Atrial Fibrillation Ablation

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Abhishek J. Deshmukh and Douglas L. Packer

Abstract

Atrial fibrillation (AF), an accruing epidemic, is projected to have an incidence of approximately 16 million by 2050. A 15% increase in the hospitalization rate for AF was reported during the past decade implying significant burden on health care delivery system. According to the 2014 AHA/ACC/HRS guidelines for management of AF, catheter ablation is indicated in patients with symptomatic, paroxysmal AF who have not responded to or tolerated antiarrhythmic medications and in selected patients with symptomatic, paroxysmal AF *prior* to a trial of medical therapy, provided that it can be performed at an experienced center. In this chapter, we summarize the state of the art of catheter ablation and how it may utilized to its maximum advantage in patients with this common arrhythmia.

Keywords

Atrial fibrillation • Pulmonary veins • Ablation

Introduction

Atrial fibrillation (AF), an accruing epidemic, is projected to have an incidence of approximately 16 million by 2050 [1]. A 15% increase in the hospitalization rate for AF was reported during the past decade implying significant burden on health care delivery system [2]. Multiple studies have shown catheter ablation to be superior to anti arrhythmic therapy in the management of patients with AF [3–6]. According to the 2014 AHA/ACC/HRS guidelines for management of AF, catheter ablation is indicated in patients with symptomatic, paroxysmal AF who have not responded to or tolerated antiarrhythmic medications (Class I) and in selected patients with symptomatic, paroxysmal AF *prior* to a trial of medical therapy, provided that it can be performed at an experienced center (Class IIa) [7]. The past decade saw electrophysiologists pursuing high success rates with extensive ablation. This helped us understand certain adverse sequelae such has, recurrent left sided flutters, pulmonary vein stenosis, atrioesophageal fistula, silent strokes and stiff left atrial syndrome. In current times, we are challenged to further clarify the complex mechanisms of AF to make ablation of

A.J. Deshmukh, M.D. • D.L. Packer, M.D. (✉)
Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic/St. Marys Campus,
200 First Street SW, Rochester, MN 55905, USA
e-mail: deshmuhk.abhishek@mayo.edu; packer@mayo.edu

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AF safer and effective. The irrefragable litmus test for success for any technology or innovation in this field is to provide a viable choice for our patients. The ultimate idea is to go beyond "one size fits all" ablation strategy and tailor to the particular AF mechanism of the particular patient. In the following sections, we discuss the current paradigm of atrial fibrillation, recent advances and a brief look into the future.

Basis for Pulmonary Vein Isolation

The seminal observation that rapid depolarizations from the pulmonary veins (PVs) can initiate and maintain AF led to the development of novel mechanistic and therapeutic paradigms [8] (Fig. 12.1).

It is well established that the PVs play a major role in triggering and maintaining AF, as established by animal and human models, especially in the setting of paroxysmal AF. Fibrillatory conduction is likely initiated by rapid discharges from one or several focal sources within the atria; in most patients with AF (94%), the focus is in one of the PVs. The role of PVs in the initiation and perpetuation of persistent AF seems less prominent than in the setting of paroxysmal AF, likely secondary to the electrical and structural remodeling associated with persistent AF (Fig. 12.2). Evidence exists to suggest that the PVs are capable of sustaining automaticity. Blom et al. [9] studying the human embryo using monoclonal antibodies to stain conducting tissue, documented the presence of cardiac conduction tissue within the PV during embryonic development. However, although node-like cells have been observed in the PVs of rats, a detailed histology of the atrial myocardial sleeves in human hearts has thus far failed to reveal any node-like structures. Experiments have demonstrated early and delayed after-depolarization and automatic high-frequency irregular rhythms related to calcium-sensitive inward currents following infusion of ryanodine, atrial distension, rapid atrial pacing, or congestive heart failure, but most groups have not observed these in normal PV cardiomyocytes [10]. A possible role for re-entry has been implicated in the genesis of spontaneous activity from the PV. Conduction delay and block (source—sink mismatch) have been associated with changing myocardial fiber orientation, producing nonuniform anisotropy and fractionated electrograms in PVs and at the PV-left atrial (LA) junction. Optical mapping studies of normal canine PVs, demonstrated both anisotropic conduction and repolarization heterogeneity [11]. Clinically, ectopy-initiating episodes of AF have been largely localized to the distal PV musculature from multiple PVs or from multiple sites within a given PV, which after isolation could occur proximal to the ablated site. Chen et al. demonstrated that the distal PV had significantly shorter refractory periods than the adjacent LA [12]. Jais et al. demonstrated distinctive electrophysiologic properties in the PVs of patients with AF (compared with controls), with shorter PV refractory periods, more frequent and greater decremental conduction to the LA, and a propensity for PV extrastimuli to initiate AF [13]. Based on these clinical and basic electrophysiologic findings, the mechanisms of PV arrhythmogenesis is likely to be a combination of abnormal automaticity, triggered activity, and multiple reentrant circuits.

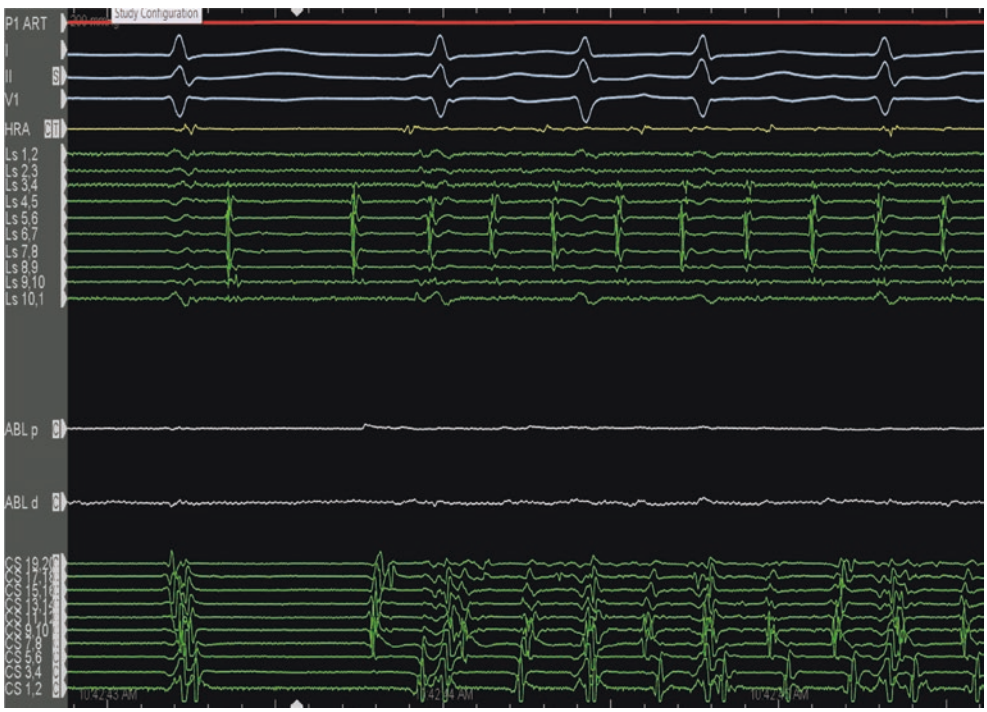

Fig. 12.1 Initiation of atrial fibrillation. Circular mapping catheter is placed in left superior pulmonary vein. Trigger noted earliest from this vein resulting in induction of atrial fibrillation

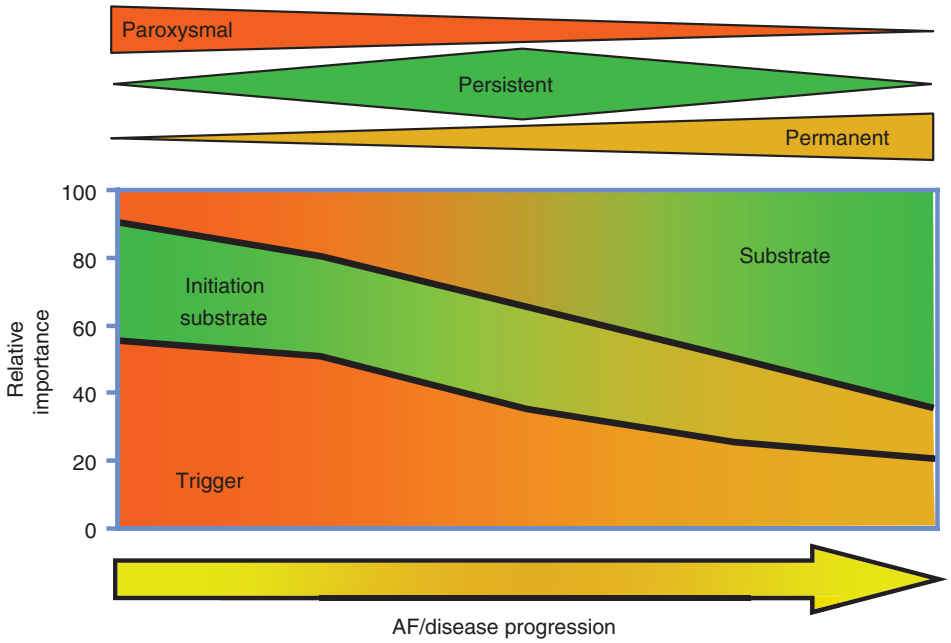

Fig. 12.2 Underlying pathogenesis of atrial fibrillation. AF is a two part disease of trigger and substrate

Pulmonary Vein Anatomy and Signals Assessment

The most important anatomic landmark relevant to AF ablation is the PV ostium. Thus regardless of the mechanism, ablation is frequently targeted to electrically isolate this substrate from the rest of the atrium. The venoatrial junctions of the pulmonary and other thoracic veins are highly complex structures [14]. Syncytial atrial myocardium extends into the veins however the orientation of the fibers typically changes around the venoatrial junction. This transition in fiber orientation, however, is gradual, and no distinct anatomic landmark (valves, ridge, etc.) clearly demarcates vein from atrium. Hence identification of true PV ostium is not possible despite advanced imaging. In some patients, the PVs may first drain into a common antrum, which then connects to the remainder of the atrium. Histologically and developmentally, the antrum, and for that matter, the proximal PVs, are no different from the atria itself showing venous and atrial myocardial components suggesting common developmental origin. During embryonic development, the common PV (sinus venosus origin) is incorporated into the left atrium. An immunohistochemical study demonstrated that the histologic characteristics of the PVs and the smooth-walled portion of the left atrium are identical explaining why the antral regions of the PVs and the posterior left atrium also are arrhythmogenic [15].

Assessing PV Potentials

PV's have its own unique electrical signature. Characteristic electrograms are recorded with single-electrode or multi-electrode mapping catheters placed within the PV. These electrograms will depend on the vein mapped, type of mapping catheter and if prior ablation has been performed. However generally an initial far-field electrogram followed by an isoelectric period, and then a sharp near-field deflection called the PV potential is recorded. The far-field signal usually represents left atrial activation. The exact reason of the isoelectric period between the left atrial potential and the PV potential is unknown, but possible explanations include ostial delay secondary to fiber orientation, ostial fibrosis, remnant nodal tissue, and a smooth muscle and cardiac syncytial interface. This delay is even better assessed with incremental coronary sinus pacing. Due to the anatomic proximity of the PVs to several other electrically active structures, complex signals may be picked up by catheter placed in the PV. For example, a catheter placed in the left upper PV may record electrical activity in the left atrial appendage, ipsilateral PV, vein of Marshall, and left atrium. In general, only the PV potential itself is near-field; all other structures picked up by the "antenna" of the mapping catheter are blunted and far-field. A mapping catheter placed in the right upper PV may record electrical activity in the right upper PV, right middle PV, right lower PV (particularly a superior branch), right atrium, left atrium, superior vena cava, and azygos vein. In fact, the far-field electrogram seen on a circumferential mapping catheter placed in the right upper PV almost always is a right atrial electrogram (not left atrial). However, this criterion alone is insufficient for identifying the true PV potential. If a catheter is deep within a PV where no PV musculature is present, then left atrial appendage electrograms will appear relatively near-field. Similarly, when radiofrequency ablation has already been performed, edema near the PV os and inadvertent ablation within the PV (more frequent than typically realized) will cause PV potentials to be less

sharp and less near-field in character. Various pacing maneuvers such as paravenous, perivenous, differential pacing are utilized to decipher each potential. We refer you to the classic reviews by Dr. Samuel Asirvatham on pulmonary vein pacing maneuvers [14, 16–18].

Techniques and Results of PVI

The initial description of PV trigger ablation consisted of focal ablation within the PVs. Initial isolation approaches were targeting specific pulmonary vein triggers utilizing induction strategies. These pulmonary vein triggers were then targeted with either focal or segmental isolation [8, 12]. However an induction strategy as a stepwise approach to pulmonary vein isolation was fraught with difficulties such as consistently initiating the arrhythmogenic foci during the electrophysiology study. In addition, during subsequent studies in patients with AF recurrence, different ectopic foci from the same or different pulmonary veins were often found to be active contributors to the arrhythmia. This approach had minimal long-term benefit, and was associated with a significant risk of PV stenosis. Subsequent evolution of the procedure involved segmental ablation at the anatomic ostium of the PVs, as defined by angiography or ICE, to isolate muscle sleeve connections between the PV and left atrium electrically. This approach is commonly referred to as segmental ostial PVI.As such, empiric isolation of all pulmonary veins became the preferred strategy [19]. However, it is important to recognize that a close examination of long-term outcomes does not demonstrate that empiric isolation of all pulmonary veins is superior to treating only those veins that are arrhythmogenic [20]. The technique further evolved targeting the left atrial tissue more proximal to the PV ostium, in a region defined as the PV antrum [21]. To achieve antral PVI, multiple approaches with different mapping systems have been described. These include electroanatomic mapping using three-dimensional nonfluoroscopic systems, and circular mapping techniques guided by imaging the PVs through ICE or angiography. Wide antral PV isolation (WACA) guided by recordings from a circular mapping catheter has been demonstrated superior to other ablation techniques in studies of direct comparison [22]. With circumferential PV ablation strategies, contiguous lesions can sometimes be created without necessarily achieving complete conduction block. Thus, post-ablation reentrant atrial tachycardias have been reported in up to 20% of patients treated with this approach [23]. Wide antral PVI is more efficacious than ostial PVI in achieving freedom from any atrial tachyarrhythmia recurrence at long-term follow-up [24]. The importance of a wider antral isolation encompassing the posterior wall between the PVs has been suggested in several preliminary studies. The main advantage of wide antral PVI is the empirical elimination of triggers arising from the left atrial posterior wall, which should be considered as an extension of the PVs from an embryologic, anatomic, and electrophysiologic standpoint. Preclinical studies have demonstrated rotors and high-frequency AF sources within the left atrial posterior wall, and observations from intraoperative AF ablation have confirmed a significant role of the posterior wall in triggering and maintaining the arrhythmia [25].

As mentioned, the majority of the studies investigating the role of PVI for the long-term maintenance of sinus rhythm have predominantly enrolled patients with paroxysmal AF; the role of PV triggers in patients with nonparoxysmal AF has not been investigated in a systematic fashion.

Pulmonary Veins Reconnection

The original promise and likely potential for this groundbreaking discovery remains largely unfulfilled due to PV reconnection. Indeed, increasing pessimism with regard to the long term outcomes for curing AF now appears to be the norm. What has remained unclear is, if our lack of progress is a fundamental flaw in the hypothesis of PV-based arrhythmogenesis, or whether we simply do not know how to permanently isolate the pulmonary veins. One basic assumption made when raising the question if pulmonary vein isolation is enough for a "cure" or durable therapy for AF is that the index ablation procedure resulted in permanent isolation of the pulmonary veins. Reconnection of the PVs represents the dominant mechanism of arrhythmia recurrence after PVI. Observational studies reporting the findings at repeat procedures showed a prevalence of PV reconnection ranging from 80 to 100% of patients [26]. In long-term follow-up study that investigated the rate of pulmonary vein reconnection after initial isolation, 53% of 161 patients were free of AF. In 66 patients, a repeat ablation was performed for repeat arrhythmia. The rate of pulmonary vein reconnection was strikingly high at 94% (62 of 66 patients) [27]. The importance of pulmonary vein reconnection has been confirmed in other studies and has led to the postulate that electrical reconnection of the veins is an important mechanism if not the sole reason for AF recurrence following catheter ablation [27, 28]. There are several potential mechanisms that may underlie pulmonary vein reconnection. First, it is possible that the initial procedure failed to achieve complete electrical isolation of the pulmonary vein. Incomplete isolation is felt to result from residual gap(s) within the encircling lesion set or lack of transmural lesions [29, 30]. As such, it is could be inferred that early recurrence of AF post ablation may be an early marker of incomplete procedural pulmonary vein isolation. This hypothesis is supported by an interesting study of 12 patients that underwent a maze procedure after a failed radiofrequency ablation. Importantly, myocardial biopsies showed anatomic gaps and/or nontransmural lesions in pulmonary veins that had reconnected [31]. Enhanced

post-procedural imaging has also added further supported to this hypothesis. In a canine study in which endocardial conduction block was demonstrated, post procedural MRI identified gaps within the line of ablation. Finally, long-term follow up data has demonstrated that those pulmonary veins with MRI identified gaps were more likely to become electrically reconnected with symptomatic recurrences [29]. Currently we can isolate the veins; however there is no real time marker to suggest if the lesions are transmural. Certain indirect assessments as discussed below can be used; however lack of real time assessment of transmural lesions remains the holy grail of modern day electrophysiology.

Maximizing Durable Pulmonary Vein Isolation

Based on available evidence, achievement of permanent PV isolation is considered the main goal of current ablation approaches for AF [32]. As of now, there are no proven ways to improve long-term durable pulmonary vein isolation, largely because we are just beginning to realize the frequency of reconnection in patients without recurrence of arrhythmia. There are several technologies and approaches that have been advocated to improve the likelihood of transmural lesion formation and durable pulmonary vein isolation. The efficacy of these technologies is largely based upon periprocedural data with the previously noted limitations, but the hope is that acute or periprocedural results will translate to enhanced long-term outcomes.

Open-irrigated catheters with contact force sensors (Thermocool® SmartTouch®, Biosense Webster, Inc., and TactiCath™, Endosense SA, Meyrin, Switzerland) have been made recently available for clinical use. These catheters contain sensors that provide real-time information on the tissue-catheter contact force and have the potential to significantly increase the safety and efficacy of PVI [33, 34]. In the Touch+ for Catheter Ablation (TOCCATA) trial, a multicenter feasibility and safety study, 32 patients with paroxysmal AF underwent PVI with the TactiCath catheter [35, 36]. In this study, tissue-catheter contact force over time (evaluated as force-time interval) was a predictor of arrhythmia-free survival over follow-up. In particular, the analysis of the force-interval integral showed a recurrence rate of 75% in patients treated with <500 g compared to 31% of patients treated with >1000 g contact force. These results have been replicated by Neuzil et al. in the EFFICAS-I trial [33]. These authors studied 46 patients with paroxysmal AF undergoing PVI with the TactiCath catheter, and operators were blinded to the contact-force information. All patients underwent a second procedure at 3 months to evaluate the presence of persistent PVI and the location of ablation gaps. Of note, 26/40 patients undergoing a repeat procedure over follow-up showed the presence of ≥1 ablation gaps; gaps were more frequently found at regions where ablation lesions were delivered with <20 g initial force and <400 g of contact force-time integral. Natale et al. recently reported the results of the SMART-AF trial evaluating the Thermocool SmartTouch catheter. In this multicenter study, 172 patients with drug-refractory symptomatic paroxysmal AF underwent PVI. At 12 months, the cumulative freedom from any atrial tachyarrhythmia recurrence was 72.5%. Of note, in this study the investigators could select the contact force parameters discretionally; when the contact force employed was in the preselected working ranges ≥80% of the time, outcomes were 4.25-times more likely to be successful [34]. A subsequent metaanalysis showed that the use of contact force technology decreases AF recurrence at a median follow-up of 12 months and also led to decreased use of RF during ablation. There was no difference in total procedure length and fluoroscopy exposure.

Methods of checking for durable lesion sets have also been explored. Dormant conduction can be identified by use of intravenous adenosine that hyperpolarizes atrial cell membranes allowing transient conduction at sites with partial ablation. Adenosine reduces LA and PV action potential duration but significantly hyperpolarizes RMP only in PV cells. This differential action on RMP is due to larger IKAdo in PV than in LA and PV cells having smaller IK1 (and therefore less negative RMPs) than LA cells. Ablation by RF energy significantly changes cellular electrophysiological properties, producing potentially reversible membrane depolarization and loss of cellular excitability. Hyperpolarization facilitates the closure of the inactivated sodium channels, making them available for activation. This results in resumption of conduction in tissue where reversible thermal heating has occurred. This premise has been used by multiple studies to assess gap in the ablation line. Although further ablation at these sites may improve AF-free period, paradoxically it also identifies those patients with a greater likelihood of AF recurrence despite additional ablation reflecting suboptimal ablation [37]. Macle et al. have recently reported the benefit of adenosine testing after initial PV isolation to improve outcomes in patients with paroxysmal AF [38]. They found that adenosine unmasked dormant PV conduction in 53% of patients studied. Further, iterative elimination of the elicited PV conduction significantly reduced the recurrence of symptomatic atrial arrhythmia after a single ablation procedure (success rate 69.4% with additional ablation vs. 42.3% with no further ablation). This absolute risk reduction of 27% translates into needing to treat 3.7 patients for benefit [38]. However no significant reduction in the 1-year incidence of recurrent atrial tachyarrhythmias by ATP-guided PVI compared with conventional PVI by another recent study [39].

Another approach to treat potential conduction gaps is to perform further ablation at sites that demonstrate pace capture along the ablation line. In a recent study investigators were able to achieve PVI in 95% of PV's using pace-guidance

alone, as assessed by circular mapping catheter data that was blinded to the operator [40]. In a prospective randomized study, same group noted 82.7% patients were free of AF at 1 year in the pace map group [41].

Beyond identification of gaps, efforts have also been directed in preventing these gaps during ablation. Steerable sheaths were designed to improve access to and contact with ablation target sites. One randomized controlled trial compared the use of steerable sheaths with the use of non-steerable sheaths in AF ablations [42]. Although the rate of acute PV isolation and total RF application time did not differ between the two groups, single procedure success was significantly higher in patients treated with a steerable sheath (76% vs. 53% at 6 months), which highlights the importance of good wall contact to achieve transmural and durable lesions.

The optimum time for ablation at each site without collateral damage is still not known. Surrogates of transmural lesions such as impedance drop change in unipolar electrograms have been studied [43–45].

Beyond electrophysiological innovation, the adoption of general anesthesia is has been shown to improve the procedural success. In a multicenter trial, Di Biase et al. randomized 257 consecutive patients undergoing a first AF ablation procedure to general anesthesia or conscious sedation. At 17 ± 8 month follow-up, 69% patients assigned to conscious sedation were free of atrial arrhythmias off antiarrhythmic drugs, as compared with 88% patients randomized to general anesthesia ($P < 0.001$). In this study, all patients with recurrence had a second procedure. Interestingly, at the repeat procedure, 42% of PVs in the conscious sedation arm had recovered PV conduction compared with 19% in the general anesthesia group ($P = 0.003$) [46]. Better and more stable tissue-catheter contact due to controlled breathing patterns and elimination of patient movements may provide an explanation to these findings. Hutchinson et al. showed similar results in an observational study [47]. The authors reported that the systematic implementation of general anesthesia and high-frequency jet ventilation together with the use of steerable sheaths and anatomic image integration with merged computed tomography/magnetic resonance imaging scans resulted in significantly better long-term arrhythmia-free survival compared to historical controls undergoing ablation under conscious sedation.

Complex Fractionated Atrial Electrograms

Complex fractionated atrial electrograms (CFAEs) during AF are thought to represent either continuous reentry of the fibrillation waves into the restricted area or an overlap of different wavelets entering the same area at different times [48]. These complex electrical activities have a relatively short cycle length and heterogeneous temporal and spatial distribution in humans. Ablation of these electrograms has been performed with the aim of eliminating wavelet reentry, thus preventing AF from perpetuating. Nademanee et al. were the first to report the success of pure CFAE ablation [49]. CFAEs are defined as low voltage atrial electrograms (ranging from 0.04 to 0.25 mV) that have fractionated electrograms composed of two deflections or more, and/or have a perturbation of the baseline with continuous deflection of a prolonged activation complex. CFAE have a very short cycle length (≤120 ms) with or without multiple potentials; however, when compared to the rest of the atria, this site has the shortest cycle length. The following key areas have demonstrated a predominance of CFAE: (1) the proximal coronary sinus; (2) superior vena cava–RA junction; (3) septal wall anterior to the right superior and inferior PVs; (4) anterior wall medial to the LA appendage; (5) area between the LA appendage and left superior PV; and (6) posterosuperior wall medial to the left superior PV. A customized software package to assist in the process of mapping (CFAE software module, CARTO, Biosense-Webster, Diamond Bar, CA, USA) has been developed [50]. The software analyzes data on atrial electrograms collected from the ablation catheter over a 2.5-s recording window and interprets it according to two variables: (1) shortest complex interval (SCL) minus the shortest interval found (in milliseconds), out of all intervals identified between consecutive CFAE complexes; and (2) interval confidence level (ICL) minus the number of intervals identified between consecutive complexes identified as CFAE, where the assumption is that the more complex intervals that are recorded—that is, the more repetitions in a given time duration—the more confident the categorization of CFAE. Information from these variables is projected on a three-dimensional electroanatomic shell according to a color-coded scale. This allows targeting and retargeting of areas of significant CFAE.

Nandemanee reported a single-procedure success rate of 63% at 12 months that improved to 77% with repeat procedures in 19 of the 64 patients. Nevertheless, similar results at that magnitude have not been replicated by other studies. Subsequent studies analyzed the additive effect of CFAE ablation to PVI. Hayward et al. performed a metaanalysis of eight controlled studies comparing the effect of PVI with CFAE ablation versus PVI alone in patients with paroxysmal and non-paroxysmal AF ($N = 481$). The authors found a slight benefit with the addition of CFAE ablation, with a relative risk of 1.15 (CI 1.2–1.31, $P = 0.03$). This statistical difference was primarily driven by studies on patients with non-paroxysmal AF. Similar results were published in a meta-analysis by Kong et al., yet this group also analyzed the drawbacks of this technique and showed that adjunctive CFAE ablation increased procedural, fluoroscopy, and RFA times [51]. Recently the STAR AF collaborators randomized patients with persistent atrial fibrillation, and found

no reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary-vein isolation.

Linear Ablation

Linear ablation paradigm is based on compartmentalization of the atria with the aim of preventing the formation of macroreentrant circuits. Ablation lines include a roof line, a mitral isthmus line, posterior box line, anterior line or any other line which could be used to compartmentalize the atrium further. Issues involved beyond collateral damage are to ensure presence of bidirectional block. If the line is not blocked, then it can further promote macroreentrant flutters.

Roof Line

Hocini et al. was the first to describe the benefits of a complete linear block by creating a roof line joining the right and left superior PVs in patients with paroxysmal AF [52]. This prospective randomized study demonstrated the feasibility of achieving complete linear block at the LA roof, which resulted in the prolongation of the fibrillatory cycle, termination of AF, and subsequent non inducibility of this arrhythmia in the electrophysiology laboratory. Roof line was also associated with an improved clinical outcome compared with PVI alone (87% vs. 69%, P = 0.04) [53].

Mitral Line

In a study by Jais et al., mitral isthmus block was achieved in 92% of patients. At 1 year after the last procedure, 87% patients with mitral isthmus ablation versus 69% without (P = 0.002) were arrhythmia free, with mitral isthmus ablation being the only factor associated with long-term success [54]. Fassini et al. showed that patients who had additional mitral isthmus ablation but did not achieve bi-directional block did not fare better than patients who had pulmonary vein isolation only [55]. In a randomized trial, Pappone et al. found that additional linear ablation (roof and mitral isthmus) significantly reduced the incidence of macroreentrant flutters without affecting AF recurrence [56, 57]. A gap in the mitral isthmus line is undoubtedly a pre-requisite for the development of postprocedure macroreentrant peri mitral flutter. It is observed from several studies that these "gaps" do not always lead to clinical tachycardia. In fact, the majority of these "gaps" do not manifest as peri mitral flutter [58]. It may be because "gaps" alone are not sufficient to support macroreentrant tachycardia and other factors may be necessary for initiation and/or perpetuation of macroreentry. In fact, Bai et al. suggested that for treatment of peri mitral flutter, the strategy of eliminating PV and non-PV triggers may be superior to mitral isthmus ablation [59].

Role of Non-PV Sources

Despite persistent PV isolation, a subset of patients may still continue to experience recurrent arrhythmia. In a recent study, Dukkipati et al. reported a 1-year AF recurrence rate of 29% despite proven permanent PVI [60]. The reasons underlying the lack of sustained response to PVI are still unclear, although the occurrence of triggers outside the PV region has been shown to play an important role in observational studies. High dose isoproterenol infusion (up to 20 μg/min) together with cardioversion of induced AF is the protocol we follow to provoke latent non-PV triggers. Typically, non-PV triggers cluster in specific regions such as the coronary sinus, the inferior mitral annulus, the interatrial septum particularly at the fossa ovalis/limbus region, the left atrial appendage, the Eustachian ridge, the crista terminalis region, and the superior vena cava [61, 62]. Other sites responsible for AF triggers are the persistent left superior vena cava and its remnant, the ligament of Marshall [63, 64]. Empirical ablation at common origins of trigger did not improve outcomes in a recent randomized trial and is not part of the standard ablation strategy at this time [62]. The optimal strategy to target non-PV sources varies according to the site of origin of the triggers. While for many areas focal ablation is typically sufficient to eliminate the triggers, isolation for triggers arising from the coronary sinus and the left atrial appendage has resulted in improved success. Once all the arrhythmia triggers have been eliminated, the incremental value of additional substrate modification with linear ablation and/ or ablation of complex fractionated atrial electrograms remains unproven [61].

Ganglion Plexi Modification

Autonomic nervous system (both sympathetic and parasympathetic) plays and important role in modulating AF triggers and substrate. High-frequency stimulation of epicardial autonomic plexuses can induce triggered activity from the PVs and potentially shorten the atrial refractory periods to provide a substrate for the conversion of PV firing into sustained AF. High-frequency stimulation is performed in the LA adjacent to the antral region of the PVs. Once identified, the location of a ganglionated plexus is tagged on the electroanatomical map. Generally, the four major LA ganglionated plexuses can be identified and localized using high-frequency stimulation in the majority of patients; though, it is not

uncommon that one or more ganglionated plexuses cannot be identified, especially in patients with persistent AF. RF is delivered after all ganglionated plexus sites have been identified. At present, no reports have suggested that targeting of ganglionated plexuses as a stand-alone procedure will consistently terminate AF or prevent its reinitiation. On the other hand, several studies combining ganglionated plexus mapping and ablation with PV-based ablation procedures for the treatment of AF have produced promising but variable results. For example, in a study of 242 paroxysmal AF patients, three groups were compared; (1) standard pulmonary vein isolation; (2) ablation of the main ganglion plexi of the left atrium; and (3) both pulmonary vein isolation and left atrial ganglion plexi ablation. Over a 2-year follow-up period freedom from AF or atrial tachycardia was achieved in 56%, 48%, and 74% of the patients, respectively (P = 0.004) [65]. Although there was increased benefit with combining ablation with ganglion plexi modification, success rates without pulmonary vein isolation were worse than the standard approach. The synergy noted with ablation of both targets may be explained in a study of 63 patients with paroxysmal AF. Ganglion plexi ablation alone before pulmonary vein isolation significantly decreased the occurrence of pulmonary vein firing in 75% of patients and reduced the inducibility of sustained AF in 68% [66].

Focal Impulse and Rotor Modulation

Localized sources for AF were postulated by Garrey, Mines, and Lewis in the early twentieth century, and reported in seminal canine studies by Schuessler, Cox, and Boineau who showed that AF is often sustained by stable, relatively large drivers [67]. Narayan et al. hypothesized that human AF may be sustained by localized sources such as electrical rotors and focal impulses. Focal Impulse and Rotor Modulation (FIRM) mapping is a novel technique to identify patient-specific AF mechanisms, by recording AF electrograms in a wide field-of-view across the majority of both atria then using physiologically-directed computational methods to produce maps of AF propagation. FIRM records AF in both atria using direct contact electrodes, the gold standard particularly for low-amplitude AF electrograms, in the form of 64-pole basket catheters each of 8 splines containing 8 electrodes. Basket catheters are advanced from the femoral vein into the right atrium (RA) or, transseptally, to the left atrium (LA). Recordings are made sequentially using one basket in each atrium in turn. Electrodes are separated by 4–6 mm along each spline and by 4–10 mm between splines. Catheters are manipulated to ensure good electrode contact and electrode locations are verified within the atrial geometry using fluoroscopy or electroanatomic mapping [68]. In an extended follow-up study, patients who underwent FIRM-guided ablation maintained higher freedom from AF versus those who underwent conventional ablation [68]. Overall, FIRM mapping revealed AF rotors or focal sources in 98% of the patients, for 1.9 ± 1.1 concurrent sources per patient, 67% of which were in the left atrium and 33% in the right atrium [68]. Importantly, AF sources were analyzed to be coincidentally ablated in 45% of conventional cases (e.g., at the LA roof or near the PVs). These data might help explain why wide area PVI is more effective than more distal PVI, and especially, why patients might remain free of AF recurrences despite PV re-connection. The encouraging results obtained by elimination of patient-specific rotors were recently confirmed in a multicenter study [69].

In the CONFIRM trial, these sources were detected in 97% of 107 patients undergoing paroxysmal or persistent AF ablation [68]. The acute end point (AF termination or consistent slowing) was achieved in 86% of cases guided by focal impulse and rotor modulation (FIRM) versus 20% of conventional ablation cases (P < 0.001). During a median follow-up of 273 days following a single procedure, FIRM-guided cases had higher freedom from AF (82.4% vs. 44.9%; P < 0.001). Interestingly, a different group from Taiwan using a distinctive optical mapping system also demonstrated the possibility of localizing rotors in the LA in a canine heart failure model in which AF was induced by infusing acetylcholine. Epicardial ablation of the rotor anchoring sites suppressed AF inducibility in 12 out of 13 Langendorff-perfused left PV–LA preparations [70]. The use of rotor mapping and ablation should be considered investigational, and a large, multicenter, randomized controlled trial comparing FIRM versus conventional ablation versus FIRM and PVI must be designed and conducted to validate the efficacy and safety of this technique.

Balloon Based Technology

Cryoballoon

Balloon-based ablation technologies have been developed with the aim of achieving PVI in shorter time and minimizing the operator dependency of manual procedures. The cryoablation balloon catheter (cryoballoon) has been evaluated quite extensively in clinical studies. The *cryoballon* is available in two diameter sizes, namely, 23 and 28 mm. Once the balloon is inflated at the ostium of the PVs, it is capable of achieving PVI within few (usually 2) cryoablation. The most important clinical study evaluating the effectiveness of ablation of AF with the cryoballoon has been the Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP-AF) trial, which has been recently published [71]. In this study, 245 patients with at least two documented episodes of drug-refractory paroxysmal AF were randomized in a 2:1 ratio to the cryoablation group or the antiarrhythmic drug therapy group. Over 12 months of follow-up, 69.9% of patients

treated with cryoablation were free of AF, compared with only 7.3% of the antiarrhythmic drug group ($P < 0.001$ for comparison). Twenty-nine patients (11.2%) developed post-procedural phrenic nerve palsy, which persisted beyond 12 months in four patients [71]. More recently, Metzner and co-workers reported a 12% incidence of esophageal thermal lesions at routine esophagogastroduodenoscopy in patients who underwent cryoballoon PVI with the 28-mm device [72, 73]. In addition, cases of atrioesophageal fistula have been reported with the cryoballoon technology [74–76]. This might reflect the higher power of the new cryoablation platform, and would suggest routine esophageal temperature monitoring also with the cryoballoon device. Prospective and retrospective large study didn't find any difference in freedom from AF when compared to radiofrequency energy [77, 78]. Further research is warranted to better evaluate the long-term arrhythmia-free survival and the safety profile of the cryoballoon device.

Laser-Balloon Ablation

The balloon-based laser ablation system (CardioFocus, Inc., Marlborough, MA) is a 12-F balloon catheter with a 2-F endoscope at the proximal end of the balloon. The balloon is designed to be inflated at the ostium of the PV to occlude the blood flow and deliver circumferential ablation. The last generation of the laser-balloon catheter is a compliant and sizeable balloon that has the capacity of delivering spot laser lesions over a wider range of energies. Dukkipati and co-workers recently reported their clinical experience with the compliant laser-balloon system in 200 patients with drug-refractory paroxysmal AF [79]. Successful PVI was achieved in 78.4% of cases with a single encircling lesion, and in 98.8% after an average of 1.3 attempts/PV. A total of 181 patients completed the 12-month follow-up achieving an arrhythmia-free survival off antiarrhythmic drugs of 60.2% (95% CI 52.7–67.4%). Phrenic nerve injury occurred in five patients, and was permanent in only one case. In addition, pericardial effusion occurred in six patients, and required pericardiocentesis in four cases [79]. In conclusion, the clinical experience with the laser-balloon catheter is very promising. It is important to emphasize that the reported results reflect the experience of high-volume institutions, and whether the reported safety and effectiveness can be generalized to less experienced operators and lower volume institutions warrants further investigation.

Complications

The specific risks of AF ablation reflect potentially extensive ablation as well as the proximity of atria to structures such as the esophagus, phrenic nerves, and other vasculature [14, 16]. Awareness of these risks has improved procedural technique, e.g., eliminating PV stenosis by ablating widely outside PVs instead of close to the thin-walled PVs, while better sheath management and anticoagulation can reduce thromboembolic risk and use of esophageal temperature probe to prevent esophageal injury. Accordingly, AF ablation procedural safety has increased with very low mortality in multicenter survey and data from both the US and Europe [80–82]. Data have consistently shown and that procedural outcomes improve with center experience. US claims data from over 93,000 patients in the U.S. national inpatient sample database showed an *in-hospital* mortality rate of 0.42%, and an overall complication rate of 6.29% which were lower in high-volume centers [83]. The possibility that complication rates are trending higher in some studies (driven by hospital volumes), although not others, may reflect treatments in less experienced centers or more complex, older patients with persistent AF in whom widespread ablation and long procedure times may cause complications. This again argues for a more targeted, mechanistic approach to AF ablation and performed by experienced operators.

Risk Factor Modification

Recently there has been interest in risk factor management to prevent recurrence of AF. Within the last decade, data on the relationship between AF and obesity, obstructive sleep apnea (OSA), alcohol consumption, and cardiometabolic risk factors have emerged [84–87]. Increased LA pressure and volume, and shortened ERP in the left atrium and PV are potential factors facilitating and perpetuating AF in obese patients with AF [88]. Furthermore, in a recently published randomized clinical study, weight reduction plus intensive general risk factor management (RFM) resulted in reduced AF symptom burden and severity. AF also has a genetic component, and a primary fibrotic atrial cardiomyopathy was described as a specific disease supplying substrates for AF, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications [89]. Pathak et al. reported the results of the ARREST-AF Cohort Study (Aggressive Risk Factor Reduction Study for Atrial Fibrillation) and their implications for catheter ablation outcomes [90]. This study comprised consecutive patients with body mass index ≥ 27 kg/m^2 and ≥ 1 risk factor (hypertension, glucose intolerance/diabetes mellitus, hyperlipidemia, OSA, smoking, or alcohol excess) undergoing catheter ablation for symptomatic AF, despite use of antiarrhythmic drugs. Patients in the RFM group ($n = 61$) attended an intensive physician-directed program in a RFM clinic, according to American College of Cardiology/American Heart Association guidelines [91]. The control group subjects ($n = 88$) continued RFM under the direction of their treating physician. RFM resulted in significantly greater weight and

blood pressure reductions, and better glycemic control and lipid profiles. Reviews were every 3 months for the first year and then every 6 months thereafter, including ambulatory 7-day monitoring at each review. At follow-up after catheter ablation, arrhythmia-free survival after single and multiple procedures was significantly greater in RFM patients compared with control subjects. On multivariate analysis, RFM was an independent predictor of arrhythmia-free survival, with an impressive hazard ratio of 4.8 [90]. This confirms and extends the growing body of evidence that a variety of cardiac risk factors affect procedural outcomes in patients with AF undergoing catheter ablation. Prior trials assessing antiarrhythmic therapy and ablation typically left these cardiometabolic risk factors untreated, these new data indicate that less invasive, lower risk, and beneficial interventions show substantial efficacy in treating AF.

Guidelines reserve ablation for patients with symptomatic AF and several studies show that ablation in such patients improves quality of life compared to pharmacologic therapy [6, 32]. Metrics of success is measured by eliminating asymptomatic and symptomatic AF. If the results of major ongoing studies, including CABANA (Clinicaltrials.gov: NCT00911508), CASTLE-AF (Clinicaltrials.gov: NCT00643188), and EAST (Clinicaltrials.gov: NCT01288352), show improved survival from ablation compared to pharmacological therapy, then AF ablation may be potentially extended to patients with asymptomatic AF.

Although cure rates remain disheartening, the remarkable success of ablation in many patients provides a foundation for future advancements. A mechanistic classification of AF will enable better guidance on how to tailor ablation in specific populations. Technical advances have already improved the ease of performing AF ablation, decreasing procedure times, and its safety profile. These trends are likely to further improve results from AF ablation in coming years as it becomes an increasingly important therapeutic option in many patients. Upstream and downstream risk factor modification has emerged as an important factor in maintaining sinus rhythm. The next few decades are exciting times for AF ablation, as it evolves from improved mechanistic understanding to innovative technology.

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