Review Article

Adjunct ablation strategies for persistent atrial fibrillation—beyond pulmonary vein isolation

Silvia Magnani[1], Daniele Muser[1], William Chik[2], Pasquale Santangeli[2]

[1]Cardiovascular Division, University of Udine, Udine, Italy; Postgraduate school of Cardiology, University of Triest, Trieste, Italy; [2]Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence to: Pasquale Santangeli, MD. Cardiovascular Division, Hospital of the University of Pennsylvania, 3400 Spruce Street, 9 Founders Pavilion, 19104, Philadelphia, Pennsylvania, USA. Email: pasquale.santangeli@uphs.upenn.edu.

Abstract: Atrial fibrillation (AF) is the most common sustained arrhythmia. Recent guidelines recommend pulmonary vein isolation (PVI) as the main procedural endpoint to control recurrent AF in symptomatic patients resistant to antiarrhythmic drugs. The efficacy of such procedure is higher in paroxysmal AF while is still unsatisfactory in persistent and long-standing persistent AF. This review will summarize the state-of-the-art of AF ablation techniques in patients with persistent AF, discussing the evidence underlying different approaches with a particular focus on adjunctive ablation strategies beyond PVI including linear ablation, ablation of complex fractionated atrial electrograms (CFAE), ablation of ganglionated plexi, dominant frequency, rotors and other anatomical sites frequently involved in AF triggers.

Keywords: Persistent atrial fibrillation; radiofrequency ablation; rotors; complex fractionated atrial electrograms (CFAE); ganglionated plexuses (GPs)

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Introduction

Atrial fibrillation (AF) is the most common atrial arrhythmias and his prevalence is continuously rising in Western countries (1). AF is a strong independent risk factor for stroke and heart failure, and is associated with a three-fold increase in mortality rates compared to patients with sinus rhythm (2). Catheter ablation is an established treatment to achieve and maintain sinus rhythm in patients with recurrent AF (3). In these patients, antiarrhythmic drug therapy typically has a suboptimal efficacy in controlling relapses. Multiple randomized clinical trials have demonstrated a superiority of catheter ablation to reduce AF, improve symptoms, quality of life and possibly reverse the AF-associated risk of thromboembolic complications (3-5). In order to develop effective ablation techniques, multiple studies have been performed to discover and validate electrophysiological and anatomic targets fundamental for triggering and maintaining the arrhythmia (6).

Pre-clinical and human studies have consistently shown that focal discharges from the pulmonary veins (PVs) are implicated in the initiation of AF in the majority of patients (7). Therefore, empirical PV isolation has been performed with high procedural success, particularly in patients with paroxysmal AF (8).

The most recent update of the guidelines has recommended catheter ablation in symptomatic paroxysmal AF refractory or intolerant to at least one Class 1 or three antiarrhythmic medications, and has also introduced new recommendations for catheter ablation in patients with persistent AF, significant left atrial dilatation and left ventricular dysfunction (9,10).

Disturbingly, the results with catheter ablation in patients with persistent and long-standing persistent AF have been shown worse compared to patients with paroxysmal AF, with a recurrence rate following pulmonary vein isolation (PVI) of up to 60% (11). Based on these findings, it has been suggested that patients with non-paroxysmal AF may require ablation of additional sites beyond the PVs to achieve success (12-15).

This review article will overview the state-of-the-art of AF ablation techniques in patients with persistent AF, with a particular focus on adjunctive ablation strategies beyond PVI.

Isolation of the left atrial posterior wall

The left atrial posterior wall should be considered as an extension of the PVs from an embryologic, anatomic and electrophysiological perspective (16). The surgical experience with AF ablation has confirmed a significant role of the posterior wall for triggering and maintaining the arrhythmia (17), with reports documenting AF localized only to the posterior wall (18,19). Oral *et al*. compared ablation of the posterior wall with circumferential PVs ablation in patients with chronic AF. In this randomized trial, 80 patients with chronic AF were assigned to circumferential PV ablation or to non-encircling linear ablation of the posterior wall. After a mean follow-up of 9 months, AF recurred in 28% of patients who underwent circumferential PVs ablation, compared to 25% of those who received posterior wall linear ablation (P=0.8 for comparison) (20).

Complex fractionated atrial electrograms (CFAE)

Persistent AF may be perpetuated even without continues ectopic discharge from PVs. One of the mechanisms supporting this may be the continuous propagation of multiple wavelets inside the atria as result of multiple functional re-entry circuits as described by Moe *et al.* (21,22). The anisotropic conduction of multiple wavelets, due to areas of slow conduction, and their clash, after turning around anatomical or functional pivots (i.e., sites of functional block), leads to the formation of (CFAE) (23). It has been postulated that reentrant circuits underlying AF substrate cannot be mapped because random but these observations demonstrate that AF substrates can be identified searching areas that have CFAEs (13). CFAE have been first systematically described by Nademanee *et al.* as low-amplitude potentials (0.06 to 0.25 mV) with consistent temporal and spatial stability and either fractionated atrial electrograms (composed by two or more deflections) or atrial electrograms with cycle length ≤120 ms. Applying a substrate-based approach targeting only areas with CFAE in patients with all forms of AF, Nademanee *et al.* reported very high success rates (91% at 1-year follow-up) (13).

After this initial report, other investigators have evaluated the adjunctive role of CFAE ablation (24). Haïssaguerre *et al.* incorporated CFAE ablation to their stepwise sequential ablation approach for patients with long-standing persistent AF. The stepwise approach included PVI, linear ablation across the roof of the left atrium between the left and right upper PVs and at the mitral isthmus, ablation at the inferior left atrium toward the coronary sinus and the base of the left atrial appendage, and left atrial ablation guided by CFAE mapping (18,19). Using this extensive ablation strategy with the procedural end-point of AF termination, the authors uniformly observed a prolongation of the AF cycle length followed by either organization in atrial tachycardia (87% of cases) or conversion to sinus rhythm (13% of cases). Atrial tachycardias were subsequently mapped and ablated (19).

In a subsequent study, Elayi *et al.* failed to find the same predictive value for periprocedural AF termination. In this study, after a mean follow-up of 25±6.9 months, 69% of patients who underwent PVI and CFAE ablation remained in sinus rhythm, without significant differences between those who had procedural termination/organization of AF and those who were converted to sinus rhythm at the end of the procedure with external cardioversion. Of note, periprocedural AF termination predicted the mode of recurrence, with a strong association with recurrent atrial tachycardia (P=0.022) (12).

Hunter *et al.* suggested a classification based on CFAE morphology (24). The authors defined different "grades" of CFAE, namely: Grade1—uninterrupted fractionated activity, that is, fractionated activity (defined as continuous deflections without pause at the isoelectric line for 70 ms) occupying 70% of the sample, and at least 1 uninterrupted episode of fractionated activity lasting 1 second; Grade 2—interrupted fractionated activity, that is, fractionated activity occupying 70% of the sample; Grade 3—intermittent fractionated activity, that is, fractionated activity occupying 30-70% of the sample; and Grade 4—complex electrograms, that is, discrete electrograms (70 ms) with complex morphology (5 direction changes), with fractionated activity occupying 30% of the sample (24). In this study, the authors hypothesized that continuous fractionated activity (i.e., Grades 1 and 2) may represent focal mechanisms, whereas less fractionated signals (Grade 4) are more likely to represent reentry. Intermittent fractionated activity (Grade 3) may be produced by passive wave front phenomena or superimposition of far-field and local electrograms, which are not critical for maintenance of AF (24). On the other hand, the available evidence does not support a clinical utility for such classification, and studies evaluating more limited CFAE mapping/ablation have provided mixed results (24-26). However, available evidence does suggest

some additional benefit with CFAE ablation in patients with non-paroxysmal AF. In a meta-analysis of six randomized controlled trials including 360 patients with persistent and long-standing persistent AF, adjuvant CFAE ablation (mostly based on visual evaluation) in adjunct to PVI increased the rate of sinus rhythm maintenance over follow-up [risk ratio (RR) 1.35, 95% confidence interval (CI): 1.04-1.75; P=0.022] (27). Such benefit in terms of arrhythmia-free survival was counterbalanced by an increased relative risk of recurrent organized atrial tachycardias (RR 1.77; 95% CI: 1.02-3.07; P=0.04), longer procedural times (245.4±75.7 *vs.* 189.5±62.3 min, P<0.001), fluoroscopy times (72.1±25.6 *vs.* 59.5±19.3 min, P<0.001), and RF energy application times (75.3±38.6 *vs.* 53.2±27.5 min, P<0.001) (28).

Moving from the scenario of paroxysmal AF to persistent and long-standing AF, the atrial substrates perpetuating the arrhythmia become more and more important as well as their mapping and elimination by catheter ablation. In the original report by Nademanee *et al.* (13) the success rate of CFAEs ablation by itself was about 91% in the setting of both paroxysmal and persistent AF. The same group reported a success rate of 85% at 2 years among 674 patients (29). Unfortunately these encouraging data were not reproduced in randomized studies. Oral *et al.*, even with some limitations as the short ablation time, didn't found a better efficacy in patients who underwent CFAEs ablation after PV isolation *vs.* PV isolation alone (30).

Realistically CFAEs ablation may improve the outcome of patients with persistent AF only in addition to systematic PV isolation.

Ganglionated plexuses (GPs)

The cardiac autonomic nervous system reflects the general organization of the autonomic nervous system with his sympathetic part is organized in adrenergic fibers from the central nervous system (CNS) terminating in big ganglia near the axial CNS and post-synaptic adrenergic fibers terminating to the target organ and his parasympathetic part organized in adrenergic fibers from the CNS terminating in small ganglia within the target organ and short post-synaptic cholinergic fiber targeting organ cells. The cardiac autonomic ganglia known as GPs are located within epicardial fat (31-33) particularly within the antrum of PVs, the crux of the heart and the junction between right atrium and superior vena cava with a wide network connecting the GPs themselves and between GPs and atrial myocardium (34).

The central role of the autonomic nervous system in triggering and maintaining AF with several mechanisms (facilitation of spontaneous premature atrial depolarization, shortening of atrial and PV effective refractory period, increasing heterogeneity of refractoriness) has been highlighted in multiple studies (35,36). On this base several authors evaluated the role of GPs ablation as an adjunct to PVs isolation (31,37,38).

Usually GPs are localized on the endocardial surface of the atria by searching sites showing vagal response to high frequency stimulation (31,38), then radiofrequency energy is delivered at each site showing a positive response to stimulation. In a randomized trial, 67 patients with paroxysmal AF were assigned to either PVI or GP ablation followed by PVI (31). After a mean follow-up of 10 months, 45.5% of patients assigned to PVI only remained free from AF recurrence, compared to 73.5% in the GP ablation plus PV isolation group (38). Pachon *et al.* have developed a system for real-time spectral mapping using the Fast Fourier Transform in sinus rhythm (39). This method is able to identify myocardial areas where unfiltered atrial bipolar electrograms contains high frequencies (i.e., AF nests) (39). Arruda *et al.* evaluated the adjunctive role of AF nest ablation in a prospective randomized study (40). A total of 157 patients underwent randomization; AF nest ablation was shown to reduce AF recurrence rate, although the absolute benefit was marginal (9% absolute risk reduction in paroxysmal AF and of 10% in persistent AF patients) (40). Of interest, the distribution of autonomic nervous targets for AF ablation seems correlated with the distribution of CFAE at the level of PV antra. Therefore, the autonomic ganglia can be targeted as bystanders during conventional PVI or CFAE ablation (41,42). To further support this concept, other studies have shown a close interaction between CFAE and GP (42,43).

Dominant frequency

Mapping studies of AF indicate repetitive periodic elements, with peculiar frequency gradients from area with high dominant frequencies (DF) to regions with low DFs. Atrial regions with high DF may serve as AF drivers and may be associated with AF maintenance, thus representing potential targets for ablation (44). Sanders *et al.* performed a real-time spectral and frequency mapping of the left atrium in AF patients. In this study, ablation at sites of high DF resulted in significant prolongation of the AF cycle length (180±30 to 198±40 ms; P<0.0001; kappa =0.77) and AF termination

during ablation in 17 of 19 patients with paroxysmal AF (45). On the other hand, none of the patients with persistent AF was terminated after targeting sites with high DF. The lack of significant benefit of high DF ablation in patients with non-paroxysmal AF has been confirmed in other studies (46,47). For instance, Verma *et al.* reported no improvement in 1-year arrhythmia-free survival with DF ablation in adjunct to PVI compared to PVI alone (46).

Rotors

Recent studies have reported the presence of stable rapid reentrant circuits within the atria of patients with AF, so called "rotors", that might provide an additional target during AF ablation (48-50).

In the pivotal work by the University of California San Diego a 64 pole basket catheter was used for panoramic right and left atrial mapping during AF. AF electrograms were analyzed using a novel system to identify sustained rotors (spiral waves), or focal beats (centrifugal activation to surrounding atrium) (51). Electrical rotors are defined as sequential clockwise or counterclockwise activation contours around a central elbow of rotation that is responsible for AF maintenance (51). Rotors and focal impulses were considered AF sources only if consistent in multiple recordings over >10 minutes, equating to thousands of cycles (51). The Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation (CONFIRM) trial provide the first demonstration that AF may be maintained by localized sources in the form of electrical rotors and focal impulses that are stable in location and can therefore be targeted for limited ablation (51). A total of 92 patients were divided in two arms and treated with ablation of focal sources [focal impulse and rotor modulation (FIRM)-Guided] followed by PVI (n=36), or PVI alone (n=71; FIRM-Blinded). Localized rotors or focal impulses were detected in 97% of patients: in particular, 80% of rotors were in the left atrium and 20% in the right atrium (51). FIRM ablation was associated with an acute termination or slowing of AF in 86% of patients, rendering AF non-inducible prior to PV isolation. Importantly, FIRM-guided ablation was associated with improved outcome over follow-up using implanted continuous electrocardiogram (ECG) monitors, with an overall freedom from AF of 82.4% versus 44.9% in the PVI-only group (P<0.001 for comparison) (51). Enlarged atria may limit the reliability of this approach, especially if the atrial volume exceeds the size of available basket catheters, as illustrated by Miller (52). Further studies are warranted to determine whether such benefits are consistent across the whole spectrum of patients with AF (52,53).

Non-PV triggers sites

The importance of non-PV trigger sites in recurrent AF following PVI has been increasingly recognized, especially in patients with non-paroxysmal AF. The coronary sinus, the ligament of Marshall (54-56), and the left atrial appendage (56) have all been implicated in recurrent AF following PVI. The ligament of Marshall usually can be ablated from the endocardial aspect of the left atrium inferior to the ostium of the left inferior PV, otherwise ethanol infusion in the vein of Marshall through an angioplasty wire and balloon has been demonstrated effective achieving electrical isolation of the ligament of Marshall in a substantial proportion of patients (57,58). Di Biase *et al.* have demonstrated a crucial role for the left atrial appendage in triggering recurrent AF in one third of cases undergoing repeat procedures. When a trigger from the left atrial appendage has been demonstrated, complete electrical isolation of the left atrial appendage should be performed in order to achieve success (59).

Final remarks

PVI is the cornerstone of current catheter ablative therapies for AF, with the highest efficacy in patients with paroxysmal AF. In patients with persistent and long-standing persistent AF, PVI alone has been associated with lower success rates. Over the last years, intense research has been directed towards the validation of adjunctive ablation strategies beyond PVI. Studies have suggested a marginal but concrete incremental benefit of extensive linear ablation strategies and atrial debulking with CFAE ablation, at the expense of increased risk of organized atrial arrhythmias, such as atrial tachycardia or flutter. Recent studies have highlighted the importance of targeting AF focal sources, such as rotors or additional non-PV trigger sites (e.g., ligament of Marshall, left atrial appendage). Further large randomized studies are warranted to better evaluate the benefits (and risks) of such adjunctive ablation strategies.

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References

1. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119-25.
2. Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2011;57:e101-98.
3. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010;303:333-40.
4. Themistoclakis S, Corrado A, Marchlinski FE, et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J Am Coll Cardiol 2010;55:735-43.
5. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA 2005;293:2634-40.
6. Oral H, Scharf C, Chugh A, et al. Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. Circulation 2003;108:2355-60.
7. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-66.
8. Marrouche NF, Martin DO, Wazni O, et al. Phased-array intracardiac echocardiography monitoring during pulmonary vein isolation in patients with atrial fibrillation: impact on outcome and complications. Circulation 2003;107:2710-6.
9. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Heart Rhythm 2011;8:157-76.
10. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace 2012;14:528-606.
11. Lin G, Lu HH, Shen Y, et al. Meta-analysis of the therapeutic effects of various methods for the treatment of chronic atrial fibrillation. Exp Ther Med 2013;6:489-496.
12. Elayi CS, Di Biase L, Barrett C, et al. Atrial fibrillation termination as a procedural endpoint during ablation in long-standing persistent atrial fibrillation. Heart Rhythm 2010;7:1216-23.
13. Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004;43:2044-53.
14. Webb S, Kanani M, Anderson RH, et al. Development of the human pulmonary vein and its incorporation in the morphologically left atrium. Cardiol Young 2001;11:632-42.
15. Voeller RK, Bailey MS, Zierer A, et al. Isolating the entire posterior left atrium improves surgical outcomes after the Cox maze procedure. J Thorac Cardiovasc Surg 2008;135:870-7.
16. Todd DM, Skanes AC, Guiraudon G, et al. Role of the posterior left atrium and pulmonary veins in human lone atrial fibrillation: electrophysiological and pathological data from patients undergoing atrial fibrillation surgery. Circulation 2003;108:3108-14.
17. Pruitt JC, Lazzara RR, Ebra G. Minimally invasive surgical ablation of atrial fibrillation: the thoracoscopic box lesion approach. J Interv Card Electrophysiol 2007;20:83-7.
18. Haïssaguerre M, Hocini M, Sanders P, Sacher F, et al. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. J Cardiovasc Electrophysiol 2005;16:1138-47.
19. Haïssaguerre M, Sanders P, Hocini M, et al. Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. J Cardiovasc Electrophysiol 2005;16:1125-37.
20. Oral H, Chugh A, Good E, Igic P, et al. Randomized comparison of encircling and nonencircling left atrial ablation for chronic atrial fibrillation. Heart Rhythm 2005;2:1165-72.
21. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. Am Heart J 1959;58:59-70.
22. Allessie MA, Konings K, Kirchhof CJ, et al.

Electrophysiologic mechanisms of perpetuation of atrial fibrillation. Am J Cardiol 1996;77:10A-23A.
23. Konings KT, Smeets JL, Penn OC, et al. Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. Circulation 1997;95:1231-41.
24. Hunter RJ, Diab I, Thomas G, et al. Validation of a classification system to grade fractionation in atrial fibrillation and correlation with automated detection systems. Europace 2009;11:1587-96.
25. Hunter RJ, Diab I, Tayebjee M, et al. Characterization of fractionated atrial electrograms critical for maintenance of atrial fibrillation: a randomized, controlled trial of ablation strategies (the CFAE AF trial). Circ Arrhythm Electrophysiol 2011;4:622-9.
26. Chou CC, Zhou S, Tan AY, et al. High-density mapping of pulmonary veins and left atrium during ibutilide administration in a canine model of sustained atrial fibrillation. Am J Physiol Heart Circ Physiol 2005;289:H2704-13.
27. Niu G, Scherlag BJ, Lu Z, et al. An acute experimental model demonstrating 2 different forms of sustained atrial tachyarrhythmias. Circ Arrhythm Electrophysiol 2009;2:384-92.
28. Li WJ, Bai YY, Zhang HY, et al. Additional ablation of complex fractionated atrial electrograms after pulmonary vein isolation in patients with atrial fibrillation: a meta-analysis. Circ Arrhythm Electrophysiol 2011;4:143-8.
29. Nademanee K, Schwab MC, Kosar EM, et al. Clinical outcomes of catheter substrate ablation for high-risk patients with atrial fibrillation. J Am Coll Cardiol 2008;51:843-9.
30. Oral H, Chugh A, Yoshida K, et al. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. J Am Coll Cardiol 2009;53:782-9.
31. Nakagawa H, Scherlag BJ, Patterson E, et al. Pathophysiologic basis of autonomic ganglionated plexus ablation in patients with atrial fibrillation. Heart Rhythm 2009;6:S26-34.
32. Wu SH, Jiang WF, Gu J, et al. Benefits and risks of additional ablation of complex fractionated atrial electrograms for patients with atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol 2013;169:35-43.
33. Zipes DP, Mihalick MJ, Robbins GT. Effects of selective vagal and stellate ganglion stimulation of atrial refractoriness. Cardiovasc Res 1974;8:647-55.
34. Scherlag BJ, Yamanashi WS, Schauerte P, et al. Endovascular stimulation within the left pulmonary artery to induce slowing of heart rate and paroxysmal atrial fibrillation. Cardiovasc Res 2002;54:470-5.
35. Scherlag BJ, Yamanashi W, Patel U, et al. Autonomically induced conversion of pulmonary vein focal firing into atrial fibrillation. J Am Coll Cardiol 2005;45:1878-86.
36. Wang J, Liu L, Feng J, et al. Regional and functional factors determining induction and maintenance of atrial fibrillation in dogs. Am J Physiol 1996;271:H148-58.
37. Pauza DH, Skripka V, Pauziene N, et al. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. Anat Rec 2000;259:353-82.
38. Katritsis DG, Giazitzoglou E, Zografos T, et al. Rapid pulmonary vein isolation combined with autonomic ganglia modification: a randomized study. Heart Rhythm 2011;8:672-8.
39. Pachon M JC, Pachon M EI, Pachon M JC, et al. A new treatment for atrial fibrillation based on spectral analysis to guide the catheter RF-ablation. Europace 2004;6:590-601.
40. Arruda M, Natale A. The Adjunctive Role of Nonpulmonary Venous Ablation in the Cure of Atrial Fibrillation. J Cardiovasc Electrophysiol 2006;17:S37-S43.
41. Verma A, Saliba WI, Lakkireddy D, et al. Vagal responses induced by endocardial left atrial autonomic ganglion stimulation before and after pulmonary vein antrum isolation for atrial fibrillation. Heart Rhythm 2007;4:1177-82.
42. Lin J, Scherlag BJ, Zhou J, et al. Autonomic mechanism to explain complex fractionated atrial electrograms (CFAE). J Cardiovasc Electrophysiol 2007;18:1197-205.
43. Lu Z, Scherlag BJ, Lin J, et al. Autonomic mechanism for complex fractionated atrial electrograms: evidence by fast fourier transform analysis. J Cardiovasc Electrophysiol 2008;19:835-42.
44. Atienza F, Almendral J, Jalife J, et al. Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. Heart Rhythm 2009;6:33-40.
45. Sanders P, Berenfeld O, Hocini M, et al. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. Circulation 2005;112:789-97.
46. Verma A, Lakkireddy D, Wulffhart Z, et al. Relationship between complex fractionated electrograms (CFE) and dominant frequency (DF) sites and prospective assessment of adding DF-guided ablation to pulmonary vein isolation in persistent atrial fibrillation (AF). J Cardiovasc Electrophysiol 2011;22:1309-16.

47. Kumagai K, Sakamoto T, Nakamura K, et al. Combined dominant frequency and complex fractionated atrial electrogram ablation after circumferential pulmonary vein isolation of atrial fibrillation. J Cardiovasc Electrophysiol 2013;24:975-83.
48. Skanes AC, Mandapati R, Berenfeld O, et al. Spatiotemporal Periodicity During Atrial Fibrillation in the Isolated Sheep Heart. Circulation 1998; 98:1236-48.
49. Ryu K, Shroff SC, Sahadevan J, et al. Mapping of atrial activation during sustained atrial fibrillation in dogs with rapid ventricular pacing induced heart failure: evidence for a role of driver regions. J Cardiovasc Electrophysiol 2005;16:1348-58.
50. Shivkumar K, Ellenbogen KA, Hummel JD, et al. Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: first multicenter experience of focal impulse and rotor modulation (FIRM) ablation. J Cardiovasc Electrophysiol 2012;23:1277-85.
51. Narayan SM, Krummen DE, Shivkumar K, et al. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012;60:628-36.
52. Miller JM, Kowal RC, Swarup V, et al. Initial independent outcomes from focal impulse and rotor modulation ablation for atrial fibrillation: multicenter FIRM registry. J Cardiovasc Electrophysiol 2014;25:921-9.
53. Lin YJ, Lo MT, Lin C, et al. Prevalence, characteristics, mapping, and catheter ablation of potential rotors in nonparoxysmal atrial fibrillation. Circ Arrhythm Electrophysiol 2013;6:851-8.
54. Hwang C, Wu TJ, Doshi RN, et al. Vein of marshall cannulation for the analysis of electrical activity in patients with focal atrial fibrillation. Circulation 2000;101:1503-5.
55. Jaïs P, Haïssaguerre M, Shah DC, et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 1997;95:572-6.
56. Elayi CS, Verma A, Di Biase L, et al. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. Heart Rhythm 2008;5:1658-64.
57. Valderrábano M, Liu X, Sasaridis C, et al. Ethanol infusion in the vein of Marshall: Adjunctive effects during ablation of atrial fibrillation. Heart Rhythm 2009;6:1552-8.
58. Valderrábano M, Chen HR, Sidhu J, et al. Retrograde ethanol infusion in the vein of Marshall: regional left atrial ablation, vagal denervation and feasibility in humans. Circ Arrhythm Electrophysiol 2009;2:50-6.
59. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. Circulation 2010;122:109-18.

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