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ORIGINAL ARTICLE

Efficacy and safety of novel epicardial circumferential left atrial ablation with pulmonary vein isolation in sustained atrial fibrillation

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Abstract The aim of this study was to examine the efficacy and safety of this novel epicardial circumferential left atrial ablation (CLAA) with pulmonary vein isolation (PVI) in sustained atrial fibrillation (AF). Thirty domestic pigs were divided equally into 3 groups: AF without ablation (AF group), AF with PVI (PVI group), and AF with CLAA and PVI (CLAA + PVI group). AF was induced by rapid atrial pacing. After AF was induced, CLAA and PVI were performed for pigs in CLAA + PVI group, and PVI was performed for pigs in PVI group. AF vulnerability, AF duration, and histology were performed in all groups. All pigs developed sustained AF after 6.27 ± 0.69 weeks of rapid atrial pacing. All pigs successfully underwent isolated PVI or CLAA with PVI on the beating heart in PVI group or CLAA + PVI group. Isolated PVI terminated AF in 3 of 20 pigs (15 %), and CLAA with PVI terminated AF in 5 of 8 pigs (62.5 %, $P = 0.022$). Compared with AF group (10/10), the incidence of sustained AF by burst pacing was significantly decreased in PVI group (3/10, $P = 0.003$) or CLAA + PVI group (0/10, $P < 0.001$). There was no significant difference between PVI group and CLAA + PVI group ($P = 0.211$). AF duration was significantly decreased in CLAA + PVI group (734.70 ± 177.81 s, 95 % CI 607.51–861.89) compared with PVI group (1217.90 ± 444.10 s, 95 % CI 900.21–1535.59, $P = 0.008$). Also, AF duration was significantly decreased in PVI group ($P = 0.003$) or CLAA + PVI group ($P < 0.001$) in comparison with AF duration in AF group (average 1800 s). Epicardial CLAA could ablate the left atrial roof and posterior wall together safely and reliably. Compared with PVI alone, CLAA with PVI may be able to improve the rate of acute termination of persistent AF. It may be useful in selecting the best ablation approaches for patients with persistent AF.

Keywords Atrial fibrillation · Ablation · Pulmonary vein isolation · Epicardial · Efficacy

Introduction

Atrial fibrillation (AF) is a very common clinical arrhythmia, with a high morbidity or stroke [1–3]. Cox-Maze III procedure has been considered as the "gold standard" to eliminate AF, but the procedure is complex and difficult [4, 5]. In the past few years, circumferential pulmonary vein isolation (PVI) was applied to treat atrial fibrillation frequently, but the results of isolated PVI were not satisfactory for persistent AF [6–10]. In order to improve the outcomes, ablation lines in the left atrium with different approaches (left atrial roof ablation, mitral annular lesion), and ganglion plexus (GP) ablation were added [11–16]. Among them, "Dallas lesion set" was considered to be one of the most classic ablation procedures. In our previous study, we have reported a novel modified bipolar radiofrequency ablation procedure for preoperative AF combined with off-pump coronary artery bypass grafting surgery [17]. In recent years, we also introduced another novel minimally invasive AF ablation procedure for lonely AF according to Cox-Maze III procedure and "Dallas lesion set", which included bilateral PVI, GP ablation, mitral isthmus line, resection of the left atrial appendage and a circumferential

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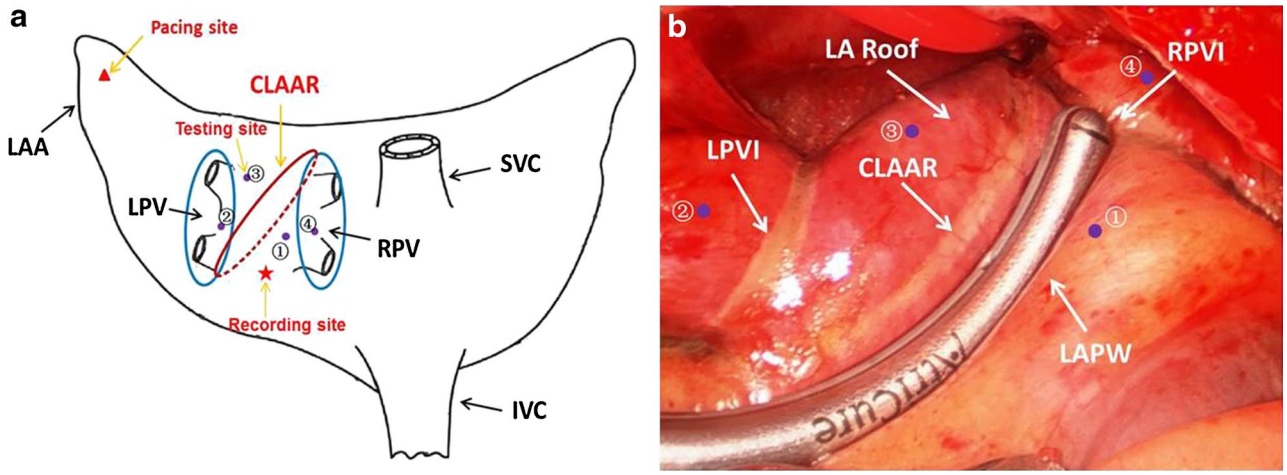

Fig. 1 Epicardial ablation procedure. Circumferential left atrial ablation ring (CLAAR, *red circle*); pulmonary vein isolation (*bule circle*); pacing site (*red triangle*); testing site (*purple dot* ①②③④). *LAA* left atrial appendage, *LPV* left pulmonary vein, *RPV* right pulmonary vein, *IVC* inferior vena cava, *SVC* superior vena cava, *LPVI* left pulmonary vein isolation, *RPVI* right pulmonary vein isolation, *LAPW* left atrial posterior wall, *LA Roof* left atrial roof

left atrial ablation (CLAA) ring connecting the left inferior pulmonary vein to the right superior pulmonary vein across the left atrial roof, anterior and posterior wall. The procedure showed satisfactory early and mid-term outcomes [18, 19]. In this procedure, we used the CLAA ring to substitute the previous left atrial roof line. The aim of this study was to examine the efficacy and safety of epicardial CLAA with PVI in sustained AF.

Methods

Animals

This protocol was approved by the Institutional Animal Care and Use Committee in Shanghai Jiaotong University School of Medicine. In this study, thirty male pigs weighing 60–78 kg were used and divided into 3 groups: (1) pigs with pacing induced AF but without ablation (AF Group); (2) pigs with pacing induced AF and isolated PVI (PVI Group); (3) pigs with pacing induced AF and CLAA with PVI (CLAA + PVI Group).

Construction of AF model

Pigs were pre-medicated with intramuscular ketamine (10 mg/kg) and anesthetized with endotracheally applied isoflurane (2–4 %) after intubation. Left thoracotomy was performed through the fourth intercostal space. A pacing lead was implanted onto the left atrial appendage and connected to a subcutaneously positioned Medtronic pacemaker. After 1 week recovery, the left atrium was continuously paced at a rate of 500 beats per minute (bpm) for 6 weeks. After the pacing, the pacemaker was turned off and electrocardiography (ECG) was recorded to confirm the presence of sustained AF (>48 h). ECG was recorded every day to ensure that the pacemaker paced properly. If sustained AF did not occur, the pacing was continued for 2 more weeks until sustained AF was recorded.

Surgical procedure

If sustained AF occurred, the pig would be anesthetized, intubated and undergo redo thoracotomy. Standard ECG was recorded during the procedure. In CLAA + PVI group, PVI and CLAA were performed in all pigs. The pericardium was opened a few centimeters anterior to the descending aorta after the chest was opened. The bilateral pulmonary veins (PVs) and the posterior left atrium were exposed after the suspension of the pericardium. Then, the right PV and left PV were bluntly dissected using the AtriCure Lumitip Dissector (AtriCure, Inc., West Chester, OH, USA). Epicardial PVI was performed by AtriCure Isolator Synergy ablation clamp (AtriCure, Inc.) at the antrum of the right and left PV on beating heart (Fig. 1). Also, epicardial CLAA ring connecting the left inferior PV to the right superior PV was also performed with ablation clamp on beating heart (Fig. 1). One jaw was inserted through the space in the front of left atrium, and the other jaw was inserted behind the left atrium. Then, left inferior PV and right superior PV were connected by two transverse ablation lines (CLAA ring). At least 10 times overlapping ablation lesions were performed to ensure the complete transmurality of ablation lines. Pigs with induced AF would be cardioverted

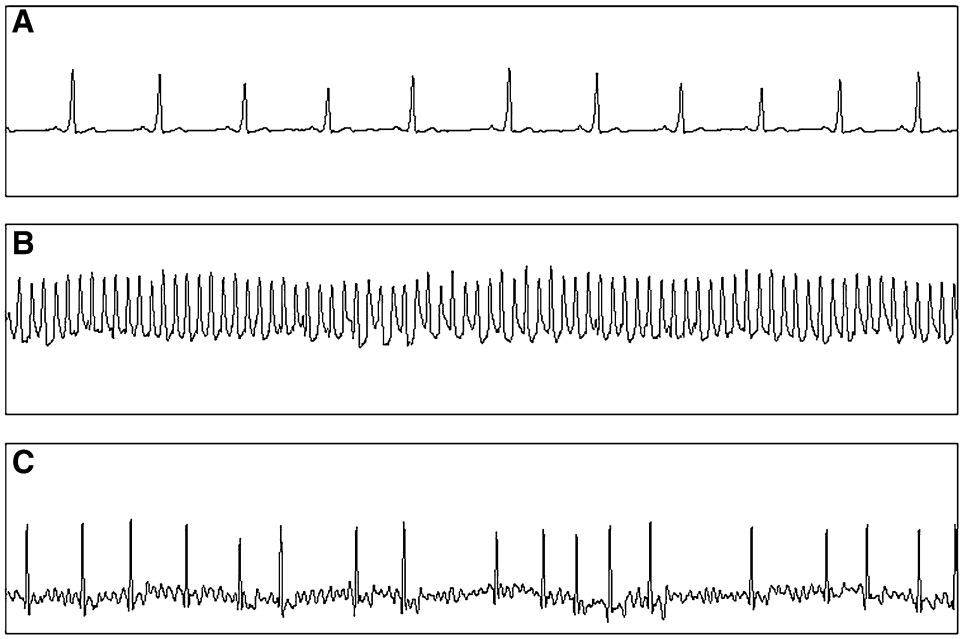

Fig. 2 ECG recording. **a** Normal sinus rhythm before pacing. **b** ECG during pacing. **c** atrial fibrillation after pacing

to sinus rhythm, if sinus rhythm did not recover after the ablation. Then, conduction block was tested using the Atricure bipolar isolator multifunctional pen (AtriCure, Inc.). Intraoperative post-ablation pacing was performed in the testing site (Fig. 1, purple dot ①②③④). Atrial and ventricular capture was defined as positive pacing result, and failure of capture was negative pacing result. Conduction block was considered successful, if area ① pacing was positive and area ②, ③, ④ pacing results were negative after epicardial ablation. In PVI group, isolated PVI was performed in all pigs. In AF group, neither CLAA nor PVI was performed.

AF vulnerability studies

All pigs were cardioverted to sinus rhythm. Then, one bipolar electrode was hooked onto the left atrial appendage for pacing (Fig. 1). AF vulnerability was assessed by 8 burst pacing (4 for 6 s, 4 for 12 s) at a cycle length of 50 ms and a stimulus output of 0.5 V plus twice diastolic threshold. AF was considered sustained if the induced episode lasted >30 min. If sustained AF was achieved at any point in the protocol, further testing was not performed and the longest AF duration was considered as 1800 s.

Histologic analysis

After electrophysiological study, 3 pieces of ablated left atrial tissue were randomly sampled and fixed in 4 % formalin for 45 min, followed by storage in 70 % alcohol. Then, the tissue was sectioned at 5-mm intervals perpendicular to the longitudinal axis of ablation line, and was stained with Masson-Trichrome.

Statistical analysis

Categorical variables were expressed as frequencies and proportions and were compared using the χ^2 test or Fisher's exact test. Continuous variables were presented as mean ± standard deviations, and comparisons were performed using Student's *t* test. Results were considered to be significant if $P < 0.05$.

Results

AF induction results

All pigs developed sustained AF after 6.27 ± 0.69 weeks of rapid atrial pacing (Fig. 2). There was no significant difference between 3 groups (AF Group, 6.40 ± 0.84 weeks; PVI Group, 6.20 ± 0.63 weeks; CLAA + PVI group, 6.20 ± 0.63 weeks; $P = 0.769$).

Ablation results

In PVI group or CLAA + PVI group, all pigs successfully underwent PVI or CLAA with PVI on the beating heart (Fig. 1b). Mean AF ablation time was 12.8 ± 1.23 min (range 11–15 min) in PVI group and 17.1 ± 1.66 min (range 15–20 min) in CLAA + PVI group. After PVI ablation, AF was terminated in 1 pig in the PVI group. In

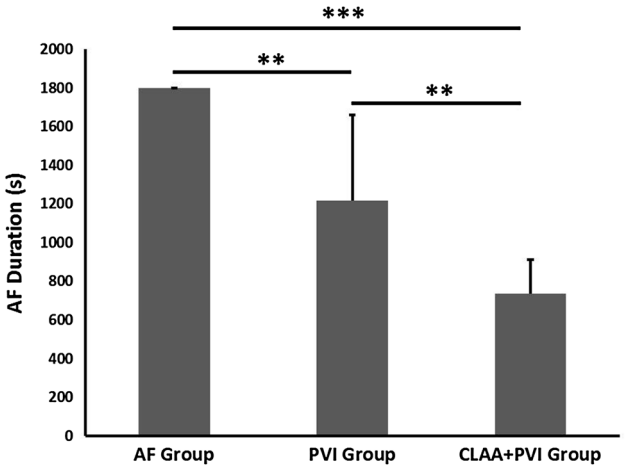

Fig. 3 AF duration in each group. $^{**}P < 0.01$; $^{***}P < 0.001$

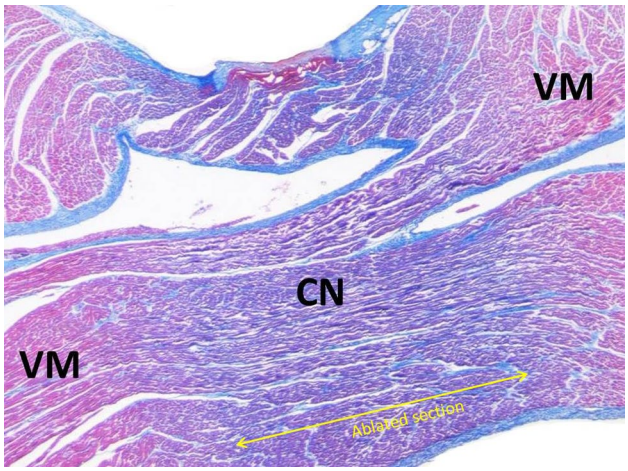

Fig. 4 Histological changes in tissues with or without ablation (Masson-Trichrome stain). Coagulation necrosis (CN) is stained *blue*, and viable myocardium (VM) is stained *red*

CLAA + PVI group, 2 pigs recovered to sinus rhythm after PVI, and AF was terminated in another 5 pigs after PVI with CLAA. That is isolated PVI terminated AF in 3 of 20 pigs, and CLAA with PVI terminated AF in 5 of 8 pigs. There was a significant difference between isolated PVI and CLAA with PVI (15 vs. 62.5 %, $P = 0.022$).

AF vulnerability

All pigs (10/10) developed sustained AF by burst pacing in AF group. Three pigs (3/10) developed sustained AF by burst pacing in PVI group, whereas no pig (0/10) developed sustained AF in CLAA + PVI group. Compared with AF group, the incidence of sustained AF was significantly decreased in PVI group ($P = 0.003$) or CLAA + PVI group ($P < 0.001$), but there was no significant difference between PVI group and CLAA + PVI group ($P = 0.211$). However, AF duration was significantly decreased in CLAA + PVI group (734.70 ± 177.81 s, 95 % CI 607.51–861.89) compared with PVI group (1217.90 ± 444.10 s, 95 % CI 900.21–1535.59, $P = 0.008$, Fig. 3). In addition, AF duration was significantly decreased in PVI group ($P = 0.003$) or CLAA + PVI group ($P < 0.001$) in comparison with AF duration in AF group (average 1800 s).

Histological examination

As shown in Fig. 4. CLAA induced histological changes in ablated section as estimated by Masson-Trichrome staining. No perforation or fracture of the tissue was observed in ablated lesion. Coagulation necrosis (CN) was observed in the ablated section, which was stained blue. Viable myocardium (VM) was observed in the sections without ablation, which was stained red. Completely transmural lesions were also observed in the ablated section.

Discussion

AF affects more and more patients in modern society and leads to increased incidence of stroke, heart failure and mortality [1–3]. PVI has been demonstrated to play a key role in eliminating AF for AF patients [20–22]. At present, the results were satisfactory for paroxysmal AF, but the outcomes of isolated PVI were disappointing for persistent AF [6–10]. Additional left atrial ablation at the roof line has been considered to be an effective method to improve the success rate of AF ablation, especially for persistent AF [11–16]. In addition, left atrial posterior wall was also considered to play a critical role in the occurrence and maintenance of AF in recent years [23–25]. Ablation of the left atrial posterior wall may have a good effect on improving the outcomes of AF ablation [26]. However, sometimes it is difficult and complex to ablate both left atrial roof line and the left atrial posterior wall together through epicardial approach on the beating heart. In order to simplify the epicardial ablation procedure and improve the outcomes of AF ablation, we used the CLAA ring to substitute the left atrial roof line with a bipolar radiofrequency clamp during the epicardial ablation procedure for AF in our previous clinical study. After the mean follow-up of 12.6 ± 2.2 months, freedom from AF was 92.1 % for paroxysmal AF and 82.4 % for persistent/longstanding persistent AF [18, 19]. We concluded that this circle not only connected the left PVI ablation ring with the right PVI ablation ring, but also ablated the left atrial roof, anterior and posterior wall together, which could block the atrial reentrant circuits and eliminate AF more effectively. This animal study examined the efficacy and safety of epicardial CLAA with PVI on suppressing sustained AF, and compared that with epicardial PVI alone.

Persistent AF is constantly associated with more complex atrial substrate remodeling than paroxysmal AF. Also, the triggers of AF include both PV foci and non-PV foci. It is generally considered that the triggers are important for the initiation of AF and the substrate of left atrium plays a key role in AF persistence [27, 28]. Therefore, isolated PVI is not enough for persistent AF, especially for AF with non-PV foci. In previous study, Nishida et al. [29, 30] found that PVI combined with left atrial roof ablation could suppress AF perpetuation in experimental model. In this present study, we also found that CLAA with PVI was more effective to terminate AF in comparison with PVI alone in this sustained AF model (3/20, 15 % vs. 5/8, 62.5 %, $P = 0.022$), which was consistent with previous study [29]. In comparison with AF group, the incidence of sustained AF by burst pacing was significantly decreased in both PVI group and CLAA + PVI group in our study. There was no significant difference between PVI group and CLAA + PVI group. However, compared with AF duration in PVI group, AF duration was significantly decreased in CLAA + PVI group. These findings may indicate that the CLAA with PVI could suppress the maintenance of sustained AF better than PVI alone.

At present, although epicardial ablation with bipolar radiofrequency clamp has been proved to be safe and effective, it is still difficult to achieve a complete transmurality on the beating heart due to atrial pathology, blood cooling, epicardial fat, poor clamp–tissue contact and tissue impedance [31–34]. In our study, the CLAA ring across the left atrial roof, anterior and posterior wall was performed on beating heart with bipolar radiofrequency clamp in a pig sustained AF model. We inserted one jaw of the clamp through the space in front of the left atrium, and the other jaw was inserted behind the left atrial posterior wall. At least 10 times overlapping ablation lesions were performed. Then, a circle connected the left and right PVI ablation ring was made across the left atrial roof, left atrial anterior and posterior wall. Complete transmurality was observed after the ablation (Fig. 4). Coagulation necrosis was stained blue and viable myocardium was stained red with Masson-Trichrome stain [35]. Compared with non-ablated tissue, transmural coagulation necrosis was shown in ablated tissue. We concluded that we were able to reliably create completely transmural lesions for CLAA using bipolar radiofrequency ablation clamp.

Clinical implications

The present study showed that epicardial CLAA could be created by bipolar radiofrequency clamp safely and reliably, and compared with PVI alone, CLAA with PVI may be able to improve the success rate of acute termination of persistent AF, and inhibit AF maintenance.

Limitations

There are few limitations in our study. Firstly, we tried to study the relationship between the CLAA and AF termination in pig sustained AF model. We constructed the AF model by rapid atrial pacing with pacemaker. The mechanism of this AF model may be different from that of human AF. So the outcomes should be demonstrated in other AF models and a larger series. Secondly, we got satisfactory short-term effects of the ablation in our study, but we did not observe the long-term effects. In human study, AF long-term recurrence is an important problem after the first ablation. Researching on the long-term effects of the ablation may be meaningful to explain the long-term recurrence of AF. Thirdly, this ablated circle was performed on beating heart using bipolar radiofrequency clamp. This method may be not suitable for patients who have larger left atrial diameters, because the jaws of the bipolar ablation clamp cannot clamp the larger left atrium completely. However, except some patients with AF and mitral valve disease may have larger left atrial diameters, left atrium were not too large in patients with AF and CAD or lonely AF.

Conclusion

Compared with PVI alone, CLAA with PVI may be able to improve the success rate of acute termination of persistent AF, and inhibit AF maintenance.

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Conflict of interest There are no conflicts of interest to report.

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