Catheter ablation for chronic atrial fibrillation

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In recent years, radiofrequency catheter ablation has become an effective treatment modality for patients with atrial fibrillation (AF). Because triggers/drivers that originate from the pulmonary veins (PVs)[1] and other thoracic veins appear to be the primary mechanism of AF in patients with paroxysmal AF,[2] ablation strategies that target only thoracic vein arrhythmogenicity have been effective in the majority of patients with paroxysmal AF.[3,4] However, elimination of PV arrhythmogenicity has been insufficient to eliminate chronic AF.[4] As the multifactorial nature of the genesis of AF has become better recognized,[5] catheter ablation has evolved into an effective treatment strategy also in patients with chronic AF.

AF is classified as paroxysmal, persistent, or permanent per American Heart Association/American College of Cardiology/European Society of Cardiology (AHA/ACC/ESC) guidelines. Episodes of AF that are not self-terminating and last >7 days are classified as *persistent,* whereas patients in whom cardioversion has failed or was not attempted are considered to have *permanent* AF. However, patients with AF also have been classified as *paroxysmal* or *chronic* in clinical practice. In general, chronic AF implies non–self-terminating episodes of AF that often recur after cardioversion. In one study, chronic AF was defined as "AF that had been present for more than six months without intervening spontaneous episodes of sinus rhythm and that recurred within one week after cardioversion."[6] In this review, chronic AF refers to persistent and mostly permanent AF. Of note, the clinical presentation of AF from paroxysmal to persistent to permanent may reflect a continuous spectrum of pathogenetic factors that come into play as AF progresses.

Mechanistic considerations

A key step in catheter-based treatment of AF has been the recognition of arrhythmogenic foci within the PVs as triggers of AF.[1] Rapid repetitive electrical activity within the PVs, that is, PV tachycardias, have been demonstrated to play a critical role not only in the initiation but also in the perpetuation of AF.[7,8]

An important observation from the early studies of PV isolation by segmental ostial ablation was that elimination of PV triggers/drivers distal to the PV ostium resulted in long-term maintenance of sinus rhythm in approximately 65%–70% of patients with paroxysmal AF but had minimal efficacy for the majority of patients with chronic AF.[4] Possible explanations include the following: (1) mechanisms other than PV arrhythmogenicity that develop as a result of progressive electroanatomic remodeling may be critical to perpetuation (and possibly initiation) of AF in patients with chronic AF, and (2) recovery of conduction from the PVs after an initially successful PV isolation is common. Although residual PV triggers/drivers still may be present, their arrhythmogenic potential may be substantially reduced due to a decrease in the total number, frequency, and duration of premature depolarizations/PV tachycardias and to rate-related exit block from the PVs. As a result of marked reduction in the arrhythmogenicity of PVs, AF can no longer perpetuate in a normal atrium. However, even a single premature depolarization may initiate sustained AF in a remodeled atrium.

Progressive electroanatomic remodeling that develops as AF progresses from paroxysmal to permanent has been well demonstrated to further facilitate AF.[9] Structural remodeling may include interstitial fibrosis, loss of gap junctions, impairment of cellular coupling, and loss of myofibrils with deposition of extracellular matrix.[10] Activation of the renin–angiotensin system may promote interstitial fibrosis.[11]

Electrophysiologic remodeling results in progressive shortening of the effective refractory period, maladaptation to changes in rate, and intracellular calcium overload leading to inactivation of inward calcium currents.[12] Shortening of the action potential duration facilitates afterdepolarizations.

As a result of progressive electroanatomic remodeling, mechanisms other than thoracic vein arrhythmogenicity may emerge to perpetuate AF. Whether these mechanisms are operational by themselves or whether they require initiation/activation by a primary driver such as PV tachycardias is unclear. A previous study demonstrated the presence of dynamic interplay between the PVs and the left atrium such that the site with the shortest cycle length, that is, the driver, alternated between the two several times per minute.[8] These observations may suggest that PV tachycardias initiate secondary drivers in the left atrium that later may recruit other potential mechanisms, similar to a form of tachycardia-induced tachycardia. Beneficial effects of ablation of the residual mechanisms of AF on clinical

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outcome after elimination of PV drivers have been demonstrated.[7,8,13,14] In these studies, rapid atrial pacing was used to assess the inducibility of AF after electrical isolation of PVs. Rapid atrial pacing may mimic the effects of PV tachycardias on the left atrium. Patients who were rendered noninducible had a more favorable clinical outcome than did patients who remained inducible. These studies demonstrated (1) the presence of left atrial mechanisms other than PVs that may have developed due to remodeling and (2) the feasibility of modification/elimination of these *other* mechanisms of AF with beneficial effects on clinical outcome.

Interstitial fibrosis, uncoupling of the myofibrils, resultant anisotropy, conduction slowing and/or block, shortening of the effective refractory period, and atrial dilation may facilitate reentry, which may be critical to perpetuation of AF.[15] On the other hand, shortening of the action potential duration and effective refractory period and facilitation of afterdepolarizations may promote triggered activity and automaticity. As demonstrated in computer and animal models, high-frequency sources often referred to as *mother rotors* may perpetuate AF.[16] Rotors develop due to anisotropic reentry, which also may be facilitated by remodeling. A study demonstrated that frequency within the PVs is higher in paroxysmal than in chronic AF, and that isolation of PVs has a lesser impact on atrial fibrillatory activity in chronic than in paroxysmal AF.[17] These findings suggest the presence of atrial remodeling in chronic AF, capable of maintaining high-frequency sources independent of the PVs. More recently, ganglionated plexi and perturbations in vagal and adrenergic innervation of the atrium with vagal dominance have been implicated in the genesis of AF.[18] An increase in vagal tone may result in shortening of the atrial effective refractory period and facilitation of spontaneous premature depolarizations. Whether autonomic influences have a more profound effect in a remodeled than a normal atrium is not clear.

Ablation strategies for chronic AF

Several ablation strategies have been successfully performed to eliminate chronic AF.[6,19–22] Elimination of PV drivers using a variety of approaches is an integral part of these ablation strategies. In addition, substrate modification is performed using different techniques. Ablation strategies for chronic AF can be classified as either *anatomic ablation* guided primarily by anatomic landmarks or *tailored ablation.* During tailored ablation, drivers identified by local electrograms are targeted in a stepwise manner until AF terminates. Some type of anatomic ablation can be integrated into tailored ablation.

Anatomic ablation

Circumferential PV ablation, also known as *wide-area circumferential ablation,* PV antrum isolation, and linear ablation (with or without PV isolation) are typical examples of anatomic ablation.

Circumferential PV ablation encircles the PVs 1–2 cm away from the ostia (except for near the left atrial appendage), often with additional linear ablation along the mitral isthmus and between the right-sided and left-sided encircling lesions. In a randomized controlled study, the efficacy of circumferential PV ablation for chronic AF was assessed.[6] Transient antiarrhythmic drug therapy and one to two cardioversions may often be used within the first several weeks after circumferential PV ablation. To account for these confounding variables, this study included a control group of patients who received exactly the same transient antiarrhythmic drug therapy as did patients in the ablation group and were allowed to undergo two cardioversions after randomization. Clinical efficacy was assessed by daily transtelephonic transmissions for 1 year. At 1-year follow-up, 74% of patients with chronic AF who underwent circumferential PV ablation were in sinus rhythm in the absence of antiarrhythmic drug therapy, whereas only 4% of patients in the control group remained in sinus rhythm. A repeat ablation procedure was performed in 30% of patients. Maintenance of sinus rhythm was also associated with improvement in left ventricular ejection fraction and quality of life and a decrease in left atrial size.

Circumferential PV ablation eliminates a variety of mechanisms that may play a role in chronic AF. During circumferential PV ablation, PV tachycardias are targeted. A significant portion of the PV antrum (if not all) also is excluded from the left atrium. The PV antrum may play an important role because arrhythmogenic fascicles from the PVs extend into the antrum; anchor points for reentrant circuits, rotors, and ganglionated plexi may be located within the PV antrum. In addition, approximately 25% of the left atrial mass is excluded after circumferential PV ablation.[23] Debulking of the left atrium may decrease the availability of a wavelength that can harbor reentrant circuits. Although complete electrical isolation of the PVs, that is, elimination of all PV potentials, may not be necessary for the clinical efficacy of circumferential PV ablation,[24] it is critical to eliminate all residual drivers within the encircling lesion sets.

PV antrum isolation has been successfully performed to eliminate chronic AF.[20] During PV antrum isolation, the antrum is mapped with a circular multipolar catheter, and all electrograms within the antrum are ablated. Ablation and energy delivery usually are guided by intracardiac echocardiography. PV antrum isolation often involves extensive ablation in the posterior left atrium.

Linear ablation has been performed with or without PV isolation. In a randomized study, circumferential PV ablation and nonencircling linear ablation were compared in patients with chronic AF.[25] Nonencircling linear ablation included lines along the septum, roof, mitral isthmus, posterior mitral annulus, and anterior left atrium. At 9-month follow-up, 68% and 60% of patients who underwent circumferential PV ablation and nonencircling linear ablation were in sinus rhythm, respectively. In another study, intraoperative left atrial linear ablation was performed between the ostia of the PVs,[26] without isolating the PVs. In a small