

## Durable Pulmonary Vein Isolation: The Holy Grail of Atrial Fibrillation Ablation

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### Abstract

The inability to achieve durable pulmonary vein isolation remains a major limitation to catheter ablation for the treatment of atrial fibrillation (AF). In this review, we discuss the research performed over the past decade investigating methods to improve lesion permanence for the goal of durable pulmonary vein isolation (PVI). Investigations evaluating procedural techniques, adjunctive pharmacologic therapy, and newer energy sources designed to improve ablation lesion permanence are discussed.

### Introduction

The safe and controlled destruction of cardiac tissue is the principle behind ablative treatments of arrhythmias. This principle implies a lack of reversibility of tissue conduction after rendering it electrically inert. However, a frustration for cardiac electrophysiologists remains the, oftentimes, unpredictable resumption of electrical conduction in ablated tissue. This phenomenon is most apparent in procedures incorporating pulmonary vein isolation, which currently serves as the cornerstone of most ablation strategies for the treatment of atrial fibrillation. Pulmonary vein isolation is achieved when the vein is electrically disconnected from atrial myocardium, as demonstrated in Figure 1, which shows an electrocardiogram with sinus rhythm and simultaneous atrial fibrillation in a pulmonary vein that has been disconnected. Intracardiac electrograms on a multipolar circular mapping catheter placed inside the pulmonary vein showing concurrent atrial fibrillation within the vein with exit block.

However, ever since the technique of circumferential pulmonary vein isolation was described, electrical reconnection was recognized as a major issue of concern. Pulmonary vein reconnection is considered to be the most important reason for recurrent atrial fibrillation<sup>1</sup> and new atypical atrial flutter.<sup>2</sup> In many cases, acute pulmonary vein

reconnection can be observed during the actual procedure despite initial disconnection with ablation.

In this review we will discuss the research performed over the past decade investigating methods to improve lesion permanence for the goal of durable pulmonary vein isolation. It should be noted that many of the studies' outcomes evaluated AF recurrence, and not specifically PV reconnection. Not all AF recurrences correlate to PV reconnection; however, particularly in patients with paroxysmal AF, pulmonary vein reconnection is nearly always related to AF recurrences,<sup>1</sup> and therefore AF recurrence is a likely proxy for lack of PV durability in these studies.

### Procedural Techniques to Ensure Adequate Lesion Formation

Prior to concerns for durable pulmonary vein isolation are addressed, the initial achievement of PVI must be considered. Rajappan et al. have characterized common anatomical sites of PV reconnection.<sup>3</sup> They found that, for left sided veins, acute reconnection typically occurred in the intervenous ridge (otherwise known as the carina) and PV-left atrial appendage (PV-LAA) ridge. For right veins, acute reconnection occurred at the roof and the intervenous ridge. Late reconnection was found to occur predominantly at the intervenous ridge and to a lesser extent at the PV-LAA ridge for left sided veins. On the right, late PV reconnection occurred on the roof, intervenous ridge, and floor.

Catheter stability, delivery of adequate power for adequate duration, and contiguous lesions encircling the pulmonary veins is required for any expectation of long-term pulmonary vein isolation. However, these requirements, while necessary though not sufficient, can sometimes be easier said than done and an operator can often be misled by conflicting data from electroanatomical mapping, electrogram analysis, and intracardiac echocardiography. In addition,

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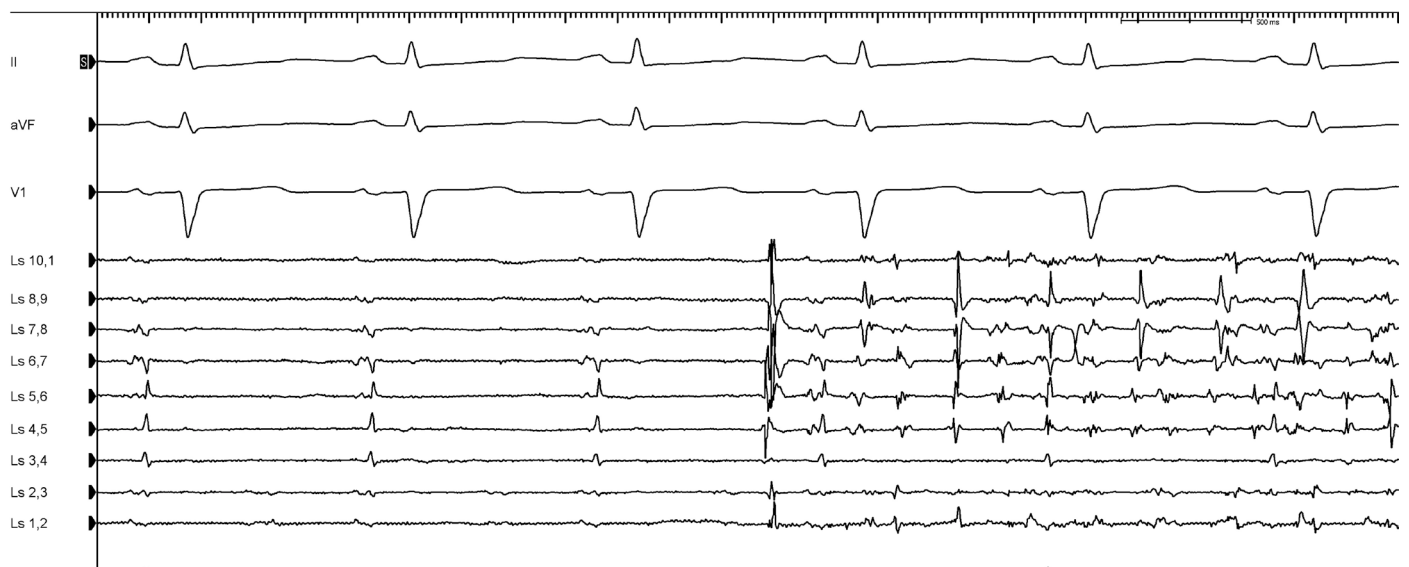
Atrial fibrillation, Ablation, Durability, Pulmonary vein

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**Figure 1:** An electrocardiogram with sinus rhythm and simultaneous atrial fibrillation in a pulmonary vein that has been disconnected. Intracardiac electrograms on a multipolar circular mapping catheter placed inside the pulmonary vein showing concurrent atrial fibrillation within the vein with exit block.

patient respiratory movement and the normal cardiac motion can result in intermittent catheter contact leading to incomplete ablation lesions and then pulmonary vein reconnection.

In an attempt to control for some of these variables, investigators at the University of Pennsylvania explored the use of a steerable sheath with Jet ventilation. In this observational study, clinical outcomes were improved when using these techniques to improve catheter contact.<sup>4</sup> The study demonstrated a significant reduction in acute PV reconnection observed during the procedure and also a reduced number of chronic PV reconnections at the time of PV remapping upon repeat procedure (Table 1). While use of a steerable sheath is one method to improve catheter contact, other measures of adequate catheter contact should be monitored, including observation of impedance decreases with ablation and attenuation of the local bipolar atrial electrogram amplitude. Furthermore, the use of intracardiac ultrasound can be invaluable to evaluate for catheter contact, as well as for assisting with a double transeptal approach and for defining the geometry and location of the esophagus.<sup>5,6</sup>

## Finding the Gaps and Dormant Conduction

### Visual Gaps

Although pulmonary vein isolation can be achieved without complete circumferential ablation lines, there is evidence that electrical pulmonary vein isolation in these situations may not be as durable. Potentially reversible effects of ablation, such as tissue edema, may lead to the initial acute isolation but then are responsible for reconnection. Visual gaps left in circumferential ablation lines were shown to be associated with dormant PV conduction, despite acute PV isolation.<sup>7</sup> Hence, an important aspect to durable PV isolation is to close this visual gap seen during electroanatomical mapping. Figure 2 shows an example of a visual gap identified during pulmonary vein isolation despite acute PV reconnection.

### Waiting Period

While ensuring the durability of the acute PV isolation at the time of the procedure intuitively makes sense to ensure durability of the

PV isolation over the long term, there is conflicting data with regards to the use of a waiting period in order to allow for the treatment of any reconnection.

Wang et al. showed that the prevalence of PV reconnection was about 30% after PV isolation, occurring mostly within 30 minutes of the initial isolation.<sup>8</sup> These investigators also demonstrated that repeat isolation of the reconnected veins contributed to improved durability of their ablation after a mean follow up of 6.7 months.

However, a recent study from Bansch et al casts some doubt as to the usefulness of a waiting period.<sup>9</sup> Likely to the authors' surprise and contrary to the study hypothesis, a waiting period of 1 hour and subsequent ablation of any recurrence did not appear to affect AF recurrence in follow-up. It is noted, however, the recurrent AF results were reported without taking into account a 3-month blanking period. Furthermore, it is of interest to note that, of those patients who underwent redo procedures for recurrent AF, there were more gaps ablated in the group who initially had a waiting period. Although this number was not statistically higher than in those patients who did not have a waiting period, it nevertheless suggests that the initial down payment in waiting periods and acute re-ablation did not appear to ameliorate the number of future ablation lesions or procedures.

### Pacing on the Line

Several early studies demonstrated that pacing to elicit tissue excitability and subsequent ablation to achieve lack of pacing capture may be effective in pulmonary vein isolation.<sup>10,11</sup> A recent randomized control trial from Steven et al. provided further evidence that ablation to achieve non-excitability to pacing along a PVI line, in addition to the bidirectional block of PV isolation, was associated with better patient outcomes (less AF/AT recurrence), compared to PV isolation alone.<sup>12</sup>

### Adenosine to Identify Dormant Conduction

Despite the use of a circular mapping catheter to demonstrate bidirectional block with PV isolation and despite ablation to avoid

visual gaps in the PV line, dormant conduction persists. The use of adenosine has been shown to unmask dormant PV conduction (Figure 3); the belief is that adenosine can assist in directing further ablation of PVs with dormant conduction in order to reduce early PV reconnection. A recent meta-analysis from McLellan et al aggregated data from nine studies that utilized adenosine following PVI, with three studies addressing freedom from AF based on whether adenosine was given or not.<sup>13</sup> Six of the nine studies addressed freedom from AF based on PV reconnection or not. Based on these studies, it was found that routine use of adenosine to assess for dormant conduction and to guide additional targeted ablation was associated with a significant decrease in AF recurrence after PVI. However, for patients who received adenosine, those with reconnection trended toward an increased risk of AF recurrence despite further ablation.

### Adjunctive Pharmacologic Therapy to Improve Lesion Durability

#### Facilitated Ablation

Recently, there have been some data looking at the use of certain pharmacologic therapies in the peri-ablation period to improve outcomes. The use of such adjunctive pharmacologic therapy to improve outcomes is a newer paradigm for electrophysiology, but it is commonly employed in interventional cardiology to preserve coronary artery patency following percutaneous intervention.<sup>14</sup> A term that is frequently used to describe this phenomenon is “facilitated PCI.” We would propose that the use of peri-procedural, adjunctive treatments to improve ablation efficiency could be similarly termed “facilitated ablation.”

#### Anti-Arrhythmic Drugs

The use of adjunctive antiarrhythmic drugs immediately after AF ablation was thought to improve long term outcomes by addressing the well-known and often quoted phenomenon of “AF begets AF.”<sup>15</sup> With this in mind, Roux et al. (5A study) randomized patients with paroxysmal AF undergoing ablation to antiarrhythmic therapy or no antiarrhythmic therapy for 6 weeks post-ablation.<sup>16</sup> They found that antiarrhythmic therapy did reduce clinically significant atrial

arrhythmia events in the 6 weeks after AF ablation. However, antiarrhythmic therapy did not appear to improve long-term AF recurrences at 6 months.<sup>17</sup> There may be several explanations for this. It is possible that early atrial arrhythmias are due to inflammation that later resolve at 6 weeks; however, this would also suggest that early inflammation has little impact on long term AF recurrence. Another potential explanation is that early AF recurrences were not of sufficient duration or frequency to “beget more AF,” or that sinus rhythm for the majority of the time was able to cause reverse remodeling sufficiently enough such that no difference was seen in late recurrences. Finally, the most likely explanation is that the durability of the PV lines is at stake, and that PV reconnection is driving the majority of recurrences. PV reconnection, for the most part, is not impacted by early recurrences. Nevertheless, early recurrence is a strong independent predictor of late recurrence.

#### Anti-Inflammatory Agents

Data on other adjunctive pharmacologic therapies appear more promising. Koyama et al randomized patients with paroxysmal atrial fibrillation undergoing ablation to intravenous hydrocortisone on the day of the procedure and then oral prednisolone for 3 days post-PVI.<sup>18</sup> Patients receiving corticosteroids had less immediate AF within 3 days post-PVI. Interestingly, there was no difference in AF burden from 4 to 30 days, suggesting that perhaps the duration of corticosteroid treatment was not long enough, although there may be risks of adverse events with prolonged steroid use. However, there was a higher AF-free rate in the corticosteroid group at 14-month follow up, suggesting that treatment of early inflammation can, in fact, improve long-term AF outcomes. However, a recent study by Andrade et al. has not shown benefits from a single dose of pre-procedural steroids. In fact, patients in this study who received the single bolus of 250 mg IV of hydrocortisone required greater RF requirements to achieve PV isolation and had higher prevalence of dormant PV conduction unmasked by adenosine. There was no difference in AF recurrence at 1 year between those who received steroids and those who did not receive steroids.<sup>19</sup>

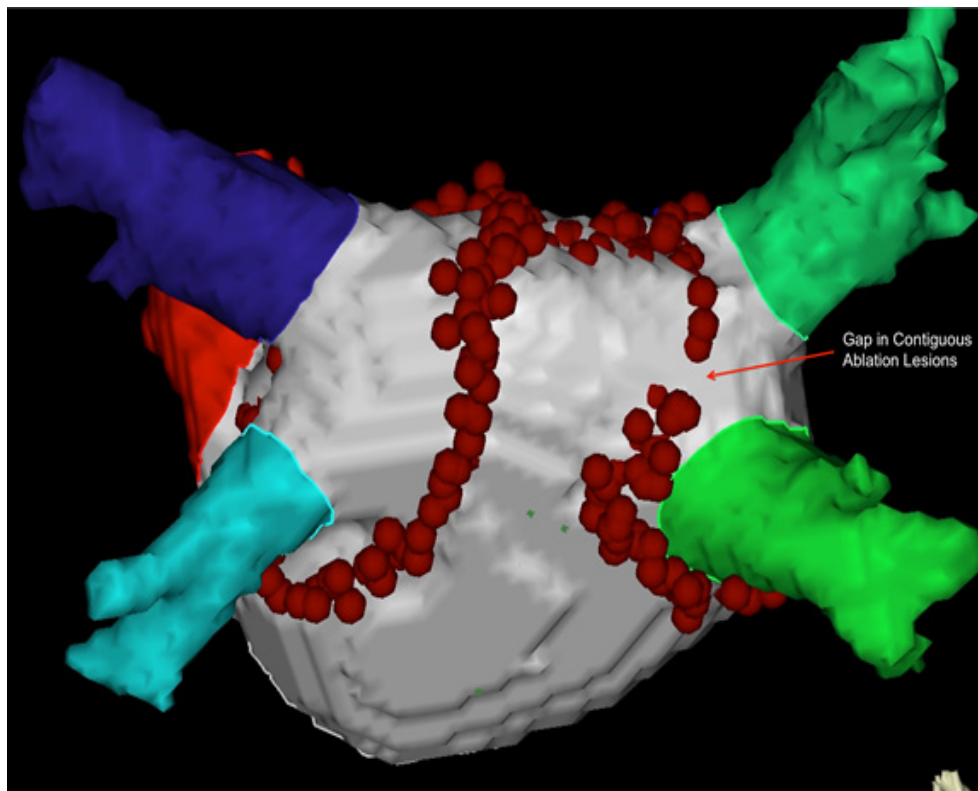
Another study addressing inflammation in the post-AF ablation period involves the use of colchicine. Investigators treated patients

**Table 1:**

**Ablation Techniques Used for Improving Outcomes after Ablation of Atrial Fibrillation**

Ablation Technique	N	Pulmonary Vein Remapping	Effect	Follow-up Period
Image Integration, Steerable Sheath, HFJV (4)	100	Yes*	Reduced Recurrence of AF, Average of 2.4 PVs chronically reconnected vs 3.9 at repeat procedure	1 year
Laser Balloon (33)	52	Yes	14% PV Reconnection Rate	3 months
Cryoballoon (26)	12	Yes	12% PV Reconnection Rate	2-3 Months
Pacing on Contiguous Lesions (10)	102	No	Improved AF/AT-free rates, 82.7% in pacing group vs. 52% in conventional group.	18 months
Use of Adenosine to Identify Dormant Conduction (13)	612	No	Meta-analysis combining three retrospective studies assessing use of adenosine and post PVI AF-free rates: 76% (adenosine) vs 61% (not tested with adenosine).	6-20 months
Closure of Visual Gaps (7)	28	Yes	8% PV reconnection rate (1 of 12 PV pairs in 6 patients)	13 months
30-60 minute Waiting Period after Initial PV Isolation (8)	90	No	Improved AF/AT-free rates, 84.3% (30 min) group vs. 86.7% (60 min) group vs. 60.7% (no waiting period).	6.7 months
1 hour Waiting Period after Initial PV Isolation (9)	107	Yes	No reduction in AF recurrence. Only those with recurrent arrhythmias refractory to anti-arrhythmics were remapped.	9.6 months

\*Pulmonary Vein Remapping at Time of Indicated Repeat Procedure due to Failed Ablation Attempt; HFJV: High Frequency Jet Ventilation; PV: Pulmonary Vein



**Figure 2:** Three-dimensional electroanatomic mapping of circumferential ablation lines around the pulmonary veins, showing a visual gap in otherwise contiguous ablation lesions.

with a 3-month course of colchicine and found that there were larger reductions of C-reactive protein and interleukin-6 with colchicine, as well as decreased AF recurrence within 3 months of ablation.<sup>20</sup> Longer follow up is needed to assess whether this reduction in early AF recurrence is translated to improved long term outcomes, given the mixed data on antiarrhythmic therapy in the post-ablation period. Another study utilizing atorvastatin as a possible agent to target early inflammation in the post-AF ablation period did not find that atorvastatin decreased AF recurrences at 3 months.<sup>1</sup>

#### Renin-Aldosterone-Angiotensin Agents

There have been conflicting data on the use of inhibitors of the renin-aldosterone-angiotensin (RAA) system to decrease AF recurrence.<sup>21-24</sup> Given the retrospective nature of these studies, the mix of patients with paroxysmal and persistent AF, and the variable follow-up, it is difficult to make conclusions regarding the benefits of RAA inhibitors such as ACE inhibitors or angiotensin receptor blockers. A recent study from Ito et al evaluated the role of eplerenone, a selective aldosterone blocker, after ablation for persistent AF in a retrospective observational fashion.<sup>25</sup> Eplerenone was associated with less AF recurrence at 23 months. Nevertheless, these promising data will need to be validated in a randomized control trial before they can be translated into wide spread clinical practice.

#### Newer Energy Sources and Future Investigations

##### Balloon Based Pulmonary Vein Ablation

One potential mechanism for the lack of durability seen with pulmonary vein isolation is failure to deliver a sufficient amount of energy to ensure trans-mural myocardial scarring. Cardiac electrophysiologists titrate energy levels and duration to safely

achieve local electrogram diminution without causing steam pops, cardiac perforation, or injury to adjacent structures such as the esophagus. Newer energy sources could potentially allow for the delivery of non-RF ablative energy for a longer duration to minimize myocardial hibernation resulting in recovery of electrical conduction.

Ahmed et al. evaluated patients undergoing balloon cryoablation for pulmonary vein isolation, 8-12 weeks after achieving initial PV isolation at the index procedure.<sup>26</sup> The investigators found that 88% of the pulmonary veins that were originally isolated remained electrically disconnected. The authors found that a "pull-down" technique used in the initial PVI procedure resulted in a 100% longer-term PVI rate in their small cohort that underwent the repeat procedure.

Acute PV isolation using balloon cryoablation ranges from 90-100%.<sup>27-29</sup> Late AF recurrence rates with balloon cryoablation have been shown to be similar to those reported for radiofrequency ablation studies.<sup>30</sup> Predictors of late PV reconnection after balloon cryoablation have been recently elucidated. Investigators assessed PV reconnection in 51 patients who were undergoing repeat ablation for recurrent AF after initially undergoing balloon cryoablation.<sup>31</sup> They found that balloon warming time was the most important predictor of pulmonary vein reconnection. Other predictors, to a lesser extent, included pulmonary vein size and vein occlusion score. A longer balloon warming time may simply be a marker of an effective cryoablation. There is also a mechanistic explanation in that a longer warming time may lead to improved lesion durability by increasing the duration of ice re-crystallization, which is known to cause further injury and thereby lead to more permanent lesions.

Pokushalov et al. compared cryoballoon versus radiofrequency ablation for patients undergoing a second procedure for recurrent paroxysmal atrial fibrillation, after a first failed RF procedure.<sup>32</sup> The

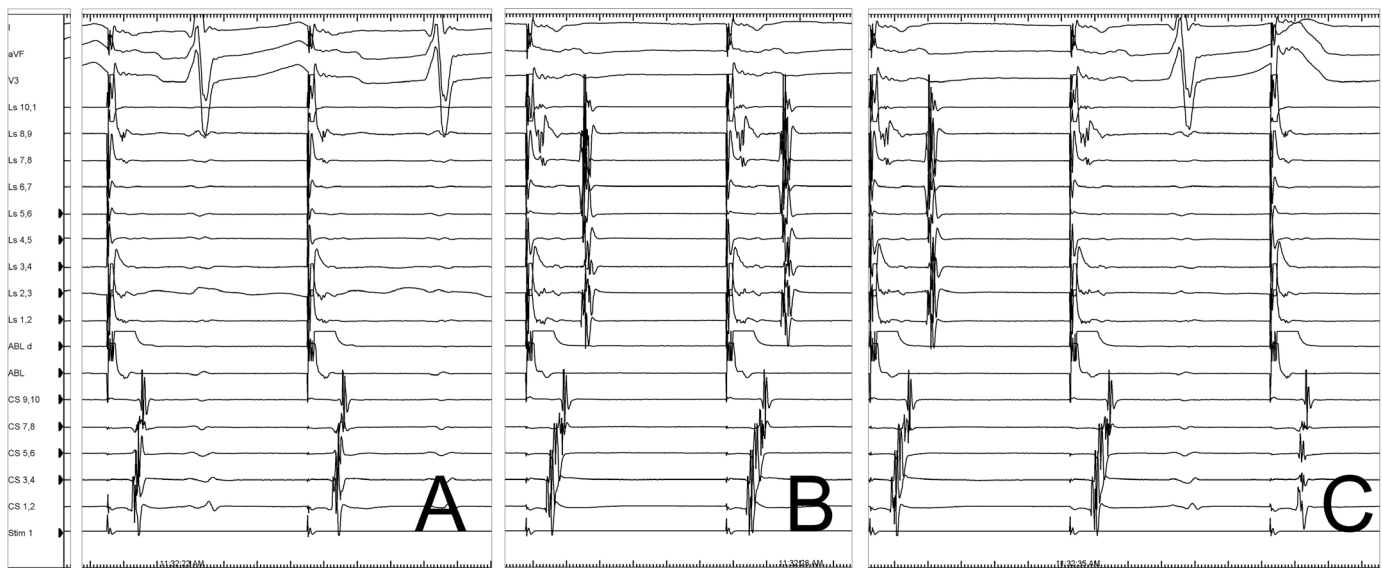


Figure 3:

**Intracardiac electrograms demonstrating adenosine-induced reconnection of a previously disconnected pulmonary vein that had both entrance and exit block. Panel (A) shows a disconnected vein with increasing PR prolongation as adenosine is given. Panel (B) shows adenosine induced heart block with pulmonary vein reconnection. Panel (C) shows that as the effects of adenosine dissipates, resumption of atrioventricular conduction occurs and pulmonary vein reconnection is no longer apparent.**

investigators found that patients undergoing RF had higher AF-free rates compared to those who underwent cryoballoon ablation. There were no complications in the RF group, while 3 out of 40 patients had temporary phrenic nerve paralysis in the cryoballoon group.

In a separate PV remapping study evaluating the durability of PVI using the visually-guided laser balloon, a similarly high rate of longer-term electrical isolation was observed.<sup>33</sup> In that study a cohort of 52 patients underwent pulmonary vein mapping 3 months after an initial PVI procedure using the laser balloon demonstrating a low PV electrical reconnection rate of 14%. In addition, the investigators observed a lower rate of PV reconnection at 3 months in those operators who had performed more than 10 procedures using the laser balloon (11% vs. 27%), suggesting a learning curve for achieving durable PVI with this new technology.

#### Future Investigations

The achievement of durable pulmonary vein isolation in all patients will continue to be an area of active research. A sequential surgical epicardial and endocardial pulmonary vein ablation has shown promise in patients with persistent atrial fibrillation who have failed previous ablation attempts.<sup>34</sup> Perhaps the combined epicardial-endocardial ablation at the level of the PV antrum is what it takes to achieve lasting transmural lesions in some patients. Novel catheters using contact force sensors to assess effective energy delivery<sup>35</sup> and the use of catheters incorporating near-field ultrasound to prevent steam pops<sup>36</sup> are some of the new technologies that will need to be evaluated for achieving this goal.

Several different ablation systems are also being actively studied. In a multicenter trial, Metzner et al. evaluated an endoscopic ablation system, which utilizes laser energy to deploy circumferential point by point lesions.<sup>37</sup> They have found that the one year success rates for patients with paroxysmal AF with this system is comparable to conventional PV isolation techniques. Furthermore, the use of a multielectrode ablation catheter, with combined bipolar and unipolar energy delivery, has been evaluated in several studies with promising

results.<sup>38-40</sup>

#### Conclusions:

Durable pulmonary vein isolation remains the major limitation to catheter ablation for the treatment of atrial fibrillation. Over the past decade, research evaluating procedural techniques to ensure adequate energy delivery with catheter stability and lesion permanence has yielded improved results. The use of adjunctive pharmacologic therapy to assist in ablation lesion maturation has shown some promise and has become an integral part to our ablation strategy. The use of new energy sources and future technology to improve the efficiency and safety of energy delivery to the posterior left atrium holds promise for achieving the ultimate goal of permanent pulmonary vein isolation for the effective treatment of atrial fibrillation. While many of these studies have been promising in demonstrating improvement of PV lesion durability, each study has evaluated a strategy in isolation. There are few studies that have compared any of these strategies to one another or to combine the various strategies together to further improve durability. However, it is plausible that as each strategy is added on top of one another, that there would be diminishing returns, as it is likely that there is overlap in the underlying mechanisms for reconnection that each strategy is trying to target. Hence, further studies are needed to delineate which strategy is superior and which strategies can be combined to garner the most sustained durability.

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