Ablation of Atrial Fibrillation: Patient Selection, Technique, and Outcome

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Ablation of atrial fibrillation (AF) has expanded from its limited application for patients with paroxysmal AF and structurally normal hearts to patients with persistent arrhythmia and more extensive structural heart disease. The cornerstone of this procedure involves pulmonary vein (PV) isolation, which is achieved by encircling lesions around the PVs. Success rates are highest for patients with paroxysmal AF, but modification of the technique to include linear lesions in the left atrium and targeting complex electrograms has improved outcomes in patients with long-lasting AF. The procedure remains complex, and the risk of complications must be balanced against the perceived benefit of maintaining sinus rhythm. For this reason, AF ablation is indicated in symptomatic patients who have failed at least one antiarrhythmic drug. Current studies will address catheter ablation's role as first-line therapy for patients with AF.

Introduction

Atrial fibrillation's (AF) deleterious effects have been well known for decades. AF can cause incapacitating symptoms and reduced exercise tolerance due to uncontrolled and irregular rates, as well as loss of atrial contribution to cardiac output. AF increases the risk of embolic stroke and has been implicated in one third of strokes in patients older than 60 years. AF is also associated with increased mortality in various populations, including patients with congestive heart failure and after cardiac surgery. In fact, AF conveys an increased risk of mortality independent of structural heart disease. The mortality related to AF may be due to heart failure, stroke, drug toxicity, and ventricular arrhythmias.

Despite these associations, randomized trials have failed to show benefits of maintaining sinus rhythm with antiarrhythmic drugs, possibly due to these agents' limited efficacy in preventing recurrent AF and drug toxicities such as proarrhythmia [1]. An analysis of one large trial (AFFIRM) showed that the presence of sinus rhythm predicted survival, and antiarrhythmic drug therapy increased the risk of death [2]. These observations suggest there are benefits to maintaining sinus rhythm, but these are counterbalanced by the drug therapy's toxicities. Furthermore, medical therapy is often unsatisfactory in controlling symptoms. Therefore, effective nonpharmacologic therapy to maintain sinus rhythm would be an appealing alternative to rate control and antiarrhythmic medications.

Rationale and Historical Development of AF Ablation

The success of the surgical Maze procedure in eliminating AF prompted electrophysiologists to develop a catheter-based procedure to treat this arrhythmia. The classic Maze procedure, developed and modified by Cox and colleagues, remains the gold standard of curative intervention for AF, with freedom from AF in 97% of patients after 5 years [3]. The rationale for this operation was the widely accepted AF model due to multiple reentrant wave fronts. Historically, the procedure required extensive atrial incisions to create multiple lines of block in the atria and thus prevent recirculating wave fronts. The Maze surgery evolved in recent years with the development of new energy sources to generate linear lesions and the possibility of epicardial ablation, but until recently, the procedure involved a thoracotomy, cardiopulmonary bypass, multiple atriotomies, and an operative mortality of 1% to 2%.

Initial attempts at catheter ablation of AF were designed to replicate or modify the Maze lesion set [4,5]. These early efforts were fraught with difficulties related to the challenge of creating continuous transmural linear lesions with endocardial catheter technology. During these efforts, Haissaguerre et al. [6] observed that paroxysmal AF often initiated from focal discharges in the pulmonary veins (PVs). This observation resurrected a different AF paradigm—that of focal sources initiating and driving the

arrhythmia. It also provided the rationale for PV isolation as a new approach to AF ablation.

The earliest catheter ablation of AF originating from the PVs involved focal ablation of discrete sources in the culprit veins [6]. However, it was recognized that more than one focus within a vein may be arrhythmogenic, and more than one vein may be arrhythmogenic in a given patient [7,8]. This led to the concept of PV isolation, which involves segmental ablation or complete encircling around a PV to achieve electrical disconnection from the atrium [9]. Modifications and variations of this technique are now the most widely used approaches to ablate AF.

Pathophysiology of AF

The importance of the PVs and posterior left atrium (LA) in AF pathophysiology has been studied intensely, but no consistent explanation has emerged to explain the localization of AF triggers to the PV region. The PVs contain sleeves of myocardium that extend up to 2 to 3 cm from the PV ostia [10]. Changes in fiber orientation and the complex architecture of the myocardial sleeves may provide the substrate for small reentrant circuits [11]. The PV ostia are also richly innervated with sympathetic and parasympathetic nerve terminals, and activating both limbs of the autonomic nervous system can trigger atrial premature beats and AF [12]. An optical mapping study of the atrial-PV junction has shown focal discharges arising from the proximal PVs and reentrant circuits at the PV ostium [13].

Experimental models demonstrate that AF can be generated by high-frequency microreentrant circuits that localize to the posterior LA [14]. Because of heterogeneities in atrial conduction and refractoriness, impulses propagating from focal sources encounter lines of block and slow conduction, a phenomenon known as "fibrillatory conduction." With increasing distance from the focal source, the local frequency of activation decreases, and the area of highest frequency defines the AF's focal source. The concept of a "dominant frequency" has been translated into the clinical arena with software to identify AF's focal drivers.

Techniques of Catheter Ablation for AF

Although high success rates can be achieved in ablating paroxysmal AF through PV isolation, persistent and chronic AF continues to present a challenge. New techniques are currently under development, with recent activity dedicated to identifying and modifying "substrate" for AF.

Most procedures now involve radiofrequency energy to produce thermal injury and coagulation necrosis. Irrigation of the ablation electrode improves the safety and efficacy of radiofrequency by allowing for therapeutic delivery of current while avoiding overheating of the electrode-tissue interface. Cryoablation is being developed as an alternative to avoid complications of radiofrequency energy, such as thrombosis from endothelial disruption or esophageal injury. Balloon catheters currently in clinical trials deliver cryoablation circumferentially around the PV ostia and have been effective in achieving PV isolation. Experimental energy sources also include ultrasound and laser ablation.

PV isolation

The current approach to treating arrhythmogenic PVs involves encircling lesions around the PV ostia. Although some variation exists in this technique, many electrophysiologists favor wide encircling lesions that target the PV antra, a relatively wide area that includes the LA's posterior wall [15]. An anatomic approach that involves wide encircling lesions—but without verification of true electrical disconnection—has been used to treat AF [16], but the complete isolation of the PVs as a physiologic end point is generally accepted as a standard for the ablation procedure. Wide encircling lesions provide the advantage of avoiding PV stenosis and isolating antral tissue that may contain arrhythmogenic foci. In theory, this technique also modifies substrate in a wide region of the posterior LA and the interatrial septum that may provide AF's substrate. Verification of PV isolation is made with a multipolar circular catheter positioned within the vein (Fig. 1). These recordings identify connections between atrial tissue and the PV and allow for targeted ablation to eliminate PV potentials. Pacing within the PV can verify exit block and thus confirm electrical isolation. Non-PV triggers occur in up to 10% of patients; these may arise from the superior vena cava, crista terminalis, posterior LA, and coronary sinus.

Complex fractionated electrograms

During AF, it is possible to record complex electrical activity in some areas of the atria. These are known as "complex fractionated electrograms" (CFEs) and are characterized by low amplitude, continuous activation. It has been proposed that these areas are critical for AF's perpetuation [17], but the origin of these complex electrograms remains to be elucidated. They may arise from small reentrant circuits ("microreentry") or areas of slow conduction in multiple wavelet reentry. It is also possible that some sites are "bystander" regions with fibrillatory conduction and are therefore not critical for AF perpetuation. An approach targeting CFEs has been used to treat paroxysmal and persistent AF, and termination of AF to atrial flutter or sinus rhythm has occurred with this technique [17,18•]. CFEs are typically identified in the PV ostia, interatrial septum, anterior LA and base of the LA appendage, inferior LA, and coronary sinus.

Linear ablation

Linear ablation has been combined with PV isolation in efforts to further modify atrial substrate for AF and

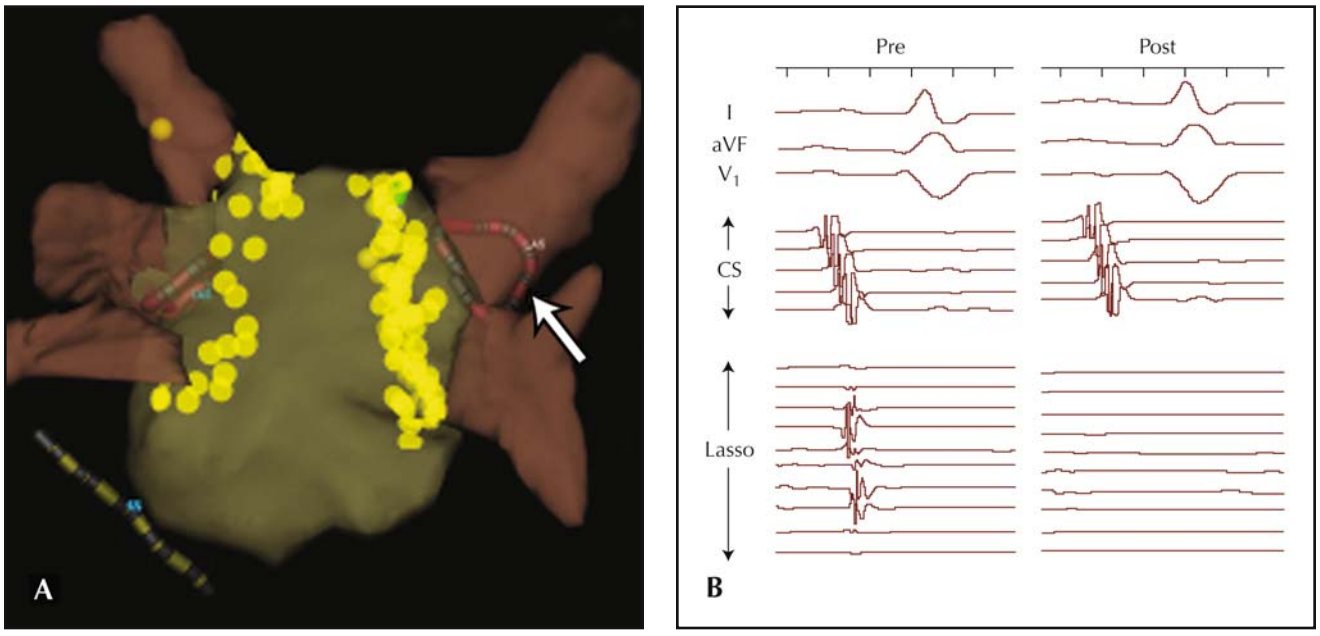

Figure 1. Pulmonary vein isolation is demonstrated with a multipolar "lasso" catheter (*arrow*) in the right superior pulmonary vein (RSPV). **A,** A posteroanterior map of the left atrium constructed with an electroanatomical mapping system (NavX; St. Jude Medical, St. Paul, MN). Radiofrequency lesions encircling the pulmonary veins (PVs) are depicted by *yellow circles*. **B,** The tracing on the left shows a single sinus beats with three surface leads, five electrograms from the coronary sinus (CS), and 10 electrograms from the lasso catheter in the RSPV. Before ablation (Pre), sharp deflections are present within the vein, which are PV potentials. After completion of the encircling lesions, the PV potentials are no longer present, which is an electrical end point for PV isolation. aVF—augmented voltage, unipolar left leg lead.

prevent macroreentrant atrial tachycardias that may occur after circumferential PV ablation. Targets for linear lesions include the roof of the LA, the posterior wall between the PVs, and the segment between the mitral annulus and the left inferior PV ("mitral isthmus"). Ablation in the cavo-tricuspid isthmus in the right atrium is often performed during AF ablation in patients with pre-existing typical right atrial flutter. It may be difficult to achieve a complete line of block in some locations, especially in the mitral isthmus, which often requires ablation within the coronary sinus [19]. Linear ablation may be proarrhythmic if lines are not complete.

Ganglionated plexi

During PV isolation procedures with radiofrequency energy, profound vagal responses are sometimes encountered, characterized by transient bradycardia, sinus pauses, and hypotension [20]. These reflexes are attributed to the presence of parasympathetic nerve terminals in the vicinity of the PV ostia. Stimulation studies and histology show that the LA is richly innervated with parasympathetic and sympathetic nerve terminals, and ganglionated plexi exist near the PV ostia. Experimental models demonstrate the importance of vagal stimulation and sympathetic activation in the induction and focal triggers of AF. Parasympathetic stimulation shortens the action potential duration of PV myocytes (as occurs in the atrial myocardium), and sympathetic stimulation provokes delayed after-depolarizations due to calcium overload [12]. The combination of parasympathetic and sympathetic stimulation is particularly arrhythmogenic.

After circumferential PV ablation, vagal denervation identified by reduced heart rate variability is associated with higher long-term success rates [20]. Some researchers have advocated an approach to identify ganglionated plexi through high-frequency stimulation with the goal of targeting these sites for ablation [21]. Sites of ganglionated plexi also demonstrate CFEs during AF, which provides another explanation for these complex recordings and a method to identify these sites in AF [22].

Combined approaches

To improve the efficacy of ablation for persistent and chronic AF, some researchers have adopted a combination of techniques, including PV isolation, linear ablation, and targeting of CFEs or non-PV triggers [18•]. PV isolation remains the cornerstone of ablation in most laboratories, but this technique alone may be insufficient to restore and maintain sinus rhythm. Using a staged approach, Haissaguerre et al. [18•,23] have shown that AF may organize to atrial tachycardia or convert to sinus rhythm during ablation, which in turn predicts long-term efficacy in patients with chronic AF. Other groups have reported that PV isolation alone—in conjunction with ablation of atrial tachycardias that occur during the procedure—can achieve relatively high success rates for long-lasting AF [24].

Table 1. Randomized ablation trials for AF

Study	Acronym	Year	*N*	AF population	Design	Follow-up, *mo*	Freedom from AF (ablation vs control), %
Wazni et al. [27•]	RAAFT pilot	2005	70	Paroxysmal	PVI vs AAD	12	87 vs 37
Pappone et al. [28•]	APAF	2006	198	Paroxysmal	CPVA vs AAD	12	86 vs 22
Jais et al. [29]	A4	2006	112	Paroxysmal	PVI vs AAD	12	75 vs 7
Oral et al. [30•]	—	2006	146	Persistent	CPVA + amiodarone + cardioversion vs amiodarone + cardioversion	12	74 vs 58
Stabile et al. [31•]	CACAF	2006	137	Paroxysmal (92), persistent (45)	CPVA vs AAD	12	56 vs 9

A4—Atrial Fibrillation Ablation vs Antiarrhythmic Drugs; AAD—antiarrhythmic drug; AF—atrial fibrillation; APAF—Ablation for Paroxysmal Atrial Fibrillation; CACAF—Catheter Ablation for the Cure of Atrial Fibrillation; CPVA—circumferential pulmonary vein ablation; PVI—pulmonary vein isolation; RAAFT—Radiofrequency Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment.

Electroanatomical mapping and image integration

AF ablation is facilitated by three-dimensional navigation systems, known as "electroanatomical mapping," that reconstruct atrial anatomy (Fig. 1). These technologies permit nonfluoroscopic catheter manipulation and the ability to sample and return to multiple sites in the atria. They can be integrated with other digital imaging modalities, such as CT, MRI, and ultrasound. Electroanatomical maps are now integrated with robotic technology and have the potential of evolving into fully automatic mapping and ablating systems.

Outcomes of AF Ablation

Procedural success rates for AF ablation depend on numerous factors, including type of AF (paroxysmal, persistent, or long-lasting persistent), clinical and anatomic considerations, ablation technique, and definition of success. Some studies report single procedural success rates, whereas others report cumulative success after multiple procedures. Recurrences of AF and atrial tachycardia within weeks after ablation are common and do not necessarily predict long-term recurrences [25]. Thus, most studies include a "blanking period" of 1 to 3 months in reporting freedom from AF. Success rates are clearly affected by the intensity of rhythm monitoring after ablation, as clinically asymptomatic AF is known to occur postablation as with medical therapy for AF [26]. Using implantable loop recorders is likely to demonstrate higher recurrence rates after ablation. Protocols for postablation treatment also differ in the use of antiarrhythmic drugs and success may be reported with or without concomitant drug therapy.

For paroxysmal AF, single procedure success rates are generally 70% or greater, whereas success rates exceeding 80% have been reported for multiple procedures. Three randomized studies of circumferential PV ablation for paroxysmal AF reported success rates of 75% to 86% at 1 year following a single procedure, with higher success rates attainable with second procedures (Table 1) [27•,28•,29]. Comparable success rates in the antiarrhythmic drug arms of these trials were 7% to 37%.

For persistent AF, early experience yielded success rates of ≤ 50% for single procedures, and multiple procedure success rates were highly variable. A randomized study for persistent AF using wide circumferential ablation as adjunctive therapy to amiodarone and cardioversions demonstrated freedom from AF in 74% of patients after 1 year, compared with 58% who did not undergo ablation (Table 1) [30•]. Another study involving circumferential PV ablation in patients with paroxysmal and persistent AF yielded an AF-free rate of 56% after 1 year, compared with 9% in drug-treated patients (Table 1) [31•]. With more intensive ablation techniques that involve the addition of substrate modification and staged ablation, success rates of ≥ 90% at almost 1 year have been reported [18•].

To date, only observational data are available regarding survival benefits after AF ablation. Pappone et al. [32] reported that survival among 589 patients who underwent AF ablation exceeded that of 582 control patients treated with antiarrhythmic drugs, with a hazard ratio of 0.46 (mean follow-up 2.5 years). In a Kaplan-Meier analysis, freedom from AF at 3 years was 78% among those treated with ablation versus 37% in the medically treated group.

Complications

Complications of AF ablation include pericardial effusion and tamponade, thromboembolism and stroke, PV stenosis, esophageal injury and atrioesophageal fistula, and phrenic nerve injury. Cardiac tamponade has been reported with a frequency generally in the range of 1% to 2% [33]. Clinically significant PV stenosis is uncommon with current techniques that involve antral isolation [34].

Using electroanatomical mapping, image integration, and intracardiac ultrasound ensures accurate lesion delivery outside the PVs. Esophageal injury may occur due to the esophagus' close proximity to the posterior LA. Atrioesophageal fistulas are usually catastrophic and associated with high mortality [35]. Fortunately, this complication is rare, and the risk may be reduced by identifying the esophagus' location and minimizing energy delivery near this structure on the posterior wall. Methods to image the esophagus include fluoroscopy with a temperature probe, barium swallow, tagging of the esophagus on the electroanatomical mapping system, and intracardiac ultrasound.

Stroke and transient ischemic attacks occur at a rate of 0.5% to 1% [33]. To prevent thrombemboli, screening for LA thrombi is often performed with transesophageal echocardiography before ablation. New research has suggested that CT with intravenous contrast holds promise for excluding LA thrombi [36]. Anticoagulation with intravenous heparin is used during LA catheterization to maintain an activated clotting time of at least 300 seconds, and oral anticoagulation is used for at least 2 months after ablation [37••]. For patients with ≥ 2 CHADS2 risk factors, continued anticoagulation beyond the initial 2-month period is recommended.

Atrial tachycardias may occur after AF ablation, particularly after wide encircling PV isolation, and the frequency may be as high as 10% to 25% [38,39]. These arrhythmias take the form of reentrant circuits that involve reconnected PVs due to gaps in the encircling lesions. In addition, circuits may occur around the mitral annulus or ipsilateral PVs. Focal atrial tachycardias also occur after AF ablation, often from tissue adjacent to ablation lines. These tachycardias are amenable to re-ablation, with relatively high acute success rates.

Patient Selection

Historically, the ideal patient for catheter ablation had paroxysmal AF, was relatively young, and had little or no structural heart disease. With improved experience and techniques, the indications for AF ablation have expanded. Now, AF ablations are performed with reasonable success and complication rates in older patients and those with persistent AF, structural heart disease, and left atrial dilatation [40]. AF ablation has improved symptoms and left ventricular function in selected patients with congestive heart failure [41]. Ablation has also been performed in patients with hypertrophic cardiomyopathy [42] and in those with prior cardiac surgery and valve disease (although LA catheterization in patients with mechanical mitral valves poses a serious risk of catheter entrapment) [43].

An expert consensus statement endorsed by three professional electrophysiology societies considers AF ablation to be indicated in symptomatic patients who failed at least one class I or III antiarrhythmic drug [37••]. In rare circumstances, ablation may be considered appropriate as first-line therapy. This latter approach is reasonable for relatively young patients who do not wish take antiarrhythmic drugs and fully understand this complex procedure's risks and benefits.

Conclusions

Ongoing clinical trials will address catheter ablation's role as first-line therapy for AF. For example, the CABANA trial is a large, prospective, multicenter, randomized study designed to test the hypothesis that catheter ablation of AF is superior to rate control or antiarrhythmic drugs for reducing total mortality (the study's primary end point). A secondary end point will be the composite of total mortality, disabling stroke, serious bleeding, and cardiac arrest. Eligibility criteria include 1) age ≥ 65 years or 2) age less than 65 years with at least one risk factor for coronary disease or stroke. Patients are randomized to drug treatment with rate control or rhythm control versus catheter ablation. The RAAFT study will compare PV isolation to antiarrhythmic drugs as first-line therapy in patients with paroxysmal AF. The primary end point is time to first AF recurrence, and primary safety data will be assessed for ablation and antiarrhythmic drug treatment. Quality of life will be assessed as a secondary end point.

Other trials will address the efficacy of different techniques, such as PV isolation, CFEs, autonomic modification, or hybrid approaches, for AF ablation. Future developments will also include evaluating new energy sources for ablation and new technology, such as integrated robotic navigation and real-time imaging.

Clinical Trial Acronyms

AFFIRM—Atrial Fibrillation Follow-up Investigation of Rhythm Management; CABANA—Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; RAAFT—Radiofrequency Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment.

Disclosure

No potential conflict of interest relevant to this article was reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Wyse DG, Waldo AL, DiMarco JP, et al.: **A comparison of rate control and rhythm control in patients with atrial fibrillation.** *N Engl J Med* 2002, **347:**1825–1833.
2. Corley SD, Epstein AE, DiMarco JP, et al.: **Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study.** *Circulation* 2004, **109:**1509–1513.

3. Prasad SM, Maniar HS, Camillo CJ, et al.: **The Cox maze III procedure for atrial fibrillation: long-term efficacy in patients undergoing lone versus concomitant procedures.** *J Thorac Cardiovasc Surg* 2003, **126:**1822–1828.
4. Swartz JF, Pellersels G, Silvers J, et al.: **A catheter-based curative approach to atrial-fibrillation in humans [abstract].** *Circulation* 1994, **90:**335.
5. Haissaguerre M, Jais P, Shah DC, et al.: **Right and left atrial radiofrequency catheter therapy of paroxysmal atrial fibrillation.** *J Cardiovasc Electrophysiol* 1996, **7:**1132–1144.
6. Haissaguerre M, Jais P, Shah DC, et al.: **Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins.** *N Engl J Med* 1998, **339:**659–666.
7. Hocini M, Haissaguerre M, Shah D, et al.: **Multiple sources initiating atrial fibrillation from a single pulmonary vein identified by a circumferential catheter.** *Pacing Clin Electrophysiol* 2000, **23:**1828–1831.
8. Haissaguerre M, Jais P, Shah DC, et al.: **Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci.** *Circulation* 2000, **101:**1409–1417.
9. Haissaguerre M, Shah DC, Jais P, et al.: **Electrophysiological breakthroughs from the left atrium to the pulmonary veins.** *Circulation* 2000, **102:**2463–2465.
10. Ho SY, Cabrera JA, Tran VH, et al.: **Architecture of the pulmonary veins: relevance to radiofrequency ablation.** *Heart* 2001, **86:**265–270.
11. de Bakker JM, Ho SY, Hocini M: **Basic and clinical electrophysiology of pulmonary vein ectopy.** *Cardiovasc Res* 2002, **54:**287–294.
12. Patterson E, Po SS, Scherlag BJ, Lazzara R: **Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation.** *Heart Rhythm* 2005, **2:**624–631.
13. Arora R, Verheule S, Scott L, et al.: **Arrhythmogenic substrate of the pulmonary veins assessed by high-resolution optical mapping.** *Circulation* 2003, **107:**1816–1821.
14. Mandapati R, Skanes A, Chen J, et al.: **Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart.** *Circulation* 2000, **101:**194–199.
15. Kanj M, Wazni O, Natale A: **Pulmonary vein antrum isolation.** *Heart Rhythm* 2007, **4:**S73–S79.
16. Pappone C, Rosanio S, Oreto G, et al.: **Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation.** *Circulation* 2000, **102:**2619–2628.
17. 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:**2044–2053.
18.• Haissaguerre M, Sanders P, Hocini M, et al.: **Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination.** *J Cardiovasc Electrophysiol* 2005, **16:**1125–1137.

This study shows the feasibility of terminating long-lasting persistent AF with a combination of techniques, including PV isolation, linear ablation, and targeting of CFEs.

19. Jais P, Hocini M, Hsu LF, et al.: **Technique and results of linear ablation at the mitral isthmus.** *Circulation* 2004, **110:**2996–3002.
20. Pappone C, Santinelli V, Manguso F, et al.: **Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation.** *Circulation* 2004, **109:**327–334.
21. Scherlag BJ, Nakagawa H, Jackman WM, et al.: **Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation.** *J Interv Card Electrophysiol* 2005, **13(Suppl 1):**37–42.
22. Lin J, Scherlag BJ, Zhou J, et al.: **Autonomic mechanism to explain complex fractionated atrial electrograms (CFAE).** *J Cardiovasc Electrophysiol* 2007, **18:**1197–1205.
23. Haissaguerre M, Hocini M, Sanders P, et al.: **Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias.** *J Cardiovasc Electrophysiol* 2005, **16:**1138–1147.
24. Ouyang F, Ernst S, Chun J, et al.: **Electrophysiological findings during ablation of persistent atrial fibrillation with electroanatomic mapping and double Lasso catheter technique.** *Circulation* 2005, **112:**3038–3048.
25. Oral H, Knight BP, Ozaydin M, et al.: **Clinical significance of early recurrences of atrial fibrillation after pulmonary vein isolation.** *J Am Coll Cardiol* 2002, **40:**100–104.
26. Neumann T, Erdogan A, Dill T, et al.: **Asymptomatic recurrences of atrial fibrillation after pulmonary vein isolation.** *Europace* 2006, **8:**495–498.
27.• 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:**2634–2640.

This was the first randomized trial of AF ablation, designed as a pilot study for a larger multicenter study of first-line ablation therapy for AF. It showed the superiority of PV isolation over antiarrhythmic drug therapy.

28.• Pappone C, Augello G, Sala S, et al.: **A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study.** *J Am Coll Cardiol* 2006, **48:**2340–2347.

This randomized study showed that circumferential PV ablation was superior to antiarrhythmic drugs for paroxysmal AF.

29. Jais P, Cauchemez B, MacLe L, et al.: **Atrial fibrillation ablation vs antiarrhythmic drugs: a multicenter randomized trial [abstract].** *Heart Rhythm* 2006, **3(Suppl):**S460.
30.• Oral H, Pappone C, Chugh A, et al.: **Circumferential pulmonary-vein ablation for chronic atrial fibrillation.** *N Engl J Med* 2006, **354:**934–941.

This randomized study showed that adding ablation to a regimen of amiodarone and cardioversion helped maintain sinus rhythm in patients with chronic AF.

31.• Stabile G, Bertaglia E, Senatore G, et al.: **Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study).** *Eur Heart J* 2006, **27:**216–221.

In this randomized study of ablation for paroxysmal and persistent AF, success rates were lower than for other controlled trials; however, recurrence rates on antiarrhythmic drugs were very high.

32. Pappone C, Rosanio S, Augello G, et al.: **Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study.** *J Am Coll Cardiol* 2003, **42:**185–197.
33. Cappato R, Calkins H, Chen SA, et al.: **Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation.** *Circulation* 2005, **111:**1100–1105.
34. Saad EB, Rossillo A, Saad CP, et al.: **Pulmonary vein stenosis after radiofrequency ablation of atrial fibrillation: functional characterization, evolution, and influence of the ablation strategy.** *Circulation* 2003, **108:**3102–3107.
35. Pappone C, Oral H, Santinelli V, et al.: **Atrio-esophageal fistula as a complication of percutaneous transcatheter ablation of atrial fibrillation.** *Circulation* 2004, **109:**2724–2726.
36. Patel A, Au E, Donegan K, et al.: **Multidetector row computed tomography for identification of left atrial appendage filling defects in patients undergoing pulmonary vein isolation for treatment of atrial fibrillation: comparison with transesophageal echocardiography.** *Heart Rhythm* 2008, **5:**253–260.

37.•• Calkins H, Brugada J, Packer DL, et al.: **HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation.** *Heart Rhythm* 2007, **4:**816–861.
Comprehensive policy statement that describes techniques, indications, outcomes, and postprocedure care for AF ablation.

38. Mesas CE, Pappone C, Lang CC, et al.: **Left atrial tachycardia after circumferential pulmonary vein ablation for atrial fibrillation: electroanatomic characterization and treatment.** *J Am Coll Cardiol* 2004, **44:**1071–1079.

39. Gerstenfeld EP, Marchlinski FE: **Mapping and ablation of left atrial tachycardias occurring after atrial fibrillation ablation.** *Heart Rhythm* 2007, **4:**S65–S72.

40. 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:**843–849.

41. Hsu LF, Jais P, Sanders P, et al.: **Catheter ablation for atrial fibrillation in congestive heart failure.** *N Engl J Med* 2004, **351:**2373–2383.

42. Kilicaslan F, Verma A, Saad E, et al.: **Efficacy of catheter ablation of atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy.** *Heart Rhythm* 2006, **3:**275–280.

43. Khaykin Y, Marrouche NF, Saliba W, et al.: **Pulmonary vein antrum isolation for treatment of atrial fibrillation in patients with valvular heart disease or prior open heart surgery.** *Heart Rhythm* 2004, **1:**33–39.