZ was localized or one LVZ was ≥2 cm away from another LVZ (Fig. 3B). Long linear ablation was deployed to connect one LVA with another and then with electrical or anatomic barrier if the LVZ was extensive or the LVZs were close to each other (<2 cm) (Fig. 3C, D).

Ablation lesions were created by saline-irrigated radiofrequency (RF) energy at 30–35 W, 43 °C, and with a saline irrigation speed of 17–20 ml/min to achieve a desired power delivery.

The endpoint of APs ablation was elimination of APs (local bipolar voltage < 0.05 mV). The endpoint of short linear ablation was elimination of local potentials (<0.05 mV) and inability to capture LA despite with maximum output of 20 mA. The endpoint of long linear ablation was bidirectional conduction block across the line, which was validated by pacing maneuver (Fig. 3D, E).

2.5. Stepwise ablation in SA group

The SA approach was described in detail in elsewhere [3,5]. Briefly four steps were involved.

Step 1, CPVI was performed, which was the same as the one described in ISM group [7,8].

Step 2, if AF was not terminated after CPVI, linear ablation at LA roof, mitral isthmus and cavo-tricuspid isthmus was applied. The endpoint of each RF energy delivery was reduction of bipolar voltage > 50%. The endpoint of linear ablation was bidirectional block across the lines.

Step 3, if AF did not terminate after CPVI and linear ablation, complex fractionated atrial electrograms (CFAEs) ablation was applied. CFAEs map was reconstructed by the automated software of CARTO3 system, which defined CFAEs as continuous electrograms or those with very short cycle length (50–110 ms) and low voltage range of 0.05–0.15 mV during a 2.5-second recording period [13]. The endpoint of CFAE ablation was prolongation of the cycle length (disappearance of continuous electrograms), abolishment of all CFAEs (bipolar voltage < 0.05 mV) or AF termination.

Step 4, if AF persisted after the above three steps, SR was restored by use of DC shock. If spontaneous ectopic foci that triggered AF or atrial tachycardia (AT) were observed, subsequent mapping and ablation