



Ablation of Longstanding Persistent Atrial Fibrillation

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Introduction

To prevent recurrence of paroxysmal atrial fibrillation (AF, events <7 days) isolation of pulmonary vein (PV) triggers results in success rates of up to 0.9 (i.e. 90%).¹ Recent evidence suggests that complete circumferential antral ablation is not even necessary for PV isolation.² When AF persists beyond one week, electrical and anatomic substrate remodeling typically occurs. Initially, when remodeling is slight, the arrhythmia can be terminated by PV isolation with only a few left atrial ablation lesions required in addition.³ However if longstanding persistent atrial fibrillation is present (defined as event duration > 6 months⁴ or > 1 year⁵) greater left atrial substrate modification is necessary.⁶⁻⁷ Since the atrial substrate is remodeled heterogeneously, the ablation protocol and outcomes are operator-biased, and left atrial flutters can occur after ablation.⁷ In longstanding fibrillation, large lesions are often needed with electrical isolation of large swaths of free wall, which may be difficult due to current limitations in catheter ablation technology.⁸ Chronically remodeled atria may become so structurally and electrophysiologically altered that arrhythmia is maintained even with extensive catheter ablation.⁹ Extensive lesion size can increase risk of collateral damage, affect atrial transport function and coronary sinus patency,^{3,7} it can promote arrhythmia development, and may even be proarrhythmic.³

To improve outcome in treatment of longstanding persistent AF, attention has centered on detection of areas of slowed conduction and wavefront pivot caused by tissue anisotropy, as well as regions of fibrotic change, both of which can cause electrogram fractionation.¹⁰⁻¹¹ Fractionated electrograms often include high frequency components, which represent potential triggers for onset and maintenance of fibrillation and are therefore candidate sites for ablation. In the time domain, high frequency components are manifested as more frequent electrogram deflections resulting in increased measured rate of occurrence. In the frequency domain, the dominant frequency (DF) i.e., the largest spectral component in the range of interest¹² can be measured to determine areas of high frequency. Indeed, in a prospective ablation study, targeting of high DF sites resulted in termination of AF in 53% of paroxysmal and 11% of persistent AF.¹³ When real-time electrogram analysis is available in the clinical EP lab, sites at which ablation prolongs cycle length are likely to be AF drivers.¹⁴ The endpoints for substrate ablation include elimination of fractionated signals or their transformation into discrete electrograms, as well as slowing or organization of local fibrillatory cycle length (thus diminishing frequency at sites of high DF).¹⁵ One significant problem with both time and frequency substrate mapping for identification of candidate sites is that changing electrogram morphology, along with motion artifact, can alter the electrogram profile and substantially affect accuracy.¹⁶⁻¹⁸

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Overview of the Study

In this journal review 'Outcomes of long-standing persistent atrial fibrillation ablation: A systematic review' by Dr. Anthony Brooks et al. is discussed.¹⁹ This comprehensive review reports on the effect of various ablation interventions on outcome in patients with longstanding persistent AF. The authors used the PubMed database to conduct a search of the literature from 1990 - 2009 for relevant studies. Included studies were separated by technique: PV isolation (PVI) alone, pulmonary vein antrum ablation with or without confirmed isolation (PVAI), linear ablation in addition to PVI/PVAI, posterior wall box isolation, the stepwise ablation approach, and targeting of complex fractionated atrial electrograms (CFAEs). A main finding was that the high variation in success, both within and between techniques, suggests that the optimal ablation method for longstanding persistent AF is as yet to be determined. However, the authors note that effective treatment is possible by using several isolation techniques in combination, with the inclusion of repeat procedures, and/or by including pharmacologic intervention when necessary. Part of the high variation between studies is likely due to the lack of uniform standards in reporting. For example, the duration from intervention to 'success' is investigator-defined.

Much of the findings of the Brooks et al. review¹⁹ is summarized in Table 1 of their study, entitled 'Single, multiple, multiple/antiarrhythmic drug-assisted clinical success and complication rates for persistent/long-standing persistent AF'. Means from their Table 1 are shown in row 1 of Table 1 below. For all studies included in the Brooks et al. review, the average number of patients enrolled was 51.7, with the success rate increasing from single ablation procedure (0.43) to multiple ablation procedures (0.62) to multiple + drug intervention (0.69). To contrast the results on the high versus

low end of the success rate scale, Table 1 of the Brooks et al. review was reordered according to the single-procedure success rate. From the reordered list, the means for all parameters when single procedure success was ≥ 0.5 are shown in row 2 of Table 1 below (greater success). The means for single procedure success ≤ 0.33 are shown in row 3 of Table 1 below (lesser success). In each case (all three rows), the mean number of patients N included in each study is similar. Additionally, the success fraction increases substantially from patients with a single procedure only to patients who have had multiple ablation procedures ($p < 0.01$ for each row). There is also an increase in success fraction from multiple procedure to multiple + drug (not significant). Although there are differences in the complication rate in Table 1, they are not significant due to the lower number of studies reporting this parameter.

Additional information can be gleaned by the types of interventions that were done for each type of procedure as compiled in Brooks et al. In the case of studies with single procedures having success rate ≥ 0.5 , five were PVI/PVAI + CFAE (one included linear ablation also), three were stepwise procedure studies, two were PVAI + linear ablation, and one each were CFAE, PVA, and posterior box only. Left atrial substrate ablation may therefore be important, particularly by targeting CFAE, to improve outcome in treatment of longstanding persistent AF. Yet, the best success rates are still at most 0.6 for single procedures, and even multiple procedures with pharmacologic intervention are maximally successful to ~ 0.8 . Hence, the Brooks et al. review highlights the need for better targeting of AF sources particularly for the 20% of patients in which the interventions were unsuccessful. In contrast, of the studies having a single procedure success rate ≤ 0.33 , four used CFAE ablation only, three used pulmonary vein isolation only, and in one there was pulmonary vein isolation with lin-

Table 1

Summary of Brooks et al. Findings

Type	# Patients	#Studies	Single	Multiple	Mult/Drug	Complic.
All	51.7 \pm 29.3	34	0.43 \pm 0.15	0.62 \pm 0.17	0.69 \pm 0.27	3.56 \pm 3.41
Single ≥ 0.5	48.0 \pm 23.7	13	0.58 \pm 0.08	0.76 \pm 0.09	0.81 \pm 0.12	3.29 \pm 2.52
Single ≤ 0.33	48.6 \pm 26.5	8	0.24 \pm 0.07	0.44 \pm 0.16	0.45 \pm 0.17	2.21 \pm 2.25

Calculated values are listed as mean \pm standard deviation. # = number, Single = single ablation procedure success rate, Multiple = multiple ablation procedure success rate, Mult/Drug = multiple ablation procedure success rate with drug intervention, Complic. = complications.

ear ablation. Thus the use of single interventions only during each procedure often have an unsuccessful outcome (Table 1).

Discussion and Future Directions

Several tools have recently emerged which may enhance targeting of arrhythmogenic left atrial sites. Although DF measurement has shown initial promise, methodological difficulties have become apparent.¹⁶⁻¹⁸ Using the standard approach to measure DF consists of filtering and rectification which distorts the electrograms, and the method is sensitive to additive random and phase noise (i.e., slight shifts in the local activation rate) which can render the measured DF less accurate.¹⁶⁻¹⁸ Recent work to reduce these effects include optimization of the bandpass and lowpass filter coefficients²⁰ as well as by using ensemble spectral analysis that does not require filtering.²⁰⁻²¹ Using these latter methods, the paroxysmal posterior - anterior-left atrial DF gradient was of greater significance as compared to the same gradient as measured with the standard approach.²⁰ Although high DF regions can represent epicardial breakthrough rather than focal drivers of arrhythmia,²²⁻²³ the significant differences in DF spatial gradient and differences between paroxysmal and persistent AF may yield important mechanistic information as well as being a tool for mapping heterogeneous areas. Additionally, CFAE are currently identified either by visual inspection or by an automated peak-counting process.²⁴ Perhaps more pertinent to characterization of CFAE is the electrogram morphology.²⁵ This new automated method was used to detect significant differences in the character of CFAE in paroxysmal versus longstanding persistent AF patients, as well as significant spatial differences in CFAE morphology at PV ostia versus the left atrial free wall. Such information is potentially useful to distinguish CFAE regions which are crucial to the arrhythmogenic process from bystander areas.

In summary, the Brooks et al. review¹⁹ is an important compilation that shows that there is a wide variation in success rates in studies of patients with longstanding persistent AF. Many of the studies with greatest single-procedure success rate included intervention by substrate mapping and ablation, particularly via targeting of CFAE,

in addition to PV isolation. The review is therefore suggestive of the need to increase accuracy in targeting arrhythmogenic zones in the left atrium. Development of new quantitative methods for substrate characterization, in combination with imaging approaches, can potentially be useful to improve mechanistic understanding of the relationship between anatomic and electrophysiologic remodeling in the left atrium, their relationship to pulmonary vein triggers, and subsequent development of longstanding persistent atrial fibrillation.

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