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Trigger Versus Substrate Ablation for Atrial Fibrillation

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Abstract

Elimination of triggers has become the hallmark of catheter ablation of atrial fibrillation (AF). In particular, much attention has been paid to the elimination of triggering impulses from the pulmonary veins via pulmonary vein ablation procedures. While this approach has a proven track record for paroxysmal AF, the efficacy in non-paroxysmal AF has been less convincing. Thus, attention has been paid to elimination of the substrate responsible for AF perpetuation, including complex fractionated electrograms, dominant frequency sites, and autonomic ganglionated plexi. None of these targets has yet become mainstream, but they are all under active investigation. As our knowledge of these targets increases and clinical studies are performed, a more refined approach to AF ablation will surely emerge.

Introduction

Radiofrequency ablation of atrial fibrillation (AF) has emerged as a very effective technique for the treatment of this common arrhythmia. When AF ablation was first described by Haissaguerre et al nearly ten years ago, the technique was focused on the elimination of focal triggers for AF, emanating largely from the pulmonary veins (PVs).[1] For patients with predominantly paroxysmal AF and little structural heart disease, this paradigm remained successful, with evidence confirming that elimination of all possible triggers via pulmonary vein isolation (PVI) would successfully prevent AF recurrence. However, in populations with more persistent and permanent AF, the high success rates of PVI procedures were not replicated. In these patients, it is believed that additional targets may be required to maximize success. In particular, there has been interest in identifying the critical elements of the atrial substrate required for maintaining AF. By targeting this so-called "substrate," it is hoped that AF ablation may achieve better cure rates in a wider spectrum of AF patients. While markers of the AF substrate have been proposed as potential targets of ablation, the efficacy of using such targets is not well known. Furthermore, whether such targets should be eliminated alone, or in conjunction with known triggers is also not well understood.

Trigger-Based Ablation

The goal of most present-day AF ablation techniques is to electrically isolate the PVs from the rest of the atrium by ablating around the origin of the veins. In their original article, Haissaguerre et al showed that in the majority of paroxysmal, lone AF patients (94%), focal triggers for AF were found in one or more of the PVs.[1] Although non-PV sites may also trigger AF, this is less common, occurring in no more than 6-10% of paroxysmal AF patients.[2] Thus, most present-day techniques are focused on ablating around the PVs. Initially,

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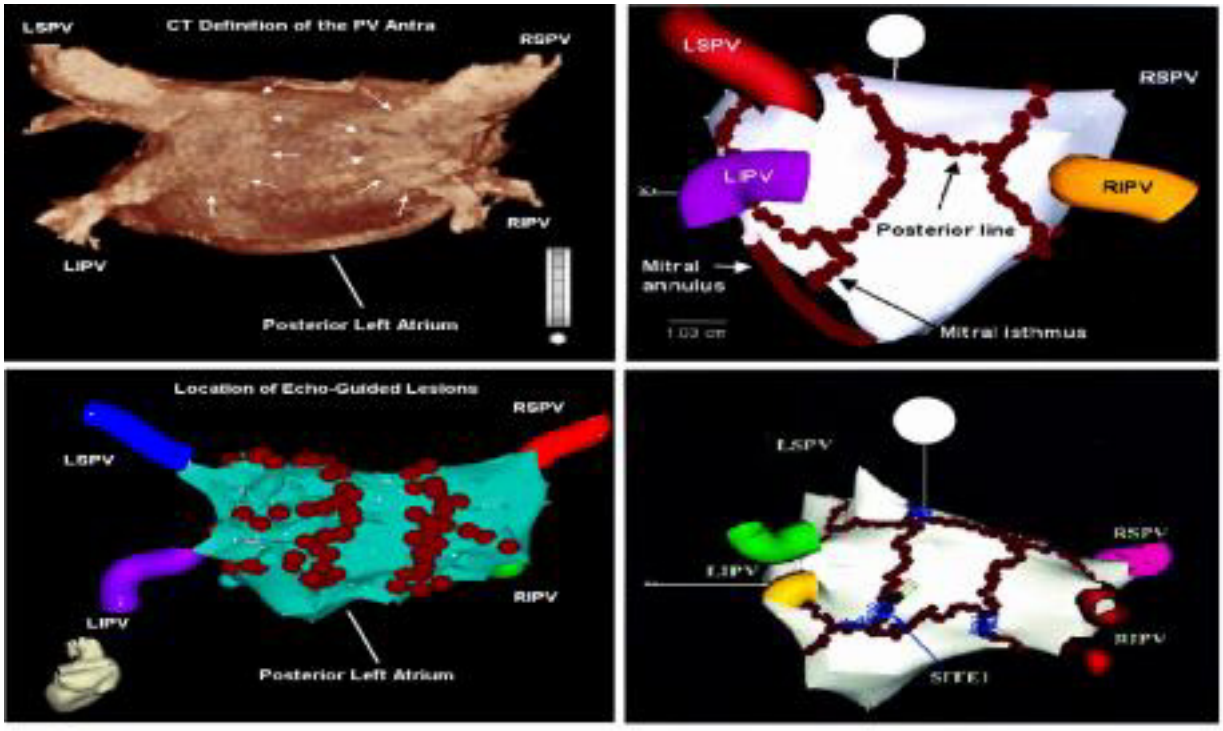
operators ablated early activation sites around the ostium of the veins – a technique often referred to as segmental, ostial isolation. However, as the understanding of the anatomy of the PV-left atrium (LA) interface increased, it was realized that the veins merge into the LA as a funnel-shaped structure, sometimes referred to as the "antrum".[3] To effectively isolate the PVs from the LA, it is necessary to isolate the entire antral region with the goal of achieving complete electrical disconnection between PVs and LA. Although this technique has many names and variations, including "pulmonary vein antrum isolation," "circumferential PV ablation," or "extraostial isolation," the lesion sets produced by the procedures are all very similar (Figure 1). Success rates are also similar, with recent pooled analyses showing success in the 80% range4.

Evidence has also suggested that the success of such ablation procedures is directly related to eliminating conduction between the PVs and the LA. Verma et al studied patients post-PV antrum isolation and found that those with successful outcomes had significantly more PVs isolated compared to those who failed.[5] Furthermore, patients who were responsive to antiarrhythmic medications had more conduction delay between the LA and PVs versus those who were not responsive. Ouyang et al also found that recurrent LA-PV conduction was the predominant finding in patients with recurrent arrhythmia post-PV antrum isolation.[6] In both studies, patients were successfully cured by re-isolating all of the PV antra. The majority of patients in these studies had paroxysmal, lone AF. These results are not necessarily appli-

Figure 1: Panels depicting the similarity in location of the radiofrequency lesions produced by various groups' approaches to atrial fibrillation ablation.



The upper left panel shows an outer view of a patient's left atrium as seen from the posterior aspect using threedimensional, multislice computed tomography. Seen clearly are the tubular portions of each of the four pulmonary veins (individually labeled). The borders between the antra of the pulmonary veins and the posterior wall of the left atrium are indicated by the small white arrows. The lower left panel shows a three-dimensional electro anatomical map (CARTO, Biosense Webster Inc.) of the left atrium (same patient as panel above) acquired during atrial fibrillation ablation guided by intracardiac echocardiography (ICE). Using ICE, the borders of the pulmonary venous antra can be accurately defined and lesions can be placed to completely surround and electrically isolate the antra. The red dots represent the anatomical locations of these lesions produced by ICE-guided ablation. The upper left panel shows the location of lesions produced using a CARTO-guided approach described by Morady and colleagues. The lower left panel shows the location of lesions produced using another CARTO-guided approach described by Pappone and colleagues. In all three cases, the location of the lesion sets is similar, encompassing the anterior and posterior borders of all four pulmonary venous antra. LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein, RSPV=right superior pulmonary vein, RIPV=right inferior pulmonary vein. (Reproduced from Verma et al, Circulation 2005, 112:1214-22 with permission from publisher Lippincott Williams &Wilkins)

cable to more persistent AF populations. Furthermore, wide PV antral isolation requires very extensive lesion sets, which presents risks including perforation and stroke. In particular, PV antral isolation requires a lot of ablation along the posterior LA wall, which presents a risk of collateral damage to the esophagus. All of these reasons have prompted investigators to search out alternative or adjuvant lesion sets that may be required to modify the atrial substrate for AF maintenance beyond trigger-based ablation.

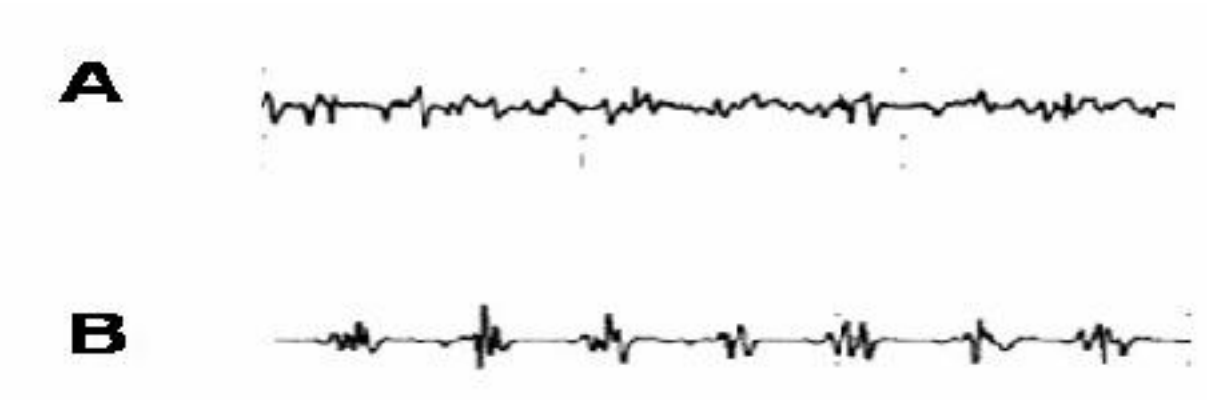
Substrate-Based Ablation

There is no general consensus on what exactly constitutes the "substrate" in clinical AF, making the use of this term somewhat problematic. It seems that when most clinicians talk about targeting the substrate for AF, they are referring to critical regions or components of the left atrial anatomy/eletrophysiology that are responsible for allowing AF to perpetuate. Investigators have proposed different ablation targets to try and identify these critical regions including complex fractionated electrograms (CFEs), dominant frequencies (DFs), and autonomic ganglionated plexi (GPs).

Complex Fractionated Electrograms

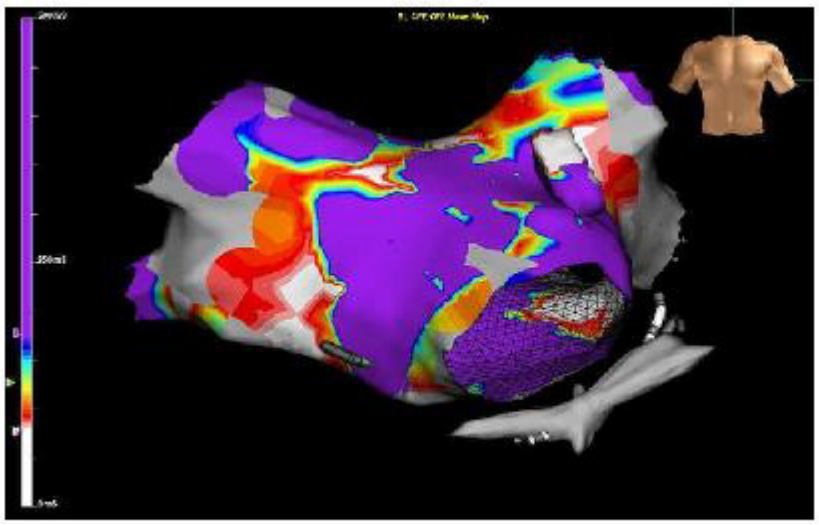
From early animal and human experiments, it was found that atrial regions exhibiting very rapid activation may represent critical rotors responsible for maintaining AF.[7] Furthermore, regions demonstrating very fragmented potentials, to the point of almost continuous baseline activity, may represent pivot points or regions of very slow conduction responsible for continued fibrillatory conduction.[8] Nademanee et al first described targeting these types of electrograms (EGMs) exclusively to ablate AF.[9] He defined so-called "complex fractionated atrial electrograms" as either EGMs with (1) two deflections or more and/or have a perturbation of the baseline with continuous deflections from a prolonged activation complex or (2) very short cycle length (<120 ms) with or without multiple potentials. These EGMs also typically have very low voltages of 0.06-0.25 mV. By ablating these targets, Nademanee described a 76% success rate after one procedure (91% after two). Others have also shown that by adding complex atrial electrograms to ablation, success rates may be increased.[10] However, targeting CFE either as a stand-lone or adjuvant technique is still subject to controversy. One reason is the subjectivity in identifying CFEs. Published articles have not been consistent in their definitions of CFE.[12] For example, some define any EGM with more than 2 components a "CFE" regardless of the cycle length or continuity of the signal (Figure 2). While an EGM with 2 or more components may technically be "fractionated," only low-voltage EGMs with rapid or continuous activity have been described as ablation targets or true complex fractionated electrograms (CFE). To this end, automated mapping algorithms have been developed to automati-

Figure 2: Examples of electro grams that have been labeled as complex fractionated electro grams



The electro grams in A are low amplitude, with multiple components to the point of having almost continuous deflection of the recording baseline. These electro grams are an example of a "complex fractionated electro grams" or CFE. The electro grams in B have two or three components and are therefore "fractionated." However, the electro grams are not low amplitude, there is not continuous electrical activity (lots of flat line between electro grams), and the cycle length is not particularly short.Thus, these electro grams would not be considered"CFE."

Figure 3: Example of a three-dimensional representation of the left atrium (AP view) with color-coded regions indicating areas of complex fractionated activity using an automated mapping algorithm (Ensite NavX, St Jude Medical, St Paul, MN).



By performing point-by-point recording of electro grams (EGMs), the algorithm automatically detects the number of local EGM peaks. By averaging the number of peaks over a period of several seconds, an average cycle length can be calculated. Regions of short cycle length (< 120 ms) represent regions of complex activity (either very

cally identify CFEs and the early results have been promising (Figure 3). Verma et al[11] reported on the use of an automated CFE mapping algorithm in a prospective, multicenter study. The study found that the algorithm accurately identified CFE when compared to independent, experienced investigators and that CFE ablation resulted in high rates of AF regularization and termination. Finally, as an adjuvant strategy, CFE ablation combined with PVI resulted in a significantly better outcome compared to PVI alone.

However, reliable, consistent identification is not the only potential limitation to the use of CFE. There is debate as to the temporal and spatial stability of CFE and whether these EGMs represent transient regions of wavefront collision as opposed to critical, stable regions of AF perpetuation.[12] These complex electrograms have been reported by some to be spatially stable and their elimination results in AF cycle length prolongation, regularization, and possibly long-term AF reduction.[9,13] More recently, Lin et al demonstrated that with an adequate sampling time of more than 5 seconds, the consistency in CFE sites both spatially and temporally is very high.[21] Some have also reported looking for such complex activity sites during sinus rhythm by examining the Fourier transform of sinus EGMs and looking for multiple late, rightward shifted frequencies or so-called "fibrillar" myocardium.[14]

Dominant Frequency

Trying to identify and interpret complex signals can be very challenging during AF. Therefore, some investigators have tried to use DF sites to identify regions of high frequency atrial activity. Sanders et al, for example, reported that AF termination or AF cycle length prolongation during ablation was usually seen while ablating over a DF site.[15] They also showed that the distribution of DF may vary from paroxysmal to permanent patients, with DFs less likely to be associated with the PVs in non-paroxysmal patients. However, like CFE, there is some question as to the temporal and spatial stability of DFs. Ng et al showed that DF values were significantly impacted by local EGM factors such as amplitude variation, frequency fluctuation, and EGM ordering or phase.[16] Thus, DF sites may not necessarily correlate with atrial regions exhibiting the most rapid or complex atrial activity. There have not yet been any studies validating the approach of targeting DF

sites for AF ablation.

Autonomic Ganglionated Plexi

It has been suggested that autonomic inputs from ganglionated plexi surrounding the heart may contribute to both the initiation and maintenance of atrial fibrillation (AF).[17] High-frequency stimulation of epicardial autonomic plexi can induce triggered activity from the pulmonary veins and also affect atrial refractory periods so as to provide a substrate for the conversion of PV firing into sustained AF.[17] Elimination of vagal inputs may prevent AF recurrence in both animal and patient models of vagal AF.[18, 19] In human AF patients, recent data has suggested that identification and ablation of autonomic ganglia during PV isolation may improve long-term success.[20] However, in another report, use of ganglionated plexus ablation alone in vagal AF patients had a success rate of less than 30%.[19] The location of these plexi has been correlated with the presence and location of CFE20, but whether targeting plexi alone will ultimately prove effective remains unclear.

The Need For Clinical Trials

Ultimately, several targets have been proposed for AF ablation, each with their own supporting evidence and limitations. It is also quite likely that for any given approach, there will be overlap in the targets that are ablated. Performing circumferential lesions around the PVs may not only isolate them, but may also eliminate some sites of CFE and some autonomic inputs. However, whether we need to systematically add other targets to PVI or whether we need to move beyond PVI as a whole remains a somewhat controversial issue. The only way to definitively determine the efficacy and utility of different approaches is to subject them to the rigor of randomized clinical trials. One such trial, Substrate versus Trigger Ablation for Reduction of Atrial Fibrillation (STAR-AF) will specifically look at the utility of targeting CFE versus PVI. In this randomized, three-arm, multicenter comparison, PVI will be compared to CFE alone as well as a hybrid procedure combining PVI and CFE in a largely persistent AF population. The primary outcome will be freedom from AF at one year. Canadian and European centers are now actively enrolling in the pilot phase of this trial and results should be available within the next year.

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