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REVIEW

Catheter Ablation of Persistent Atrial Fibrillation

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ABSTRACT

Catheter ablation of atrial fibrillation (AF) has been widely accepted as an important therapeutic modality for the treatment of patients with symptomatic, drug-refractory AF. Ablation strategies which target the pulmonary veins (PVs) and/or the PV antrum (segmental or large circumferential lesions) are the cornerstone of AF ablation procedures, irrespective of the AF type. Successful electrical PV isolation results in maintenance of sinus rhythm in 60 to 85% of patients in patients with paroxysmal AF. However, PV isolation is usually insufficient to eliminate persistent or long-lasting persistent AF leading to significantly lower success rate of this method. Up to now, no single strategy is uniformly effective in patients with persistent and long-lasting persistent AF. Many centers follow a stepwise ablation approach including (i) PV isolation as the initial step; (ii) electrogram-based ablation at all sites in the left atrium and the coronary sinus exhibiting complex fractionated atrial electrograms; (iii) If AF sustains, linear ablation (mainly roof and mitral isthmus lines) is then carried out; and (iv) the right atrium and superior vena cava are finally mapped and ablated. However, such an extensive ablation strategy lead to longer procedure time, longer fluoroscopy time, higher complication rates and higher rates of post-procedural atrial tachycardias. Therefore, the risk/benefit ratio of an extensive ablation approach has to be carefully evaluated. Catheter ablation of persistent and long-lasting persistent AF still remains challenging for the electrophysiologists. The long-term efficacy of certain ablation strategies need to be evaluated in randomized trials.

KEY WORDS: *atrial fibrillation; catheter ablation; cardiac arrhythmias; pulmonary vein isolation; transseptal catheterization*

Abbreviations

AF = atrial fibrillation
AT = atrial tachycardia
CFAE = complex fractionated atrial electrogram
LA = left atrium
PV = pulmonary vein
PVI = pulmonary vein isolation
GP = ganglionated plexi

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice with an increasing prevalence in relation to age, ranging from 0.1% in people younger than 55 years to more than 9% by 80 years of age.[1,2] AF is associated with a 2-fold risk of cardiac and overall mortality.[1] In our days, the mainstay of treatment of AF remains pharmacological. Data from the AFFIRM,[3] the RACE,[4] and the PIAF[5] trials have shown a comparable outcome for both rhythm and rate-control pharmacological strategies. However, in subgroup analysis, survival is improved in patients who achieve sinus rhythm, an event that is negated by the deleterious effects of the antiarrhythmic drugs.[6] Thus, the restoration and maintenance of sinus rhythm is of major importance if it can be accomplished without the use of antiarrhythmic drugs.

Catheter ablation of AF has been widely accepted as an important therapeutic modality for the treatment of patients with symptomatic AF, refractory or intolerant to at least one class I or III antiarrhythmic medication.[7,8] The current AHA/ACC/ESC guidelines state that catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no left atrial (LA) enlargement (Class: 2A; Level of Evidence: C).[2] However, recent data have clearly demonstated the superiority of catheter ablation over antiarrhythmic drug treatment.[9-14]

Following the pioneering work of Haissaguerre et al. electrical isolation of all pulmonary veins (PVs) is the end point of ablation for paroxysmal AF.[15] Successful PV isolation (PVI) results in maintenance of sinus rhythm in 60 to 85% of patients.[16,17] On the contrary, PVI is insufficient to eliminate persistent or long-lasting persistent AF leading to significantly lower success rate of this method.[7,8,18-19] This difference suggests that the mechanisms underlying the maintenance of persistent AF are different in relation to paroxysmal AF.[7,8] Elimination of PV drivers and additional substrate modification are required in the setting of persistent and long-lasting persistent AF.[18-19] Although different ablation strategies have been reported for persistent AF, the reproducibility of these techniques is considered inconsistent. This review article highlights on the current catheter ablation strategies for persistent and long-lasting persistent AF.

DEFINITION OF DIFFERENT TYPES OF ATRIAL FIBRILLATION

Based on the updated AHA/ACC/ESC guidelines[2], AF is classified as *paroxysmal, persistent, or permanent*. In the setting of two or more episodes, AF is designated recurrent. If the arrhythmia terminates spontaneously, recurrent AF is characterized as *paroxysmal*. In the case that maintains for more than seven days, AF is characterized as *persistent*. Termination with pharmacological therapy or direct-current cardioversion does not change the designation. First-detected AF may be either paroxysmal or persistent. The category of persistent AF also includes cases of *long-lasting* AF (greater than one year) and *permanent* AF, in which cardioversion has failed or has not been attempted. These categories are not mutually exclusive in a particular patient, who may have several episodes of paroxysmal AF and occasional persistent AF, or the reverse.

PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

The pathophysiology of AF is multifactorial, complex, and not well-defined. Up to date, two main theories have been reported for the initiation and maintenance of AF. The single-focus hypothesis advocates that AF is due to a single automatic focus or a microreentrant circuit.[2,20] The wavefronts emanating from the primary driver circuit (rotor) break against regions of varying refractoriness and give rise to irregular global activity.[2,20] A single focus can fire at a regular but very rapid rate that cannot be followed by the rest of the atrial tissue, resulting in fibrillatory conduction.[20] A variety of different potential sources of triggers for AF have been reported[2]; however, triggers that originate from the PVs and other thoracic veins appear to be the primary mechanism of AF, particularly in subjects with paroxysmal AF.[2,15,21] Atrial tissue within the PVs in patients with AF display shorter refractory period and decremental conduction properties compared to control patients leading to a marked heterogeneity of conduction that promotes reentry and form a substrate for sustained AF.[2,7,8]

The multiple re-entrant wavelet hypothesis as a mechanism of AF was described by Moe and colleagues in 1959,[2,22] with supportive experimental work by Alessie.[23] This theory was the premise on which Cox's Maze procedure was developed and provides the rationale for ablation procedures leading to LA compartmentalization.[24] The multiple re-entrant wavelet hypothesis supports that fractionation of wavefronts propagating through the atria results in self-perpetuating 'daughter wavelets'. Multiple re-entrant wavelets are separated by lines of functional conduction block. The lines of the conduction block can occur around the anatomical structures within the atria with different inherent electrophysiological properties, such as scars, patchy fibrosis and myocardium, at different stages of recovery and excitability. The number of wavelets at any given time depends on the conduction velocity, atrial mass and refractory period in different parts of the atria. Thus, AF is perpetuated by slowed conduction, increased atrial mass and shorter refractory periods.

The relationship between these mechanisms is complex, and they often coexist in the same patient, particularly in the setting of persistent AF or long-lasting persistent AF.[25] In addition to these models, the role of the local autonomic nervous system in the initiation and perpetuation of AF has been demonstrated in both animal and human models. Parasympathetic ganglionated plexi (GP) are located near the PV-LA junction and may be important targets for ablative therapy.[7,8] Autonomic factors have also been implicated in the generation of complex fractionated atrial electrograms (CFAEs), an important substrate of AF.[7,8]

Progressive electroanatomic remodeling that develops as AF progresses from paroxysmal to persistent and permanent has been well demonstrated to further facilitate AF.[26] Atrial dilation, interstitial fibrosis, uncoupling of the myofibrils, loss of myofibrils, deposition of extracellular matrix, loss of gap junctions, resultant anisotropy, conduction slowing and/or block, and shortening of the effective refractory period may facilitate reentry, which is critical to perpetuation of AF.[2,7,8] As a result of progressive electroanatomic remodeling, mechanisms other than PV arrhythmogenicity are strongly involved and perpetuate AF.

ABLATION STRATEGIES AND SUCCESS RATES IN PERSISTENT AF

1. PULMONARY VEIN ISOLATION

Ablation strategies which target the PVs and/or the PV antrum are the cornerstone of AF ablation procedures, irrespective of the AF type. Initial attempts were targeted the arrhythmogenic activity within the PVs using a focal approach.[15] Due to the high risk of PV stenosis and the high rate of recurrence, complete electrical isolation of the PVs by segmental ostial ablation quickly replaced the initial approach.[27,28] Successful PV isolation was defined by loss of PV potentials (entrance block) and failure to capture left atrium during pacing from the PV (exit block). Figure 1 shows an example of electrical isolation of the left superior PV in a patient with persistent AF. A clinically satisfactory result can be achieved in more than 80% of patients with paroxysmal AF using a segmental PVI approach.[27,28] However, this approach had minimal efficacy in patients with persistent AF.[27,28] Pappone et al. introduced the circumferential PV ablation without PV isolation with higher success rate even in patients with persistent and permanent AF.[29] This technique involves applications of radiofrequency energy 1-2 cm away from the ostia of the PVs. The PV ostium is identified by a combination of venography, electrogram, and the drop-off site of the mapping catheter during its withdrawal from the vein. Each target site is usually ablated until the local electrogram amplitude decreased by ≥80% or to <0.1 mV. Lemola et al. have additionally shown that complete electrical isolation of the PVs is not a requirement for a successful outcome after left atrial circumferential ablation.[30] In a randomized trial, Arentz et al. have demonstated that isolation of a large circumferential area around both ipsilateral PVs with verification of conduction block is a more effective treatment of AF than isolation of each individual PV using a segmental approach.[31] Figure 2 shows the three-dimensional reconstruction of the left atrium with large circumferential ablation lesions around both ipsilateral veins and additional ablation lines on the interpulmonary isthmus creating a "figure of eight" model. Up to now, PVI or PV antral isolation confirmed by absence or dissociation of PV potentials is the most effective strategy for treatment of most patients with paroxysmal AF.[32-34] Despite achieving a very high rate of electrical PVI, PVI strategies alone have consistently demonstrated a lower success rate in patients with persistent AF compared to paroxysmal AF.[7,8,35-37]

FIGURE 1. Left superior PV isolation in a patient with persistent AF. Map indicates distal bipole of the ablation catheter; PV indicates Lasso catheter bipoles.

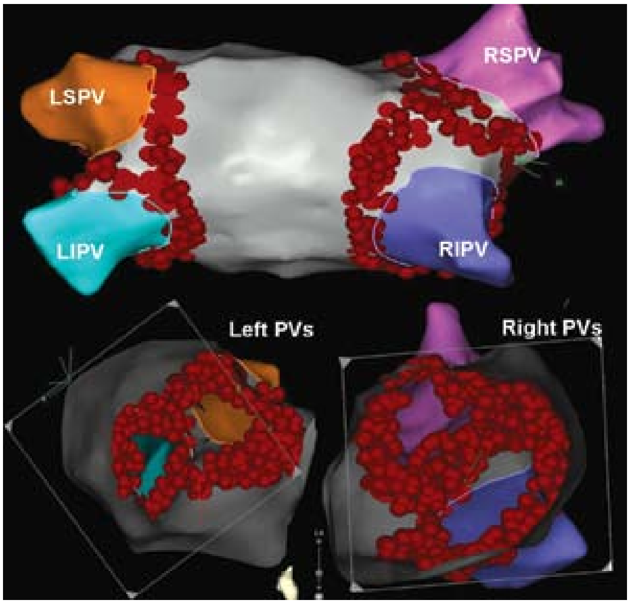

FIGURE 2. Three-dimensional reconstruction of the left atrium using the CARTO 3 map system (Biosence-Webster, Johnson & Johnson, USA) showing large circumferential ablation lesions around both ipsilateral veins. In this example, additional radiofrequency energy was applied on the interpulmonary isthmus following the large circumferential lesion creating a "figure of eight" model.

2. LINEAR ABLATION

As previously stated, PVI alone is insufficient for restoration and maintenance of sinus rhythm in most patients with persistent AF. Based on the high success rates of surgical MAZE procedures,[24] several attempts have been made to reproduce these results by percutaneous catheter-based linear ablations. Linear lesions usually include a roof line connecting the left and right superior PVs (Figure 3), and a mitral line connecting the mitral annulus to the left inferior PV (Figure 3 and Figure 4).[35-38] Addition of linear lesions is intended to modify the arrhythmogenic LA substrate and atrial macro-re-entrant circuits involved in maintenance of AF.[35-39] Linear lesions have been associated with conversion of AF either directly to sinus rhythm or to atrial tachycardia (AT), demonstrating that such lesions significantly modify the substrate for AF.[39] Linear lesions applied at the mitral isthmus or the roof of the LA increase the AF cycle length by a mean of 20 ms, and exert a favourable impact on elimination of AF.[38] Bidirectional block across the linear lines has to be confirmed in order to assess completeness of linear lesions.[38,39] However, LA linear ablation still remains technically challenging. In the study of Jais et al, 68% of patients required an ablation within the CS facing the endocardial aspect of the mitral isthmus because of persisting epicardial conduction.[38]

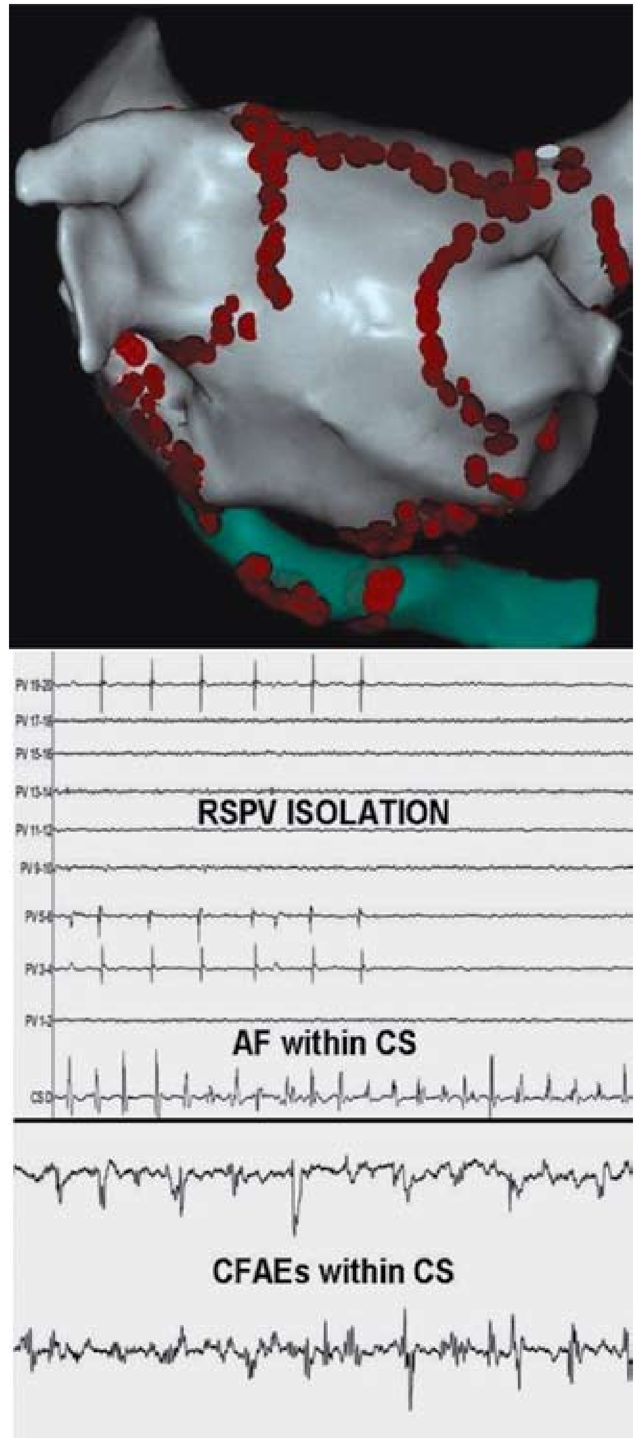

FIGURE 3. Three-dimensional reconstruction of the left atrium using the CARTO 3 map system (Biosence-Webster, Johnson & Johnson, USA) showing large circumferential ablation lesions around both ipsilateral veins and extensive ablation lines including roof, mitral isthmus and coronary sinus line. This figure also shows right superior PV (RSPV) isolation and an example of CFAEs recorded within the coronary sinus (CS).

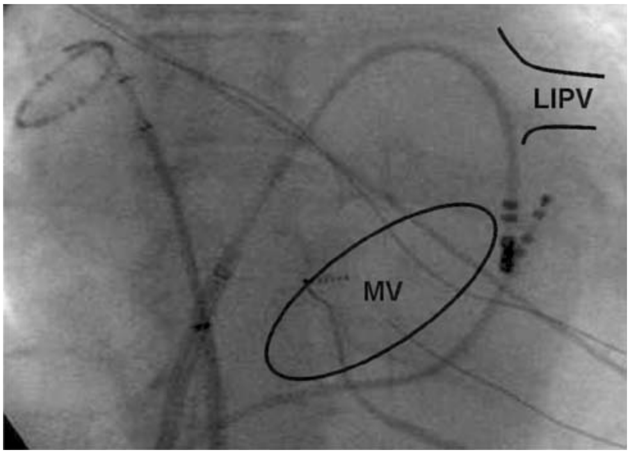

FIGURE 4. Mitral isthmus line connecting the mitral valve (MV) annulus to the left inferior PV (LIPV).

Willems et al. have investigated the effectiveness of additional substrate modification by left atrial linear lesions as compared with PVI alone in patients with persistent AF in a prospective randomized study.[40] After a mean follow-up time of 487 days, only 20% of patients undergoing stand alone PVI remained in sinus rhythm when compared with 69% following PVI combined with substrate modification. This study clearly shows that PVI alone is insufficient for the treatment of patients with persistent AF. In a similar study, Fassini et al. confirmed the additional benefit of mitral isthmus ablation in patients with persistent AF.[41] Yao et al. attempted to convert AF to sinus rhythm using a linear catheter ablation approach.[42] This approach initially utilized a *figure of seven* lesion line between the right and left superior PV on the roof of the left atrium and then extended along the ridge between the left appendage and the left PVs until the mitral valve annulus, as the primary lesions. AF was converted to sinus rhythm in 81.6% of patients (90.8% of paroxysmal and 51.1% of persistent AF) with this technique. During a mean follow-up of 18.2 months follow-up, 88.3% of patients were free of atrial tachyarrhythmias without medication.

3. COMPLEX-FRACTIONATED ATRIAL ELECTROGRAMS

CFAEs areas represent potential AF substrate sites and are now considered as important targets for AF catheter ablation.[7,8] CFAEs indicate sites of slow conduction, wavefront collision, conduction block, or anchor points for reentrant circuits based on the findings of an epicardial unipolar mapping study in humans.[43] CFAEs have also been proposed to indicate sites of ganglionated plexi, as shorter effective refractory period at these sites would allow higher-frequency activation.[44] CFAEs are defined as (i) atrial electrograms that are fractionated and composed of two or more deflections averaged over a 10-s recording period; and (ii) atrial electrograms with a very short cycle length (≤120 ms) with or without multiple potentials when compared with the atrial cycle length recorded from other parts of the atria.[45] End points for ablation at sites of CFAEs include complete elimination of CFAEs or slowing and organization of local electrograms.[45,46] An example of CFAEs is showing in Figure 3. The preferential sites of AF termination or regularization have been found around the pulmonary veins, at the anterior wall of the LA and at the interatrial septum. Nademanee et al. have shown that demonstrated that ablation of CFAEs alone resulted in termination of AF without external cardioversion in 95% of patients persistent or paroxysmal AF and at 1-year follow-up, 91% of patients were free of arrhythmia and symptoms.[45] On the contrary, Oral et al. have demonstrated a modest short-term efficacy of the ablation procedure when targeting only the CFAEs.[46] In particular, only 33% of patients were in sinus rhythm without the use of antiarrhythmic drugs after the index ablation.[46] Bencsik et al. have recently demonstrated that CFAEs ablation guided by a dedicated software algorithm and performed after circumferential PVI outside of the circular PVI lines had no significant impact on the fibrillatory process and displayed a minor role in achieving higher rates of termination and non-inducibility in patients with persistent AF.[47]

Ablation of CFAE as a stand-alone ablation strategy seems insufficient for the treatment of patients with persistent AF.[48] A combined approach of PVI and CFAE ablation in persistent AF leads to acute AF termination in 66% and long-term maintenance of sinus rhythm in 74% of cases.[49] The role of ablation of CFAEs following PV antral isolation was investigated in two recent randomized studies. Elayi et al. have conducted a multicenter, randomized controlled study of three different catheter ablation strategies in patients with long-lasting persistent AF (≥1 year, median duration 28 months): anatomic circumferential PV ablation, electrophysiologically guided PV antral isolation, and ablation of complex fractionated atrial electrograms (right and left atria and coronary sinus) followed by PV antral isolation (CFAE plus PV antral isolation). CFAE plus PV antral isolation (61%) outperformed PV antral isolation (40%), which was superior to circumferential PV ablation (11%).[50] Oral et al. randomized 119 consecutive patients with long-standing persistent AF to PVAI or PVAI and further CFAE ablation. These authors found that up to 2 h of additional ablation of CFAEs after PVAI does not appear to improve clinical outcomes in patients with long-lasting persistent AF.[51]

4. NON-PULMONARY VEIN FOCI

Although the PVs are a dominant source of AF, non-PV ectopic activity can trigger AF, and ablation of these ectopic activities can eliminate AF in a specific group of patients. Non-PV triggers are more commonly observed in patients with persistent (8.2%) and long-lasting persistent AF (19.1%) in relation to those with paroxysmal AF (2.9%).[52] Ablation of non-PV foci following PVI can organize persistent AF into focal or macro-re-entrant atrial tachycardias, which can be eliminated, resulting in maintenance of sinus rhythm in the majority of patients.[53,54] The majority of non-PV foci responsible for initiation of AF are located in the superior vena cava, crista terminalis, coronary sinus, LA free wall, LA appendage and ligament of Marshall.[53,54]

5. AUTONOMIC GANGLIONATED PLEXI

Experimental and clinical data suggest that activation of the autonomic nervous system may play a critical role in the initiation and maintenance of AF.[55] The majority of GPs are located over the LA and in fat pads at the superior vena cava-aorta and the PV-LA junctions, and ablation of these sites can effectively denervate the LA.[56] GP activation includes both parasympathetic and sympathetic stimulation of the atrium surrounding the GP and the closest PV. Parasympathetic stimulation markedly shortens action potential duration, while sympathetic stimulation increases calcium loading and calcium release from the sarcoplasmic reticulum leading to early afterdepolarizations and triggered activity.[57,58] GPs can be easily mapped using high-frequency stimulation. Vagal denervation after circumferential PV ablation was associated with a higher probability of maintenance of sinus rhythm.[59] Limited data exist regarding GP ablation in AF, particularly in persistent AF. It is unclear whether ganglionated plexi should be specifically targeted, given that these sites may be concomitantly ablated in the course of above described ablation targets.

COMBINATION OF ABLATION TECHNIQUES: THE BORDEAUX EXPERIENCE

According to the Bordeaux group,[18,19,34,36,60,61] catheter ablation sequence for persistent AF should be as follows: (i) *PV isolation* is the initial step aiming at elimination of PV electrograms; (ii) *Electrogram-based ablation* is then performed at all sites in the LA and the CS exhibiting any of the following electrogram features: (a) *CFAEs*, especially continuous activity; (b) *activation gradient* of at least 70 ms between the distal and proximal recording bipoles of the mapping catheter; (c) *frequency gradient* in regions with a cycle length shorter than the mean LA appendage cycle length. The endpoint of electrogram-based ablation is transformation of complex fractionated electrograms into discrete electrograms and slowing of the local cycle length compared with LA appendage cycle length or finally elimination of electrograms; (iii) If AF sustains following PV isolation and electrogram-based ablation, *linear ablation* is carried out. The roof line is primarily performed followed by the mitral line if AF persists. During AF, the endpoint of linear ablation is significant reduction or abolition of the local electrograms on the line. After restoration of sinus rhythm, bidirectional block across the linear lines is confirmed in order to assess completeness of linear lesions; (iv) Finally, the *right atrium (RA) and superior vena cava* are targeted for ablation if implicated as a source perpetuating AF and only after all LA ablation steps. The perpetuating influence of the RA is likely when RA appendage cycle length is shorter than the LA appendage cycle length by more than 20 ms after completion of LA ablation. Using this sequential ablation, the Bordeaux group reported termination of chronic AF (including patients with persistent AF) by conversion to either sinus rhythm or atrial tachycardia in 87% of patients during the index procedure and freedom from AF after an 11-month follow-up period in 95% of patients.[18,19] Interestingly, AF was terminated in only 5% of patients by PVI, in 60% after electrogram-based ablation, and in 84% following linear ablation.[18] AF cycle length was the strongest independent predictor of procedural AF termination.[61] A recent systematic review of the literature with regards to the impact of ablation technique on the outcomes of persistent and long-lasting persistent AF ablation showed a significant variation in success rates suggesting that the optimal ablation technique is unclear.[62] Table 1 summarizes the main findings of this systematic review.

TABLE 1. The impact of ablation technique on the outcomes of persistent and long-lasting persistent AF ablation.[62]

Ablation technique	Success rate
Segmental PVI	21-22%
Circumferential PV antrum ablation with electrical isolation	38-40%
Circumferential PV antrum ablation without electrical isolation	37-56%
Linear ablation in addition to PV antrum ablation	11-74%
Linear ablation in addition to PV antrum isolation	38-57%
CFAEs ablation alone	24-63%
CFAEs ablation as an adjunct to PV antrum ablation	50-51%
CFAEs ablation as an adjunct to PV antrum isolation	36-61%
CFAEs ablation as an adjunct to PV antrum isolation and linear ablation	68%
A combination ablation approach	38-62%

END-POINTS OF CATHETER ABLATION FOR PERSISTENT AF

The goal of catheter ablation in persistent AF is trigger elimination and substrate modification. However, there is no clear end-point for persistent AF ablation. Four procedural end-points are accepted for AF catheter ablation: (i) *electrical PVI*; (ii) *completion of a predetermined linear lesion*; (iii) *termination of AF during ablation*; and (iv) *non-inducible AF after ablation*.[7,8,33,34] Although restoration of sinus rhythm by ablation appears an intuitively ideal end point, data are limited to support such an end-point. In a prospective study of 153 patients who underwent catheter ablation of persistent AF, a lower incidence of AF recurrence was demonstrated in those patients in whom AF was terminated during the index procedure compared to those without termination (5 vs. 39%, mean follow-up 32+11 months).[60] During ablation of persistent AF with various strategies, the arrhythmia often organizes into a regular AT and sometimes even terminates into sinus rhythm.[18] In a recent prospective study, Elayi et al. assessed the AF termination mode during catheter ablation in 306 patients with long-lasting persistent AF and whether it predicts long term sinus rhythm maintenance.[63] During AF ablation, only 6 out of 306 patients converted directly to sinus rhythm and 172 patients organized into AT. The presence or absence of organization during ablation clearly predicted the predominant mode of recurrence, respectively AT or AF. Authors showed that AF termination during ablation (conversion to AT or sinus rhythm) predict the mode of arrhythmia recurrence (AT vs. AF), but did not impact on long term sinus rhythm maintenance after a single or two procedures. Non-inducibility of AF following catheter ablation seems to be associated with an improved outcome. However, there is no current consensus on the definition of non-inducibility and the induction protocol used.

In clinical practice, the ideal end-point for AF catheter ablation is freedom from AF without the use of antiarrhythmic medications. There is much controversy regarding the monitoring period as well as the minimum acceptable AF burden. Current definitions of freedom from AF include absence of AF, AF episodes lasting up to 30s, and absence of symptomatic AF.[7,8,33] A 'blanking period' of up to 3 months after ablation, during which antiarrhythmic medications may be continued and direct current cardioversion can be performed for early recurrences of arrhythmias, appears to be adequate in order to access the efficacy of an ablation strategy.[7,8] However, clear definitions of freedom from AF and the 'blanking period' are needed in order to be able to compare and interpret the results of different AF ablation trials.

WHICH IS THE PRICE FOR AN EXTENSIVE ABLATION PROCEDURE IN THE SETTING OF PERSISTENT AF?

Longer procedure time, longer fluoroscopy time, higher complication rates and high rates of post-procedural ATs are the main consequences of an extensive ablation procedure carried out in the setting of persistent and long-lasting persistent AF. In a recent systematic literature review of studies with persistent and long-lasting persistent AF ablation, complications have been reported in 4.4% of patients.[62] Death is an uncommon complication of AF ablation, occurring in 0.1-0.15% of subjects.[64,65] These fatal events have been related to different steps of the ablation procedure including the transseptal puncture, a prolonged catheter manipulation in the left atrium, and a high cumulative RF energy delivered in the left atrium in the context of a high level of systemic anticoagulation. Cardiac tamponade is by far the most common fatal complication of AF ablation.[7,8,62,64,65] In a recent worldwide survey on the safety of catheter ablation of AF including 16.309 patients, there were 213 episodes of tamponade (1.31%), 37 strokes (0.23%) and 115 transient ischemic attacks (0.71%).[64] PV stenosis requiring intervention was observed in 0.29% of patients.[64] Femoral pseudoaneurysm and artero-venous fistulae were observed in 0.92% and 0.54% of patients, respectively.[64] Atrio-esophageal fistulas, esophageal damage, and perforation are rare, but usually fatal complications of AF ablation (0.04%).[64] Finally, transient ST-segment elevation, usually in inferior leads, is rarely observed during AF ablation and has been related to coronary artery spasm secondary to autonomic modulation or air emboli.[66] ATs following AF ablation are a rapidly growing clinical problem due to the expansion of the ablation strategies in the setting of persistent AF.[7,8,64,65] These secondary ATs are often incessant and very poorly tolerated by the patient. ATs have been shown to occur in about 40% of patients who undergo the stepwise ablation approach.[18]

We have recently shown that peri-procedural maintenance of sinus rhythm lead to similar success rates in patients with paroxysmal and persistent AF.[67] After a relatively long follow-up period (18±10 months), 70.1% of patients with paroxysmal and 68.5% with persistent AF were in sinus rhythm without antiarrhythmic drugs. The peri-procedural maintenance of sinus rhythm ("*sinus rhythm begets sinus rhythm*" theory) may contribute to this improved success rate in the setting of persistent AF possibly by facilitating reversed LA remodeling. In addition, the acceptable long-term efficacy of large circumferential electrical PVI around both ipsilateral PVs in the setting of persistent AF may be explained by the adequate LA substrate modification following these lesions. As shown in Figure 5, arrhythmogenic ostial foci, parasympathetic innervation (GPs), and CFAEs that are possible mechanisms for the initiation and perpetuation of AF may be concomitantly

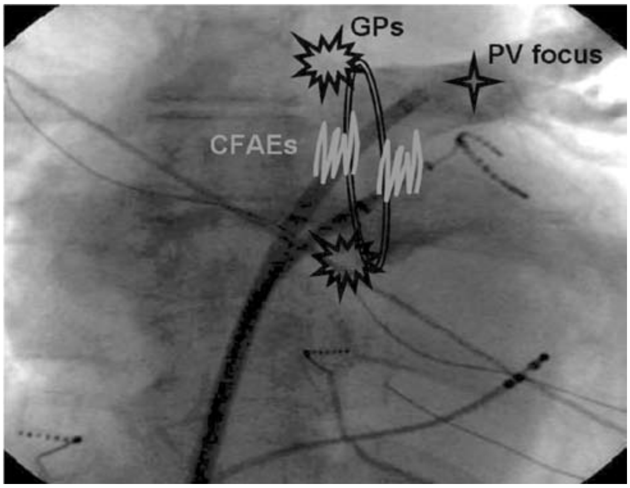

FIGURE 5. Arrhythmogenic ostial foci (PV), parasympathetic innervation (GPs), and CFAEs are possible mechanisms for the initiation and perpetuation of AF and can be concomitantly ablated in the course of large circumferential lesions.

ablated in the course of these large circumferential lesions. This study shows that a less extensive ablative approach has favourable long-term efficacy in the setting of persistent AF.[67] A similar approach is taking place in our Laboratory at Evagelismos Hospital, where large circumferential lesions are performed during sinus rhythm in all patients with paroxysmal and persistent AF using the CARTO™ 3 3-D mapping system (Biosense Webster, Inc., CA, USA). CFAEs ablation and/or linear lesions are performed in the setting of long-lasting persistent AF (>12 months AF).

EVOLVING ABLATION TECHNOLOGIES

A number of technical advances regarding mapping systems as well as catheter designs and energy sources are tacking place playing a major role on AF ablation, and more are expected. Fluoroscopy-guided catheter manipulation in the LA requires extensive previous experience and carries a higher risk of complications. The use of 3-D mapping systems, with or without intracardiac echocardiography, facilitates real-time assessment of LA anatomy, and can help operators to target the ablation sites. The Carto™ XP (Biosense Webster, Inc., CA, USA) and NavX™ (St Jude Medical, Inc., MS, USA) are the most known 3-D mapping systems used in clinical practice.[33] Both of them provide an accurate electroanatomic map facilitating the ablation procedure and minimizing fluoroscopy and procedural times. A randomized trial has recently shown that the three-dimensional magnetic resonance imaging of the LA reconstruction merged with the electroanatomical map does not significantly improve the clinical outcome, but significantly shortens the X-ray exposure.[68] Two relatively new remote navigation systems are now available for clinical use: the magnetic navigation system (Niobe II system, Stereotaxis, Inc., MO, USA) and the robotic navigation system (Sensei system, Hansen Medical, Inc., CA, USA).[69-72]

Traditional catheter ablation is performed in a single-tip, point-by-point ablation process. This technique requires a high degree of operator skill and procedures are long-lasting, often more than 4 hours. New catheter designs and energy sources for ablation are now under active investigation. The PVAC multipolar circular mapping and ablation catheter (Medtronic, Ablation Frontiers, Inc., Carlsbad, CA, USA) is a relatively new catheter that delivers both duty cycled bipolar and unipolar radiofrequency energy at a relatively low power through multiple electrodes at once, potentially making it faster and easier to isolate the PVs. This catheter has a bidirectional steering mechanism and an over-the-wire design. Initial studies have shown that PV isolation can be effectively and safely accomplished using the duty-cycled unipolar/bipolar RF ablation catheter.[73-75] The Mesh catheter (Bard Electrophysiology, Inc., MA, USA) consists of an expandable, braided-wire, electrode array, designed to perform a high-density, 36-electrode (18 bipoles) mapping and to deliver radiofrequency by the same electrodes.[76-77] Once the ostium is reached, RF energy is delivered to the annular perimeter of the umbrella-shaped catheter. The circumferential exposed wire segment is divided into four quadrants, each containing a thermocouple at its central point, allowing RF delivery in a temperature control mode. The safety and efficacy of the Mesh system in both mapping and ablating the PVs have been reported. The success rate for PV isolation varies between 63% and 100%.[77] No procedure related complications occurred using this type of catheter.[77,78] Long-term results of the clinical efficacy of this system need to be further evaluated.

Balloon-ablation catheters have emerged as promising new technology that may allow rapid and effective isolation of all PVs. Cryoballoon ablation appears to be the most completely tested. The cryoballoon system is a deflectable catheter (Cryocath Technologies Inc., Quebec, Canada; Medtronic Inc., MN, USA) with a balloon-within-a-balloon design wherein the cryo refrigerant (N2O) is delivered within the inner balloon.[78] The balloon is inflated at each PV ostium to temporarily occlude blood flow from the targeted PV. Tissue injury by freezing occurs due to direct cellular damage as well as microcirculatory failure shortly after tissue thawing. The prime mechanism of cell death is formation of intracellular ice crystals at rapid freezing rates, which occurs only close to the cryoballoon, highlighting the need for good tissue contact. Initial trials have demonstrated efficacy similar to radiofrequency ablation with limited applications and reduced procedure times.[79-82] An uncommon, but important complication of this system is right phrenic nerve paralysis.[79-82] Other novel energy sources for ablation include high-intensity ultrasound and laser ablation. The high-intensity focused ultrasound (HIFU) balloon catheter (ProRhythm Inc., Ronkonkoma, NY, USA) uses a focused ring of ultrasound energy to ablate myocardial tissue.[74] Borchert *et al.* have shown that treatment with the HIFU ablation system led to an increased incidence of atrio esophageal fistula.[83] As a result, all clinical trials with the ProRhythm focused ultrasound ablation system have now been terminated. The CardioFocus (Marlborough, MA, USA) ablation system is a balloon-based laser ablation.[78] Limited data are available on the outcomes of AF ablation using this energy source.[78] Large studies will be needed to determine the safety and efficacy of the CardioFocus laser balloon ablation system.

CONCLUSIONS

In conclusion, catheter ablation of persistent and long-lasting persistent AF remains challenging for the electrophysiologists. Up to now, no single strategy is uniformly effective in patients with persistent AF. The risk/benefit ratio of an extensive ablation approach has to be carefully evaluated. More lesions prolong not only procedure and fluoroscopic times, but also increase the risk of complications including ATs. For this purpose, the long-term success rates of certain ablation strategies need to be evaluated in randomized trials.

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