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Predictors of Recurrence After Radiofrequency Ablation of Persistent Atrial Fibrillation

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Abstract

Radiofrequency catheter ablation that targets the pulmonary veins is well established as a mainstay for drug-refractory, paroxysmal atrial fibrillation (AF). However, in patients with persistent AF, the ideal approach remains elusive. Further, despite the various additional ablation strategies that have been investigated in patients with persistent AF, the rate of recurrent atrial tachyarrhythmias after ablation remains relatively high. In this review, the predictors of recurrent atrial tachyarrhythmias after catheter ablation of persistent AF will be discussed.

Introduction

While there is consensus regarding the ablation strategy in patients with paroxysmal atrial fibrillation (AF),[1] the ideal strategy for patients with persistent AF remains unclear. Patients with persistent AF do not respond well to pulmonary vein (PV) isolation as the sole strategy.[2] Although outcome in patients with persistent AF is improved with extra-PV ablation, e.g., ablation of complex fractionated atrial electrograms (CFAEs) and linear ablation, patients frequently require repeat ablation procedures for organized arrhythmias.[3] Identifying the predictors of recurrence is of obvious clinical importance in enhancing efficacy and achieving better long-term outcomes. This review focuses on predictors of recurrent atrial tachyarrhythmias after ablation of persistent AF.

Predictors of Recurrent Atrial Arrhythmias

Several studies have reported various factors as predictive of arrhythmia recurrence. These include demographic factors such as age[4,5] and duration of AF,[6] and comorbid conditions such as metabolic syndrome[7] and obstructive sleep apnea.[8] The impact of coexisting heart diseases may also contribute to AF recurrence.[9] Apart from demographic and historical factors, structural remodeling as revealed by imaging modalities such as echocardiography,[10] computed tomography,[11,12] and magnetic resonance imaging[13,14] have also been shown to be associated with arrhythmia outcome. Invasively determined factors such as AF cycle length,[15,16] atrial pressure,[17] and volume[18] have also been evaluated. More sophisticated techniques such as substrate mapping,[19] AF frequency,[20] and integrity of linear lesions[21,22] have also shown to be important in predicting arrhythmia recurrence after catheter ablation. These factors will be each discussed in detail below.

Patients Characteristics

Age

Advancing age is a strong risk factor for the development of AF and is associated with arrhythmia recurrence following catheter ablation of persis-

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tent AF.[4,5] Aging is related to structural remodeling culminating in low voltage areas/scar and conduction slowing associated with atrial fibrosis.[23-26] Atrial fibrosis may increase the complexity of the fibrillatory process by causing formation of multiple drivers.[27] In fact, advancing age was the only predictor of left atrial (LA) scarring in a recent study.[28] In the absence of randomized data or observational data from large studies, it is not clear whether the elderly fare worse with catheter ablation as compared to younger cohorts. Prior studies have reported that outcomes in the elderly are not significantly different than in younger patients.[29,30] More recent studies have reported discordant results. For example, a study by Yoshida et al. concluded that age is associated with recurrence in patients undergoing an extensive ablation strategy for persistent AF.[5] In a more recent study, it was shown that the efficacy and complication rates are in keeping with those of younger patients.[28] It is probably fair to conclude that arrhythmogenic substrate in the elderly is likely to be more complex that in younger patients, and elderly patients with significant structural remodeling probably do not respond as well to catheter ablation. However, patients should not be excluded from undergoing ablation on the basis of age alone.[31]

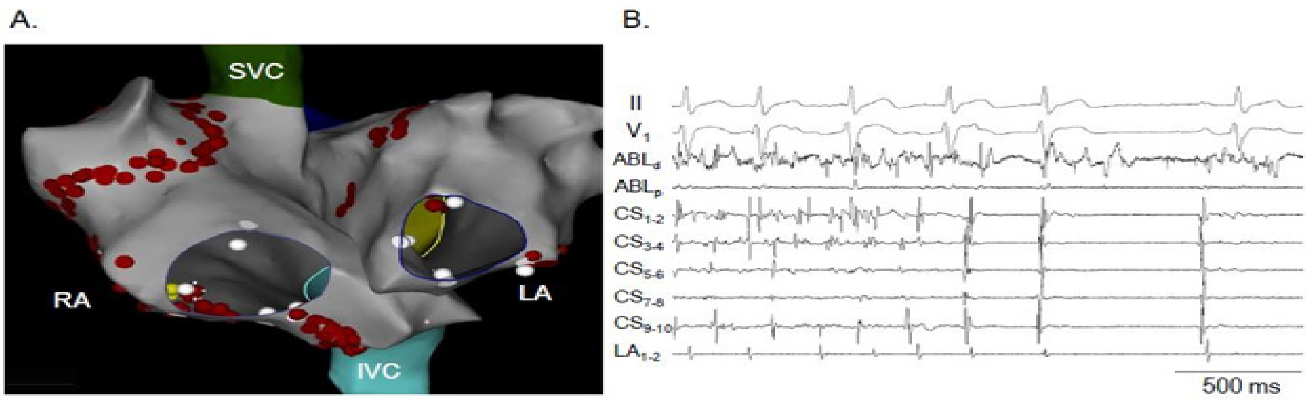
Duration of AF

Longer duration of AF is associated with shortening of the atrial effective refractory period, which further perpetuates AF.[6] The perpetuation of AF itself contributes to electric and structural remodeling of the atria. Patients with longer duration of persistent AF do not respond as well to antiarrhythmic medications, catheter or surgical ablation,[32] and are more likely to have recurrence of atrial arrhythmias after the ablation.[33,34] A recent study suggested that the distribution of the atrial substrate differs among patients depending on the duration of AF.[33] In patients with long-standing AF, the fibrillatory substrate includes not only the left but also the right atrium (Figure 1). These patients not only require additional ablation during the index procedure, but may also require repeat ablation procedures after elimination of the LA contribution. The potential targets in the right atrium include the right atrial appendage, free wall along the tricuspid annulus, the septum, roof of the right atrium, ostium of the coronary sinus, and the posterior wall.[35] Identification of complex electrograms at these candidate sites is key to eliminate right atrial drivers in these patients.

Structural Heart Disease

The presence of structural heart disease such as valvular heart disease,[36,37] nonischemic cardiomyopathy,[36] hypertrophic cardiomyopathy38 and coronary disease[39] is likely associated with higher recurrence rates after AF ablation. Patients with valvular heart disease may have a higher degree of atrial disarray and irreversible fibrosis which curtail the successful outcome after the ablation. The advanced valvular disease could develop irreversible atrial myopathy. AF recurrence of hypertrophic cardiomyopathy often accompany with diastolic dysfunction, elevated LA pressure, and LA enlargement. The progressive atrial remodeling, fibrosis by collagen metabolism abnormali-

Figure 1: Additional ablation of complex fractionated atrial electrograms at the base of the right atrial appendage (A) resulted in termination of atrial fibrillation (AF) to sinus rhythm during ablation in a patient with long-standing persistent AF (B). ABL= ablation catheter; CS= coronary sinus; IVC= inferior vena cava; LA= left atrium; RA= right atrium; SVC= superior vena cava



ties, atrial stretch and enlargement exacerbated by rising left ventricular filling pressure could have contributed substantially to AF recurrence in patients with structural heart disease, even when the procedure is initially successful. The challenges in these patients include not only the severely enlarged atria, but also the presence of atrial scarring. These findings should be taken into consideration when selecting patients for ablation of persistent AF.

Metabolic Syndrome

Metabolic syndrome defined as obesity, hypertension, dyslipidemia, diabetes and glucose intolerance is associated with a larger LA size and may increase the risk for recurrence after AF ablation.[7] Hypertension is associated with diastolic ventricular dysfunction, left ventricular hypertrophy and elevated intracardiac pressure.[40] Obesity is associated with impaired ventricular diastolic performance and may promotes atrial remodeling due to the chronic elevation in the intracardiac pressures.[41] In obese patients, elevated plasma volume, enhanced neurohormonal activation along with oxidative stress and subclinical inflammation conditions may play a role in the perpetuation of AF.[42] A recent study demonstrated that baseline inflammatory markers such as C-reactive protein and total white blood cell count are associated with metabolic syndrome predicted higher recurrence rate after AF ablation.[43] Although patients with metabolic syndrome may be more likely to experience arrhythmia recurrence, these patients should not be denied catheter ablation based on this factor alone. These patients may be more likely to require repeat procedures and perhaps, an extra-PV approach, but the expectation is that the majority of these patients with drug-refractory AF should benefit from catheter ablation.

Obstructive Sleep Apnea

Obstructive sleep apnea is associated with an increase in the probability of AF recurrence after ablation.[8] Possible mechanisms by which obstructive sleep apnea predisposes to AF include intermittent hypoxemia, hypercapnia, autonomic imbalance with surges in sympathetic tone. Hypoxemia and hypercapnia have direct adverse effects on cardiac electrical stability. The sympathetically mediated vasoconstriction increases arterial pressure and cause diastolic dysfunction followed by LA dilatation. Atrial stretch also may promote emergence of new triggers and perpetuate AF. Recent study demonstrated that treatment of continuous positive airway pressure improved success rate of AF ablation in patients with obstructive sleep apnea.[44] Continuous positive airway pressure may decrease frequency of hypoxemic episodes, prevent atrial stretch and raise the nadir value for lower nocturnal oxygen saturation.

Atrial Remodeling

LA Size

LA size is a predictor of freedom from atrial arrhythmias after single and repeat ablation procedures.[10] Remodeling of the atria during persistent AF is a time-dependent process, and typically results in the enlargement of LA dimensions.[5] Atrial dilatation has been recognized as a major pathophysiological factor in the perpetuation of AF.[45] An enlarged atrium modulates the electroanatomic substrate with the increased nonuniform anisotropy and a conduction disturbance, which could contribute to the heterogeneity of the LA. A prior experimental study showed that atrial stretch resulted from LA dilatation also may promote AF maintenance by high-frequency focal discharges that generate fibrillatory conduction and wave break.[46]

LA diameter measured from the parasternal long-axis view on transthoracic echocardiography, has been widely used to assess the LA size. However, recent studies have suggested that LA volume may be more accurate in the estimation of the LA size and may be a more robust marker of recurrrence.[18] Patients with severe LA enlargement (>5.5 cm on transthoracic echocardiography) should be counseled that they are probably more likely to require multiple procedures prior to achieving sinus rhythm. These patients may harbor AF drivers that are not addressed by PV isolation or ablation of complex electrograms. Further, in patients with severe chamber dilatation, technical issues such as catheter stability may also play a role in arrhythmia recurrence. Lastly, the processes (other than AF) that contribute to chamber enlargement, e.g., hypertension, sleep apnea, heart failure, and others need to be constantly addressed to prevent further adverse remodeling. Patients with an LA diameter >6.5 cm probably should not be offered catheter ablation since their outcomes are likely to be suboptimal despite multiple procedures of long duration.

Atrial Pressure

The atrial stretch imparted by elevated LA pressure may contribute to the maintenance of AF by stabilizing high-frequency sources and make it less likely to spontaneous terminate.[17] The higher LA pressure in patients with persistent AF results in a greater degree of stretch-related electrical remodeling, resulting in a higher AF frequency.[17] A stretch-related mechanisms of AF has been proposed in a number of clinical conditions, such as mitral valve disease, heart failure and obstructive sleep apnea. Treatment of the underlying conditions, such as hypertension, sleep apnea, heart failure, and obesity may be protective in preventing ongoing structural remodeling related to atrial stretch.

Preexistent LA Scarring

Fibrosis in the LA may help to anchor reentrant circuits, alter the wave-front propergation and cause wave break and conduction delay.[7] Patients with LA scar were less likely to respond to catheter ablation.[13,14] Recently, delayed enhanced magnetic resonance imaging using gadolinium contrast has been used to analyze scar burden.[13,14] The LA voltage during catheter mapping may be representative of the structural integrity of the atria and a lower voltage is a predictor of recurrent atrial tachyarrhythmias after AF ablation.[19] The posterior wall is preferentially scarred in patients with persistent AF.[13] The posterior LA scarring could be associated with a lower contribution of PV arrhythmogenicity, making antral PV isolation less likely to be effective. These patients obviously require mapping of AF drivers outside the PV antrum. Possible strategies include linear ablation and ablation of CFAEs.

Procedural Parameters

AF Cycle Length

AF cycle length may be used as a surrogate parameter for the acute efficacy of ablation.[47-49] A shorter AF cycle length reflects a short refractory period and higher number of perpetuating activities, both of which are characteristic of persistent AF.[47] AF termination is more likely to occur in patients with a longer AF cycle length at baseline.[43] However, this may not be the case in patients with LA scar.[28] Although the baseline AF cycle length is longer in patients with scar, this does not necessarily make it easier to terminate AF with the ablation. It is possible that AF cycle length is not a reliable marker of acute efficacy of ablation in patients with LA scar.[28] A recent study using fast Fourier transform analysis demonstrated that a reduction in the dominant frequency by 11% or more by the ablation was a predictor of successful outcome with less radiofrequency energy and a shorter procedure time than those of termination of AF.[20] Whether tailoring the ablation procedure with respect to real time frequency analysis is associated with an improved outcome is unknown.

PV Reconnection

Although the clinical efficacy of pulmonary vein isolation is much lower when AF is persistent than when it is paroxysmal, PV isolation is the cornerstone of AF ablation.[51] A recent study reported that in patients who underwent repeat ablation for arrhythmia recurrences after ablation of persistent AF, more than 1 PVs reconnected in all patients and only re-isolating these PVs resulted in no recurrence in 80% of patients.[52] The preprocedural recognition of specific patterns and variants of PV anatomy may be helpful as a roadmap to help achieve PV isolation. Computed tomography and magnetic resonance imaging acquired before the ablation provide detailed anatomic features and morphological changes. Anatomical variations of the PVs may be detected in up to 30% of patients and the most frequent variant is the common ostium of the left-sided PVs.[53] Since a common ostium usually is larger than the diameter of available circular mapping catheters, precise mapping and localization of PV fascicles may be challenging. Further studies are needed to clarify the clinical utility of preprocedural imaging to detect specific patterns and variants of PV anatomy. Recently, cryoablation has emerged as a promising tool allowing PV isolation in a safe and effective manner. However, in some patients, electrical isolation of all PVs cannot be achieved using a single size cryoballoon because of unfavorable angulations of the

PV ostia and the size of the PV ostia relative to the ablation catheter.[54]

Ablation of CFAE as a Risk Factor for AT

CFAEs may indicate sites of slow conduction, collision, anchor points for reentrant circuits, wavebreak and fibrillatory conduction at the periphery of a rotor.[55-57] Although ablation of CFAEs has been reported to achieve long-term arrhythmia freedom after a single procedure in up to 70% of patients with persistent AF,[56] there has been difficulty reproducing these results using CFAE ablation alone.[57] The potential explanations for the discrepancy were the inconsistency in interpretation of CFAEs, inadequate CFAE ablation and proarrhythmic effect of CFAE ablation by creating zones of slow conduction.[58] A prior study suggested that extensive ablation creates extremely slow conduction that allows for small circuits.[59] The localized reentrant atrial tachycardias were found predominantly within regions in which CFAEs were ablated. However, CFAEs remain an important target in patients undergoing catheter ablation of persistent AF.[60]

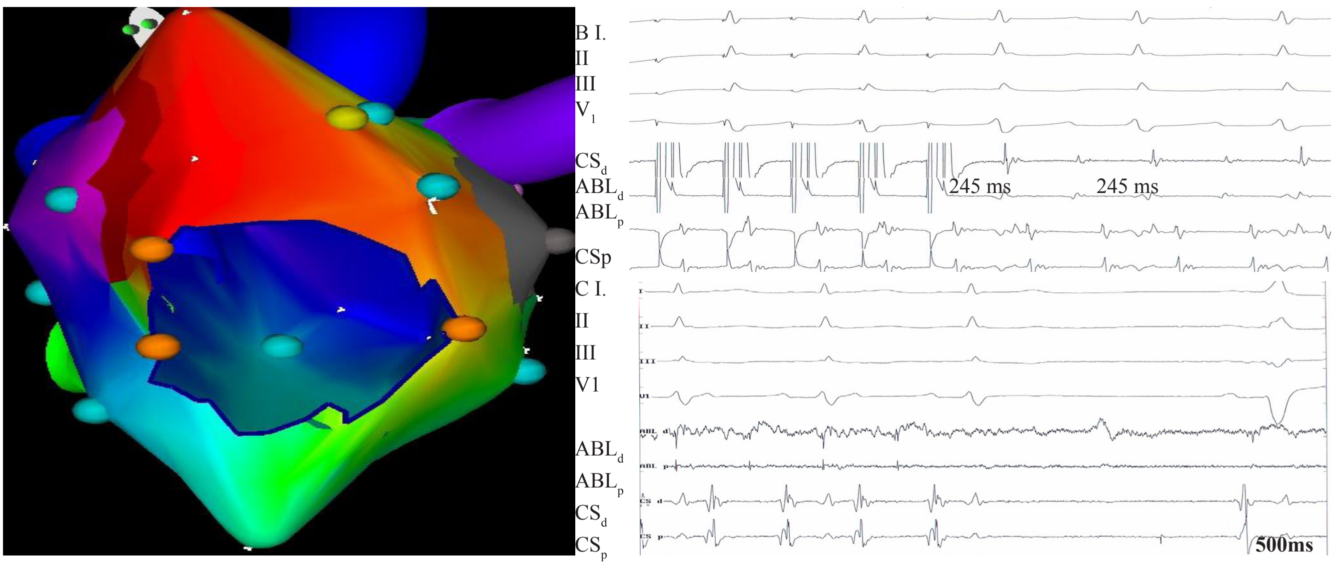
Linear Block

Linear ablation of the LA roof and the mitral isthmus have a role in elimination of AF following PV isolation.[61,62] Linear ablation has been demonstrated to be necessary to terminate AF in large percentage of patients with long-standing persistent AF in a prior study.[48] Documentation of conduction block across these lines is critical and has been shown to be associated with a lower risk of recurrent atrial tachycardias. Indeed, incomplete mitral isthmus or roof lines may serve as a significant substrate for gap-related proarrhythmia (Figure 2).[21,22]

A previous study demonstrated that the morphological characteristics of the mitral isthmus and its anatomical relationship to the adjacent vasculature affect the achieving conduction block.[12] A pouch morphology, greater isthmus depth, and the circumflex artery are associated with challenging linear ablation at the mitral isthmus. An interposed circumflex artery is also predictive of unsuccessful linear ablation at the mitral isthmus. The heat-sink effect of blood flow in the circumflex artery may prevent adequate heating of the atrial myocardium during ablation. If an interposed circumflex artery is found on computed tomography or magnetic resonance imaging, it is probably best to avoid empiric ablation at the mitral isthmus in patients with persistent AF. In patients with a pouch morphology, it may be difficult to achieve adequate tissue contact during endocardial ablation and hence, very frequently require ablation within the coronary sinus to achieve complete block.

Conduction block of the LA roof was reached more

Figure 2: Activation map during peri-mitral reentry (A: left anterior oblique projection). Entrainment mapping from the lateral mitral annulus demonstrates that the post-pacing interval is 245 ms, matching the tachycardia cycle length (B). Endocardial ablation at the mitral isthmus failed to terminate the tachycardia. Radiofrequency energy delivery in the distal coronary sinus (CS) terminated the tachycardia to sinus rhythm. (C). ABL= ablation catheter; MA= mitral annulus



frequently compared with the mitral isthmus.[62] However, it may be challenging in some patients. Several studies have analyzed the anatomy of the LA roof in patients undergoing AF ablation.[11,63] A recent study suggested that there was no significant difference in the myocardial thickness of the LA roof, curvilinear length, distance to the right pulmonary artery, angulation with respect to the superior pulmonary veins, or other morphological aspects of the LA roof in patients with and without complete block.[64] A left (from the circumflex artery) sinus node artery was the only independent predictor of incomplete conduction block at the LA roof.[64] The left sinus node artery may act as an epicardial heat-sink, preventing adequate heating of the LA roof during linear ablation.

Termination of AF during Catheter Ablation

Termination of persistent AF during ablation usually requires extensive ablation beyond the PVs, including ablation of CFAEs and multiple linear lesions. Termination of AF may represent suppression of AF drivers and perpetuating activities and has been associated with good outcomes.[47-49] However, recent studies suggested that AF termination did not impact the long-term sinus rhythm maintenance.[5,65,66] After extensive ablation, patients may not longer have AF but instead may require repeat procedures for atrial tachycardias.[65]

We need to find out how much ablation is required to eliminate AF and to avoid excessive ablation which may be detrimental not only in terms of pro-arrhythmia but also LA mechanical function. To be sure, some patients require ablation of organized atrial tachycardias as an intermediate step before sinus rhythm is achieved. The challenge is to reduce the prevalence of atrial tachycardias while maintaining the efficacy of AF elimination.

Spectral Characteristics of AF

A recent study that analyzed the spectral characteristics of AF suggested that atrial tachycardias to which AF converts during the ablation may represent organized tachycardias that coexist with AF despite a lower frequency.[67] Those spectral components were more prevalent at baseline among patients in whom AF persisted than in those in whom AF terminated during ablation.[68] In addition, linear ablation resulted in a significant decrease in the prevalence of spectral components.[68] Whether the prevalence of spectral components can be used as a predictor of recurrent atrial tachyarrhythmias after ablation of persistent AF remains to be determined.

Early Recurrence of Atrial Tachyarrhythmias

Early recurrence of atrial tachyarrhythmias has typically not been equated with procedural failure. A transient increase in atrial vulnerability caused by an acute inflammatory changes due to radiofrequency energy and autonomic remodeling after ablation may cause early recurrences of atrial tachyarrhythmias.[69] A recent study suggested that transient use of corticosteroids shortly after AF ablation may inhibit inflammatory responses and decrease early AF recurrences.[70] Corticosteroid treatment may also halt electrical or functional remodeling and prevent late AF recurrences.[70] Early recurrence of atrial tachyarrhythmias has also been associated with late arrhythmia recurrences after ablation of persistent AF.[52,71] However, the mechanisms of early recurrence of atrial tachyarrhythmias needs further study and the optical timing for the second procedure needs to be defined.

Conclusions

Knowledge of the predictors of recurrent atrial tachyarrhythmias may play an important role to improve long-term outcome after catheter of persistent AF. Further studies are needed to clarify the clinical significance of these predictors in large cohorts of patients and identify the strategies to maintain sinus rhythm after the ablation in patients with persistent AF.

Disclosures

No disclosures relevant to this article were made by the authors.

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