

Substrate Ablation in Treatment of Atrial Fibrillation

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Substrate Ablation in Treatment of Atrial Fibrillation. From the time catheter ablation of atrial fibrillation (AF) was first reported, of the two dominant approaches for AF ablation, only pulmonary vein (PV) isolation has been modified, while circumferential pulmonary vein ablation (CPVA) as performed by our group in Milan has remained substantially unmodified. In fact, PV isolation as initially performed by Haissaguerre et al. has undergone rapid evolution toward substrate modification with significantly higher success rates without major complications. Modification of such technique was due to modification of the substrate. It is now evident that substrate modification is indeed crucial for curing AF particularly in patients with long-lasting or permanent AF. Indeed, to achieve good outcomes, any ablation technique should simultaneously include elimination of all triggers associated with modification of both anatomic and autonomic substrate, as we started to do many years ago by performing CPVA. (*J Cardiovasc Electrophysiol*, Vol. 17, pp. S23-S27, Suppl. 3, December 2006)

catheter ablation, atrial fibrillation, mapping

Introduction

Over the past decade, catheter ablation techniques for treating atrial fibrillation (AF) have evolved considerably. At present, as most approaches are mainly based on empirical observations, such as pulmonary vein potentials or fractionated electrograms, rather than on understanding of mechanisms of AF, variable success rates are reported in most major electrophysiology laboratories worldwide.¹⁻¹⁶ It is well known that the pathogenesis of AF is multifactorial, complex, and not yet well defined. In addition, there are different mechanisms for each clinical form of AF (paroxysmal, persistent, and permanent) and even within each form. The variable progression times from the initial episode to recurrent and/or persistent AF and from persistent AF to permanent AF within the wide AF population further suggest that AF is a highly heterogeneous and complex disease, with different mechanisms of AF, as well as of progression from one to another form of AF in different patients, which ultimately depend on baseline clinical and electrophysiologic variables. Therefore, variable success rates in catheter ablation techniques will essentially depend on the ablation timing as well as on the different effect that each ablation technique has on multiple factors involved in the pathogenesis of AF. Currently, a potential tailored approach may be intriguing yet speculative since it implies the exact and complete knowledge of all the mechanisms involved in the pathogenesis of AF in each and every patient. Unfortunately, the lack of knowledge of all factors initiating and maintaining AF has obliged most electrophysiologic laboratories to adopt standardized techniques, which necessarily have included a predefined set of lesions. The pioneering approach by Haissaguerre et al.¹ was based on discovery of pulmonary vein foci associated with AF initiation, while other approaches were mainly based on substrate modification by surgery. The most popular pioneering standardized approaches included the “pulmonary vein

isolation” (PVI) as proposed by Haissaguerre et al.¹ and the “circumferential pulmonary vein ablation” (CPVA) as proposed by Pappone et al. in Milan.^{2,3} The initial much higher success rates following CPVA, even in patients with persistent and permanent AF compared with PVI alone, suggested that CPVA unlike PVI alone affects almost all AF mechanisms. In the last few years, despite the excellent results of CPVA in curing AF, other substrate-based approaches such as ablation of fractionated atrial electrograms have been proposed for patients with either persistent or permanent AF. In our experience, fractionated potentials are a random phenomenon being transient, not reproducible and ubiquitous, raising the question whether complex fractionated atrial electrograms should really be considered as targets for ablation. We still should clarify if such potentials are the cause or the effect of AF. What appears to be local reentry may be passive as well, and in all probability they do not represent the same process.

Success of AF Ablation Strategies: Substrate Modification, PVI, or Both?

With the Maze III approach, Cox⁴ reported the maintenance of sinus rhythm in almost all patients (95%) at long-term follow-up, and success rates appeared to be equivalent in patients with and without structural heart disease, as well as in those with paroxysmal and persistent AF. However, application of this surgical approach has been limited by high morbidity and risk associated with sternotomy/thoracotomy and cardiopulmonary bypass. The encouraging results of this approach essentially based on substrate modification formed the initial basis for percutaneous catheter ablation techniques by performing linear lesions in the right and left atrium, but most trials were terminated prematurely due to high complication rates and poor efficacy. On the basis of these preliminary observations and the rapid advances in ablation of AF targeting initiating focal triggers, catheter-based linear ablation strategies for AF were abandoned too early. Unfortunately, initial ablation techniques based on substrate modification were neglected when pulmonary veins were found to be the dominant source of triggers initiating AF, and the initial technique for AF ablation was to ablate the “culprit”

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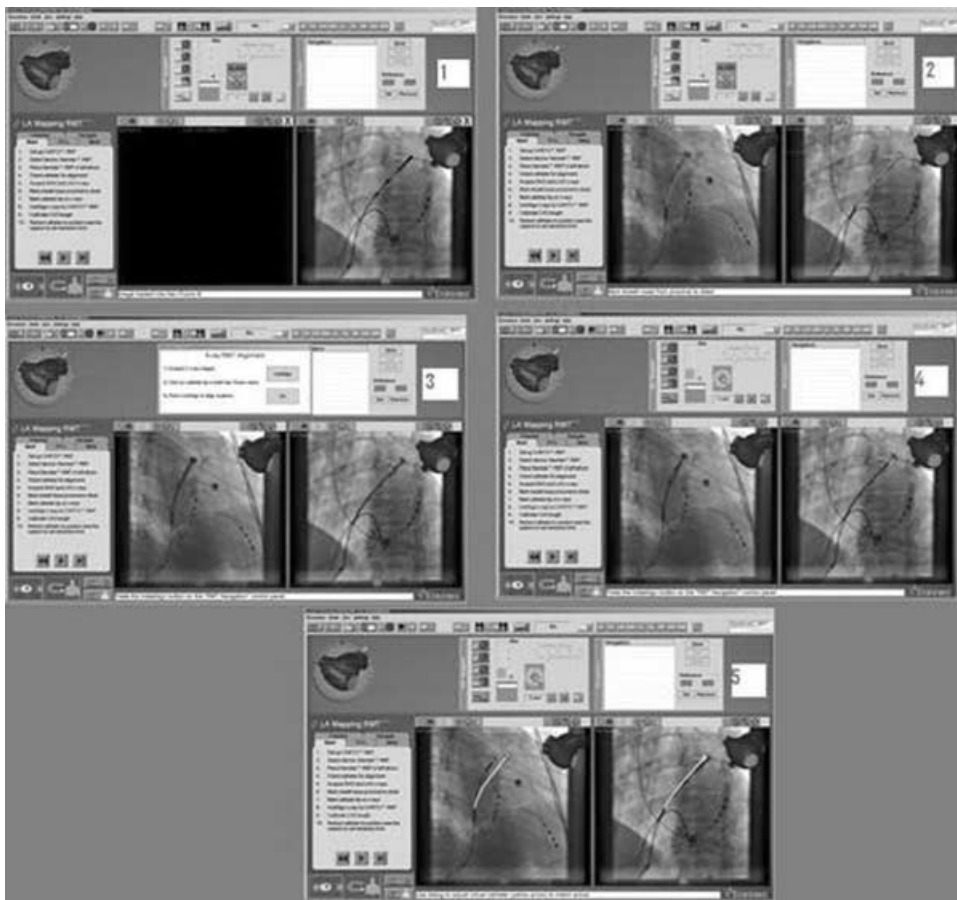


Figure 1. Remote magnetic navigation with Niobe II system (Stereotaxis, Inc., St. Louis, MO, USA). Sequence of five images on Navigant screen showing setup for navigation and auto-map navigation. Phase 1, acquisition of two Fluoro views (LAO and RAO); phase 2, the base (end of introducer) of the catheter and its tip are depicted and marked on both Fluoro views; phases 3-4, alignment with CARTO system (RMT) of the catheter tip, which appears on the Navigant screen (phase 4); phase 5, calibration of the catheter length by using Cardiodrive (Stereotaxis, Inc.). These phases are important to both synchronize Navigant and CARTO and to allow automap.

focus within the pulmonary vein.¹ However, the focal approach was limited by the complication of pulmonary vein stenosis and the recognition that multiple veins were involved in most patients with paroxysmal AF. Enthusiasm was also tempered by long procedure times and limited success rates, frequently with the need for repeat procedures. This technique rapidly evolved to aim for electrical disconnection of all pulmonary veins, which was obtained by segmental ablation guided by potentials from a multiple catheter positioned within the ostium of the vein. Certainly, segmental ostial PVI represented an advance in catheter treatment of AF over the focal strategy essentially for patients with paroxysmal AF with poor results for persistent and permanent AF. Based on the concept that substrate modification is indeed important in curing AF concurrently with PVI, we developed in Milan an approach alternative to that proposed by Haissaguerre et al.¹ We first performed circumferential lesion lines around each vein or a single large circumferential radiofrequency (RF) lesion set with the endpoint of ablation being the absence or marked reduction (80%) in the amplitude of electrical signals within the encircling lesions.⁵ Ablation was guided by three-dimensional electroanatomic mapping, and initial results on clinical outcome of patients with paroxysmal and permanent AF were much higher than those reported by electrophysiologically guided segmental pulmonary vein

disconnection. Our results were confirmed in a randomized prospective study comparing the two techniques in paroxysmal AF, with 88% of patients who underwent CPVA free of symptomatic AF at 6 months, compared with 67% of those who underwent segmental disconnection.⁶ Therefore, it has become increasingly evident that to improve the clinical outcome of ablation elimination of PV triggers alone may not be sufficient, particularly in patients with long-lasting persistent AF, but must be combined with substrate modification. Several potential mechanisms could coexist to form the substrate for AF after PVI; these include localized high-frequency activity (focal or reentrant), meandering multiple wavelet reentry, and macroreentry. The last strategy of Haissaguerre et al.¹⁵ also involves substrate modification. In all patients with long-lasting persistent AF, additional substrate modification is used to improve the outcome of ablation, while in those with paroxysmal AF, additional substrate modification is used only if patients remain inducible. The accumulating evidence of the crucial role of substrate modification as emphasized by our initial experience with CPVA has led to the development of other empirical techniques that are based on nonlinear atrial lesions. In particular, Nademanee et al.⁷ have identified areas with complex fractionated atrial electrograms and have performed “nonlinear” atrial ablation to eliminate these sites on the basis of their potential role in the maintenance of AF.

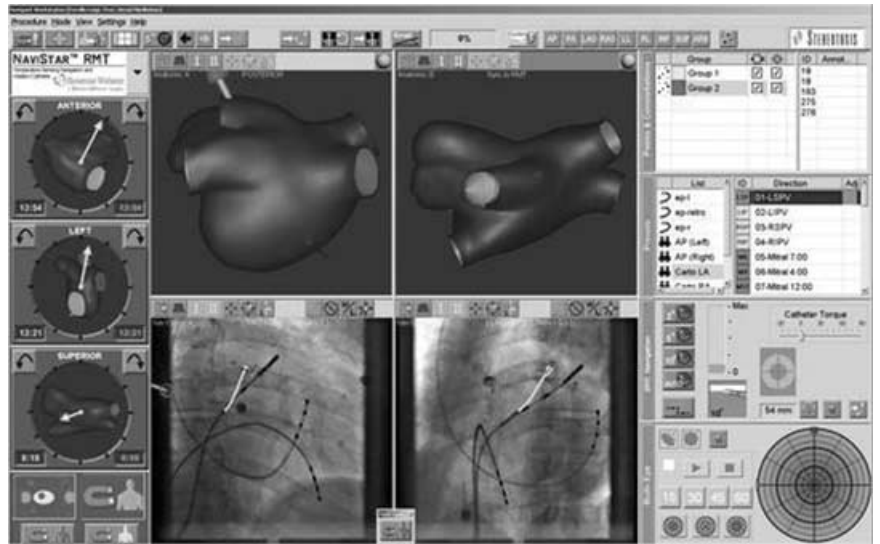


Figure 2. Remote magnetic navigation with Niobe II system (Stereotaxis, Inc.). The figure shows Navigant screen during remote navigation toward the left superior PV. A pre-set (as a stored vector, LSPV) was selected from the pre-set list indicated on the right side and applied to the desired direction. The RAO and LAO appear on the bottom. On the top two anatomic images of the left atrium are shown.

They targeted specific electrogram patterns, not only in the left atrium but also in the right atrium (mostly the septum), as well as in the coronary sinus. They also reported that the left atrial roof represents a region demonstrating highly fragmented electrograms, perhaps indicating the presence of substrate capable of sustaining localized reentry or focal activity that may maintain fibrillation. These sites, hypothesized to be pivot points for reentrant wavelets, were targeted for ablation with acute success rates of 91%. At 12-month follow-up, 70% of patients were free of AF off antiarrhythmic drugs; with a second procedure, success rate increased to 83%. Other recent ablative strategies for substrate modification include frequency mapping to eliminate selective substrate areas by identifying high-frequency electrograms. Actually, we believe that most of these empirical strategies focusing on substrate modification are also included into CPVA, which acts simultaneously on PV triggers and autonomic substrate modification.⁸ Taken together, recent results from other groups, while confirming our initial good outcomes after CPVA, indicate that more extensive lesions with substrate modification remain the key element of any AF ablation strategy. The fact that during RF applications AF may spontaneously convert to atrial tachycardia before conversion to sinus rhythm in many patients with persistent AF is convincing proof that transient substrate modification is involved in acutely restoring sinus rhythm. Accordingly, we consider spontaneous conversion of postablation left atrial tachycardia as a transient response to stable substrate modification after CPVA.⁹ Tachycardia may persist up to 2 months after the procedure, particularly in patients with persistent/permanent AF, and in up to 50% of them, tachycardia resolves spontaneously. Our extensive experience on more than 8,000 patients undergoing AF ablation (59% with permanent AF, 45% with structural heart disease, and 44% with enlarged atria) indicates that rapid or fractionated electrograms usually may be ubiquitous in the right and left atrium in patients with long-standing AF or permanent AF.

AF Ablation and the Role of Autonomic Substrate Modification

RF ablation strategies to cure AF have focused on the empirical destruction of myocardial tissue, but recent clinical

and basic studies suggest that selectively targeting autonomic nerves and ganglia can result in AF suppression with little, if any, damage to healthy myocardium. It is well known that standardized approaches may require more than 100 RF application in a single patient. In addition, ablation may create gaps, particularly in patients receiving linear lesions, providing slow conduction areas for macroreentrant tachycardias that may require further RF applications to eliminate the iatrogenic arrhythmia either at the initial ablation procedure or at a later time due to a new arrhythmia occurrence. The inability to achieve the same success for AF ablation as has been attained for Wolff-Parkinson-White syndrome, atrioventricular node-reentry tachycardia, and atrial flutter has been thought to be related to the greater electrophysiologic complexity of AF, compared to the other syndromes. However, the mechanism for focal firing has not been discerned and there is no rationale for PVI, as suggested by the limited success rates with PVI alone. The initial report and landmark article by Haissaguerre et al.¹ on identification of PV foci raises several basic questions: How does focal tachycardia in the PV become AF and not atrial tachycardia? How does a single premature depolarization in a PV become AF and not an atrial premature beat? How do PVs develop focal firing in the first place? Our clinical study for the first time has begun to address some of these questions and suggests possible answers to determine whether vagal reflexes during RF ablation predict long-term success and maintenance of sinus rhythm.⁸ We have recently localized vagal fibers and/or ganglia around PV ostia at the veno-atrial junction by eliciting vagal reflexes.⁸ Elimination of vagal reflexes by RF ablation during CPVA results in parasympathetic attenuation up to 6 months after the index procedure and no AF recurrences, confirming that PV ectopy and PVI are only the tip of the iceberg. CPVA also attenuates vagal tone, which results in enhancement of the long-term benefit of the procedure with success rates approaching 100%.⁸ Parasympathetic stimulation is involved in AF induction and maintenance, as vagal stimulation dramatically shortens the atrial refractory period, increasing the probability that multiple reentrant circuits can exist simultaneously, and further increasing the maintenance of AF. A recent study has confirmed our findings by identifying four major autonomic ganglionated plexuses outside the PV ostia in patients with AF.¹⁰ Simultaneously, the Bordeaux

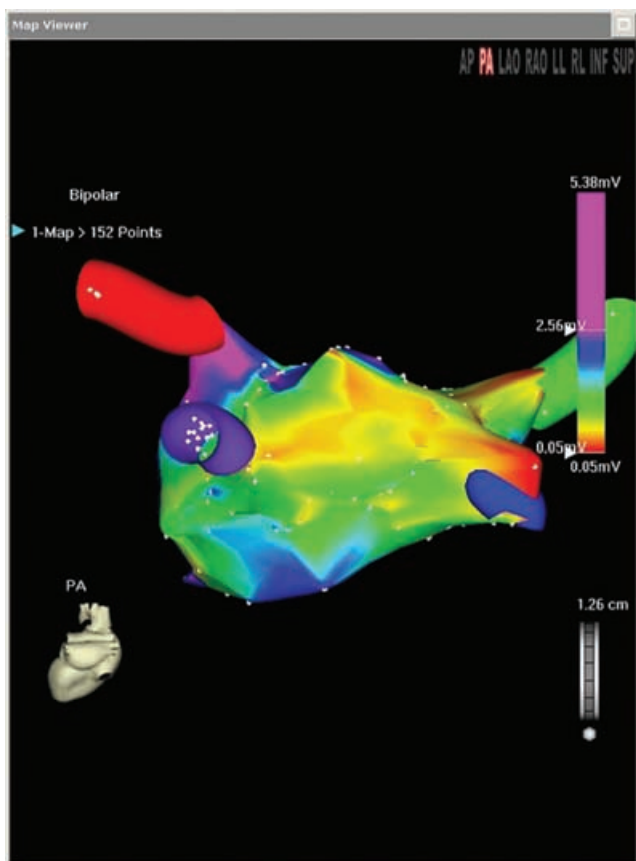


Figure 3. Preablation color-coded voltage map of the posterior left atrium using remote navigation with Niobe II system (Stereotaxis, Inc.).

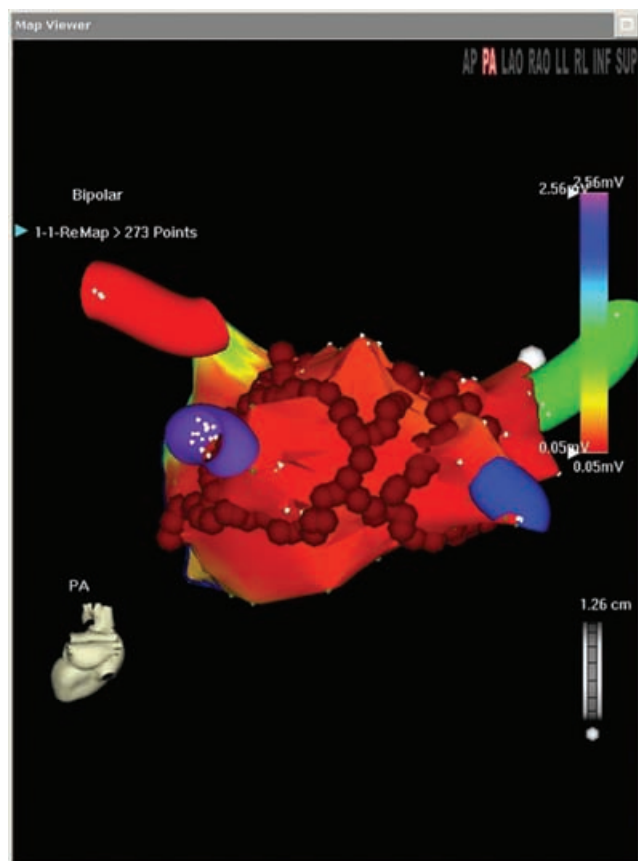


Figure 4. Postablation color-coded voltage remap of the posterior left atrium. The lesion set is clearly designated (red circles) and includes circumferential lesions, additional posterior lines, and the mitral isthmus line.

group reported that vagal excitation may enhance pulmonary vein arrhythmogenicity and maintenance of AF. These observations open new doors for curing AF offering a specific lesion set, which is included in our approach. More recently, 60 patients underwent ablation for paroxysmal and persistent AF.¹⁰ Thirty-three had standard PVI plus ganglionated plexi ablation at all PV antra; 27 received PVI alone. The former group showed a 91% freedom from AF recurrence, while the latter had a 71% success rate. Of interest, ganglionated plexi ablation prior to antrum isolation eliminated focal firing from PV in 95% of patients.¹⁰ These data taken together suggest that autonomic substrate ablation is extremely important in increasing the success rate or freedom from AF recurrence, substantially reducing overall substrate elimination.

Circumferential Pulmonary Vein Ablation from Late 1990s to 2006

CPVA, which is our current strategy, was developed at the San Raffaele University-Hospital in Milan, Italy.⁵ From 1999 to 2005, more than 8,000 patients with AF underwent CPVA with overall success rates of about 90%. Now, we are also performing remote magnetic navigation with soft catheters by using a video workstation that allows us to reach PVs (Figs. 1 and 2). Remote ablation can be safely performed using a CARTO-RMT integration system (Stereotaxis, Inc.) (Figs. 3 and 4). Remote ablation has a short learning curve, so that ablation of AF may be performed also by less experienced

hands.¹⁷ Over time, our approach has slightly evolved to a more proximal placement of encircling lesion sets, more ablation energy application at sites eliciting a vagal response, and more extensive ablation within the encircling lesion sets. At first, the CPVA strategy focused on encircling each PV ostium by circumferential RF lesions performed at least 5 mm from the ostia to prevent PV stenosis. To perform this technique, we used an electroanatomic mapping system (CARTO), which generates three-dimensional reconstructions of the left atrium and displays the spatial locations of the pulmonary veins. Four-millimeter-tip catheters were used at first, with maximal energy of 50 W and a temperature of up to 60°C. We reported that AF was controlled in 80% of the patients with paroxysmal AF, and that no pulmonary vein stenosis was found during a mean 1-year follow-up. To achieve better results, particularly in patients with persistent AF and associated heart diseases, we have enlarged the encircled area of the periostial tissue, expanding circumferential lines around the pulmonary veins and isolating them two at a time. We have added a posterior line connecting the two encircled areas and another one from the left pulmonary veins to the mitral valve annulus, similar to the surgical techniques (Fig. 4). RF ablation of the cavotricuspid isthmus has been systematically introduced. For this purpose, we use catheters with 8-mm-tip electrodes and 100 W RF power to produce transmural atrial lesions. While performing RF applications in the left atrium, we elicited in about 30% of the patients a vagal reaction, suggestive of autonomic

ganglia stimulation, which disappeared as the ablation went on. Clinical follow-up of these patients showed that 99% were free of AF without antiarrhythmic drugs. These data suggest that even after the partial ablation of ganglia and fibers of the left atrium, autonomic nervous system is important to control AF episodes. On the basis of our extensive experience, complication rates were as follows: hemopericardium: 0.2%; stroke: 0.23%; atrial-esophageal fistula: 0.03%; PV stenosis: 0%; incisional left atrial tachycardias: 6%. Our data on success rates during follow-up are based on accurate and intensive electrocardiographic monitoring (i.e., serial 48-hour Holter recordings and daily 60-second transtelephonic electrocardiograph recordings for at least 1 year after ablation). The benefits of maintaining sinus rhythm have been questioned by the "rate versus rhythm" debate, with evidence of possible harm from a pharmacologically based, rhythm control strategy.¹¹ However, there is growing evidence that maintenance of sinus rhythm after catheter ablation without the use of antiarrhythmic drugs is more desirable than AF providing clinical and prognostic benefits. A nonrandomized study from our group¹² in a large cohort of patients with AF has provided evidence of significant clinical improvement and a return to baseline community mortality rates after CPVA (589 patients), compared with drug therapy (582 patients).

Conclusions

In the last years since catheter ablation of AF was first reported, CPVA has remained substantially unmodified^{13,14} while PVI has undergone rapid evolution toward substrate modification with corresponding improvement in success rates minimizing complications.^{15,16} Although the increasing knowledge of the mechanisms of AF has paralleled the development of different interventional electrophysiology techniques, we still need to learn much more about the mechanisms of AF and the progression times of the various forms of AF and how to apply this information to ablation timing, as well as to tailor ablation strategy to each individual case. The excellent clinical success of our standardized strategy on more than 8,000 cases has addressed several important questions that suggest that catheter ablation of AF may soon become more broadly performed, particularly using remote navigation and ablation. Indeed, in our experience, to achieve the maximum clinical success without major complications, any ablation technique should include (1) triggers isolation, as documented by elimination of atrial potentials on ablation lines as well as within encircled areas to be sure of distal disconnection, (2) substrate modification, and (3) ablation of the local vagal innervation. In the past, AF ablation strategies focused their attention mainly on one of these targets, but recent strategies have focused on substrate modification. They include ablation of low-amplitude and fragmented electrograms and ablation of autonomic ganglia with initial high success rates, even in patients with persistent and permanent AF. These data, while confirming the critical role of substrate modification, indicate that AF may be a curable condition, and the Milan approach to CPVA is an extremely effective standardized strategy without major complications.

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