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MINIREVIEWS

Paroxysmal atrial fibrillation ablation: Achieving permanent pulmonary vein isolation by point-by-point radiofrequency lesions

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Abstract

Pulmonary vein isolation by point-by-point radiofrequency catheter ablation constitutes the cornerstone of catheter ablation strategies for the treatment of atrial fibrillation. However, despite advances in pulmonary vein isolation ablation strategies, long-term success rates after ablation remain suboptimal, which highlights the need to develop techniques to achieve more durable lesions. Strategies proposed to improve the durability of pulmonary vein isolation can be divided into two groups: Those addressed to improving the quality of the lesion and those that optimize the detection of acute PV reconnection during the ablation procedure. This manuscript reviews the role and potential benefits of these techniques according to current clinical evidence.

Key words: Atrial fibrillation; Pulmonary vein isolation; Lesion durability; Contact force; Pulmonary vein reconnection

Core tip: Results of pulmonary vein isolation remains suboptimal in terms of long-term outcomes. Improving lesion durability could reduce atrial fibrillation recurrence rate after pulmonary vein isolation. This manuscript reviews current techniques proposed in order to achieve more durable pulmonary vein isolation by point-by-point radiofrequency ablation. The role and potential benefits of these techniques are discussed according to current clinical evidence. Furthermore a stepwise approach to achieve permanent pulmonary vein isolation is proposed.

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INTRODUCTION

Atrial fibrillation (AF) is one of the major causes of stroke, heart failure, and cardiovascular morbidity worldwide[1]. Since Haïssaguerre *et al*[2] identified the pulmonary veins (PVs) as triggers capable of initiating AF paroxysms, radiofrequency (RF) catheter ablation through pulmonary vein isolation (PVI) has been developed and now constitutes the cornerstone of catheter ablation strategies for the treatment of AF[3]. Current indications for PVI include symptomatic paroxysmal or persistent AF, in general as second-line treatment after failure of or intolerance to antiarrhythmic drug therapy, but also as first-line therapy in selected cases[4].

According to the most recent consensus statement on catheter ablation of AF[3], the technique for achieving PVI should target a wide area around the PVs, called the antrum, with complete electrical isolation as the endpoint of the procedure. However, despite advances in PVI ablation strategies, long-term success rates after ablation remain suboptimal, which has led to the development of new techniques to achieve more durable lesions.

PV RECONNECTION AS THE MAIN CAUSE OF AF RECURRENCE AFTER PVI

In the majority of patients with AF recurrence, an electrical reconnection between the PV and LA can be observed[5-7]. The probability of AF recurrence during follow-up after a PVI procedure has been linked with the presence of gaps, defined as poor isolation areas between the PV and LA, due to suboptimal RF lesions[8]. A recent meta-analysis of 11 studies[9] including 683 patients showed that 85.5% of patients with AF recurrence had at least one PV reconnected, opposed to 58.6% of those without AF recurrence. Although not fully established, it has been suggested that the biological mechanism underlying PV reconnection may be related to the recovery of tissue conduction after a transient phase of reversible tissue injury with inflammation and edema[10]. Therefore, achievement of permanent PV isolation should be considered the main goal of current AF ablation approaches in order to avoid recurrences.

PERMANENT PV ISOLATION AS THE ENDPOINT OF AF ABLATION: HOW TO ACHIEVE IT?

The reasons for long-term failure of AF ablation are largely based on a suboptimal ability to effectuate a durable transmural lesion using the contemporary ablation toolset. While electrical PVI may be achieved acutely, the combination of inadequate electrode-tissue contact, insufficient power delivery, and tissue edema may prevent RF-induced heating of myocardium to lethal temperatures. With time, as the acute effects of RF energy resolve, the transient injury induced at the time of index ablation recovers, revealing gaps in the initial line of ablation and allowing PV triggers to excite the adjacent LA and induce AF[6,10]. Several techniques to improve the durability of PVI have been proposed, and can be divided into two groups: Those addressed to improving the quality of the lesion and those that optimize the detection of acute PV reconnection during the ablation procedure.

TECHNIQUES TO IMPROVE LESION DURABILITY

The use of irrigated catheters for PVI was associated with a dramatic decrease in PV reconnection rate[11]. However, even when irrigated catheters are used, the recurrence rate after a single PVI procedure remains high (30%-35%)[12]. Further strategies are required in order to improve long-term durability of the lesions obtained with this type of catheters.

Use of sheaths

Efficient catheter contact can be facilitated through the use of non-steerable and steerable sheaths that allow easy maneuverability, access, and contact to target sites. Piorkowski *et al*[13] compared the use of steerable sheaths with the use of non-steerable sheaths during AF ablations in a prospective randomized trial. Although the rate of acute PVI and total RF application time did not differ between the study groups, single procedure success was significantly higher in patients treated with a steerable sheath (76% *vs* 53% at 6 mo). The difference persisted at 12 mo (75.7% success) after a single AF catheter ablation procedure using steerable sheath[14]. Therefore, use of a steerable sheath may help to improve the maneuverability of the ablation catheter, catheter stability, and tissue contact. This could potentially reduce recurrence through the enhancement of lesion continuity and transmurality.

General anesthesia

In a multicenter trial, Di Biase *et al*[15] randomized 257 consecutive patients undergoing a first AF ablation procedure to general anesthesia or conscious sedation. During follow-up (mean 17 ± 8 mo), fewer patients randomized to conscious sedation were free of atrial arrhythmias while off antiarrhythmic drugs (69% *vs* 88% of patients randomized to general anesthesia). In their study, all patients with recurrence had a second procedure. Interestingly, 42% of PVs in the conscious sedation arm at the repeat procedure had recovered PV conduction, compared with 19% in the general anesthesia group[15]. Better and more stable tissue-catheter contact due to controlled breathing patterns and elimination of patient movements may explain this finding.

Contact force sensing catheters

Contact force (CF) sensing is a novel technology used to assess the degree of catheter-tissue contact through a sensor at the distal tip of the ablation catheter. Studies based on animal models have shown that catheter-tissue CF is directly correlated with lesion size, and that excessive CF (> 50 g) could even provoke steam pops[16,17]. The concept of force-time integral (FTI) has also been proposed as a major factor in RF lesion size[18]. Shah *et al*[18] calculated the FTI by measuring the area under the CF curve beyond 60 s and found a linear correlation with lesion size during RF ablation. Despite similar power and peak CF values, lesions were larger with constant contact and smaller with intermittent contact.

CF and lesion transmurality

Several studies have assessed the relationship between CF and lesion transmurality by means of electrogram analysis, cardiac imaging, and histopathology. Squara et al assessed the CF and FTI needed to create effective transmural lesions during AF ablation by analyzing bipolar electrograms before, during, and after RF application. Based on post-ablation changes in electrogram characteristics, they identified a cutoff FTI of > 392 gs to predict transmurality with 89% sensitivity and 93% specificity[19]. Two cardiac MRI studies have demonstrated a direct correlation of CF and FTI with lesion transmurality. In the first study, Sohns *et al*[20] performed contrast-enhanced cardiac MRI in patients treated with AF ablation using CF catheters. They found a correlation between regions where higher FTI (> 1200 g) was maintained during ablation and those showing increased late gadolinium enhancement on MRI at 3 mo after ablation[20]. In the second study, Andreu et al performed cardiac MRI at 3 mo after PVI ablation to assess CF thresholds required to create permanent lesions using a dragging catheter (as opposed to a point-by-point lesion delivery) technique[21]. They reported that PV segments where MRI gaps were seen had lower maximal CF values, compared to segments without gaps, and a CF threshold of > 12 g predicted the formation of a complete PV lesion with 94% specificity and 91% positive predictive value.

Results from a recent study question the correlation between CF and chronic lesion formation. Williams *et al*[22] placed linear intercaval right atrial lesions in eight pigs using high (> 20 g) or low (< 10 g) CF, intentionally leaving a gap between segments. Voltage maps and cardiac MRI were performed before, immediately after, and 2 mo after ablation. The authors found that tissue edema was greater in the acute post-ablation setting with high CF, but there was no difference in chronic lesion size or volume by voltage mapping or cardiac MRI between high *vs* low CF regions at 2 mo. Their results suggest that a transmural lesion can be created whenever continuous tissue-catheter contact is achieved (independently of the CF value) and adequate power is delivered with a stable catheter position throughout the lesion.

CF variability according to left atrium anatomy

Obtaining adequate CF can be difficult in certain portions of the LA, and certain LA regions may require less CF to achieve transmurality with RF ablation. This may explain the observation that PV reconnection tends to recur at specific regions in the LA. For example, Schluermann *et al*[23] reported lower CF obtained in left PVs than in right PVs and found the lowest values in the anterior segments, where the ridge between the left upper PV and the LA appendage represents anespecially challenging region for obtaining appropriate CF. Consistently with these data, our group observed that when operators were blinded to CF, the lowest CF values were recorded at the anterior segments of left PVs[24] (Figure 1).

On the other hand, given the differences in LA wall thickness, the amount of CF needed to achieve transmural lesions may vary in different portions of the LA. Sotomi *et al*[25] showed that higher CF may be necessary in certain regions such as the inferior right PV and posterior-superior right PV regions (22 g CF), while other areas such as the posterior-inferior right PV region may require only 10 g CF to assure acute PVI. Knowledge of CF requirements in various regions of the LA can improve safety during ablation by allowing the operator to control RF power based on CF to prevent steam pops without compromising lesion durability.

Impact of CF on ablation outcomes-clinical studies

Several studies (Table 1) have assessed the role of CF technology in short and long-term ablation outcomes.

The TOCCATA study was the first multicenter, prospective study to demonstrate the safety of CF-sensing catheters (Tacticath, Endosense) for ablation of cardiac arrhythmias[26]. The study included 34 patients undergoing PVI for paroxysmal AF and showed that low CF was associated with higher rates of AF recurrence[26]. Specifically, all patients treated with a CF < 10 g experienced AF recurrences, whereas 80% of the patients treated with an average CF > 20 g remained free from AF recurrence at 12 mo[26].

In order to demonstrate the correlation between CF parameters during initial procedure and PV reconnection, the EFFICAS-I study of PVI using CF-sensing catheters assessed the incidence of isolation gaps at 3-mo follow-up (Tacticath, Endosense)[27]. Interestingly, operators were blinded to CF information during the initial procedure. Isolation gap sites correlated with lower minimum CF and FTI during the initial ablation, and the authors proposed an optimal CF target of 20 g with minimum FTI of 400 gs. These cut-off values were prospectively tested in the EFFICAS-II study, which showed that 85% of PVs treated within the proposed CF guidelines were chronically isolated, suggesting a more durable PVI[28].

The SMART-AF trial, a prospective, multicenter, non-randomized single-arm study, examined the efficacy

Table 1 Clinical studies on contact force monitoring and mid/long-term outcomes

Study	*n*	Type of study	CF catheter	Control catheter	Follow-up (mo)	Findings
Andrade *et al*[55], 2014	75	Prospective observational	Thermocool SmarTouch	Navistar Thermocool	13.3	CF reduced dormant conduction (16% *vs* 52%) and improved long-term arrhythmia-free survival (88% *vs* 66%)
Kimura *et al*[31], 2014	38	Randomized controlled trial	Thermocool SmarTouch	Thermocool SmarTouch (blinded operador)	6	CF reduced procedure time and additional touch-up ablation
Marijon *et al*[61], 2014	60	Prospective observational	Thermocool SmarTouch	EZ Steer Thermocool	12	CF reduced AF recurrence at 12 mo (10.5% *vs* 35.9%)
Shurrab *et al*[33], 2015	42	Observational	Thermocool SmarTouch	Navistar Thermocool	2.5	CF reduced reconnection rate at 30 min postablation
TOCCASTAR, 2015	300	Randomized controlled trial	Tacticath	Thermocool Navistar	12	No differences in arrhythmia-free survival
Pedrote *et al*[24], 2016	50	Randomized controlled trial	Thermocool SmarTouch	Thermocool SmarTouch (blinded operador)	12	CF reduced PV gaps (20% *vs* 68%). No benefits in arrhythmia-free survival
Ullah *et al*[34], 2016	117	Randomized controlled trial	Thermocool SmarTouch	Thermocool SmarTouch (blinded operador)	12	CF reduced acute reconnections (22% *vs* 32%). No benefits in arrhythmia-free survival

CF: Contact force.

and safety of AF ablation using a SmartTouch CF-sensing catheter[29]. Only 2.5% of the 172 patients included had severe complications, suggesting that safety was not inferior to non-CF-sensing catheters. On the other hand, CF-sensing ablation that remained within target range > 80% of the time resulted in superior 1-year ablation success (81% of patients free from AF recurrence *vs* 66%, $P = 0.005$)[29].

The TOCCASTAR study was a prospective, multi-center, randomized clinical trial that compared AF ablation with CF (TactiCath) *vs* non-CF (ThermoCool Navistar) catheters in 300 patients[30]. Achieving optimal CF resulted in higher rates of acute PVI and no differences were observed in long-term success (freedom from AF or atrial tachycardia recurrence at 12 mo, excluding 3-mo blanking period).

Kimura *et al*[31] compared acute bidirectional block after PVI in 38 patients randomized to non-CF guided *vs* CF-guided (target CF 10-20 g) ablation using Thermocool Smart Touch catheter. This study showed that CF-guided PVI reduces procedure time and the need for additional touch-up ablation. Furthermore, a nonsignificant trend towards lower AF recurrence rate at 6 mo post-PVI was observed in the CF-guided group.

Two large meta-analyses have compared AF ablation with CF *vs* non-CF catheters. Afzal *et al*[32] examined data on 1148 patients in 9 studies and found that the use of CF-sensing technology reduced AF recurrence 37% overall at a median 12 mo of follow-up. Those treated with CF catheters also had reduced RF ablation duration, although no significant difference was seen in total procedure length or fluoroscopic exposure, compared to non-CF catheters. Shurrab *et al*[33] subsequently published another meta-analysis, which included 1428 patients from 11 studies (an overlap of 6 studies from the previous meta-analysis). They found a similar 38% overall reduction in AF recurrence at long-term follow-up. However, in addition to reduced RF ablation time, overall procedure length and fluoroscopic exposure duration were significantly lower in patients treated with CF technology. This meta-analysis also demonstrated a non-significant trend toward lower complication rates in the CF group.

It should be noted that the studies mentioned above assessed the impact of CF parameters in PVI performed with a circular catheter inside the PV. The use of circular catheters allows continuous recording of the electrical signal inside the PV, which can condition the endpoint of the procedure and prevents "naïve" assessment of the potential benefit of CF monitoring. In order to test the benefits of CF monitoring in PVI with an exclusively anatomic approach (blinded to the PV catheter), our group conducted a randomized, controlled study in which 50 patients with paroxysmal atrial fibrillation were randomized into CF-on (CF > 10 g) or CF-off (CF blinded; $n = 25$) groups. In the CF-on group, there was a reduction in the PV gaps at the expense of the left PVs and shortening of the procedure and radioscopy times. This confirms the benefits of operator monitoring and control of a mean CF > 10 g during PVI[24]. However, at 12 mo the AF recurrence rate was similar in both groups[24]. Consistent with these data, a larger study by Ullah *et al*[34] using the same methodology showed that access to CF data during the procedure was associated with reduced acute PV reconnection, although no benefit was observed in terms of 1-year success rate. These results suggest that CF monitoring during PVI may not impact long-term clinical outcome because it is only one of multiple factors that determine lesion durability.

Ablation index

As has been explained, previously described endpoints (CF and FTI) do not take the power used during RF

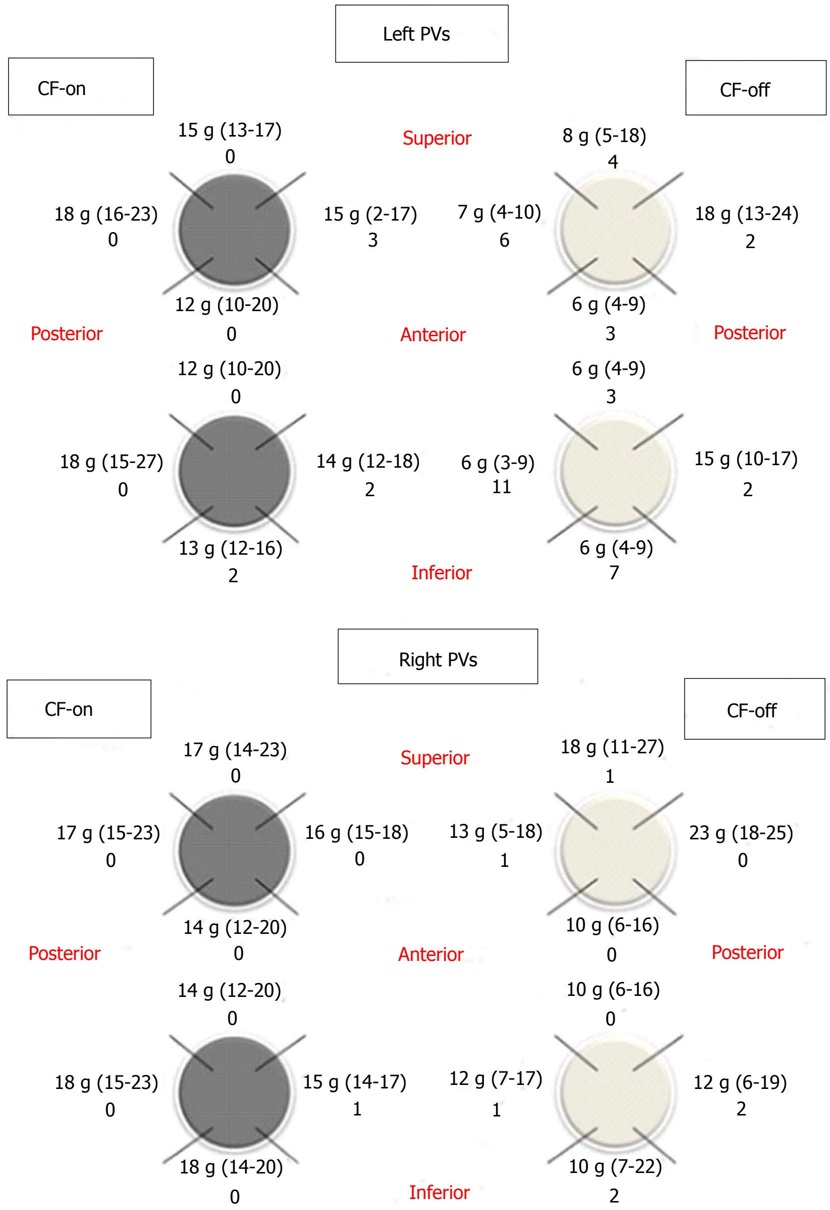

Figure 1 Contact force variability according to left atrium anatomy. Contact force (CF) is expressed in grams (g; median and 25^{th}-75^{th} percentile) and the number of pulmonary veins segments with conduction gaps (bold) in the CF-on group (dark gray) and the CF-off group (light gray). Reproduced with permission from Pedrote *et al*[24].

application into account. In order to resolve this limitation, the ablation index has been proposed as a marker of ablation lesion quality that incorporates CF, ablation time, and RF power in a weighted formula (the greater the impact of power over CF, the greater the impact on the initial phase of ablation). A recent study by Das *et al*[35] showed that the minimum ablation index was an independent predictor of conduction recovery after PVI. Furthermore, in this study, higher ablation index values were required to prevent reconnection of anterior/roof segments, compared to posterior/inferior segments[35].

Lesion contiguity

The EFFICAS-II study demonstrated that lesion contiguity is an essential component of effective PVI. The analysis of the contiguity index revealed that even with effective use of optimized CF, 15% of PVs were reconnected after ablation due to non-contiguity between point-by-point lesions along ablation line[28]. Consistent with these data, Park *et al*[36] showed that acutely durable PVI can be achieved in CF-guided ablation when RF lesions are delivered with a mean CF > 10 g and an inter-lesion distance < 5 mm.

A novel automated technology for tagging ablation lesions (VisiTag module) allows real-time assessment of catheter stability, contact force, power, and impedance drop during radiofrequency applications (Figure 2). This technology improves lesion efficiency and reduces the number of ineffective applications[37]. Catheter stability tracking during PVI is essential in order to achieve appropriate lesion contiguity. Okumura *et al*[38] reported

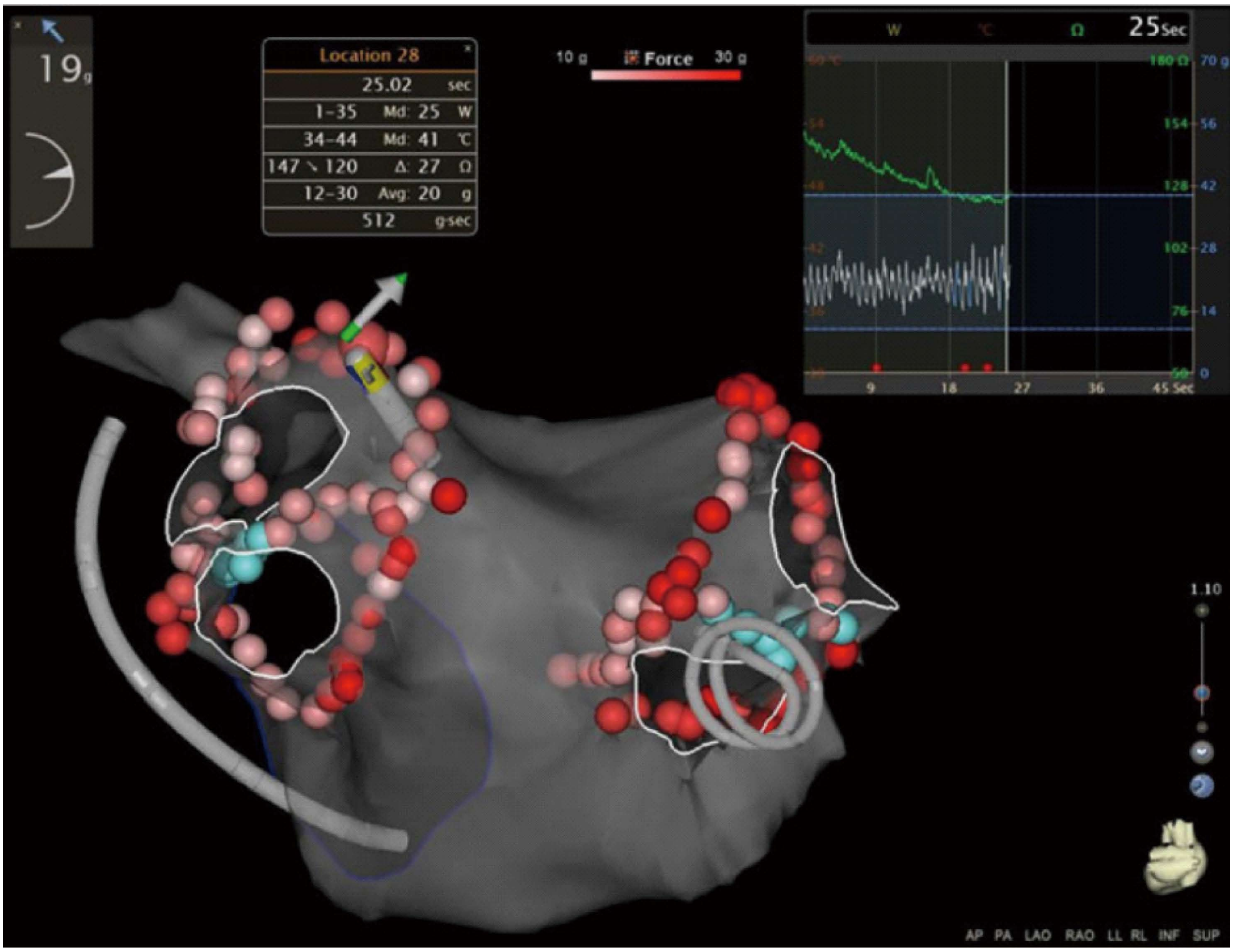

Figure 2 Automatic tagging of radiofrequency lesions. The contact force (CF) of each application is color-coded (color bar). The manually acquired RF applications are displayed in green. The central box shows the information collected by the VisiTagTM module on each point, including average CF, time, force-time integral, temperature, power, and delta impedance. The force and impedance graphs from this RF point are shown on the right, and the real-time CF and direction dashboard are shown on the left. Reproduced with permission from Pedrote *et al*[24]. RF: Radiofrequency.

that a strict stability setting (3-mm distance limit for at least 10 s) for VisiTag reduced acute PV reconnection, although no benefit was observed in mid-term outcomes.

HOW TO OPTIMIZE THE DETECTION OF ACUTE PV RECONNECTION DURING THE ABLATION PROCEDURE

Circular mapping catheters

Circumferential PVI guided by nonfluoroscopic electro-anatomic mapping systems, without confirmation of electrical isolation with a circular mapping catheter, has been shown to be ineffective in achieving long-term arrhythmia control[39]. Additionally, a randomized study comparing PVI guided by circular mapping catheter *vs* PVI using only RF catheter showed that the use of circular mapping catheter is associated with better acute results and lower recurrence rates[40]. Therefore, 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 arrhythmia-free survival.

Identification of dormant conduction

The identification of dormant tissue that has been rendered unexcitable by "stunning" or edema is a significant challenge that may potentially increase risk of AF recurrence. The detection of such "dormant conduction" during the initial ablation procedure may therefore help identify PVs with the potential to reconnect after the index procedure, and targeted ablation at these sites may reduce the risk of recurrent AF. Adenosine has been shown to effectively uncover dormant conduction. Following ablation, adenosine selectively hyperpolarizes PV cells by increasing inward rectifier potassium current, thereby restoring excitability of inactivated voltage-dependent Na^+ (INa) and reestablishing conduction in dormant PVs[41]. Multiple studies have shown that adenosine is clinically useful in identifying PV reconnection, as well as cavotricuspid isthmus reconnection[42]. An early study reported that

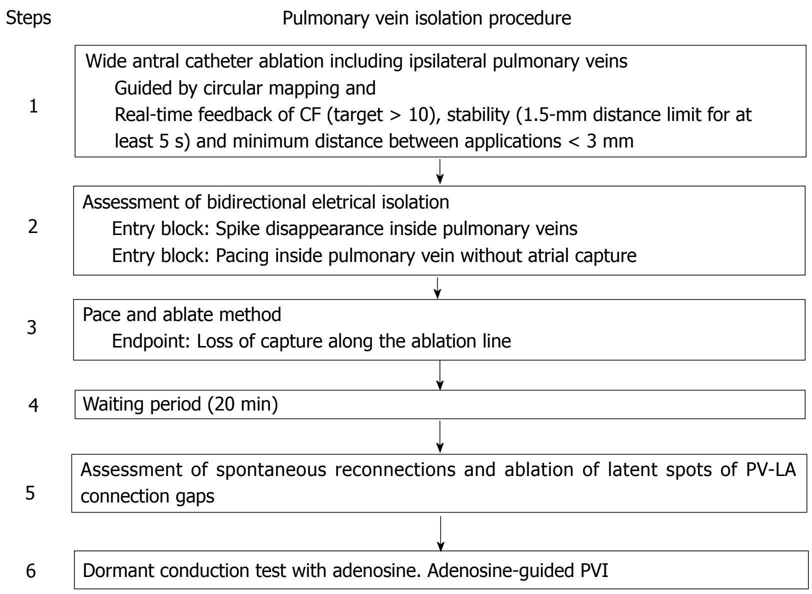

Figure 3 Stepwise approach for permanent pulmonary vein isolation. CF: Contact force; PVI: Pulmonary vein isolation.

adenosine induced reconnection in 25% of PVs immediately after successful isolation[43]. Tritto *et al*[44] further demonstrated that delivering additional RF lesions at electrical gap sites elicited by adenosine definitively eliminated recovery of PV reconnection in all cases. Subsequent studies have shown that AF recurrence after PV isolation could be reduced by delivering additional ablation lesions to eliminate adenosine-induced dormant PV conduction[45-47]. Other studies[48,49] did not confirm the usefulness of adenosine in AF recurrence after PVI, fueling a need for randomized trials.

Two randomized trials (ADVICE and UNDER-ATP) have assessed whether elimination of dormant PV conduction after PVI is better than conventional PVI in terms of arrhythmia-free survival. The ADVICE study showed that the use of adenosine to identify and target areas of dormant conduction significantly improved long-term arrhythmia-free survival, compared to PVI alone[50]. In contrast, the UNDER-ATP trial found no significant reduction in arrhythmia-free survival by ATP-guided PVI, compared with conventional PVI[51]. The discrepancy between ADVICE and UNDER-ATP trials may be due to differences in the rate of dormant conduction, around 50% in the ADVICE trial and 28% in UNDER-ATP. This suggests that the benefit of using adenosine after PVI depends on how frequently dormant conduction is observed; which is highly affected by the ablation procedural method.

Pace and ablate

Entrance and exit block confirmed by the absence of PV potentials and by pacing inside the PVs is a common procedural endpoint of encircling PVI. However, it has been suggested that pacing along the ablation line may identify latent spots of PV-LA antrum connection gaps not detected by circular mapping catheters. Steven *et al*[52] showed that more RF ablation energy was required to achieve loss of pace capture along the ablation line than for entrance block into the PVs, suggesting that reaching the endpoint of loss of capture along the ablation line may be associated with more durable lesions. Consistent with this hypothesis, a randomized study confirmed that the use of pacing to ensure an unexcitable gap along the ablation line improved success rates at 12 mo post-PVI, compared to reliance on bidirectional block alone (83% *vs* 52%, respectively)[53]. However, it should be noted that adenosine was not used to identify dormant conduction after PVI in this study. In contrast to these findings, two recent studies showed that although PVI followed by the pace and ablate method reduced dormant PV conduction unmasked by adenosine, there was no difference in 1-year AF recurrence, compared to adenosine-guided ablation[54,55].

Although the available results suggest that both techniques achieve similar long-term outcomes, the potential effect on recurrence rates of combining pace and ablate with adenosine-guided PVI remains unknown. A recent study by Kogawa *et al*[56] showed that sites with adenosine-induced dormant PV reconnection did not match the excitable gaps identified by pacing, suggesting a difference in the underlying mechanism to elucidate potential PV-antrum gaps. Thus, the authors proposed that an adenosine provocation test followed by pace and ablate method could be useful in reducing AF recurrence. Further prospective and randomized studies are required to confirm this hypothesis.

NON-PV SOURCES OF AF RECURRENCE

It should be noted that a variable proportion of patients may have AF recurrence despite persistent PVI. This could be due to the existence of non-PV triggers[57]. Typically, these non-PV triggers are located in specific regions such as the crista terminalis, the superior vena cava, the Eustachian ridge, the fossa ovalis, the left atrial appendage, the inferior mitral annulus and the coronary sinus. Empirical ablation of these common origins of triggers is not recommended. However, once a trigger is identified, it should be eliminated in order to achieve better outcomes[58].

EXPERT RECOMMENDATIONS

Based on our own experience, we propose the following step-wise approach to achieve permanent PVI (Figure 3). Our unit adopted this strategy two years ago, with good arrhythmia-free survival at 12 mo (84%), a very low complication rate (1%), and no increase in procedure time[24,59].

FUTURE PERSPECTIVES

The implementation of non-fluoroscopic navigation systems in the electrophysiology laboratory has improved anatomic definition of cardiac structures. However, the increased complexity of ablation procedures demands better intra-procedural anatomic definition and improved accuracy in catheter positioning. Novel non-fluoroscopic systems have been proposed for catheter guidance during PVI procedures. In animal studies, Ranjan *et al*[60] showed the feasibility of catheter tracking, electrogram recording, and RF energy delivery in a real-time MRI environment. Intra-procedural MRI allowed real-time visualization of lesion formation and tissue characterization, which could permit the assessment of lesion depth and transmurality. Furthermore, their work demonstrates the utility of MRI-guided PVI to identify gaps intra-procedurally and guide catheter positioning to target them. However, this proof-of-concept has not been tested in humans. In order to use this technology in clinical settings, several technical challenges must be overcome to obtain better signals and develop more maneuverable and easily visible catheters. However, this promising technology will provide considerable benefits by delivering accurate anatomic definition and monitoring of RF lesions.

CONCLUSION

PVI is the cornerstone of catheter-based therapies for AF. PV reconnection after PVI represents the main limitation of AF ablation techniques. Efforts should be made to develop strategies that achieve more durable lesions. Current techniques associated with better acute (and probably long-term) outcomes include antral PVI guided by circular mapping catheters, the use of CF catheters, lesion contiguity, and the assessment of dormant PV conduction by adenosine and/or pace and ablate. Finally, a subset of patients may still have AF recurrences despite persistent PVI, due to the presence of non-PV triggers. Efforts should be made in order to individualize the treatment according to each patient's specific mechanism of recurrence (drivers, rotors, focal activity...).

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