Review article

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Invasive strategies for rhythm control of atrial fibrillation: a narrative review

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Atrial fibrillation (AF) is the most common sustained tachyarrhythmia and its increasing prevalence has resulted in a growing health-care burden. A recent landmark randomized trial, the EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial), highlighted the importance of early rhythm control in AF, which was previously underemphasized. Rhythm control therapy includes antiarrhythmic drugs, direct-current cardioversion, and catheter ablation. Currently, catheter ablation is indicated for patients with AF who are either refractory or intolerant to antiarrhythmic drugs or who exhibit decreased left ventricular systolic function. Catheter ablation can be categorized according to the energy source used, including radiofrequency ablation (RFA), cryoablation, laser ablation, and the recently emerging pulsed field ablation (PFA). Catheter ablation techniques can also be divided into the point-by-point ablation method, which ablates the pulmonary vein (PV) antrum one point at a time, and the single-shot technique, which uses a spherical catheter to ablate the PV antrum in a single application. PFA is known to be applicable to both point-by-point and single-shot techniques and is expected to be promising owing to its tissue specificity, resulting in less collateral damage than catheter ablation involving thermal energy, such as RFA and cryoablation. In this review, we aimed to outline catheter ablation for rhythm control in AF by reviewing previous studies.

Keywords: Atrial fibrillation; Catheter ablation; Cryosurgery; Pulse field ablation; Radiofrequency ablation

Introduction

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia and its global incidence and prevalence are increasing. AF is associated with increased morbidity and mortality related to stroke, congestive heart failure, impaired quality of life, and an increased risk of dementia [1-6]. The comprehensive management of AF, known as the "ABC pathway" suggested by the 2020 European Society of Cardiology Guidelines, includes stroke prevention, rate control, rhythm control, and management of comorbidities [5]. Rhythm control treatments include antiarrhythmic drugs, direct-current cardioversion, catheter ablation, and surgical ablation. Rhythm control therapy for AF has not been emphasized in the past. Many clinical trials, including the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and the RACE (Rate Control Versus Electrical Cardioversion) trials, which compared rate control and rhythm control treatments, did not demonstrate any clear benefits of the rhythm control strategy and, instead, reported higher rates of adverse events [7-12]. However, since the results of the EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial), the benefits of early rhythm control therapy for AF have been highlighted, and real-world data support the advantages of early rhythm control, marking a paradigm shift in AF management [13,14]. Differences

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in the classification of AF as paroxysmal or persistent, the timing of rhythm control treatment initiation, modalities of rhythm control treatment, extent of left atrial remodeling, and anticoagulation strategies have contributed to the different outcomes observed in recent studies compared with those of past trials. Recently, many studies have focused on early catheter ablation of AF. A recent randomized trial reported no difference in clinical outcomes even after delayed catheter ablation for up to 12 months [15]. However, that study had some limitations, as it utilized the referral date to a tertiary hospital, rather than the diagnosis date of AF, as the starting point for survival analysis. Other observational studies have shown that the shorter the time from the diagnosis of AF to catheter ablation, the better the clinical outcomes [16-19]. This article reviews rhythm control therapy for AF with a focus on catheter ablation.

Epidemiology and risk factors

The estimated prevalence of AF was 50 million cases worldwide in 2020. Using a back-calculation methodology, it is estimated that approximately 11% of the more than 5.6 million AF cases in the United States are undiagnosed [20-22]. According to South Korea's statistics, the prevalence of AF has gradually increased, reaching 1.53% in 2015, approximately twice that in 2006, using data from the Korean National Health Insurance database. The projected prevalence of AF is expected to increase by approximately 5.81% by 2060 [23]. The risk of AF increases with age. According to the Framingham Heart Study, AF will occur in 26% of Caucasian men and 23% of Caucasian women after 40 years of age [24]. There are various risk factors for AF. These include modifiable risk factors such as hypertension, obesity, endurance exercise, sleep apnea, thyroid disease, and alcohol consumption, as well as non-modifiable risk factors such as age, sex, family history, height, ethnicity, and history of valvular heart disease [25-29].

Catheter ablation of atrial fibrillation

1. Pulmonary vein isolation: the cornerstone of catheter ablation for atrial fibrillation

The concept of AF catheter ablation originated from the maze procedure, which was developed by Cox et al. [30]. This procedure involves the creation of transmural incisions in the left atrium. It has evolved into Cox-Maze III, which has impressive efficacy, achieving > 90% freedom from AF recurrence at 12 months [31-33].

The Cox-Maze procedure involves making incisions around the pulmonary veins (PVs); however, the significance of the PVs in AF was not widely recognized until the study by Haïssaguerre et al. [34]. Following that study, which identified PVs as a key source of ectopic beats in AF, catheter ablation has emerged as a treatment option for AF [34,35]. Subsequently, Pappone et al. [36,37] performed PV antral ablation using three-dimensional (3D) electro-anatomic mapping for AF management. Consequently, PV isolation (PVI) is a crucial milestone in catheter ablation for AF, and circumferential PVI has become the standard treatment for AF catheter ablation. In cases of persistent AF, additional ablation procedures, such as linear ablation in the left atrium, ablation of areas with fragmented local electrograms, and ablation of ganglionated plexi, have been attempted to achieve better outcomes. However, the results of these additional ablation procedures have not been satisfactory [38-42], and they have received class IIb recommendation in the clinical guidelines [5,43].

2. Energy sources of catheter ablation

1) Radiofrequency ablation

Radiofrequency (RF) is currently the most widely used energy source [5,44]. While the RF spectrum ranges from 30 to 300 GHz, the energy sources used for ablation typically operate at frequencies between 350 and 750 kHz [45]. When an RF current is delivered through the catheter tip electrodes, it generates resistive heating owing to the high resistance of the tissues, converting the RF energy into the thermal energy necessary for ablation [46]. Significant advancements have been made in the RF catheter ablation (RFCA) procedure through the development and refinement of two key technologies: open-irrigated catheters and contact force (CF)-sensing RF technology (Fig. 1A). CF-sensing RF technology has improved long-term procedural effectiveness and enabled operators to avoid excessive force and reduce procedure-related complications such as cardiac tamponade and rupture, thereby enhancing safety and efficiency [47-51]. Open-irrigated catheters decrease thrombus and char formation at the catheter tip, providing more accurate temperature feedback and improving safety [52]. The recently developed TactiFlex catheter (Abbott Inc., Chicago, IL, USA) exhibits enhanced flexibility and delivers irrigation flow directly to the tissue-tip interface, resulting in a lower incidence of steam pops than previous open-irrigated catheters [53].

Until recently, RFCA was performed using conventional power (20–40 W) for long durations (20–40 seconds). However, this method faced several issues: optimal lesion formation was highly dependent on catheter stability, procedure times were relatively long, and the incidence of PV reconnections was high [48]. To address these challenges, efforts have been made to use high power (40–90 W) with relatively short durations (≤ 15 seconds) for RFCA [54]. High-power short-duration (HPSD) ablation has

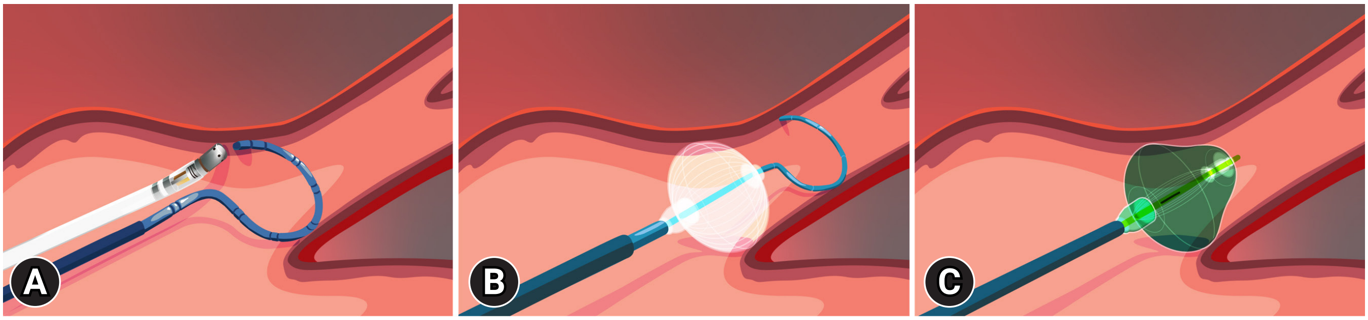


Fig. 1. Types of ablation catheters for atrial fibrillation. (A) Open-irrigated contact force-sensing radiofrequency ablation catheter (SMARTTOUCH catheter; Biosense Webster Inc., Diamond Bar, CA, USA). (B) Cryoballoon catheter. (C) Laser balloon catheter (HeartLight; CardioFocus, Marlborough, MA, USA). Illustrated by Yeungnam University College of Medicine research support team.

been attempted based on the theoretical background that it creates immediate and transmural lesions while overcoming catheter instability and minimizing subsequent tissue edema by limiting the application time. Additionally, reduced passive heat conduction may result in less collateral damage to the surrounding structures. However, the safety and efficacy windows are narrow, and the lesion depth is shallow, which may make HPSD ablation less suitable for thick tissues [55]. A human study indicated that while the efficacy and incidence of esophageal injury were similar, the procedure time was significantly shorter in patients with HPSD [56]. Additionally, a meta-analysis showed that although conventional RFCA was superior in terms of freedom from atrial arrhythmia, HPSD was advantageous not only in reducing acute PV reconnection but also in shortening the procedure time [57]. Very high-power, short-duration, temperature-controlled RFCA has also been applied in clinical settings. The QDOT MICRO catheter (Biosense Webster Inc., Diamond Bar, CA, USA), the first and only temperature-controlled CF-sensing catheter, is based on a spring-loaded CF catheter platform. It features two ablation modes: a very high-power, short-duration (vHPSD) mode (90 W, ≤ 4 seconds) and a conventional-power temperature-controlled (CPTC) mode (≤ 50 W). The vHPSD mode automatically modulates the power upon reaching maximum temperature, whereas the CPTC mode adjusts the irrigation flow and power based on temperature feedback to maintain a stable tissue temperature. Studies on vHPSD ablation have indicated that it is more efficient and effective than conventional RFCA without compromising safety. vHPSD ablation is now widely used in clinical practice [58,59].

2) Cryoablation

The cryoballoon catheter technique, in which cryoenergy is applied via a balloon catheter introduced into the left atrium through a single transseptal puncture, is also gaining attention owing to its efficacy and safety. Through the application of cryoenergy at mild freezing temperatures ranging from –10°C to –25°C, extracellular ice formation induces cell dehydration, intracellular acidification, and ionic imbalance. These physiological disruptions lead to cell membrane injury and the cessation of cardiac electrical activity. The duration of exposure to freezing temperatures correlates with the extent of permanent cellular damage. Conversely, at extreme freezing temperatures below –50°C, intracellular ice formation occurs, resulting in immediate and permanent tissue injury [60,61]. This technique, specialized for PVI using a single-shot procedure, has a relatively lower complication rate and shorter procedure time than conventional RFCA. Cryoablation is non-inferior to RFCA in reducing clinical recurrence after paroxysmal AF ablation [62]. However, in the case of persistent AF, the effectiveness of cryoablation is limited because of its primary design for creating antral PV lesions, making it less effective in targeting non-PV triggers than RFCA, which uses a point-by-point ablation technique [63-66]. A circular mapping catheter is introduced into the PV via an over-the-wire balloon catheter to confirm PVI after ablation and to monitor PV potentials in real time during the procedure. Phrenic nerve injury (PNI) is the most common complication of cryoablation, occurring in approximately 1.1% to 6.2% of cases [62,67-70]; however, it is usually temporary. According to the recent YETI registry (worldwide survey on outcome after iatrogenic phrenic nerve injury during cryoballoon based pulmonary vein isolation), when using second-generation cryoballoons, PNI occurs in 4.2% of cases, with 53.9% recovering by the end of the procedure, only 0.1% persisting with permanent PNI, and 0.06% with permanent and symptomatic PNI after 12 months (Fig. 1B).

3) Laser ablation

Laser balloon ablation (HeartLight; CardioFocus, Marlborough, MA, USA) is one method that uses laser energy to induce circumferential cell necrosis around the PV and achieve PVI. A compliant balloon adjusts to the PV size irrespective of PV dimensions and then emits a laser source onto the PV antral tissue [71]. The laser energy is titrated from 5.5 to 12 W [72]. PNI is a frequent but temporary complication. A recent meta-analysis showed that this laser balloon technique was comparable to conventional AF ablation techniques (Fig. 1C) [73].

3. Point-by-point ablation versus single-shot technique

Conventionally, AF catheter ablation involves point-by-point RF ablation with an irrigated catheter. However, this approach can be problematic owing to its complexity, longer procedure time, and the potential for increased procedure-related complications. Additionally, extensive left atrial mapping using multiple catheters is required. Gaps between the ablation lines are also inevitable during point-by-point ablation.

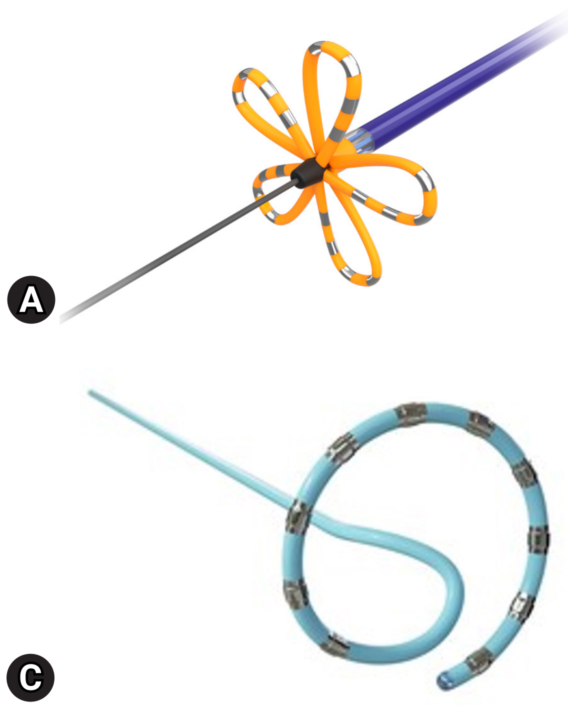
Efforts have been made to apply single-shot techniques using RF energy. Multi-electrode radiofrequency ablation catheters such as the PV ablation catheter (PVAC; Medtronic Inc., Minneapolis, MN, USA) and nMARQ (Biosense Webster Inc.) have been developed. PVAC demonstrated high procedural success rates and shorter procedure and fluoroscopy times and did not require a 3D mapping system. However, electrode overheating and tissue contact can lead to a high incidence of silent cerebral lesions. Consequently, despite the development of the improved PVAC Gold system, it was eventually withdrawn from the market [74-77]. During the study period for nMARQ, there were two cases of serious adverse events involving atrioesophageal fistulae, both of which were fatal, leading to its withdrawal from the market owing to safety concerns [78-80]. Subsequently, other catheters such as HELIOSTAR (Biosense Webster Inc.) and LUMINIZE (Apama Medical/Boston Scientific Corp., Marlborough, MA, USA) were introduced, but they are no longer commercially available [81,82]. Therefore, currently, the single-shot techniques available on the market are cryoablation using cryoenergy and, as will be discussed next, pulsed field ablation (PFA).

4. Novel method of catheter ablation: pulsed field ablation

PFA is a novel nonthermal ablation technique that utilizes irreversible electroporation (IRE) by applying an electrical field to the target tissue. When high-voltage currents are applied to the target tissue, cell membrane permeabilization increases owing to the formation of irreversible pores, which leads to the leakage of cell contents and finally, cell death [83,84]. Various tissues have specific thresholds for necrosis induced by PFA, with myocardial tissue having the lowest threshold, making it the most sensitive. Consequently, compared to other energy sources, PFA has the advantage of minimizing collateral damage, including esophageal and nerve injuries, when ablating the myocardial tissue. Additionally, because of the tissue selectivity of IRE and its rapid energy delivery, PFA is expected to have a relatively short procedure time. Experimental data from animal studies have demonstrated the safety of IRE ablation near important structures, including the coronary arteries, right phrenic nerve, and esophagus [85-87]. Observational studies on humans have also been published [88,89]. Recently, the results of a randomized controlled trial (ADVENT [Pulsed Field or Conventional Thermal Ablation for Paroxysmal Atrial Fibrillation] trial) comparing PFA to conventional thermal ablation for paroxysmal AF were published, which demonstrated that PFA is non-inferior to conventional thermal ablation methods such as radiofrequency ablation and cryoablation in terms of procedural efficacy and safety at 1 year [90]. A recent study using a variable-loop circular catheter (VARIPULSE, Biosense Webster Inc.) with a 3D mapping system (CARTO, Biosense Webster Inc.) confirmed the safety and effectiveness of this novel mapping-integrated PFA system [91]. Currently, PFA is used in both point-by-point ablation and single-shot techniques. The FARAWAVE catheter (Boston Scientific Corp.) is a five-spline-shaped PFA catheter that performs ablation by rotating in the PV antrum after positioning and changing its morphology to balloon and flower shapes [89] (Fig. 2A). The OMNYPULSE catheter (Biosense Webster Inc.) is a multi-electrode CF-sensing PFA catheter with a 12-mm-diameter spherical cage [92] (Fig. 2B). It is compatible with the 3D CARTO electroanatomical mapping system (CARTO3, Biosense Webster Inc.). The VARIPULSE multi-electrode variable-loop circular catheter (Biosense Webster Inc.) can also perform short-duration, high-voltage bipolar biphasic PFA using the CARTO3 system [91] (Fig. 2C). Additionally, the TRUPULSE 2 multimodality generator (Biosense Webster Inc.) enables point-by-point PFA using conventional CF-sensing THERMOCOOL SMARTTOUCH catheters (Biosense Webster Inc.) and is compatible with the CARTO3 system [93]. OMNYPULSE, VARIPULSE, and TRUPULSE 2 are currently under development.

Conclusion

In this review, we discussed invasive rhythm control strategies for AF. Conventional RFCA and cryoballoon catheter ablation using cryoenergy are well-established, and recent developments in PFA have either been utilized clinically or prepared for clinical use. In the past, rhythm control for AF was underemphasized; however, with the development of antiarrhythmic drugs and catheter ablation technologies, its importance has been increasingly recognized, particularly the significance of early rhythm control. Therefore, rhythm control therapy, including catheter ablation techniques,



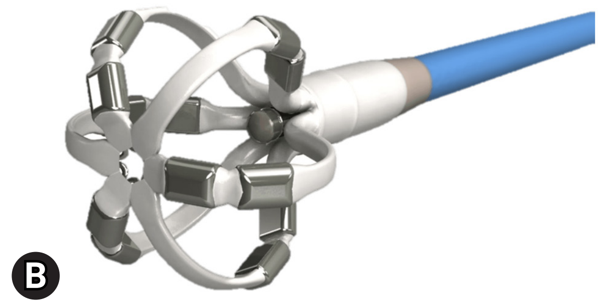


Fig. 2. Types of pulsed field ablation catheters for atrial fibrillation. (A) FARAWAVE (Boston Scientific Corp., Marlborough, MA, USA). Images provided courtesy of Boston Scientific Corp. (©2024 Boston Scientific Corp. or its affiliates. All rights reserved). (B) OMNYPULSE (Biosense Webster Inc., Diamond Bar, CA, USA) and (C) VARIPULSE (Biosense Webster Inc.). Adapted with permission from Johnson & Johnson.

should always be considered in comprehensive management strategies for patients with AF.

Article information

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization, Formal analysis, Supervision: CHL; Funding acquisition: HJK; Writing-original draft: HJK; Writing-review & editing: HJK, CHL.

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