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Review

Current strategies for non-pharmacological therapy of long-standing persistent atrial fibrillation

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ABSTRACT

Non-pharmacological rhythm control of atrial fibrillation (AF) is becoming increasingly important in our aging society. Advancement of catheter ablation techniques in the last decade has provided a cure for AF patients, with a nearly established efficiency for paroxysmal cases. However, since ablation of persistent/chronic AF cases is still challenging, early treatment of paroxysmal AF before transformation to the persistent/chronic form is mandatory. Although there is a consensus that pulmonary vein isolation is the first-line approach for ablation of long-standing persistent AF, similar to that for paroxysmal AF, there are still wide variations in the adjunctive approach to modify the atrial substrate of persistent AF (anatomical linear ablation, electrogram-based complex fractionated atrial electrogram ablation, ganglionated plexus ablation, etc.). Since data comparing the effectiveness of these adjunctive approaches are still lacking, large-scale controlled trials evaluating the effect of catheter ablation in diverse patient populations on a long-term basis are needed to establish the appropriate approach for long-standing persistent AF. Furthermore, the development of de novo ablation methods (new energies, new targets, etc.) is expected to improve ablation outcome in patients with long-standing persistent AF.

Contents

1. Introduction

Since the landmark paper published by Haissaguerre et al. demonstrating the pulmonary veins (PVs) as the dominant triggers of paroxysmal atrial fibrillation (AF), the efficacy of radiofrequency catheter ablation for atrial fibrillation has been established. After the initial attempt to ablate the firing foci of the PVs, PV isolation (PVI) has become the main target in cases of paroxysmal AF. In contrast, the role of the atrial substrates that maintain atrial fibrillation increases during AF progression from paroxysmal to the long-persistent form, which requires adjunctive treatment in addition to PVI. Years have passed since the numerous novel catheter-based approaches for long-persistent AF have been addressed; therefore, the debate still remains concerning the indications for catheter ablation, the approaches appropriate in each case, and the endpoints of ablative therapy. In this review, we focus on the current approaches for catheter ablation of long-lasting persistent AF cases.

This review summarizes the current ablative techniques and emphasizes the appropriate applications and limitations of catheter ablation for long-lasting persistent AF.

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2. Baseline ablation strategies targeting PVs

It is well known that PVI was first developed to eliminate the triggers that initiate attacks of paroxysmal atrial fibrillation [1]. Subsequently, the additional function of the PV myocardium to perpetuate atrial fibrillation has been a focus [2]. Now, most approaches for eliminating long-persistent atrial fibrillation include PVI as the baseline procedure to reduce both the trigger and the maintaining factor of persistent AF. Although variations still exist in the procedures that target the PVs, including circumferential PV ablation (CPVA), [3] extensive encircling PV isolation (EEPVI), [4] PV antrum isolation (PVAI), [5] and BOX isolation [6] (Fig. 1), there is a common consensus among them [7]. To reduce the risk of PV stenosis and eliminate the firing foci around the PV ostium, ablations should be performed in the atrial tissue located in the antrum rather than the PV ostium. If the PVs are targeted, complete electrical isolation should be the goal. Radiofrequency (RF) energy can be applied either segmentally, guided by a circular mapping catheter, or by a continuous circumferential ablation lesion created to surround the ipsilateral right or left PVs.

Analysis of 4 major articles in which antral encirclement of PVs in cases with long-standing persistent AF underwent a single-procedure, showed a drug-free success rate ranging from 37% to 56% at approximately 1 year (Fig. 2) [8]. Integration of repeat procedures (mean, 1.3 per patient) increased the drug-free success rate to 59%. The combination of drugs and multiple procedures yielded a success rate of approximately 77%.

3. Adjunctive ablation strategies (electrogram-guided ablation and linear ablation)

Although ablation strategies targeting the PVs are the cornerstone of AF ablation procedures for both paroxysmal and persistent AF, continued efforts are underway to establish additive strategies to improve ablation outcome. Currently, one of the most popular methods for AF-substrate modification in the atrium is to apply RF energy and create lesions targeting the areas with complex

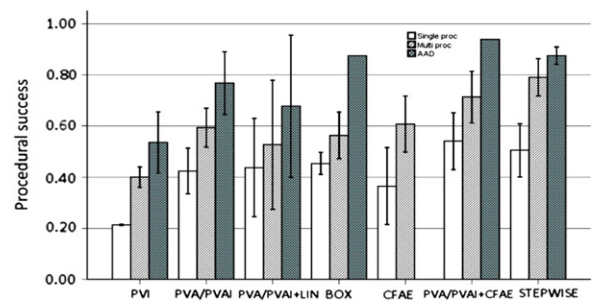

Fig. 2. Clinical success of various ablation techniques for persistent/long-standing persistent AF. The rates shown are for single-procedure, drug-free success (white), multiple-procedure success (diagonal crosshatch), and antiarrhythmic drug (AAD)-assisted success (dark double hatch). LIN=conventional linear ablation; PVA=pulmonary vein antrum ablation; PVAI=PV antrum isolation. Reproduced from Ref. [8].

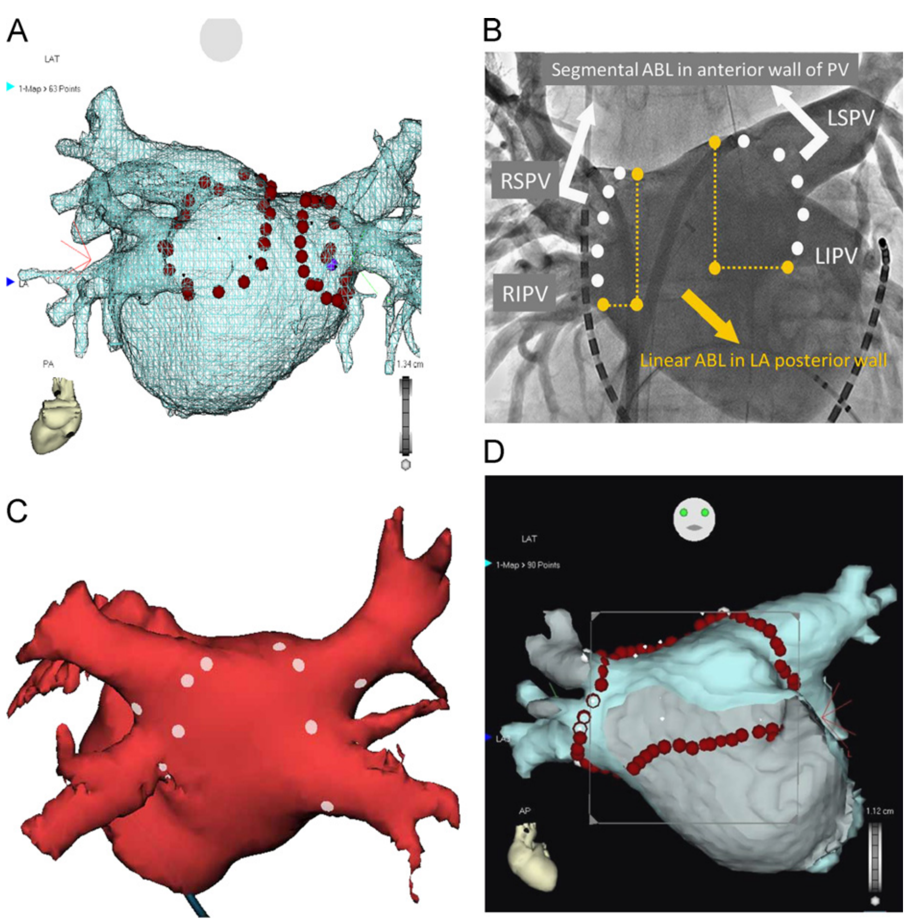

Fig. 1. Variations in the pulmonary vein isolation methods. (A) CPVA/CPVI (Circumferential PV ablation/isolation), (B) EEPVI (Extensive encircling PV isolation), (C) PVAI (PV antrum isolation), and (D) BOX isolation.

fractionated atrial electrograms (CFAEs), which was developed by Nademanee et al. (Fig. 3) [9]. CFAEs are believed to represent slow conduction or pivot points where wavelets turn around at the end of arcs of functional blocks, and are defined as atrial electrograms with fractionations, continuous activity, or rapid firings with very short cycle lengths of ≤ 120 ms averaged over a 10-s recording period. The primary endpoint of ablation in their original work was either complete elimination of the area with CFAEs or conversion of AF to sinus rhythm. CFAE ablation terminated AF in 49 of 57 patients with paroxysmal AF (86%) and 40 of 64 patients with chronic AF (63%) without the use of antiarrhythmic drugs. The AF-free rate at 1-year follow-up was 91% in 110 patients, including those who underwent repeat procedures (16%).

Although this method is well accepted, its role in ablation has not yet been fully established. CFAE ablation only targets the substrate that perpetuates AF, in fact only a modest effect on chronic AF has been reported thus far [10]. More recently, a general consensus has been established that CFAE ablation is regarded as a combination strategy for modifying the AF substrate as discussed below.

A recent meta-analysis of randomized controlled trials on the effectiveness of additional CFAE ablation on PVI [11–13] showed no benefit for CFAE ablation as a single approach. However, a significant benefit was shown for adjunctive CFAE ablation in addition to PVI in persistent AF cases, but not in paroxysmal AF cases (Fig. 4).

Based on advancements in 3D mapping systems, CFAEs can be targeted either in a subjective (physician interpretation) or objective (online CFAE detection algorithms) manner. One of

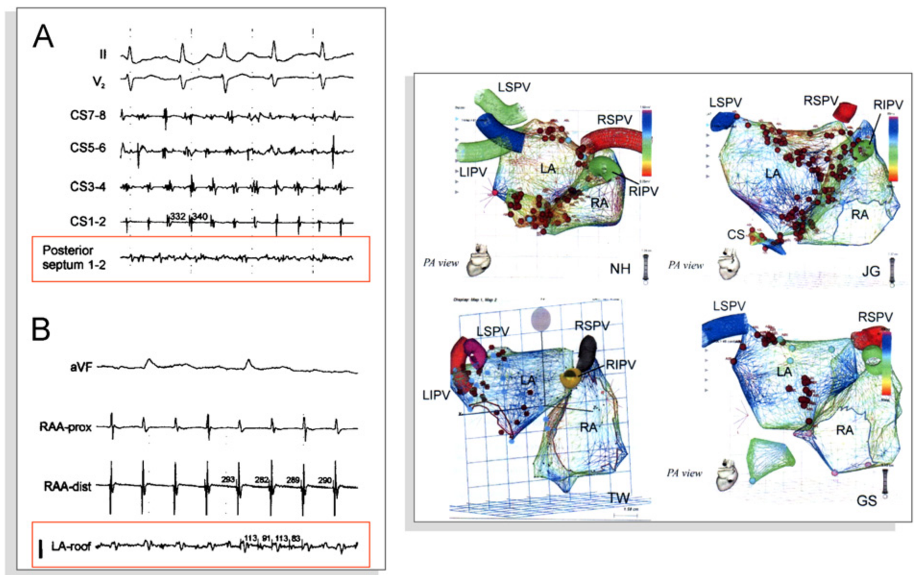

Fig. 3. Electrogram-guided complex fractionated atrial electrogram (CFAE) ablation: CFAEs are targeted with the help of the CARTO system (reproduced from Ref. [9]).

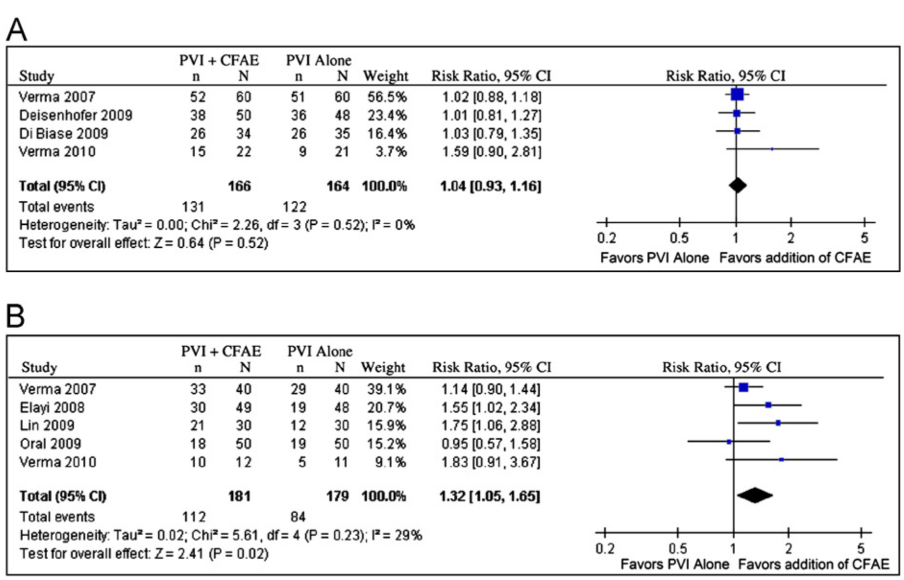

Fig. 4. Meta-analysis demonstrated that adjunctive CFAE ablation only provided a benefit in non-paroxysmal AF cases, but not in paroxysmal cases. (A) Freedom from atrial tachyarrhythmias for paroxysmal AF. (B) Freedom from atrial tachyarrhythmias for nonparoxysmal AF.

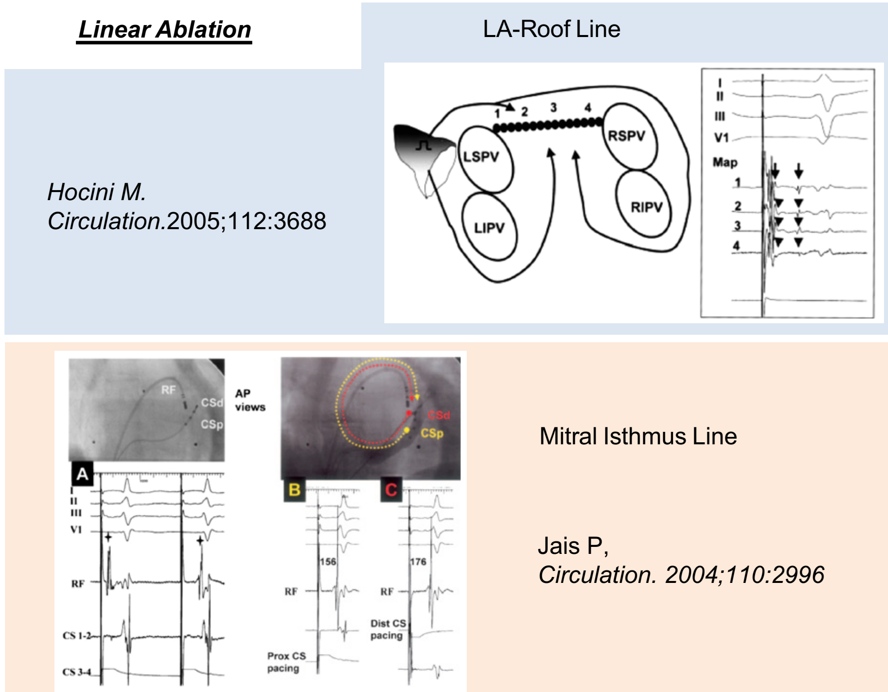

Fig. 5. Left atrial linear ablation targeting the roof and the left isthmus between the mitral valve and the left inferior PV. Reproduced from Refs. [15,16].

the first attempts to objectively quantify (CARTO, Biosense Webster, Diamond Bar, CA, USA) and target CFAE in addition to conventional ablation was reported by Hayward et al. [13]. The algorithms yielded primary CFAE sites in the atrium in an average of 24% of the cases, which were accordingly ablated. PVAI and other line ablations (roof and mitral isthmus) were also performed. During the follow-up period (> 1 year), they reported a 68% clinical (drug-free) success rate after a single procedure in long-standing persistent AF patients [14].

The efficiency of 2 additional strategies for eliminating the substrate for AF maintenance in addition to PVI has been described. Linear lesions are commonly made at the roof between the contralateral superior PVs (roof line), and at the isthmus between the mitral valve and the left inferior PV (mitral isthmus line) (Fig. 5). This concept was based on previous reports by Hocini et al. [15] and Jaïs et al. [16], in which the combination of both the roof line and the mitral isthmus line improved the AF-free ratio in paroxysmal AF cases from 69% to 87%; however, epicardial RF applications were required in 60% of the cases to achieve the mitral isthmus block. Meta-analysis showed that although the addition of linear lesions did not confer a significant benefit in freedom from AF over PVI alone, a significant benefit was observed for the addition of linear lesions to PVI in persistent AF cases (RR, 0.53) [11].

Adding ganglionated plexus (GP) ablation as an adjunctive approach to other targets may improve ablation success. The 4 major left atrial (LA) GPs (superior left, inferior left, anterior right, and inferior right GP) are located in epicardial fat pads at the border of the PV antrum and can be localized at the time of ablation using high frequency endocardial stimulation [17]. RF current can be applied endocardially at each site with a positive vagal response to high frequency stimulation until the vagal response to high frequency stimulation is eliminated. Although ablation of the left atrial GP has been shown to produce promising results in terms of eliminating the paroxysmal form of AF, its role in ablation of persistent AF remains unclear. Pokushalov et al. [18] demonstrated that GP ablation alone showed only limited effectiveness (38.2%) for long-term maintenance of sinus rhythm in

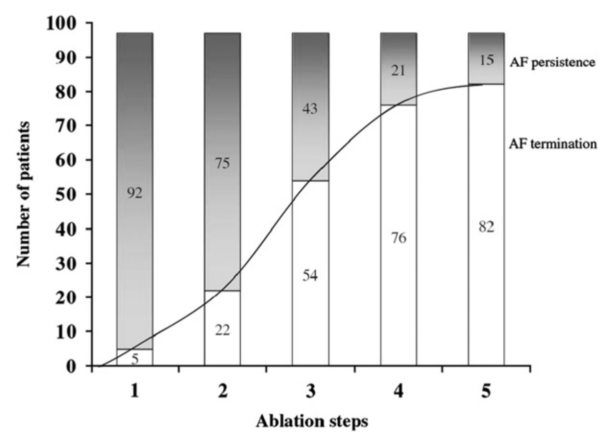

Fig. 6. Sigmoidal relationship between the progression of stepwise ablations and the AF termination rate. Reproduced from Ref. [20].

long-standing persistent AF, while the addition of antral PVI resulted in a better success rate (59.6%) over a follow-up period of approximately 1.5 years.

4. Sequential multifaceted ablation strategy for chronic AF

Multiple strategies consisting of various procedures, including PVI, anatomy- or electrogram-guided left atrial ablation, linear ablation, and thoracic vein isolation, have been developed as discussed above. Each strategy alone has been shown to yield similar success rates (50–70%), suggesting various coexisting targets and factors as modifiers of AF substrates. The stepwise ablation approach is an integration of most of the aforementioned techniques in a bid to additively improve the success of long-standing persistent AF ablation [19]. Each region is targeted in sequence, with the effect of ablation assessed by measuring AF cycle length. The procedure endpoint is the termination of AF to sinus rhythm. According to the progression of the stepwise procedure, the AF-termination rate increased in a sigmoidal fashion (Fig. 6) [20]. Thus far, 5 studies have reported the clinical success associated with the stepwise ablation approach for persistent/long standing persistent AF [19–24]. In an original article by Haissaguerre et al. [19] the single-procedure, drug-free success rate was 62% in 11 ± 6 months, which increased to 88% when repeat procedures were performed in almost 50% of patients. Subsequent articles have demonstrated substantially lower outcomes with success rates of 23–55% when using a single procedure [21–24]. Integration of repeat procedures, mostly for focal atrial tachycardia and flutter, increased the drug-free clinical success rate to 70–88%, and the allowance of previously ineffective antiarrhythmic drug treatment further improved clinical success to 84–90% (Fig. 2) [8].

5. A comparison of and the relationship between 2 approaches for long-standing persistent AF: CFAE ablation and linear ablation

As mentioned above, both electrogram-based ablation targeting the CFAEs and linear ablation in the left atrium, including roofline ablation and mitral isthmus ablation, have been performed in combination with PVI to eliminate long-persistent atrial fibrillation. Although all these strategies have been shown to be effective, there have been only a few reports demonstrating the relationship between these approaches. PVI has been shown to significantly reduce CFAE regions, and additional ablation targeting the residual CFAE can terminate and eliminate AF during subsequent observation. Matsuo et al. [25] recently demonstrated that both PVI and LA linear ablation resulted in a significant reduction of CFAE areas, not only in the areas where RF was applied, but also in remote regions

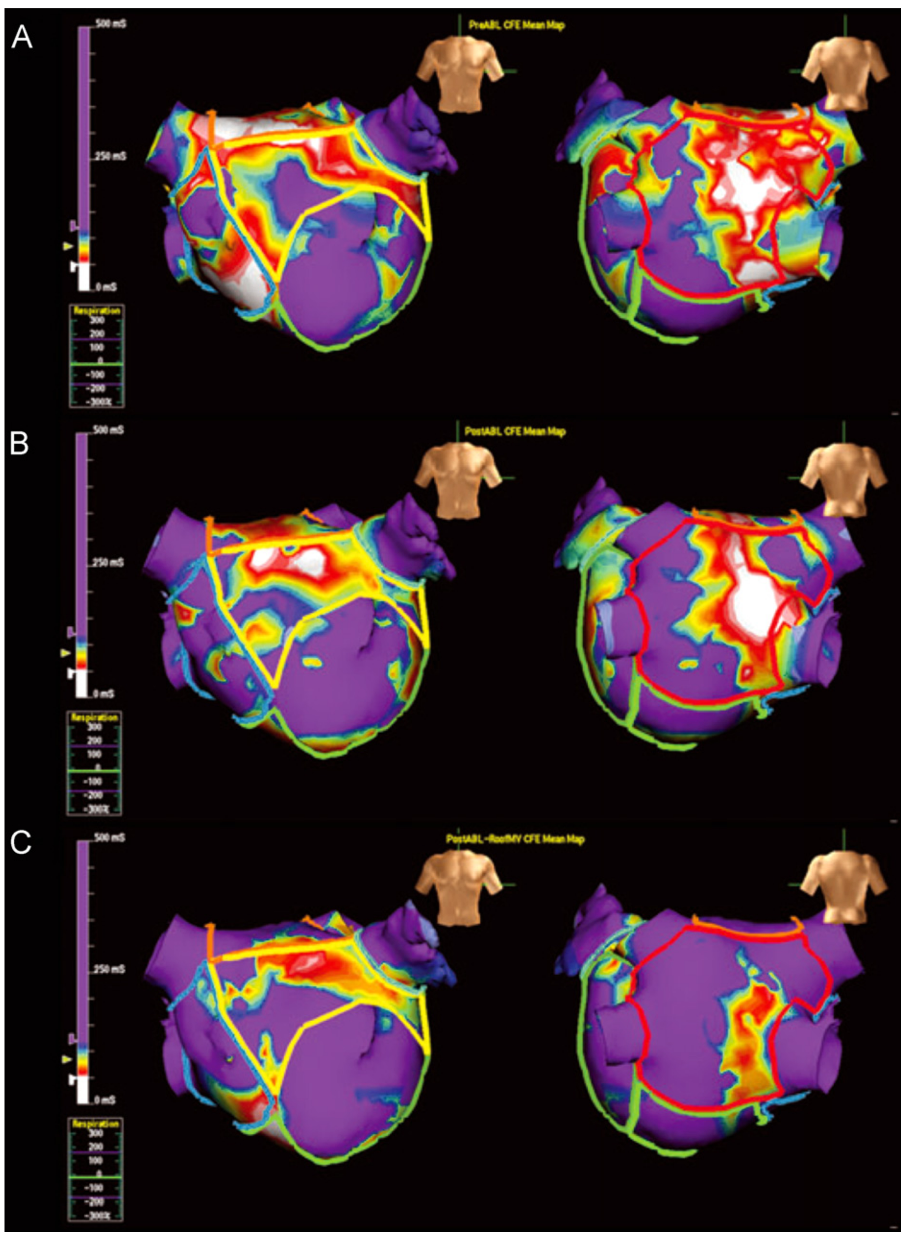

Fig. 7. A representative case demonstrating a significant reduction of continuous fractionated atrial electrograms (CFAEs) through pulmonary vein (PV) isolation and linear ablation in the left atrium. (A) The regions presenting CFAEs were demonstrated by high-density mapping prior to radiofrequency application. (B) Following the PV isolation, the regions demonstrating CFAEs were decreased. (C) The linear ablations resulted in a significant reduction of the CFAE areas. Reproduced from Ref. [25].

without RF energy application (Fig. 7). Therefore, reducing the CFAE areas through LA linear ablation could be useful for decreasing the RF energy required for CFAE ablation.

Data comparing the effectiveness of CFAE ablation and LA linear ablation for eliminating long-standing persistent AF is lacking. However, Estner et al. recently showed that CFAE ablation plus PVI in patients with persistent AF ablation approached the same effectiveness as circumferential PVI plus line within the first year after a single ablation procedure [26]. Prospective, randomized studies comparing the effectiveness of CFAE and line ablation with the baseline PVI protocol are needed to determine the actual effectiveness of each adjunctive ablation method.

6. Endpoint of catheter ablation for long-standing persistent AF

There remains a debate on the endpoint of ablation for long-standing persistent AF cases. O'Neill et al. reported that procedural AF termination during stepwise ablation, involving PVI, CFAE-ablation, and linear atrial ablation, had a better subsequent clinical outcome than cases without procedural AF termination, and suggested AF termination as the desirable endpoint of the procedure [22]. However, this result has not been reproducible in other studies. Recently published data by Lo et al. [27] and Elayi et al. [28] showed similar results; cases both with and without procedural AF termination had similar subsequent clinical outcomes and AF termination is a phenomenon that is likely to be achieved only in less advanced cases. When we look back at the paper by O'Neill et al. [20], we observed a significant difference in the baseline characteristics of patients with and without procedural AF termination, which suggests that AF termination itself may only be a surrogate for less advanced atrial disease. It is still not clear whether continued RF applications with prolonged procedure time using AF termination as the endpoint will provide a benefit to patients or not.

7. Indication for catheter ablation for long-standing persistent AF

As shown above, the clinical outcome following the ablation procedure has demonstrated that not all patients can benefit from ablation. We now focus on how we can determine who will be a good candidate for operation prior to the procedure. Several clinical variables have been shown to be correlated with ablation procedure outcome in patients with long-standing persistent AF, including the left atrial dimension on echocardiogram and the duration of persistent AF. McCready et al. [29] demonstrated that LA size (larger than 43 mm) was an independent predictor of AF recurrence following ablation of persistent AF. In contrast, Matsuo et al. [30] showed that both the surface electrocardiographic AF cycle length (≤ 142 ms) and the duration of continuous AF (>21 months) are predictive of AF recurrence after persistent AF ablation. To avoid harmful procedures in highly advanced cases, we need additional criteria to determine the appropriate indications for catheter ablation in patients with long-standing persistent AF.

8. Conclusions

Non-pharmacological rhythm control of atrial fibrillation is of increasing importance in our aging society. Advancement in catheter ablation techniques over the last decade has provided a cure for AF patients, with a nearly established efficiency for paroxysmal cases. Since ablation of chronic AF cases is still challenging, early treatment of paroxysmal AF before transformation to the persistent or chronic form is mandatory. For ablation of long-standing persistent AF, there is a consensus that PVI is the first-line approach, similar to paroxysmal AF. However, there are wide variations in the adjunctive approaches to modify the atrial substrate in persistent AF, and data comparing the effectiveness of these adjunctive approaches are still lacking. Large scale controlled trials evaluating the effect of catheter ablation on diverse patient populations over the long-term are necessary to establish the appropriate approach for long-standing persistent AF.

Conflict of interest

There is no conflict of interest.

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