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CATHETER ABLATION OF PAROXYSMAL ATRIAL FIBRILLATION: HAVE WE ACHIEVED CURE WITH PULMONARY VEIN ISOLATION?

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Abstract

Pulmonary vein isolation (PVI) is the cornerstone of current ablation techniques to eliminate atrial fibrillation (AF), with the greatest efficacy as a stand-alone procedure in patients with paroxysmal AF. Over the years, techniques for PVI have undergone a profound evolution, and current guidelines recommend PVI with confirmation of electrical isolation. Despite significant efforts, PV reconnection is still the rule in patients experiencing post-ablation arrhythmia recurrence. In recent years, use of general anesthesia with or without jet ventilation, open-irrigated ablation catheters, and steerable sheaths have been demonstrated to increase the safety and efficacy of PVI, reducing the rate of PV reconnection over follow-up. The widespread clinical availability of ablation catheters with real-time contact force information will likely further improve the effectiveness and safety of PVI. In a small but definite subset of patients, post-ablation recurrent arrhythmia is due to non-PV triggers, which should be eliminated in order to improve success. Typically, non-PV triggers cluster in specific regions such as the coronary sinus, the inferior mitral annulus, the interatrial septum, the left atrial appendage, the Eustachian ridge, the crista terminalis region, the superior vena cava, and the ligament of Marshall. Focal ablation targeting the origin of the trigger is recommended in most cases. Empirical non-PV ablation targeting the putative substrate responsible for AF maintenance with ablation lines and/or elimination of complex fractionated electrograms has not been shown to improve success compared to PVI alone. Similarly, the role of novel substrate-based ablation approaches targeting putative localized sources of AF (e.g., rotors) identified by computational mapping techniques is unclear, as they have never been compared to PVI and non-PV trigger ablation in an adequately designed randomized trial. This review highlights PVI techniques and outcomes in treating recurrent drug-refractory AF and discusses the potential role of additional non-PV ablation.

Introduction

Pulmonary vein isolation (PVI) is the cornerstone of current catheter ablation techniques for the treatment of atrial fibrillation (AF),[1] with efficacy uniformly demonstrated in multiple randomized trials.[2-4] The techniques for PVI have undergone a profound evolution over the years, moving from focal PV ablation of AF triggers to empirical ostial isolation of the PVs and, more recently, to wide circumferential isolation of the PVs, which includes a large portion of the left atrial posterior wall, the so-called PV antrum.[5,6] To achieve PV antrum isolation, multiple approaches with different mapping systems have been described, including electroanatomic mapping using three-dimensional nonfluoroscopic systems,[5,7] and circular mapping techniques guided by imaging the pulmonary veins through intracardiac echocardiography (ICE) or angiography.[6, 8-10] The technique currently endorsed by the Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS) expert consensus statement on catheter and surgical ablation of AF is antral PV isolation confirmed by a circular mapping catheter. Although studies have evaluated the role of different non-PV targets for the treatment of AF (either alone or as an adjunct to PVI), there is no conclusive evidence that additional non-PV ablation is necessary once durable PV isolation is achieved. Indeed, PV reconnection remains the dominant finding at repeat procedures in patients experiencing post-ablation AF recurrences. In this article, we review the techniques and outcomes with PVI for the treatment of recurrent drug-refractory AF and discuss the potential role of additional non-PV ablation.

Techniques and Outcomes of PVI

Triggers from the PVs represent the dominant mechanism that initiates AF. The initial description of PV trigger ablation consisted of focal ablation within the PVs.[11-13] This approach had minimal long-term benefit and was associated with a significant risk of PV stenosis.[7, 11-14] Subsequent evolution of the procedure involved segmental ablation at the anatomical ostium of the PVs, as defined by angiography or intracardiac echocardiography (ICE), in order to electrically isolate muscle sleeve connections between the PV and left atrium. This approach is commonly referred to as segmental ostial PVI.[15] Initial attempts targeted only the PVs with evidence of arrhythmogenic activity. However, it soon became clear that isolation of all PVs was necessary to increase the procedural success since the majority of patients presented with multiple arrhythmogenic PVs. In addition, symptomatic PV stenosis remained an important risk with ostial PVI, and AF triggers localized in the more proximal antral region were not addressed with such strategy. The technique further evolved targeting the left atrial tissue more proximal to the PV ostium, in a region defined as the PV antrum.[5-7] To achieve antral PV isolation, multiple

approaches with different mapping systems have been described. These include electroanatomic mapping using three-dimensional nonfluoroscopic systems[5,7] and circular mapping techniques guided by imaging the PVs through ICE or angiography.[6, 8-10] Wide antral PV isolation guided by recordings from a circular mapping catheter has been demonstrated superior to other ablation techniques in studies of direct comparison.[6,16] Circumferential PV ablation guided by nonfluoroscopic electroanatomic mapping systems, without confirmation of electrical isolation with a circular mapping catheter, has been demonstrated ineffective in achieving long-term arrhythmia control.[7,16] In a randomized comparison between CARTO®-guided circumferential PV ablation (Biosense Webster, Inc., Diamond Bar, CA) and PV antrum isolation with ICE and a circular mapping catheter,[16] Khaykin et al. studied 60 patients with drug-refractory AF with the end point of long-term procedural success defined as the absence of atrial tachyarrhythmias off antiarrhythmic drugs. After a mean follow-up of 24 ± 12 months, antral PVI was more likely to achieve control of atrial tachyarrhythmias off antiarrhythmic drugs (57% vs. 27%, $P = 0.02$).[16] Similar results were shown by Karch et al. in a study that randomized 100 patients to circumferential PV ablation or segmental PVI guided by a circular mapping catheter.[17] At 6-month follow-up, 42% of patients allocated to circumferential PV ablation and 66% of those receiving segmental PVI were free of atrial tachyarrhythmia episodes ($P = 0.02$ for comparison). In conclusion, electroanatomic mapping-guided circumferential PV ablation without use of the circular mapping catheter has been demonstrated to be less reliable to achieve PVI and significantly less effective than circular mapping catheter-guided PVI in terms of long-term arrhythmia-free survival. With circumferential PV ablation strategies, contiguous lesions can sometimes be created without necessarily achieving complete conduction block. As a result, post-ablation reentrant atrial tachycardias have been reported in up to 20% of patients treated with this approach.[18]

As far as PV imaging modalities are concerned, ICE has shown to be of incremental value compared to PV angiography.[9] Marrouche et al. reported the outcome of PVI in 315 patients; of these, 56 underwent ablation guided by circular mapping catheter and PV angiography, 107 underwent circular mapping catheter and ICE-guided PVI, and 152 underwent circular mapping-guided ablation with titration of radiofrequency energy based on visualization of microbubbles by ICE. After a mean follow-up of 13 ± 4 months, patients who underwent PVI guided by ICE had significantly lower rates of recurrent arrhythmias ($P < 0.01$ for comparison). Notably, no cases of severe PV stenosis were reported in patients undergoing PVI guided by a circular mapping catheter and radiofrequency energy titration based on visualization of microbubbles with ICE, whereas patients who underwent PVI guided by PV angiography had a rate of 3.5%.[9]

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.[19] 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.[20] To better evaluate the benefit of wide antral PVI compared to ostial PVI, Proietti et al. recently performed a systematic review and meta-analysis comparing the effectiveness of the two ablation

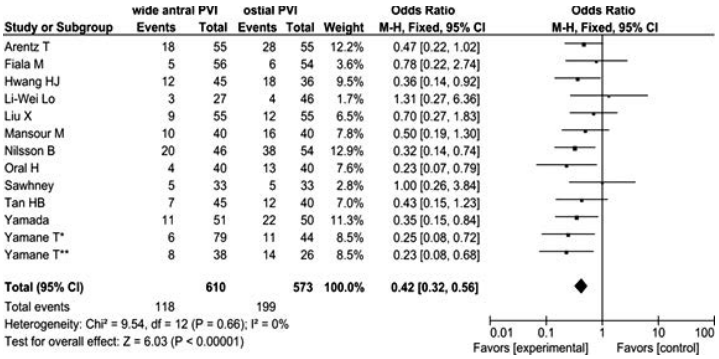

Figure 1. Combined evidence that wide antral pulmonary vein isolation improves long-term arrhythmia-free survival compared to ostial pulmonary vein isolation. From Proietti et al. with permission.[21]

techniques.[21] A total of 12 studies with 1,183 patients were included in the meta-analysis with a follow-up ranging from 6 to 48 months. Compared to ostial PVI (OR = 0.42, 95% confidence interval [CI] 0.32 to 0.56; $P < 0.001$), wide antral PVI was associated with a significantly lower rate of arrhythmia recurrence, which was driven by a reduced rate of AF at follow-up (OR = 0.33, 95% CI 0.24 to 0.46; $P < 0.001$). On the other hand, the wide antral group had a nonsignificant trend towards a higher incidence of left atrial tachycardias (OR = 1.53, 95% CI 0.88 to 2.69; $P = 0.13$) (Figure 1).[21] No significant difference between the two ablation techniques were found in terms of periprocedural complications. Based on the results of clinical studies evaluating different PVI techniques, several conclusions can be drawn: (1) empirical isolation of all PVs is necessary to eliminate the majority of AF triggers and improve arrhythmia-free survival; (2) PVI should be verified with a circular mapping catheter; (3) a wide antral PVI empirically encompassing the left atrial posterior wall between the PVs is associated with improved success at follow-up compared to ostial PVI.

Mechanisms of Arrhythmia Recurrence after PVI

PV Reconnection

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 (Figure 2).[22-26] Although the biological mechanisms underlying PV reconnection have not been fully elucidated, recovery of tissue conduction after a transient phase of reversible tissue injury with inflammation and edema has been claimed as the primary process underlying PV reconnection. Kowalski et al. reported the histopathologic and electrophysiologic findings in patients with recurrent AF after PVI who underwent a surgical maze procedure.[27] The authors collected full-thickness surgical biopsy specimens in areas of the PV antrum where endocardial scar was visible. Interestingly, the authors found that presence of conduction block did not consistently correlate with the presence of transmural lesions at histopathological analysis. In addition, the authors noted histopathological findings consistent with reversible cellular response to injury up to 37 months after the index endocardial PVI procedure. The latter finding might well explain the occurrence of very late PV reconnection, a rare but well-documented phenomenon.

Based on available evidence, achievement of permanent PV isolation should be considered the main goal of current ablation approaches for AF. Over the past years, investigators have been evaluating strategies to increase the chances of achieving permanent PV isolation. The adoption of general anesthesia is one such

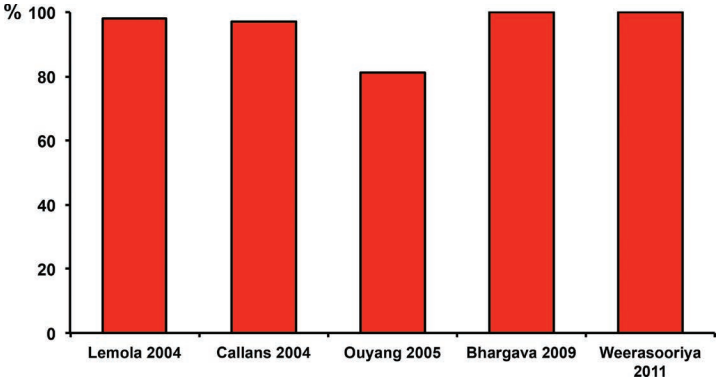

Figure 2. Prevalence of pulmonary vein reconnection in patients undergoing repeat catheter ablation procedures.

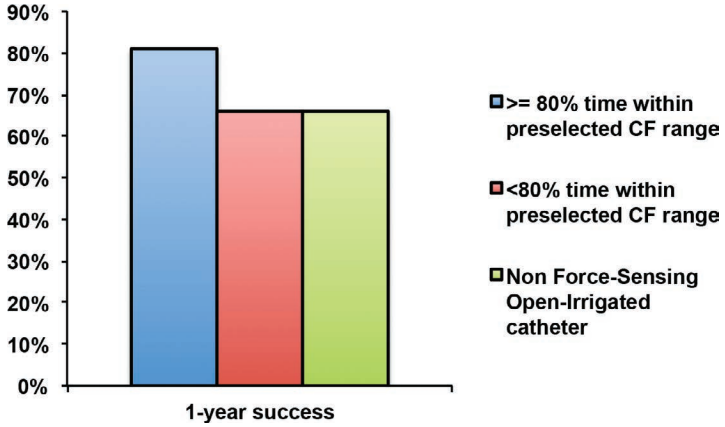

Figure 3. Outcomes of pulmonary vein isolation with the SmartTouch (Biosense Webster, Diamond Bar, CA) force-sensing catheter. Data from Natale et al.[31]

strategy 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 (n = 129) or conscious sedation (n = 128).[28] At 17 ± 8 month follow-up, 88 (69%) patients assigned to conscious sedation were free of atrial arrhythmias off antiarrhythmic drugs, as compared with 114 (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 ($P = 0.003$).[28] 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.[29] 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.[29] Recently, open-irrigated catheters with contact force sensors (Thermocool® SmartTouch®, Biosense Webster, Inc., and TactiCath™, Endosense SA, Meyrin, Switzerland) have been made 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.[30,31] 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. In this study, tissue-catheter contact force over time (evaluated as force-time interval) was a predictor of arrhythmia-free survival over follow-up.[32,33] In particular, the analysis of the force-interval integral showed a recurrence rate of 75% in patients treated with < 500 gs compared to 31% of patients treated with > 1000 gs contact force. These results have been replicated by Neuzil et al. in the EFFICAS-I trial.[30] 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 gs of contact force-time integral.[30]

Natale et al. recently reported the results of the SMART-AF trial evaluating the Thermocool SmartTouch catheter (Figure 3).[31] 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.[31]

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.[34] The reasons underlying the lack of sustained response to PVI are still unclear, although the occurrence of triggers outside the PV region have been shown to play an important role in observational studies.[35-39] High-dose isoproterenol infusion (up to 20 µg/min) together with cardioversion of induced AF is the protocol validated at our institution 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,[40] the Eustachian ridge, the crista terminalis region, and the superior vena cava.[41,42] Other sites responsible for AF triggers are the persistent left superior vena cava and its remnant, the ligament of Marshall.[43-46] Once a trigger has been identified, it should be eliminated with catheter ablation to improve procedural success.[41,42] Empirical ablation at common origins of trigger did not improve outcomes in a recent randomized trial by our group and is not part of the standard ablation strategy at this time.[42] 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.[40,47] 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.[42,48,49] Recently, Narayan et al. developed a computational mapping technique capable of identifying AF localized sources that may correspond to organized reentrant circuits (i.e., rotors) or focal impulses that have been reported in animal models of AF.[50] The benefit of ablation of these localized sources—called Focal Impulses and Rotor Modulation (FIRM) ablation—has been

tested against conventional ablation in a multicenter observational study including 92 patients with predominantly persistent AF (72%).[51] Localized rotors or focal impulses were found in 97% of cases, and ablation of these sites resulted in AF termination or consistent slowing in 86%. After a median follow-up of 273 days, patients who underwent FIRM ablation had higher freedom from recurrent AF compared to conventional ablation (single procedure success: 82.4% vs. 44.9%, $P < 0.001$). Overall, the results reported by Narayan et al. are promising; however, the extent to which they are consistently reproducible by other investigators and applicable to more challenging forms of AF (i.e., long-standing persistent AF) warrant further investigation. In particular, the benefit of FIRM ablation should be formally tested against conventional PVI plus non-PV trigger ablation in an adequately designed randomized trial to fully evaluate the potential benefit of this novel strategy.

Conclusions

Pulmonary vein isolation is the cornerstone of catheter-based therapies for AF. Over the years, techniques for PVI have undergone a profound evolution; current guidelines recommend a wide antral PVI with confirmation of electrical isolation with a circular mapping catheter, which has been demonstrated to optimize clinical success compared to other PVI approaches. Available ablation tools for PVI are still imperfect, and PV reconnection following PVI represents the dominant mechanism of recurrent arrhythmia. Although different non-PV targets have been evaluated to improve outcomes of PVI alone, it is important to emphasize that none of the studies comparing PVI alone with other non-PV ablation strategies (with or without PVI) ever achieved the desired goal of durable PVI. Future research efforts should prioritize the achievement of durable PVI to facilitate the identification of patients who truly do not respond to PVI and may require different ablation approaches and/or targets.

Conflict of Interest Disclosure: The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords: atrial fibrillation, catheter ablation, pulmonary vein isolation

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