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REVIEW

Catheter Ablation of Atrial Fibrillation: Where Are We?

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Abstract

Atrial fibrillation (AF) is the commonest cardiac arrhythmia, with significant morbidity and mortality. More than half of patients with AF are still symptomatic despite adequate anticoagulation and rate control. If antiarrhythmic drugs are ineffective or poorly tolerated, AF patients are then typically treated with catheter ablation to restore sinus rhythm. In the past 20 years, AF ablation has developed from a specialized, experimental procedure into a common treatment in the cardiovascular field. Various ablation techniques and mapping technologies have been described and are continuing to evolve for increased safety and efficacy. An incomplete list of such techniques and technologies would include focal and segmental, circumferential and linear, complex fractionated atrial electrogram, ganglionated plexus, focal impulse and rotor modulation, body surface potential mapping–guided, real-time MRI–guided, cryoballoon, visually guided laser balloon, radiofrequency hot balloon, contact force sensing catheter, multielectrode catheter, and hybrid ablations. This review examines the history of invasive AF treatment and its evolution into catheter ablation but mainly focuses on the discussion of various ablation techniques and technologies leading to our current understanding of the ablation therapy of this most common arrhythmia.

Keywords: Atrial fibrillation; Catheter ablation; Invasive cardiology; Cardiac arrhythmia

Introduction

Atrial fibrillation (AF) is the commonest cardiac arrhythmia, with significant morbidity and mortality. The causes of AF or the medical conditions that can contribute to the development of AF are many [1]. Despite more than a century of investigations, the cellular mechanisms and pathophysiology of AF remain incompletely understood [2–8]. The burden of AF to society is tremendous: the worldwide estimate of the number of patients with AF was more than 33 million in 2010 [9], with an overall prevalence of approximately 3% in adults aged 20 years or older [10], being higher in men and the elderly, and in those with hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus, or chronic kidney disease [10–14]. AF mortality is 3.5% per year, and results from cardiovascular death, sudden cardiac death, or death as a result of heart failure or stroke [15, 16]. Each year, approximately 20% of patients with AF need to be hospitalized [17, 18], and stroke occurs in 1.5% of patients with AF who are receiving anticoagulant drugs [19]. AF prevalence is projected to increase from 5.2 million in 2010 to 12.1 million by 2030 in the United States [20, 21], and from 14 million to 17 million in the European Union by 2030 [5].

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For adults aged 55 years, the lifetime risk of AF was approximately 1 in 5.3 in a Chinese study [22], compared with 1 in 4.3 in the Rotterdam study [23] and about one in 4.1 in the Framingham study [24]. A recent analysis of medical costs associated with AF in 38 million individuals in the United States demonstrated that individuals with AF had 73% higher medical costs compared with matched control individuals. The incremental cost was $8075 per individual with AF in the United States, resulting in a total national incremental expenditure of $26.0 billion dollars in 2008 [25].

AF diagnosis is straightforward. The 12-lead electrocardiogram (ECG) remains the gold standard diagnostic test even though AF had already been recorded when the ECG machine was invented a century ago [26, 27]. A major challenge in the diagnosis of this arrhythmia is its paroxysmal and often asymptomatic nature, particularly in its early stages [28]. Recent studies have shown that more frequent or longer monitoring can improve AF detection, but contemporary monitoring technologies used for AF detection in clinical practice are costly and sometimes burdensome. The treatment of AF can be considerably more challenging and complex. Anticoagulation for thromboembolic event prevention should be considered for all AF patients who have a CHA_2DS_2-VAsc score of 2 or greater [3–5, 18, 19]. Symptomatic improvement is usually achieved with one of two strategies: rate control or rhythm control. Rate-control strategies do not directly address the presence of AF, but rather aim to reduce the ventricular response. More than half of patients with AF are still symptomatic despite adequate anticoagulation and rate control [13, 14]. By contrast, rhythm-control strategies target directly the restoration of sinus rhythm and prevention of AF recurrence. The first line of therapy in rhythm-control strategies is usually antiarrhythmic drugs and/or direct current cardioversion. Detailed discussions of antiarrhythmic strategies and therapies can be found in many excellent reviews [29–33]. In the United States, the most commonly used drugs belong to the class Ic (flecainide and propafenone) and class III (amiodarone, dronedarone, sotalol, dofetilide, and ibutilide) categories, although class Ia agents (quinidine, procainamide, and disopyramide) are used occasionally in some particular AF patients. If these agents are ineffective or poorly tolerated, patients are then typically treated with catheter ablation to electrically isolate the pulmonary veins (PVs). While catheter ablation is most probably not a "curative" therapy and should not be considered an alternative to oral anticoagulation, it has shown moderate efficacy in maintaining sinus rhythm and reducing symptoms and improving quality of life as compared with antiarrhythmic drug therapy. Whether rhythm control using ablation to restore sinus rhythm will actually lead to reductions in stroke incidence and mortality has not been demonstrated in prospective studies [3–5]. The ongoing CABANA trial, which began in 2009 to compare AF ablation versus antiarrhythmic drug therapy for a composite end point of total mortality, disabling stroke, serious bleeding, or cardiac arrest in patients with untreated or incompletely treated AF, will hopefully provide further evidence of clinical benefits supporting AF ablation therapy.

Early Development

In the past 20 years, AF ablation has developed from a specialized, experimental procedure into a common treatment to prevent AF recurrence [34, 35]. This is primarily achieved through isolation of the PVs. All PVs should be completely isolated for full effectiveness [36], and sometimes additional ablation in the posterior left atrial wall may be required as well. Despite a stronger recommendation from current guidelines [3–5] for paroxysmal AF (PAF) ablations, persistent AF (PeAF) and long-standing PeAF (LPeAF) ablations are also performed with increasing prevalence worldwide. AF ablation, when performed in experienced medical centers by adequately trained teams, was reported to be more effective than antiarrhythmic drug therapy in maintaining sinus rhythm, and the complication rate, though not negligible, is similar to or lower than the complication rate for antiarrhythmic drugs [37, 38]. It is worth noting that the SARA-AF study used only ECG or 24-h Holter monitoring to assess AF recurrence for PeAF [38]. When 7-day Holter monitors were used in the MANTRA-PAF study, there were no significant differences between the ablation and drug-therapy groups in the cumulative burden of AF in the first 18 months for PAF, although the benefit of AF ablation could be seen after 24 months [37].

From the very beginning, AF ablation was attempted to be cellular mechanism driven, but the cellular and, in particular, the molecular mechanisms of AF remain elusive for most individual patients even now. More than a century ago "the nature of fibrillary contraction of the heart" was found to require a "critical tissue mass" of the atrium to allow the fibrillation to continue [39]. The effects of vagal stimulation on AF induction and its reentry mechanism were described shortly afterward [40]. Rapid-firing ectopic focus of the atrium serving as the triggering mechanism for AF was proposed nearly 70 years ago [41]. The aforementioned pioneer investigations helped pave the way to the "multiple wavelet" hypothesis for AF that was published a half century ago by Moe et al. [42, 43]. While supporting reentry as the major mechanism of AF, Moe et al. also concluded that the irregular activation of the atria could be produced by several factors, including a single rapidly discharging ectopic focus, multiple rapidly discharging foci, or rapidly circulating circus movement [42–44].

On the basis of the understanding of AF mechanisms then (e.g., requirement of critical mass and the reentry hypothesis), the nonmedical treatment of AF – the benchmark surgical Cox maze (CM) procedure – was serially described by Cox et al. [45, 46] during the late 1980s and early 1990s. By cutting and sewing, the procedure interrupts all potential myocardial substrates for reentrance and AF signal propagation while creating a "maze" of functioning atrial myocardium (Figure 1), through which normal impulses can travel from the sinus node to the atrioventricular node [47]. The initial procedure was very effective, with freedom from AF greater than 94% at 12 months on the basis of recurrent symptoms and/or office ECG findings, but was associated with significant chronotropic incompetence and high rates of pacemaker implantations [48, 49]. Serial modifications to address these issues and to technically simplify the procedure have been developed, culminating in what is known as the CM-III and CM-IV procedures these days [49–51]. The major events leading to the development of current AF ablation techniques and technologies are chronologically shown in Figure 2. The creation of the CM procedure and the description of focal segmental PV ablation (discussed later) can certainly be regarded as the landmark events.

Evolving Ablation Techniques and Technologies

Segmental and Focal Ablations

The major limitations of these surgical techniques, however, remained the need for a fairly long cardiopulmonary bypass time and the implicit surgical risks and complications of opening the chest and the patient undergoing total anesthesia. For these reasons AF ablation was, at that time (from the 1980s to the mid-1990s), primarily performed in patients with concomitant surgical indications such as septum/valvular repair/replacement and coronary bypass [52]. Efforts to avoid the complications and limitations of the surgical approach combined with the proven success of percutaneous catheter ablation of Wolff-Parkinson-White syndrome and other supraventricular tachycardias led to the earliest attempts at linear catheter ablation of AF in both the right atrium and the left atrium some 20 years ago [53–56]. Linear ablation in the right atrium and/or left atrium was initially proposed with the purpose of replicating the surgical "maze" procedure. Linear lesions for substrate modification of AF represented the goal of catheter AF ablation procedures until the seminal work of Haïssaguerre et al. [57] in 1998. In this milestone study performed on 45 patients with frequent AF episodes refractory to drug therapy, spontaneous initiation of AF was mapped with the use of multielectrode catheters designed to record the earliest electrical activity preceding the onset of the arrhythmia. Ectopic foci as the triggers of AF were found in 94% of patients (65 of 69 foci) in the PVs. Ablation of the focus with local radiofrequency energy achieved a 62% freedom from symptomatic AF in an 8-month period, and no acute complications were reported. This study led to the shift in the attention of interventional electrophysiologists from mazelike linear lesions to isolation of ectopic foci within the PVs by means of focal and segmental ablations [57–61].

Circumferential and Linear Ablations

Learning while burning applies unfortunately to the evolving AF ablation. Even in the earlier days, extensive, biatrial linear ablations appeared to be effective in restoring sinus rhythm in medication-refractory,

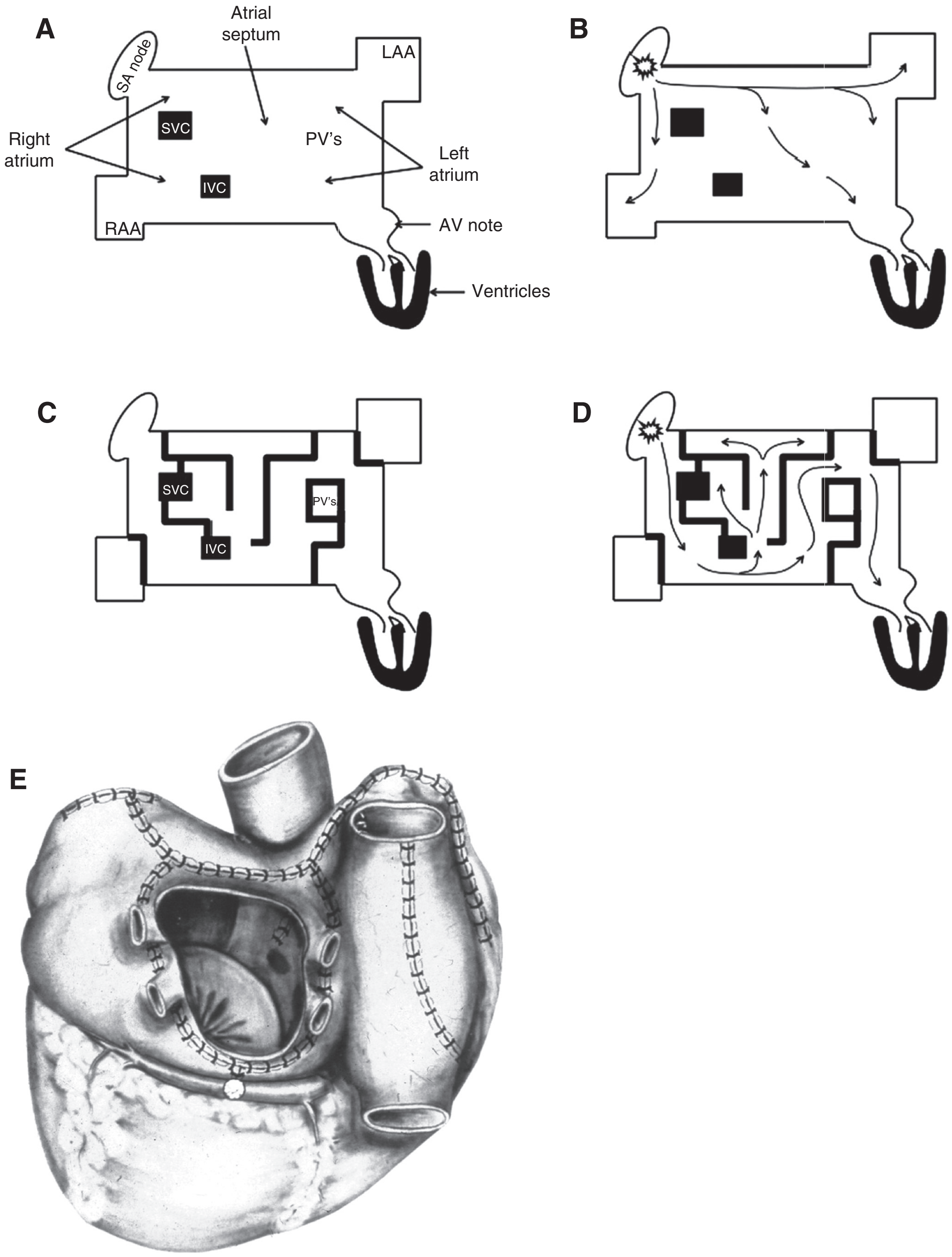

Figure 1 Original Maze Concept.
The diagrams demonstrate the concept of the maze procedure first envisioned in early 1987. (A) Two-dimensional representation of the anatomy of the atria with the right atrium harboring the orifices of the superior vena cava (SVC) and inferior vena cava (IVC), as well as the right atrial appendage (RAA). The left atrium has the pulmonary veins and left atrial appendage (LAA). The atrial septum divides the two, with the sinoatrial (SA) node in the top of the right atrium near the septum and the atrioventricular (AV) node at the bottom of the septum connecting to the ventricles. (B) *Arrows* depict the propagation of a normal sinus rhythm beat from its source (starburst) in the SA node to all of the atrial myocardium and then to its termination at the AV node. (C) *Thick lines* represent lines of conduction block created by lesions in the atria. (D) If the lesions are placed in the pattern of a maze, they can be placed close enough to prevent the development of macro reentry anywhere in either atrium and still allow the sinus impulse to activate all of the atrial myocardium except the encircled pulmonary veins and excised atrial appendages. (E), Three-dimensional representation of the original maze I procedure. A ‘‘window’’ has been drawn in the posterior left atrium to allow visualization of the location of the mitral valve, atrial septum, and AV node. PV's, pulmonary veins. (Modified from [47]).

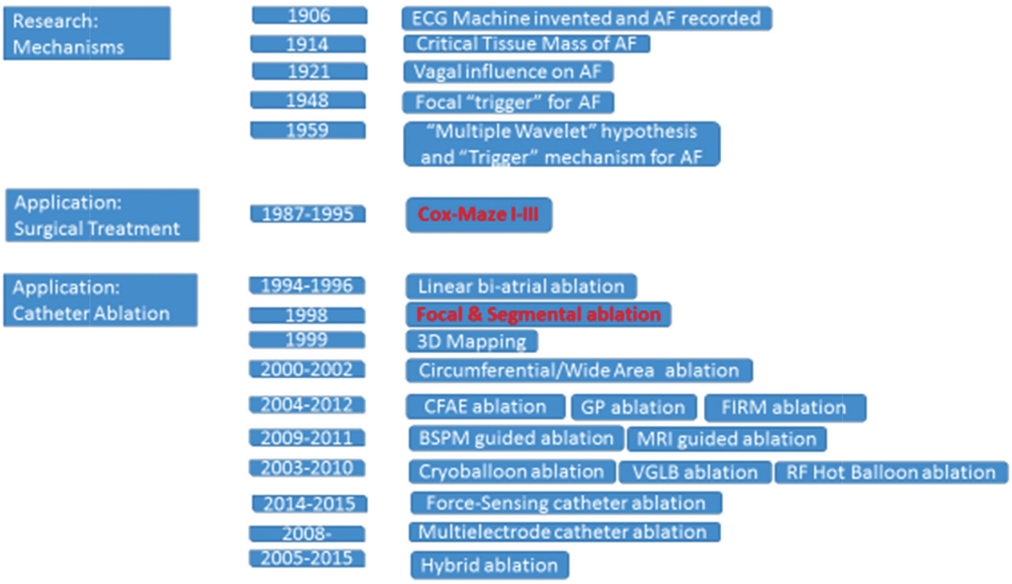

Figure 2 Major Events Leading to the Development of Atrial Fibrillation (AF) Catheter Ablations.
BSPM, body surface potential mapping; CFAE, complex fractionated atrial electrogram; ECG, electrocardiograph; GP, ganglionated plexus; FIRM, focal impulse and rotor modulation; RF, radiofrequency; VGLB, visually guided laser balloon.

chronic AF patients [62]. Linear ablation, which was originally targeted toward reentry and multiple wavelength mechanisms, never faded despite the paradigm shift to focal trigger ablation [61–64]. The first important innovation in AF ablation was introduced by technology advancement in 1999 [65, 66]. Application of a nonfluoroscopic electroanatomical mapping system (CARTO system) permitted safer navigation in the atria. This new technique for catheter-based endocardial mapping that enables the generation of 3D electroanatomical maps of the heart chambers had been described barely a few years earlier [67–69]. Together with the ability to create 3D activation maps, the long continuous linear lesions with regard to the anatomical markers of the atria became visible to the AF ablators. In some of these early studies [62, 65] the biatrial, extensive linear ablations actually included lesions "encircling the two superior veins" and the mitral isthmus lines extending from the two inferior veins to the lateral and medial mitral annulus.

The ability to visualize ablation points in the left atrium under 3D mapping guidance allowed precise applications of radiofrequency energy around the PV ostia, so a new anatomical approach to AF ablation was described in 2000 and 2001 by the same group of investigators [63, 64], namely "circumferential radiofrequency ablation." Despite significant success in targeted focal trigger ablation inside the PVs and the segmental ostia of the PVs [57–59], stenosis of the veins could occur in as many as 42% of the cases because of presumed scar formation from lesions inside the vein [59]. The new anatomical approach, in which circumferential radiofrequency lesions are created around the ostia of each PV, aimed to electrically isolate these veins from the left atrium while reducing the risk of PV stenosis. A modification of the circumferential technique, named "left atrial catheter ablation" or "wide area circumferential ablation" (WACA) further reduced the risk of PV stenosis and increased the mid-term success rate in maintaining sinus rhythm in PAF patients [61, 70]. The rationale for the WACA (two circular lesions encircling the two PVs on each side of the left atrium) was to isolate the AF triggers inside and near the PV ostia, and the two linear lesions targeted the reentry or multiple wavelength mechanism for the perpetuation of AF. Of the two linear lesions, one was applied at the posterior wall close to the roof [61] or in the roof [71] joining the two circular lesions and the other was applied at the mitral isthmus joining the left inferior PV to the posterolateral mitral annulus.

Modifications of AF ablation in the early days were based on solid clinical experience and scientific knowledge accumulations. The linear lesion line concept confined to the left atrium targeting specifically the left atrial “anchor” reentrant circuits eliminated AF in approximately 90% of patients with PAF and PeAF who were treated with intraoperative radiofrequency ablation using surgical or minimally invasive surgical techniques [45, 72]. On the other hand, circumferential catheter ablation around the PVs at the atrial level was demonstrated [57, 65, 70] to be highly effective in patients with PAF and PeAF. While the risk of PV stenosis was significantly decreased by the WACA technique, the linear lesions indiscreetly added to the ablation in PAF patients significantly increased the occurrence of postablation complications such as left atrial flutter or left atrial tachycardia, a lesson well learned a decade ago [61, 70]. However, PV isolation alone was found to be insufficient for restoration and maintenance of sinus rhythm in patients with PeAF and especially LPeAF. Additional linear lesions at the roof and mitral isthmus were intended to eliminate more arrhythmogenic substrates and specifically to prevent large atrial reentrant circuits potentially involved in perpetuation of AF. A combination of circumferential PV ablation and adjunctive roof and mitral isthmus ablation significantly reduced the AF burden in patients (80% PAF, 20% PeAF) at 12-month follow-up as measured by 7-day Holter monitoring [72]. Given these considerations, a tailored approach to apply linear lesions such as the “2C3L” technique [73] only in PeAF and LPeAF patients appears more appealing.

Complex Fractionated Atrial Electrogram Ablation

It is likely that in humans most AFs are caused by more than one mechanism [42–44, 74, 75]. AF ablation continues to evolve on the basis of our understanding or incomplete understanding of the cellular mechanisms of AF, such as PV triggers to initiate AF and multiple wavelet reentry to sustain AF or the interplay of those known mechanisms for the progression of the arrhythmia. During intraoperative mapping of animal and human AF, the complex fractionated atrial electrograms (CFAEs) were found mostly in areas of slow conduction and/or at pivot points where the wavelets turn around at the end of the arcs of functional blocks. Such areas of CFAEs during AF could represent either continuous reentry of the fibrillation waves into the same area or overlap of different wavelets entering the same area at different times [45, 76, 77]. If such areas were to be selectively eliminated by catheter ablation, wavelet reentry should stop, thereby preventing perpetuation of AF. Indeed such a new strategy targeting the presumed “substrate” of AF was initially described to have a high success rate (>90%) in restoring and maintaining sinus rhythm [78]. In that study the CFAEs were defined as (1) atrial electrograms that are fractionated and composed of two or more deflections, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-s recording period, and (2) atrial electrograms with a very short cycle length (<120 ms) averaged over a 10-s recording period. The same group of investigators also reported that at a mean follow-up of 2.3 years after CFAE ablation, the sinus rhythm maintenance rates were 89, 85, and 71% for those whose presenting rhythm was PAF, PeAF, and permanent AF respectively [79]. Unfortunately such a high success rate by targeting CAFEs could not be repeated by other high-volume AF ablation investigators [80–82]. Furthermore, multiple meta-analyses [83, 84] and the recent STAR-AF trial [85] failed to show additional benefits of CFAE ablation on top of PV isolation for either PAF or PeAF. Thus it is important to recognize other potential causes of electrogram fractionation that may not be related to underlying AF processes. CFAEs may reflect purely local effects, but may also be caused by remote activity at the recording site where deflections that result from local and distant activity merge (e.g., the right superior PV and the superior vena cava). Some CFAEs may represent sites of passive wavelet collision (and therefore are not important for the maintenance of AF) or barely normal atrial tissue response to rapid PV firings [86]. In addition to prolonging the procedure time, CFAE ablation appears to increase the postablation atrial tachycardia or left atrial flutter. While mapping and ablation of *all* CFAEs are much less favored by most cardiac electrophysiologists nowadays, the higher success rate of WACA compared with the focal segmental strategy is believed to be partly due to the encircling of some CFAE areas located within 1 cm of PV ostia.

Ganglionated Plexus Ablation

While circumferential PV isolation or WACA has been the mainstay of AF ablation since its inception, ganglionated plexus (GP) ablation emerged a decade ago as an alternative technique to improve outcomes in patients with AF [87–93]. This evolutional development also involves significant scientific knowledge accumulation. In human heart, most GP were initially described in the posterior surfaces of the atria and superior aspect of the ventricles [94]. Four major GP near the antrum of the PVs have been described: the superior left GP is located on the roof of the left atrium, near the medial side of the left superior PV; the anterior right GP is located anterior to the right superior PV; the inferior left GP and the inferior right GP are located at the inferior aspect of the posterior left atrial wall, just below the left and right inferior PVs. The density of nerves around the PV junction is greatest in the left atrium within 5 mm of the left atrium–PV junction, and higher in epicardium than in endocardium [95]. GP contain a variety of sympathetic and parasympathetic neurons and communicate with the extrinsic cardiac autonomic nervous system. Parasympathetic stimulation releases acetylcholine, which activates acetylcholine-sensitive K^+ current in atrial myocytes, resulting in shortening of the action potential duration and effective refractory period. This effect decreases the wavelength of reentrant circuits that facilitate initiation and perpetuation of AF. Sympathetic stimulation releases catecholamine, which (1) activates calcium inward current I_{ca-L}, causing intracellular calcium overload and generating delayed afterdepolarizations as well as early afterdepolarizations to trigger AF (from atrial myocytes, especially those inside or near the PVs), and (2) enhances delayed rectifying K^+ current, resulting in fast repolarization and shortening of action potential duration as well as the refractory period just like vagal stimulation mentioned before.

Parasympathetic stimulation has for decades been used for the induction and maintenance of AF in experimental protocols [44]. Increased vagal tone is frequently involved in the onset of AF in patients with structurally normal hearts [96–99]. An animal study also demonstrated that long-term vagal denervation of the atria rendered AF less easily inducible [100]. In humans, complete vagal denervation near and around the PVs during circumferential PV ablation was found to significantly decrease the recurrence rate of AF at a follow-up of 12 months [87]. Targeted GP ablation then emerged in increasing frequency in the AF ablation literature, and was achieved by either a selective or an anatomical approach [88–93]. Selective GP ablation caused by high-frequency stimulation does not eliminate PAF [92] or short-term induction of AF [101] in most patients. An anatomical approach for regional ablation at the sites of GP seems to give better results [92]. However, in patients with PAF, anatomical GP ablation yields a significantly lower success rate over the long-term follow-up period when compared with circumferential PV isolation [90, 102]. Arrhythmia recurrences include AF and macro reentrant atrial tachycardias [90–102]. Currently, GP ablation remains controversial: addition of GP ablation to PV isolation seems to result in a higher success rate compared with either PV isolation or GP ablation alone in patients with PAF but in patients with PeAF or LPeAF [91, 103]; GP ablation during thoracoscopic surgery for PeAF and LPeAF has no detectable effect on AF recurrence but results in more major adverse events, major bleeding, sinus node dysfunction, and pacemaker implantation [104, 105]. Many questions remain, such as how to achieve complete GP ablation and avoid partial denervation by localizing the true boundary of GP, and how to prevent reinnervation and end-organ hypersensitivity. It is clear that novel technologies and strategies will be needed to improve current GP ablation techniques to treat patients with AF.

Focal Impulse and Rotor Modulation Ablation

The success rate of PeAF or LPeAF ablation is dismal even with repeated ablation procedures [106]. This poor outcome is likely due to incomplete understanding of the optimal ablation technique and the best targets to achieve freedom from arrhythmia [107]. It is indeed unclear whether substrate ablation alone, the elimination of triggers of AF, or a combination of both is the ideal ablation approach in these subsets of the AF population. PeAF and LPeAF are chronic diseases associated with progressive atrial fibrosis and evolving PV and non-PV triggers. Once triggered, the mechanisms that sustain PAF, PeAF, or LPeAF are not well defined. Of the two currently prevailing hypotheses, the continuing multiple wavelets hypothesis [75] does not readily explain spatial nonuniformities in AF [108, 109], and CFAE ablations targeting this mechanism result in no improvement in short-term or long-term success, as discussed previously. The localized source hypothesis is based on experimental models in which organized reentrant circuits, the rotors [110, 111], or focal impulses [109] disorganize into AF. The CONFIRM trial was designed to test this hypothesis by targeting patient-specific AF sources, the focal impulse and rotor modulation (FIRM), in 92 patients, including PAF, PeAF, and LPeAF patients [112]. During a median of 9 months of follow-up, the FIRM-guided ablation had a much higher freedom from AF than the conventional ablation using the WACA technique. While similar results could be obtained by some experienced investigators [113–115], the long-term outcome (18±7 months) was poor, with freedom from AF being only 37% [116]. FIRM-identified rotor sites did not exhibit quantitative atrial electrogram characteristics expected from rotors and did not differ quantitatively from surrounding tissue [117]. Poor outcome was also reported by other independent investigators [118–120]. Adding to the controversy was the recently retracted OASIS trial paper that reported for patients with PeAF and LPeAF a significantly low sinus rhythm with a FIRM-only ablation strategy compared with FIRM plus circumferential PV isolation or conventional circumferential PV isolation plus posterior wall and additional linear ablations, for a mean follow-up of 12 months [121].

At the cellular level, whether rotors can be demonstrated as the drivers of PeAF remains arguable [122, 123]. High-resolution mapping of human AF during open heart surgery demonstrated highly complex activation patterns that varied from beat to beat. Rotational activity was either not detected at all [75, 124] or observed only occasionally [125, 126]. If present, rotors were always transient and ceased to exist after only a couple of cycles. High-resolution mapping of human AF points to endocardial–epicardial dissociation as the main mechanism for long-lasting AF, a third mechanism independent of focal or reentrant activity (the double-layer hypothesis [75, 124, 127]). The 2016 European Society of Cardiology guidelines [5] state that "ablation of so-called 'rotors', guided by body surface mapping or endocardial mapping, is under evaluation and cannot be recommended for routine clinical use at present."

Body Surface Potential Mapping–Guided Ablation

Thus the possibility remains that the inconsistent outcome of FIRM-guided AF ablation is related to inaccurate identification of the rotors and drivers in the population of PeAF and LPeAF patients. While the standard 12-lead ECG is insufficient to characterize the complex electrical activation in AF, body surface potential mapping (BSPM) using 56 torso leads in addition to the standard limb leads could demonstrate four different patterns of wavefront propagation during AF [128]. Simultaneous BSPM and intracardiac real-time electroanatomical mapping demonstrated good correlation between the highest dominant frequency sites in the right and left atria and the corresponding right- and left-sided surface leads [129]. By integrating unipolar body surface potentials obtained from a 252-electrode vest with biatrial geometry obtained with high-resolution thoracic computed tomography, the activation pattern, dominant frequency, and cycle length maps could be constructed. The presumed AF drivers were identified and classified into focal and reentry (either functional or fixed anatomical). With the guidance of BSPM and despite the fact that rotors were seen only rarely [130] and were not stationary for more than two rotations [131], ablation at these "driver" locations could abruptly convert AF into sinus rhythm or atrial tachycardia [131, 132]. Driver-alone ablation terminated 75% of PeAF and 15% of LPeAF, with a success rate in sinus rhythm maintenance at 12 months (85%) comparable to that for patients with conventionally ablation (87%). It remains to be seen if this experience from a single-center study of 103 patients can be repeated by other investigators and to what extent BSPM increases the long-term efficacy of AF ablation.

MRI-Guided Ablation

AF burden correlates with atrial fibrosis [133, 134]. Progression of PAF to PeAF and LPeAF parallels increase in atrial fibrosis and scar formation, which predict high recurrence of AF after catheter ablation [135]. AF itself appears to promote atrial fibrosis [136]. Since atrial fibrosis leads to a range of conditions that favor the development of AF, conventional scar mapping using CARTO or EnSite system–guided additional ablations after PV isolation appear to provide a better sinus rhythm maintenance rate [137–142].

Significant limitations with the conventional endocardial voltage scar mapping include inaccurate estimates of the extent of atrial scar and variability in the density of atrial voltage maps, resulting in variable mapping resolution. In addition, mapping completed during AF versus sinus rhythm and significant heterogeneity between studies due to different criteria for defining left atrium scar further hinder generalization of such a principle to wider applications. An atrial voltage cutoff less than 0.5 mV is most appropriate to detect atrial scar/fibrosis [143, 144] but only applies to data acquisition in sinus rhythm. Voltage data collection during AF may require distinct cutoffs to accurately discern normal myocardium from scar [145].

Delayed gadolinium enhancement MRI (DEMRI) has been widely used to identify ventricular fibrosis and scar. Recent studies have established that the extent of left atrial scar/fibrosis can be identified though DEMRI and the degree of atrial scar/fibrosis can be a predictor of procedural success [146, 147]. These results have been reproduced in a multicenter study led by the same group [148]. In addition to DEMRI, T1 mapping is another MRI-based technique that has shown encouraging results in the preprocedural planning of AF catheter ablation as it allows direct signal quantification. In a controlled study of 112 patients undergoing radiofrequency ablation, the T1 time was the only predictor of 12-month arrhythmia recurrence in multivariate analysis [149]. Despite promising data emerging from a few academic centers, DEMRI for the evaluation of atrial scar has not been widely adopted because of its well-known technical challenges [150].

The real-time intraprocedural application of MRI to guide ablation was reported in 2008 [151]. With use of a 3-T MRI system in a swine model, real-time MRI tracking of catheters with electrogram recording to guide radiofrequency ablation and visualization of lesion formation was proved feasible [152]. The same group used real-time DEMRI to identify and target gaps in AF ablation lesions sets [153]. While real-time MRI is radiation-free and allows the accurate visualization of the location and extent of lesion formation, its disadvantages may include the compatibility of catheters and existing ablation technology, its cost, and incompatibility with implantable cardiac devices or other hardware. A consensus statement from the European Heart Rhythm Association [154] reads “up to now, there is neither recommendation nor expert consensus on the role of DEMRI to assist AF ablation procedures”.

Balloon-Based Catheter AF Ablation

Cryoballoon

In the past decade cryoballoon PV isolation has been increasingly used for the treatment of PAF and short-lasting PeAF because of the relative technical simplicity and short learning curve [155–157]. The ability to isolate a PV with a single deployment of a catheter is very appealing. Moreover, the use of a balloon-based system eliminates the need for complex imaging techniques and may shorten the procedure duration [155, 157–159]. Acceptable 75% success rates, with low adverse event rates, have been reported for cryoballoon ablation in high-volume centers [155, 157, 159–161]. Currently all three generations of cryoballoon catheter are available (depending on the geographic areas/countries) but the most frequently used one is the second generation (Figure 3A). The improved design of the second-generation and third-generation cryoballoon catheters allows faster, broader, and homogenous application of freezing energy at the tissue contact hemisphere. Despite several advantages over radiofrequency ablation, such as preserved tissue architecture, uniformity of lesions, and lower rate of thrombus formation, the FIRE AND ICE study [162] and a recent meta-analysis [163] of studies comparing the two approaches have not demonstrated one to be more effective at preventing AF recurrences or improving quality of life. The predominant difference has been a higher risk of perforation and tamponade with radiofrequency ablation and a higher risk of phrenic nerve paralysis with cryoballoon ablation.

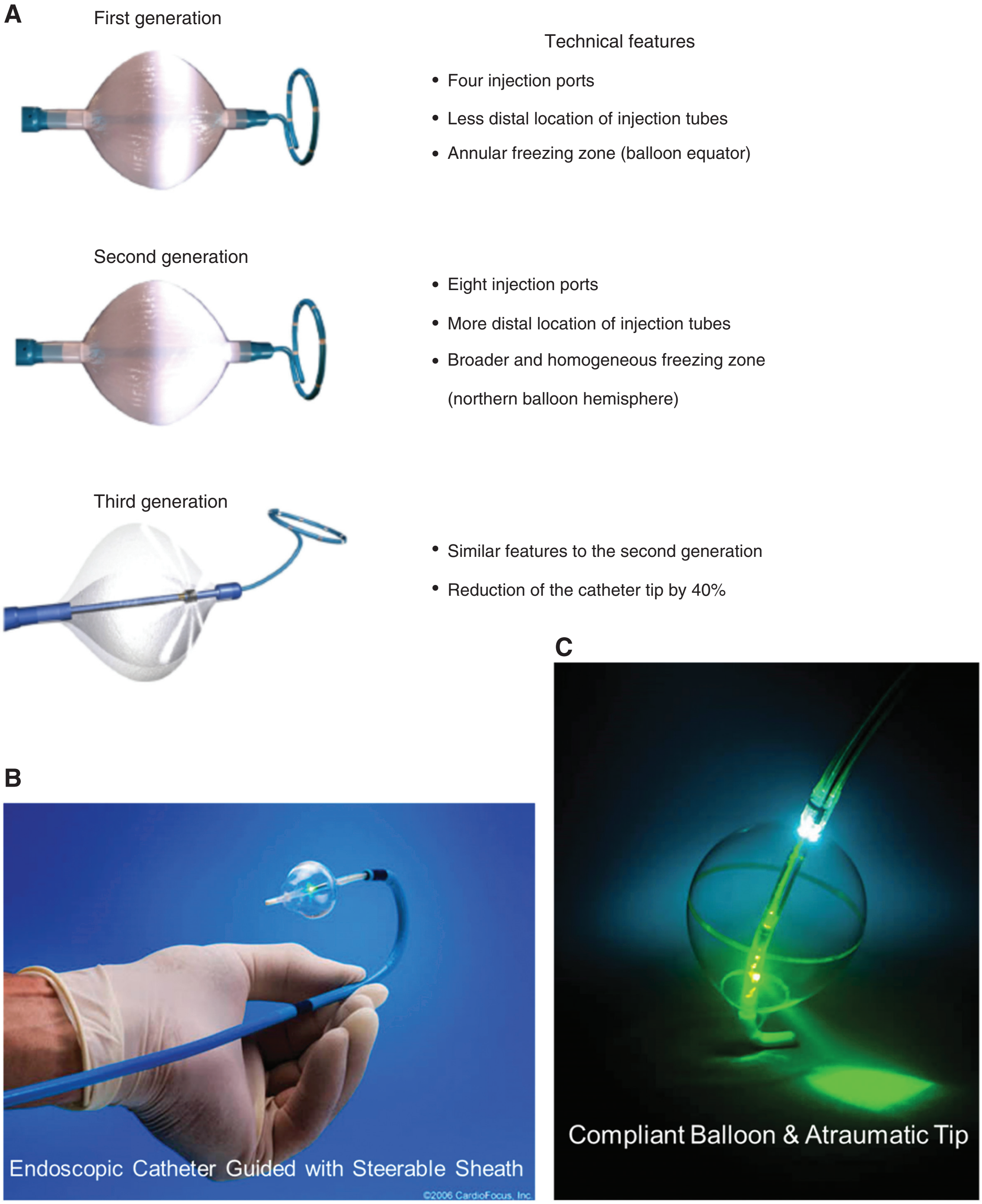

Figure 3 Cryoballoon Catheters and Visually Guided Laser Balloon Catheter.
Panel (A) illustrates the three generations of cryoballoon catheters, with major differences in technical features. Panel (B) and (C) show the visually guided laser balloon catheter with steerable sheath (left) and atraumatic tip (right).

While the technical approach to radiofrequency ablation is relatively mature, continued questions arise as to the optimal technical approach for cryoballoon ablation. The initial cryoballoon ablation experience was obtained from the first-generation balloon and generally incorporated 4 min or more of freezing as well as two or more freeze applications for each PV. Because of technical advancements the second-generation cryoballoon was positioned to create more uniform cooling over a larger surface area of the distal hemisphere of the balloon. This change has been shown to result in more complete circumferential lesions and PV isolations for the second-generation cryoballoon versus the first-generation cryoballoon

[164]. As a result, the clinical success with regard to sinus rhythm maintenance rate has increased significantly, while the commonest complication with cryoballoon ablation, phrenic nerve paralysis, has shown a considerable decrease. The increased freezing efficiency permits a shorter ablation time (3 min for each freeze circle) although the optimal freezing time and number of freeze circles for the second-generation cryoballoon remain unsettled. With rapid time to isolation (<40 s) and long warming times, particularly on the right PVs, where the risk of phrenic nerve palsy is higher, a single successful freeze may be sufficient. Veins that require longer durations (>70 s) to achieve isolation and have rapider warming may benefit from an additional freeze.

Visually Guided Laser Balloon

A visually guided laser balloon (VGLB) ablation catheter (HeartLight, CardioFocus) is another balloon-based catheter for AF ablation (Figure 3B). This technology has not yet been approved in the United States (but has been approved in Europe) for AF ablation. This catheter is unique in that it uses (1) a compliant, variable-diameter balloon, thus allowing a single balloon catheter to accommodate multiple PV sizes/shapes, (2) a 2-F endoscope to provide real-time direct visualization of the target tissue, and (3) a maneuverable (30°) aiming arc that allows the operator to easily target the location of the PV ostium/antrum and titrate the amount of laser energy (980 nm) delivered. Isolation of the PV can be confirmed with the use of a different circular mapping catheter. In principle, the laser generates a very similar tissue effect compared with the radiofrequency energy source, and histologic findings represent fibrous tissue with much sharper edges compared with those from radiofrequency ablation. The feasibility of the VGLB system for PAF ablation was demonstrated in 27 patients and published in 2010 [165]: 100% of the PVs were isolated after 1.3 attempts per PV, 84% of which were isolated after the initial visually guided lesion set. At 3 months, 61 of 68 PVs (90%) continued to be electrically isolated. In a subsequent study of 56 patients, short-term and 3-month isolation was documented in 98 and 86% of PVs respectively [166], while another study of similar size demonstrated an arrhythmia-free rate of 60% 1 year after ablation. In a multicenter trial [167] involving 200 PAF patients, 98.8% (95% confidence interval 97.8–99.5%) of targeted PVs were isolated with a mean of 1.07 catheters per patient. The fluoroscopy and procedure times were 31±21 min (mean±standard deviation) and 200±54 min respectively, with a 2% incidence of cardiac tamponade and a 2.5% incidence of phrenic nerve palsy. At 12 months, the drug-free rate of freedom from atrial arrhythmias after one or two procedures was 60.2%. In the US feasibility study of 86 PAF patients, the mean fluoroscopy, ablation, and procedure times were 39.8±24.3 min, 205.2±61.7 min, and 253.5±71.3 min respectively. Short-term PV isolation was achieved in 314 of 323 targeted PVs (97.2%) [168]. Freedom from symptomatic or asymptomatic AF was 61%. The primary adverse event rate was 16.3% (pericarditis 8.1%, phrenic nerve injury 5.8%, and cardiac tamponade 3.5%). The findings of a larger prospective, multicenter, and randomized comparison of VGLB ablation with standard radiofrequency ablation (open-irrigated catheter) in 353 PAF patients (178 VGLB ablation patients, 175 controls) at 19 clinical sites were recently released [169]. With a mean follow-up of 12 months, the noninferiority was met with no significant differences in the primary efficacy end point (61.1 vs. 61.7%) and adverse event rate (11.8 vs. 14.5%). While the rate of diaphragmatic paralysis was higher (3.5 vs. 0.6%; P=0.05), the rate of PV stenosis was lower (0.0 vs. 2.9%; P=0.03) with VGLB ablation. Whether this technology can gain wide application depends on a number of factors, including at least the cost of the equipment, the easiness to learn and adopt the technique, and long-term outcome data.

Radiofrequency Hot Balloon

The proof of concept for radiofrequency hot balloon AF ablation was published originally in a study of 11 porcine hearts [170]. In 18 PVs that had PV potentials, PV isolation was performed successfully in 15 (success rate 83%, 95% confidence interval 58.0–96.3%; failure rate 17%, 95% confidence interval 3.7–42.0%). After successful isolation, the PV potentials completely disappeared and the histologic examination revealed circumferential, transmural necrosis around the PV trunks. No major early complications, such as PV stenosis or macroscopic thrombosis, were observed. The first human study was performed in 20 patients for the isolation of the two superior PVs only [171]. Nineteen of 20 left superior PVs and all 20 right superior PVs were successfully isolated by this technique. The total procedure time was 1.8±0.5 h, which included a fluoroscopy time of 22±7 min. With a mean follow-up time of 8.1±0.8 months, 17 of the 20 patients were free from AF and 10 of them were not taking any antiarrhythmic drugs.

The newer system is composed of a 1.8-MHz radiofrequency generator, a 13-F deflectable guiding sheath, a two-lumen catheter shaft, and a highly elastic and compliant 20-μm-thick polyurethane balloon which is inflated from 26 to 33 mm in diameter with ionized contrast medium diluted with normal saline. Radiofrequency energy is delivered between a coil electrode inside the balloon and four cutaneous electrodes on the patient's back to induce capacitive-type heating of the balloon. With further maturation of the technique, all PVs could be isolated in a study of 100 consecutive patients, including 63 PAF and 37 PeAF patients [172]. The total procedure time was 129±26 min, inclusive of a fluoroscopy time of 29.9±7.3 min. Follow-up during 11.0±4.8 months confirmed that 92 patients (60 PAF patients, 32 PeAF patients) were free from AF without antiarrhythmic drugs, and in the remaining patients except for two with left atrial tachycardia, sinus rhythm was maintained with antiarrhythmic drugs. No esophageal fistula or permanent phrenic nerve injury occurred, but three cases of asymptomatic PV stenosis were found. The same group recently published [173] the long-term outcomes for 238 consecutive PAF patients. During 6.2-years (75 months) of follow-up, 154 patients (64.7%) were free from atrial tachyarrhythmias without antiarrhythmic drugs. Reablation was performed in 69 of 84 patients with atrial tachyarrhythmia recurrence using a 3D-mapping system and a conventional catheter. There were four patients (1.7%) with PV stenosis with more than 70% reduction in diameter but none of these cases required intervention. Phrenic nerve palsy was detected in eight patients (3.4%), and all cases resolved during the 3-month follow-up. Despite a promising outcome, the same limitations as for VGLB ablation discussed earlier will likely will affect the adaptation of this technology by many other interventional electrophysiologists.

Contact Force Sensing Catheters

Ablation electrode–tissue contact is an important determinant of lesion size and ultimately of durability. This has been traditionally assessed by the operator using a combination of fluoroscopic and electroanatomical imaging of catheter tip motion, tactile feedback, and local electrogram attenuation and impedance reductions during energy delivery. Too much force increases the risk of perforation, while too little force decreases lesion depth, resulting in incomplete PV isolation or line blockade. Thus contact force (CF) sensing allows real-time estimation of the CF between the tip of the catheter and the target myocardium, providing the operator with accurate quantitative assessment of tissue contact. Two FDA-approved CF radiofrequency ablation catheters have become available in the last 2 years: ThermoCool SmartTouch™ (Biosense Webster) and TactiCath™ Quartz (St Jude Medical). With use of spring microdeformation or fiberoptic technologies, catheter tip direction and CF amplitude are sampled in rapid cycles of 50–100 ms and displayed in real time. The prospective, multicenter SMART-AF trial demonstrated that the irrigated CF-sensing ThermoCool SmartTouch™ catheters was safe and effective for the treatment of drug-refractory symptomatic PAF, with no unanticipated device-related adverse events [174]. The TOCCASTAR study demonstrated that the TactiCath™ Quartz catheter met the primary safety and effectiveness end points [175]. Additionally, optimal CF was associated with increased effectiveness [175]. The sensitivity of both catheters is 1 g or less.

Preclinical experimental studies have shown that (1) for constant radiofrequency power and application time, radiofrequency lesion size significantly increases with increasing CF, (2) the incidences of steam pop and thrombus also increase with increasing CF, and (3) modulation of radiofrequency power based on CF (i.e., high radiofrequency power at low CF and lower radiofrequency power at high CF) results in a similar and predictable radiofrequency lesion size [176]. Clinical experience confirmed a poor relationship between CF and the signal amplitude of either unipolar or bipolar radiofrequency energy, or impedance. Within the left atrium, the most commonest high-CF site was found at the anterior/rightward left atrial roof, directly beneath the ascending aorta (confirmed by the merging of the computed tomography image and map). The outcomes of CF sensing catheter AF ablation are not consistent: while some reported higher freedom from AF recurrence [177–181], others reported no significant differences in comparison with the use of regular open-irrigated radiofrequency catheters [182–185]. In one published study of 600 patients including PAF (n=200), PeAF, and LPeAF patients, CF sensing catheter use independently predicted higher success only in PAF patients and not PeAF and LPeAF patients [186]. In general, patients who underwent ablation with an average CF of less than 10 g experienced higher AF recurrence, whereas patients with ablation using an average CF of more than 20 g had lower AF recurrence. However, even with a CF of 10–25 g, atrioesophageal fistula was reported to occur in two patients from a high-volume center recently [187]. In addition to cost-effective analysis, long-term follow-up data will also be needed to address if there is any certain superiority of the CF sensing catheters compared with the regular open-irrigated catheters.

Multielectrode Ablation Catheters

Multielectrode ablation catheter systems were designed to overcome some of the limitations of point-by-point radiofrequency ablation, such as the potential for noncontiguous and/or nontransmural ablation lesions, the risk of injury of adjacent structures with extensive unipolar radiofrequency energy application, and the long procedure and fluoroscopy times, especially in the case of PeAF and LPeAF. Currently there are two systems that have gained increasing adoption although neither has been approved by the FDA. The PV ablation catheter (PVAC; Medtronic Ablation Frontiers) is a circular, decapolar mapping and ablation catheter with a 25-mm-diameter array at the distal tip with adjustable diameter allowing positioning in PVs of variable diameter (Figure 4A). Another circular ablation catheter (nMARQ™, Biosense Webster) has ten openly irrigated electrodes arranged in a circle with an adjustable diameter (20–35 mm). Mapping is performed with the same catheter using the CARTO system (Biosense Webster) and radiofrequency energy can be delivered in unipolar or bipolar fashion (Figure 4B).

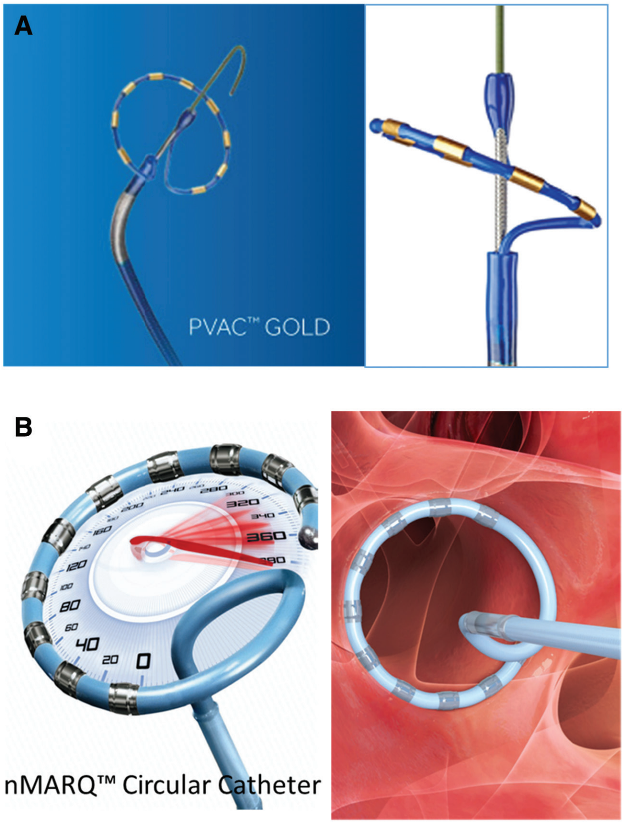

Figure 4 Multielectrode Ablation Catheters.
(A) PV Ablation Catheter, (B) nMARQ™ Circular Catheter.

Although the safety and effectiveness of multielectrode ablation catheters were demonstrated in 93 PAF and 50 LPeAF patients [188, 189], the failure to meet the predefined short-term safety end point (within 7 days of ablation, serious adverse event rate of 12.3%) in the larger TTOP-AF trial [190] led to the FDA nonapproval of the PVAC device. This multicenter trial randomized 240 PeAF and LPeAF patients in a 2:1 ratio for ablation or medical treatment. At 6 months, 55.8% of the ablation patients achieved effectiveness without antiarrhythmic drugs (77 of 138) compared with 26.4% from the medically treated group (19 of 72). Significant differences were also observed in quality of life and symptom severity in favor of the ablation group. Although the long-term safety events did not differ significantly between the two groups, the high short-term serious adverse event rate caused significant concerns. A more recent multicenter, randomized clinical trial with 120 PAF patients demonstrated that the PVAC and the conventional ablation catheter had similar rates of single-procedure short-term PV isolation without serious adverse events in the first 30 days. The PVAC group had slightly lower long-term freedom from arrhythmia, but marked and significantly shorter procedure, fluoroscopy, and radiofrequency energy times [191]. A large-scale real-world registry of the second-generation PVAC GOLD catheter is currently under way in several European centers. Hopefully the improved design with the platinum electrodes replaced with gold electrodes will improve thermal delivery while being less thrombogenic, and therefore result in a lower thromboembolic event rate.

The feasibility and efficacy of the nMARQ catheter system was demonstrated in a number of small-scale studies [192–195]. In a multicenter registry study of 180 patients (140 with PAF, 40 with PeAF), irrigated multielectrode radiofrequency ablation using nMARQ proved feasible and achieved a high rate of PV isolation. The procedure and fluoroscopy times and success rates were comparable with those for other techniques, with a low complication rate [196]. Despite comparable outcomes, important device-related limitations in achieving PV isolations and other concerns were raised in other studies [197–201].

Compared with the SmartTouch force sensing catheter, the nMARQ catheter results in similar PV isolation of both PAF and PeAF but the procedure time was shorter with the nMARQ catheter in PAF [199]. However, the need for crossover from the nMARQ catheter to the SmartTouch catheter occurred in 2.7% of PVs ablated [199]. Comparison of the two circular ablation catheters has also been reported recently. Both technologies have short procedure and fluoroscopy times, comparable complication rates, and comparable short-term and 1-year success rates. The number of applications was lower and the total procedure and burning times were shorter with the nMARQ catheter. The nMARQ catheter was more suitable for larger atria and PVs, suggesting a patient-based preablation anatomy definition is probably warranted for appropriate selection of the technology type [202].

Hybrid Ablation

From the surgical perspective the high success but significant invasiveness and morbidity of the "cut-and-sew" maze procedure has led to the development of alternative minimally invasive surgical options for AF patients. Bilateral video-assisted thoracoscopic PV isolation with excision of the left atrial appendage was reported to be feasible and safe a decade ago [203]. There are several important limitations of thoracoscopically guided AF ablation: the recovery period remains long; most techniques do not confirm PV isolation or adequacy of posterior left atrium ablation; several areas of the right atrium and the left atrium are unreachable epicardially (e.g., mitral isthmus and cavotricuspid isthmus). Thus a combination of epicardial ablation and the conventional endocardial lesion sets may increase the success rates of the ablation procedure. This strategy was first described in five patients [204] but the epicardial ablation was performed by percutaneous pericardial puncture with a subxiphoid approach. The hybrid approach using thoracoscopic guidance has proved to be safe and effective with favorable outcomes in patients with all types of AF but mostly PeAF and LPeAF [205–207]. The staged hybrid epicardial-endocardial ablations of LPeAF seem to be highly effective in maintenance of normal sinus rhythm compared with radiofrequency catheter or surgical ablation alone [208]. However, data to the contrary have also been reported from high-volume centers. In patients with LPeAF and an enlarged left atrium, a concomitant combined surgical and endocardial ablation approach increases the complication rate and does not improve outcomes when compared with extensive endocardial ablation only [209]. In a study of 83 patients (52 same day, 31 staged), staged hybrid ablation significantly increased the likelihood of discovering incomplete PV isolation at the time of endocardial mapping versus a same-day procedure. However, the staged approach did not increase the time to first atrial tachycardia or AF recurrence [210].

Because of the absence of guidelines for hybrid ablation [3–5], operating approaches and perioperative care differ among medical centers. There are several variations of hybrid AF ablation, but the primary components are PV isolation with left atrial linear lesions, and endocardial confirmation and additional lesions to ensure conduction block. Adjunctive measures include targeting GP and the ligament of Marshall, complete left atrial "box lesion," right atrial linear lesions, endocardial cavotricuspid ablation, and left atrial appendage occlusion. Hybrid thoracoscopic AF ablation is generally reserved for symptomatic patients with PeAF and LPeAF especially those in whom endocardial ablation has failed and symptomatic PAF patients in whom catheter ablation has failed and whose PAF is still refractory to medical management. However, consensus recommendations for hybrid approaches do not exist in the 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines for the treatment of patients with AF [3]. The committee did issue a class IIB recommendation for surgical ablation in stand-alone AF. Currently, lack of matching data hinders the drawing of conclusions and the creation of guidelines. Despite early encouraging results, more data are awaited and needed.

Summary and Future Directions

Despite a century-long investigative effort, the precise understanding of AF, with regard to its underlying mechanisms, relation to other cardiovascular diseases, and propensity to progression, has remained a challenge. We still do not know the mechanism of AF in individual patients. Most data strongly suggest that triggered activity, automaticity, and reentry all play a role in the initiation and maintenance of AF, but these mechanisms likely differ depending on the pathophysiologic conditions present. The last two decades have seen substantial progress in the understanding of the mechanisms of AF, clinical implementation of ablation for maintaining sinus rhythm, and new drugs for stroke prevention. On the basis of the current guideline recommendations and the general practice patterns, a partial list of the ablation techniques and technologies commonly used for different types of AF is summarized in Figure 5. In general, linear ablations should be avoided in PAF and perhaps in some PeAF cases that last only a relatively short time (e.g., ≤4–6 weeks) to avoid iatrogenic macro reentry atrial tachycardia or flutter. While significant inconsistency exists for the ablation of PeAF, a simple PV isolation will be inadequate for maintenance of sinus rhythm for LPeAF and most recurrent PeAF cases after the initial ablation. For those patients, a balance of extensive ablation-related iatrogenic arrhythmias and complications versus an acceptable sinus rhythm maintenance rate with the "substrate modifications" in addition to PV isolation remains the most challenging issue in AF ablation. Further studies are urgently needed to better inform clinicians about the risks and benefits of therapeutic options for an individual patient. Continued research is also required into the mechanisms that initiate and sustain different types of AF in individual patients. It is hoped that better understanding of these molecular, genetic, cellular, and tissue

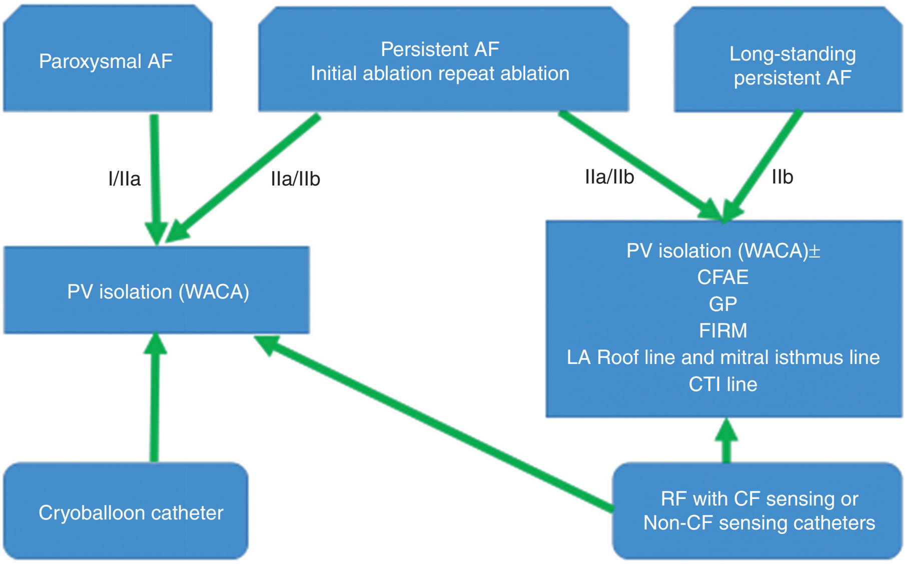

Figure 5 The Atrial Fibrillation (AF) Ablation Techniques and Catheters Commonly Used for the Different Types of AF. I, IIa, and IIb refer to the guideline indications for the different types of AF. CF, contact force; CFAE, complex fractionated atrial electrogram; CTI, cavotricuspid isthmus; FIRM, focal impulse and rotor modulation; GP, ganglionated plexi; LA, left atrium; PV, pulmonary vein; RF, radiofrequency; WACA, wide area circumferential ablation.

mechanisms will lead to more defined approaches to treating and abolishing AF. This certainly includes new methodological approaches and technologies for AF ablation that would favorably impact survival, thromboembolism, and quality of life across different patient profiles. The ever-evolving new mapping and ablation technologies discussed in this review show promise in that direction. The operator learning curve, costs, and, most importantly, superior safety and effectiveness profiles in comparison with those for established strategies will be important for the widespread adoption of new technologies, which should be tested and their effectiveness confirmed in multicenter prospective randomized trials.

Conflicts of Interest

The authors declare no conflict of interest.

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