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Journal Review
Journal of Atrial Fibrillation
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Should Adenosine Test Be Performed Systematically At The End Of Atrial Fibrillation Ablation Procedure?

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Abstract

Pulmonary vein (PV) reconnection is a major limitation of atrial fibrillation (AF) ablation and is a significant contributor for arrhythmia recurrence, particularly in patients with paroxysmal AF. Recent technological advances, including the use of steerable sheaths and force sensing catheters resulted in reduced incidence of PV reconnection; however its incidence remains unacceptably high. Additional efforts to reduce pulmonary vein reconnection include the use adenosine to detect dormant PV to left atrial (LA) electrical conduction as well as identification of non-PV triggers. While this strategy is associated with an increased detection rate of reconnection that can be further targeted with ablation, its effect on long-term arrhythmia control is controversial. Still, adenosine-induced PV reconnection appears to be an independent predictor of arrhythmia recurrence despite additional ablation. We favor its use in patients with paroxysmal AF as an additional step for risk stratification and prediction of arrhythmia recurrence.

Introduction

Catheter ablation is an effective therapy for patients with symptomatic atrial fibrillation (AF), however the recurrence rate of AF at one year post-procedure remains high, approximately 16-25% and 29-35% for paroxysmal and persistent AF, respectively.[1-3] Pulmonary vein isolation (PVI) is the cornerstone for AF ablation, especially for patients with paroxysmal AF. Recurrences in these patients are often associated with recovery of pulmonary vein (PV) to left atrial (LA) electrical conduction.[4-6] Despite advances in operator expertise and technological advancement including the use of steerable sheaths, high-frequency jet ventilation,[7] and contract force sensing catheters,[8-10] durable PVI remains a clinical challenge.

For a subgroup of patients, recurrence is related to the presence of non-PV triggers,[11] accounting for 2-18% of AF relapses following PVI. Common sites of non-PV triggers include the superior vena cava (SVC),[12, 13] fossa ovalis, ligament of Marshall,[14] mitral annulus, Eustachian ridge, and the left atrial appendage (LAA).[15]

However, the recovery of PV conduction is by far the most common cause of procedural failure, being present in up to 90% of patients with AF recurrence presenting for a redo procedure.[5, 6] That said, recent data suggests that the incidence of PV reconnection is similar between patients with and without clinical recurrence, again highlighting our limited understanding of AF pathophysiology.[16]

Adenosine can reveal dormant PV conduction or re-connection during acute and repeat PVI,[13] thus allowing operators to treat ablation gaps and potentially improve procedural outcomes.[17] In this review, we describe the electrophysiological properties of adenosine that facilitate the detection of dormant PV conduction, its role in improving procedural outcome and its value for clinical use.

Electrophysiological Effects of Adenosine

Adenosine is an endogenous nucleoside that elicits its electrophysiological effects after binding to the A1 cardiac receptor. In atrial tissue, it activates a specific outward potassium (K+) current (IKAdo) leading to shortening of the action potential (AP) duration and refractoriness, as well as hyperpolarization of the resting membrane potential. Adenosine also suppresses the automaticity of the sinoatrial nodal cells through the hyperpolarizing effect, and depresses the AP of atrioventricular (AV) nodal cells, resulting in bradycardia and transient AV block, respectively.[18, 19] These actions are mediated by the same G protein system and couple K+ channels (Kir3.1/3.4) as the acetylcholine-regulated K+ current (IKAch),[20, 21] suggesting similarities with the effects of vagal stimulation to facilitate AF.[22] Lastly, the activation of the adenosine effector cascade produces secondary sympathetic activation mediated through baroreflex activity and chemoreceptor stimulation, corroborated by transient sinus tachycardia.

The initial correlation between adenosine and AF was derived from clinical observations in patients with supraventricular tachycardia treated with adenosine and acutely developed AF.[23-26]

Datino et al. demonstrated the mechanisms through which adenosine promotes the initiation and perpetuation of AF.[27] In a canine model, adenosine had a differential effect in the LA and PVs,

Key Words:
Atrial Fibrillation, Catheter Ablation, Adenosine, Reconnection, Recurrence, Dormant Conduction.

Disclosures:
None.

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Table 1: Impact of adenosine-induced dormant conduction on arrhythmia recurrence after PVI.

Study		N	Paroxysmal AF (%)	Follow-up*	Acute PV Reconnection†	Recurrence Rate‡	
Group	Design					Adenosine(+)	Adenosine(-)
Arentz et al., 2004[39]	Prospective	29	68.9	12	25%	71	35
Tritto et al., 2004[40]	Prospective	29	72.4	6.3±2.4	35%	31	31
Hachiya et al., 2007[41]	Retrospective	252	78.1	6.1±3.3	41%	27	40
Matsuo et al., 2007[42]	Retrospective	148	64.8	19.9±6	56%	20	40
Kumagai et al. 2010[43]	Retrospective	212	84.4	16±5.2	51%	23.6	37.7
Matsuo et al., 2010[44]	Retrospective	233	62	30.1±13.1	59.7%	37.4	34
Gula et al., 2011[45]	Prospective	72	100	12	35%	24	26
Miyazaki et al., 2012[46]	Prospective	109	100	12	35.8%	48.7	27.2
Cheung et al., 2013[47]	Prospective	156	64	12.5	30%	36	24
Anter et al., 2014[17]	Prospective	44	55	12	36.4%	50	10.7

N=sample size; AF=atrial fibrillation; PV=pulmonary veins; *follow-up in months; †rates expressed as percentage; ‡recurrence rate in percentage. See text for details.

reducing the AP duration in both, yet significantly hyperpolarizing the resting membrane potential only in PV cells. This phenomenon was attributed to a larger IKAdo current in PVs when compared to LA cardiomyocytes, as well as to a smaller IK1 current that leads to a less negative resting membrane potential in PVs. In consequence, hyperpolarization of these myocytes in the thoracic veins leads to improved conduction and creation of a functional conduction gap allowing initiation and perpetuation of re-entry circuits.

Radiofrequency (RF) ablation not always results in myocardial cell death, but instead may cause injury associated with partial depolarization of the membrane to about (-) 60 mV. At this stage, Na+ channels are inactive and non-excitable, producing functional block that is susceptible to recovery over time. In fact, clinical studies have noted that a third of PVs that initially demonstrated bidirectional block following PVI reconnect spontaneously following a waiting period of 30-60 minutes.[28, 29] Adenosine hastens the recovery of PV conduction in areas of RF-induced partial tissue injury and edema by hyperpolarizing these cells and restoring electrical excitability (Figure 1).

Clinical Use Of Adenosine During AF Ablation

PVI is usually performed using RF ablation delivered circumferentially around each pair of PVs.[30] Acute endpoints are functional in nature and include establishment of entrance and exit block at each vein.[31] However, anatomical (substrate) endpoints including confirmation of non-reversible transmural lesion formation are still lacking. As such, the current standard is susceptible to potential gaps in the ablation lesion set and the false impression of acute PV-LA disconnection that is not durable.[32] Evidence from magnetic resonance imaging experiments suggests that this transient injury and functional isolation is related to the presence of tissue edema that is prone to recovery. Patients with more extensive reversibility of injury, detected as a higher T2 signal on acute scans and greater decline in delayed enhancement seen on chronic imaging have an increased susceptibility to PV reconnection and AF recurrence.[33] Histopathologic analysis of RF lesions supports the observation that partial thickness lesions correlate with persistent PV conduction and clinical relapse.[34]

The limitations in achieving transmural lesions are multifactorial and include anatomical variability with different wall thickness, such as the ridge between the left PVs and the LAA,[12, 35-38] inadequate catheter-tissue contact and /or stability during ablation.[7]

Adenosine And Dormant PV Conduction

The ability of adenosine to reveal PV reconnection following PVI was first described by Arentz et al., in a prospective, observational study including patients with paroxysmal and persistent AF. Twenty-nine patients were followed, accounting for 83 studied PVs. Following adenosine injection, 25% of initially isolated veins showed dormant conduction in sinus rhythm and during coronary sinus pacing. The rate of arrhythmia recurrence was higher in patients exhibiting PV reconnection, with 71% having recovery of conduction in at least one vein seen at repeat ablation compared to only 35% in those that did not.[39] This observation was further studied by Tritto et al. in a prospective study analyzing a similar number of patients and documenting an incidence of acute reconnection in 35% of the analyzed PVs. Of note, this was the first study with a systematic attempt to detect the sites of reconduction and approach them with further RF ablation. After a follow-up of 6 months, there was no difference in the rate of recurrence for patients that exhibited dormant conduction in response to adenosine.[40]

Since these original reports, different groups including ours have conducted similar studies demonstrating an adenosine-induced dormant conduction or PV reconnection incidence rate in the range of 25-60%.[17, 39-47] These studies are summarized in Table 1. Overall, the majority of these studies showed that resumption of LA to PV conduction during adenosine challenge was associated with increased recurrence rate. Specifically, of the eight studies where dormant PV conduction was treated with additional ablation, two of them showed no significant difference in the rate of arrhythmia recurrence;[40, 44] three studies prior to 2012 reported an improvement in AF freedom;[41-43] while the latest three studies showed higher risk of recurrence despite eliminating the sites of PV reconnection.[17, 46, 47] Still, these studies report comparisons between patients where the outcomes of adenosine-induced PV reconnection are contrasted to those without recovery of PV conduction or patients that were not tested. No study to date has randomized patients with evidence of PV-LA reconduction to observation versus additional ablation in order to analyze the impact of treatment on arrhythmia recurrence.

As suggested from the experimental animal model,[27] the adenosine effect is probably related to restoration of conduction through hyperpolarization of partially depolarized cardiomyocytes injured but

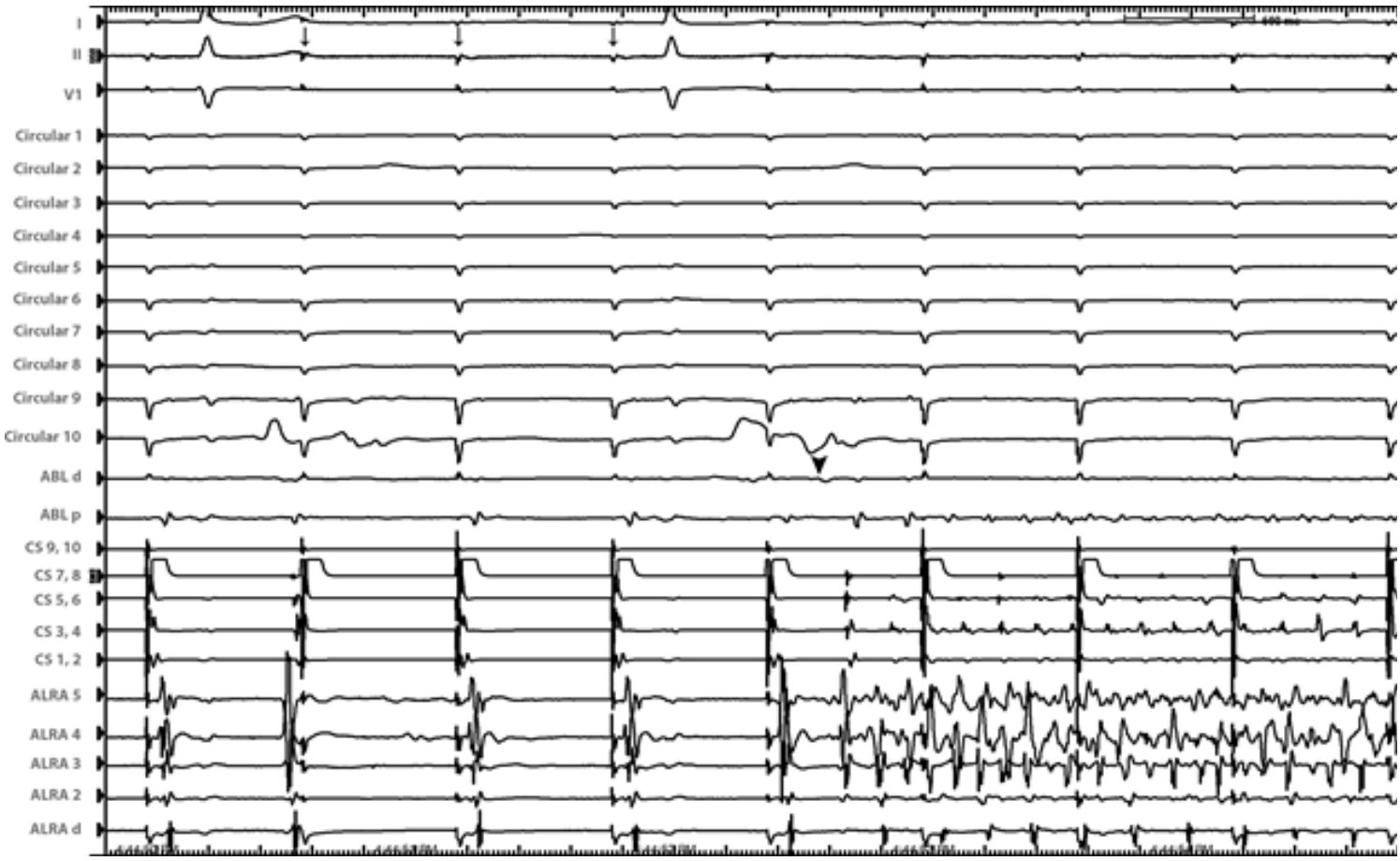

Figure 1: **Adenosine-induced Dormant PV Conduction**

PV reconnection in the right PVs (ABL) as evidenced by a circular mapping catheter localized to the left superior PV. After the administration of an intravenous bolus of 24mg of adenosine during coronary sinus (CS) pacing, transient AV block is induced (arrows) followed by re-initiation of atrial fibrillation and resumption of conduction along the right PVs (arrowhead).
PV=pulmonary veins; ABL=ablation catheter; CS=coronary sinus; AV=atrioventricular

not destroyed with RF energy, re-establishing PV-LA conduction. A similar phenomenon has been observed with RF ablation outside of the PVs, such as after formation of a cavo-triscuspid isthmus line in atrial flutter[48,49] or isolation of the SVC.[12,36]

Clinical Implications of Adenosine-Induced PV Reconnection

The clinical utility of recognizing dormant PV conduction in response to adenosine and its effect on clinical outcome has become a subject for intense clinical research. A series of studies initially documented improved outcomes when adenosine-induced PV reconnection was treated with additional ablation. Hachiya et al.[41] performed a retrospective analysis comparing the outcome of PVI between 82 patients challenged with adenosine and further ablated as necessary with a cohort of 170 patients not challenged with adenosine. In this study, the group subjected to adenosine challenge and further ablation showed a trend towards higher arrhythmia-free survival rate (73% vs. 60%, p=0.04) at 6 months. Matsuo et al.[42] did a similar comparison among cohorts before and after the routine use of adenosine as a mean to evaluate the significance of identifying and treating dormant conduction and reported very similar results. In this case, ablation of the gaps led to an increase in the efficacy of PVI from 60% to 80% after a mean follow-up period of 19.9±6 (6-28) months. A consistent trend was evident even when a larger retrospective series was analyzed by Kumagai and colleagues.[43] In this particular study, 212 consecutive patients with predominantly paroxysmal AF were equally divided in two groups, with and without the administration of adenosine after PVI. Once again, those with evidence of dormant conduction were treated with further ablation and had lower rates of AF recurrence at 23.6% vs. 37.7%. Despite the plausibility of these initial results, these studies were retrospective in nature, compared to historical cohorts with some including different ablation technologies, thus limiting their clinical validity. Subsequent prospective and retrospective studies were performed in large cohorts of patients with paroxysmal AF where adenosine was used to routinely evaluate for the presence of dormant PV conduction. Matsuo et al.[44] analyzed outcomes of 233 consecutive patients and identified PV reconnection induced by adenosine in 59.7%. Ninety-eight percent of the ablation gaps were successfully isolated, yet the success rates of the index PVI was similar to those without dormant conduction (62.6% vs. 66%). Subsequently, Gula et al.[45] went further and prospectively analyzed 72 patients with paroxysmal AF in which no further intervention was performed despite acute PV reconnection. Remarkably, patients with untreated transient conduction recovery had very similar rates of recurrence compared to those without evidence of dormant conduction, suggesting a limited ability of adenosine to predict recurrence of clinically significant atrial arrhythmias.

Since the report by Gula et al., three recent prospective studies systematically reviewed the significance of adenosine-induced

reconnection in arrhythmia freedom. Paradoxically, the results suggest that even when conduction gaps are adequately treated by further RF application, patients with dormant conduction have higher rates of AF recurrence. Moreover, proportional hazards modeling consistently associated the presence of PV reconnection, whether transient or sustained, with a higher risk of arrhythmia recurrence.

The first of these studies was reported by Miyazaki et al.,[46] analyzing the response to adenosine of 109 consecutive patients with paroxysmal AF immediately after PVI. Thirty-six percent of subjects had evidence of dormant conduction and experienced higher rates of recurrence at one year post-procedure, 48.7% in the group with conduction recovery vs. 27.2% in those without PV reconnection. The presence of adenosine-provoked dormant PV conduction was associated with a 38.7% increased risk of recurrence after a single PVI. Cheung et al.[47] followed a similar study design that also included subjects with non-paroxysmal AF. In this report, 156 patients received an adenosine challenge after PVI and were classified as exhibiting transient or sustained PV reconnection as different markers of dormant conduction. All sites exhibiting resumption of conduction were targeted with further ablation. Fourteen percent of PVs had evidence of adenosine-induced transient PV reconduction, accounting for 30% of patients. A similar proportion of patients, 29%, exhibited sustained PV reconnection and underwent further RF ablation. After a year of follow-up, freedom from AF was significantly lower in those with evidence of dormant conduction, 63% vs. 76%. Similar to the results obtained by Miyazaki et al., patients with PV ectopy in response to adenosine had a greater risk of recurrence estimated at 90%, while the combination of PV ectopy and reconnection was associated with a hazard ratio of recurrence of 2.9 (95% CI 1.28-6.37, p=0.01) during the first year of follow-up even when reconnection was successfully eliminated by ablation at the index procedure.

Our group recently reported consistent findings. In a prospective cohort of 44 patients,[17] adenosine induced dormant conduction in as much as 36.4% of subjects. The group of patients with a positive response to adenosine underwent further ablation to eliminate dormant conduction. Despite further ablation, the 1-year recurrence rate was 50% in the group of patients with positive response to adenosine compared to only 10.7% in those with negative adenosine response. We also performed a multivariate analysis that included covariates such as LA dimension, type of AF and OSA and found that PV reconnection was an independent risk factor for arrhythmia recurrence despite further ablation. A positive response to adenosine resulted in a 6-fold increased risk of relapse in the year following initial PVI despite evidence of isolation at the end of the procedure. Comparatively, a meta-analysis[50] pooling the results of the trials performed prior to 2013 and described previously, associated adenosine-induced transient reconnections post-PVI with a non-significant trend to reduction in freedom from AF of approximately 9% (HR 0.91, 95% CI 0.79-1.94, p=0.149).

Therefore, while we have a partial understanding on the mechanism through which adenosine reveals dormant PV conduction, the data available today provides limited insight into the implications of such findings. These results are from observational, non-randomized trials that are subjected to the inherent limitations and bias associated with their design. Similarly, they reflect variable periods in the evolution of AF ablation with gradual addition of technical improvements to the approach, including the use of electroanatomical mapping systems, general anesthesia, use of steerable sheaths, and changes in power limit and duration of RF applications, all of which can impact the effectiveness of individual lesions. Nevertheless, there is a clear trend showing that acute PV reconnections revealed by adenosine most likely reflect an inability to achieve durable PVI lesions and are a marker of an increased risk of recurrence. At the time of this writing, a multi-center, prospective randomized clinical trial named ADVICE is being conducted to better address the mechanism and implications of adenosine-induced PV reconnection.[51] As part of its design, patients with dormant conduction will be randomized to no additional ablation or to additional targeted ablation with the primary endpoint of time to first recurrence.

The limited impact of treating dormant conduction with further ablation on the incidence of chronic PV reconnection and arrhythmia recurrence is intriguing. Potential mechanisms include the inability to precisely map and ablate the focal area of reconnection due to multiple ineffective lesions with variable degrees of edema and partial injury, limiting adequate recording and even effective energy delivery. Similarly, there may be areas of more significant, yet still reversible, tissue injury that fail to reconnect within the allowed time period or that are only partially repolarized in response to traditional doses of adenosine that subsequently become the sites of relapse. In support of this observation, chronic PV reconnections have been shown to occur also at a distance from the previously documented acute reconnection sites[17] as well as in PVs that had negative response to adenosine challenge.

Impact of Time in Revealing Dormant PV Conduction

Studies that have examined the incidence of PV reconnection following PVI have showed a positive relationship between time interval after PVI and incidence of PV reconnection, suggesting a time-dependent tissue recovery. The available data suggest a steady increase in PV reconnection rates at 30, 60 and 90 minutes[28, 29, 52] where the majority of acute PV reconnections occur during the initial 60 minutes. This time effect of the incidence of PV reconnection is additional and independent of identification of dormant PV conduction in response to adenosine.[17, 37, 53] Thus, we advocate for at least 30 if not 60 minutes of waiting time in addition to adenosine in the evaluation of acute reconnection.

Limitations of Adenosine Use During AF Ablation

Clinical evidence supports the role of adenosine as a powerful tool in the armamentarium of the electrophysiologist to achieve durable PVI. Its use throughout the years has provided insights into some of the mechanisms that initiate and perpetuate AF, as well as on the effect of RF injury to the electrical properties of atrial tissue. The main limitation of adenosine in the acute procedural setting relies in its inability to accurately identify and localize all sites of conduction gaps.[38] In order to maximize its benefit, operators should follow a systematic approach to detect sites of earliest activation after resumption of conduction, a phenomenon that may be transient. Nevertheless, the use of adenosine following PVI may help in two other manners: (1) it may identify non-PV triggers[54] particularly when other efforts have been completed to ensure adequate PVI, and (2) may identify patients with increased recurrence rate who would potentially benefit from closer clinical follow-up and decisions regarding medical management. Last, all studies assessing the short- and long-term impact of adenosine-induced PV reconnection have been observational, which predisposes to bias inherent to their design.

Despite a consistent trend in their findings, there is still a need for a prospective, randomized controlled trial aimed at guiding the role of adenosine in modern AF ablation.[51]

Novel Tools to Improve Ablation of AF

The success of catheter ablation for the treatment of AF depends on simultaneous efforts to achieve durable PVI.[55-57] Emerging technologies offer strategies aimed to overcome the anatomical and functional limitations of delivering adequate and durable lesions for PV-LA isolation. Amongst them are the use of contact-force catheter[8, 9, 58, 59] and objective annotation of ablation lesions that is based on catheter stability, tissue contact and impedance decrease.[37]

Cryoballoon ablation, particularly with the second-generation cryoballoon catheters, offers the advantage of a larger and homogeneous contact area along the PV. In the studies published to date, this approach has been proven effective and promising in the management of AF after short follow-up period. A recent study analyzed 50 patients with AF (82% paroxysmal, 200 PVs) treated with the use of the 28mm cryoballoon.[60] Successful PVI was achieved in 95% of PVs after a single application. The incidence of PV reconnection after a waiting time of 30 minutes and subsequent use of adenosine was very low, with a combined incidence of 4% of PVs and 12% of patients. Specifically, the rate of adenosine-induced PV reconnection was only 2%. After re-isolation, subjects with targeted PV reconduction remained free of AF after 7 months of follow-up. In this study, nadir temperature of < -51 ˚C and rewarming time >28 seconds were significantly associated with successful ablation and absence of PV reconnection. Similar results were obtained by Kumar and colleagues,[61] with a rate of adenosine-induced PV reconnection of 5%.

Conclusion:

Adenosine is a powerful tool during AF ablation procedures. It allows identification of dormant PV conduction and/or acute PV reconnection and identification of non-PV triggers. Although outcome data following identification and treatment of dormant conduction with further ablation is limited and awaits further studies, its presence is associated with worse clinical outcome and identifies patients with increased recurrence rate. We recommend a multi-level approach for achieving durable PVI during catheter ablation of AF that includes adequate patient selection, meticulous technique, objective feedback during lesion creation and functional testing of the ablation lines evaluated by a combination of a waiting period of at least 30 minutes and adenosine provocation. Further studies are needed to fully understand the mechanism behind the increased risk of recurrence for patients that exhibit acute reconnection despite successful isolation of these sites, as well as the variability of this risk as newer technologies are adopted for the management of atrial fibrillation.

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