

## Recurrent Atrial Fibrillation After Catheter Ablation: Considerations For Repeat Ablation And Strategies To Optimize Success

Andrew E. Darby, MD, FHRS

*Assistant Professor, University of Virginia, Charlottesville, VA.*

### Abstract

Recurrent AF after catheter ablation occurs in at least 20 to 40% of patients. Repeat ablation is primarily considered for those with symptomatic AF recurrences (often drug-refractory) occurring at least 3 months or more post-ablation. Pulmonary vein reconnection is almost universally encountered, and repeat isolation of electrically connected pulmonary veins should be the primary ablation strategy. Beyond repeat PVI and possible ablation of non-PV triggers, there is little to no evidence that additional substrate modification improves outcomes. In addition to repeat ablation, it is critical to address and treat comorbid conditions which increase arrhythmia risk post-ablation. Specifically, obesity, hypertension, and sleep-disordered breathing should be targeted and modified to increase the likelihood of success.

### Introduction

Catheter ablation of atrial fibrillation (AF) has become an increasingly frequent procedure performed in electrophysiology laboratories worldwide. It is most often performed for maintenance of sinus rhythm in patients with symptomatic, drug-refractory paroxysmal or persistent AF or as an initial rhythm control strategy in lieu of anti-arrhythmic drug therapy in patients with paroxysmal AF.<sup>1</sup> The increased efficacy of catheter ablation over anti-arrhythmic drug therapy to maintain sinus rhythm has been demonstrated in a number of randomized, controlled trials and meta-analyses.<sup>2-12</sup> Unfortunately, recurrent atrial fibrillation or atrial tachycardia after an index AF ablation procedure results in repeat ablation in 20 to 40% of patients.<sup>13</sup> A number of dilemmas are presented by patients with recurrent AF after catheter ablation: Which patients should be considered for a second procedure and when should repeat ablation be performed? What is the optimal approach to ablation in a patient undergoing a repeat procedure? What additional interventions may reduce the likelihood of recurrence post-ablation? The purpose of this review is to summarize the available relevant data surrounding repeat ablation for atrial fibrillation and identify areas needing further investigation.

### Key Words:

Atrial Fibrillation Ablation, Repeat Catheter Ablation, Pulmonary Vein Reconnection, Atrial Fibrillation Lifestyle Modification.

**Disclosures:**  
None.

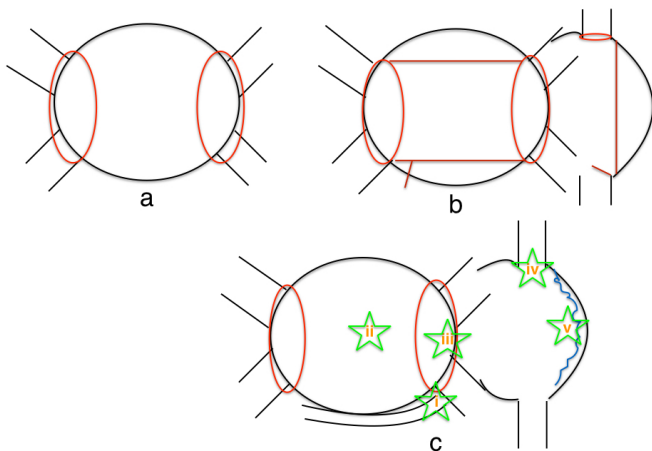
**Corresponding Author:**  
Andrew E. Darby,  
Assistant Professor  
University of Virginia Health System  
Charlottesville, VA 22908.

### Rationale For Repeat Catheter Ablation

The primary ablation strategy for AF is creation of electrical isolation of all pulmonary veins (PVs) with demonstration of bidirectional (entrance and exit) conduction block post-ablation.<sup>1</sup> The most commonly reported finding at repeat catheter ablation is resumption of conduction to (and from) previously targeted pulmonary veins.<sup>14-17</sup> Durable PV isolation (PVI) may be so difficult to achieve after a single AF ablation that some have reported recovery of conduction in 1 or more PVs in all patients undergoing repeat ablation.<sup>18-19</sup> Amazingly, pulmonary vein reconnection has been identified in up to 92% of patients undergoing a third or greater procedure.<sup>20</sup> Electrical isolation of the pulmonary veins is more likely to be permanent after a repeat ablation procedure. Consequently, one rationale for repeat ablation is to “finish” what was started during the first procedure and attempt to ensure permanent electrical isolation of all pulmonary veins. In addition, studies have shown incremental success with higher rates of long-term freedom from AF with repeat ablation possibly resulting from a higher rate of permanent PV isolation.<sup>12,19,21</sup>

### Timing Of Repeat Catheter Ablation

Among patients with recurrent arrhythmias post-ablation, there are a number of considerations impacting patient management. First, the patient’s symptoms should heavily influence subsequent management strategies. Patients with minimal to no symptoms who are adequately rate-controlled may be suitable for a rate-control and anticoagulation strategy rather than continuing to pursue sinus rhythm. The timing of recurrence is also important when considering a repeat procedure. Recurrent arrhythmias within the first two to three months post-ablation may resolve spontaneously or not recur after cardioversion so a repeat procedure is often deferred in this timeframe.<sup>1</sup> The mechanism of recurrent arrhythmia (AF versus atrial



**Figure 1:** Potential ablation strategies during repeat AF procedures: a) repeat pulmonary vein isolation only with confirmation of entrance and exit block from each vein; b) pulmonary vein isolation with additional linear lesions (posterior wall isolation with linear lesions connecting the superior and inferior pulmonary veins; mitral isthmus ablation; +/- right atrial linear lesions); c) pulmonary vein isolation and ablation of non-pulmonary vein triggers (i = coronary sinus; ii = LA posterior wall (and left atrial appendage, not pictured); iii = fossa ovalis/interatrial septum; iv = crista terminalis/right atrium; v = superior vena cava)

tachycardia/flutter) may also play a role in decision-making. Patients typically considered for repeat ablation have recurrent, symptomatic AF more than 3 months after initial ablation. Early repeat ablation may be considered for recurrent arrhythmia (particularly atrial tachycardia or atrial flutter) that is difficult to manage medically and recurs despite cardioversion. Recurrent atrial flutter or tachycardia post-ablation may be better managed with a repeat procedure as such arrhythmias can be difficult to rate control, frequently recur after cardioversion, and are often due to gaps in areas of prior ablation and have a relatively high success rate with repeat ablation. The focus of this re-view is recurrent atrial fibrillation after catheter ablation and not management of post-ablation atrial flutter or tachycardia.

An additional consideration is the likelihood of success with repeat catheter ablation. Factors shown to negatively impact recurrence rates include left atrial properties (volume, fibrosis), associated systemic disease (hypertension, obstructive sleep apnea), concomitant heart disease (particularly mitral valve disease and hypertrophic cardiomyopathy), and duration of atrial fibrillation (e.g., longstanding persistent AF has a higher recurrence rate than paroxysmal AF, table 1).<sup>1</sup> Patients with multiple negative prognostic factors for recurrence perhaps are best managed medically (if possible) rather than exposed to the risks of ablation with low likelihood of success. It would not be appropriate to pursue repeat ablation in asymptomatic patients with the hope of obviating need for long-term oral anticoagulation when the CHA<sub>2</sub>DS<sub>2</sub>-VASc score indicates a moderate to high risk of stroke. Repeat catheter ablation is most commonly accepted for patients with well-documented arrhythmia recurrences who are symptomatic (despite a trial of anti-arrhythmic drug therapy) and are more than 3 months removed from the initial procedure.<sup>1</sup>

### Strategies For Repeat Catheter Ablation

When AF recurs after PVI and PV reconnection is identified at repeat ablation it seems prudent to re-isolate any reconnected PVs. If the PVs have reconnected, however, how does one know that PV reconnection is the cause of recurrent arrhythmia? Going a step further, should additional ablation beyond repeat PVI be performed?

If the PVs have not reconnected what ablation strategy should be employed? Considerations include using different energy delivery sources to repeat PVI (e.g., using cryoablation if radiofrequency was used initially), creation of linear lesions in the left and/or right atrium, isolation of the superior vena cava or coronary sinus, ablation at atrial sites with fractionated electrograms during AF, ablation at sites of vagal inputs to the atria, and targeting non-PV triggers (figure 1). It is important to note there are no randomized controlled trials addressing these issues in patients with recurrent AF. The data reporting outcomes with repeat AF ablation are derived from retrospective and observational cohort and case-control studies. The most recent consensus statement on catheter ablation of AF suggests the first step when performing a repeat procedure is to check each PV for electrical reconnection followed by re-isolation of PVs as necessary as there is data showing reasonably good outcomes with repeat PVI alone.<sup>1,15</sup> If there is little to no evidence of PV reconnection, non-PV foci should be sought and consideration should be given to modification of the arrhythmogenic substrate although no particular linear lesion set or alternative ablation approach is recommended in the guidelines.<sup>1</sup>

### Techniques To Enhance Durability Of Pulmonary Vein Isolation

As pulmonary vein reconnection is near universal among patients undergoing repeat ablation, it is prudent when re-isolating PVs to employ techniques shown to increase the likelihood of durable PVI. This is more likely to occur with the delivery of contiguous, transmural lesions regardless of the energy delivery system. It is postulated that improved acute lesion delivery will translate to enhanced long-term outcomes. A number of procedural techniques have been advocated to improve the likelihood of transmural lesion formation thereby increasing the likelihood of durable PVI and (hopefully) freedom from arrhythmia. General anesthesia compared to conscious sedation lowers reconnection rates among patients with recurrences who underwent repeat ablation (19 vs 42%).<sup>22</sup> Efforts to minimize respiratory motion, particularly using high-frequency jet ventilation, have also been shown to improve freedom from AF at 1 year post-ablation.<sup>23</sup> Catheter stability may be further enhanced by manipulation through a steerable sheath, and use of such technology has been shown to improve short-term AF freedom rates post-ablation.<sup>24</sup> Ablation using multi-pore irrigated tip catheter technologies results in lower peri-procedural PV reconnection rates compared to standard irrigated tip catheters.<sup>25</sup> Contact force sensing technologies provide continuous feedback regarding catheter contact force and stability, and ablating with a contact force > 10 grams is associated with a lower likelihood of acute pulmonary vein reconnection and improved outcomes at 1 year.<sup>26,27</sup> Pulmonary vein reconnection rates were no different between standard radiofrequency ablation (using an open-irrigation RF catheter) and the first generation cryoballoon system among patients presenting for repeat ablation in a small study of 50 patients with paroxysmal AF.<sup>28</sup>

Rigorous testing to confirm bidirectional (entrance and exit) conduction block post-ablation improves long-term success rates.<sup>29</sup> A reasonable post-ablation wait period to assess for acute PV electrical reconnection seems to improve outcomes, and a study of 181 patients suggests waiting at least 35 minutes after acute isolation is the optimal observation time.<sup>30</sup>

Assessing for non-capture along the circumferential lesion set is

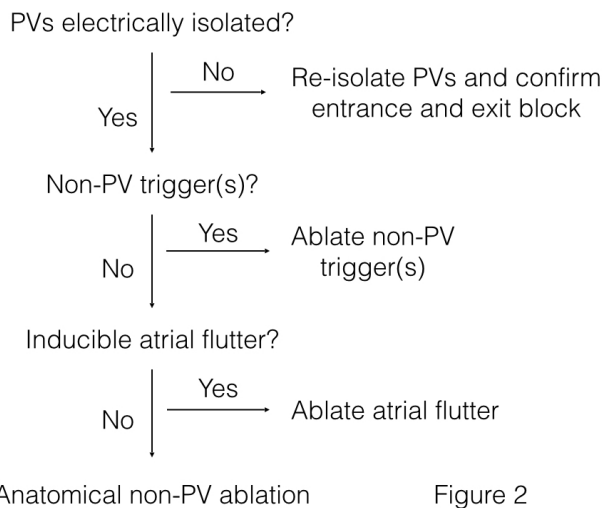


Figure 2

**Figure 2: Rational approach to a repeat AF ablation procedure**

one method for testing the integrity of the ablation line, and re-ablating sites of pace capture resulted in greater AF freedom (83 vs 52%) at 1-year follow-up in a prospective study.<sup>31</sup> Administration of adenosine to assess for dormant conduction can be useful for identifying gaps in the ablation line and pulmonary veins with higher risk of reconnection.<sup>32</sup> Additional ablation of acutely reconnected pulmonary veins after adenosine administration may or may not improve long-term outcomes as data is mixed.<sup>33,34</sup>

It is important to note that none of these approaches has been systematically studied to determine their true impact on promoting durable pulmonary vein isolation. It is also worth noting that absence of AF recurrence does not necessarily indicate permanent pulmonary vein isolation, and PV reconnection noted at repeat procedure may be incidental and not causative with regard to arrhythmia recurrence. That being said our initial approach during a repeat AF ablation procedure is to first and foremost ensure pulmonary vein isolation by ablating any reconnected pulmonary veins and confirming bidirectional conduction block (figures 2 and 3). Our standard approach is to use a contact force sensing catheter within a steerable sheath guided by an electroanatomic mapping system and intracardiac echocardiography. A circular mapping catheter is used to confirm bidirectional conduction block, and adenosine is routinely administered with re-ablation of any sites exhibiting dormant conduction. A comprehensive EP study is then performed to assess for other inducible arrhythmias or non-PV triggers with additional ablation as needed.

### Options Beyond Pulmonary Vein Isolation: Ablation Of Non-Pulmonary Vein Triggers And Substrate Modification

As pulmonary vein electrical reconnection is a common finding at repeat ablation, it seems prudent to re-isolate any reconnected PVs as an initial repeat ablation strategy as mentioned above. The decision to pursue additional ablation beyond PVI is difficult, and there is little data to guide whether additional ablation, if any, should be performed during a repeat procedure. Several studies have reported improved outcomes with a strategy of PVI and additional ablation of spontaneous or inducible non-pulmonary vein AF triggers.<sup>15,16,20,35,36</sup> One of these studies reported outcomes among 169 patients with recurrent AF despite 2 or more prior ablation procedures.<sup>20</sup> Astonishingly, only 8% of patients had all PVs isolated at baseline despite more than 1 prior ablation. Non-pulmonary vein triggers

were rigorously sought with incremental doses of isoproterenol (3, 6, 12, and 20  $\mu\text{g}/\text{min}$  and/or burst atrial pacing to provoke AF followed by cardi-overversion with or without low-dose isoproterenol). The majority of AF triggers localized to the pulmonary veins, although other triggers were identified (Eustachian ridge and crista terminalis; coronary sinus; SVC; LA posterior wall; left atrial appendage; interatrial septum). With a strategy of repeat PVI and targeting non-PV triggers, 81% of patients had arrhythmia control at up to 1-year follow-up.

Beyond PVI and ablation of non-PV triggers, there is very little data to guide whether additional substrate modification should be performed during a repeat ablation procedure. On one hand, it could be argued that recurrent AF is a failure of the initial strategy so a different strategy (i.e., substrate modification) should be attempted. Alternatively, one could postulate that the primary goal of repeat ablation is to ensure durable PVI, and non-PV based ablation strategies should be reserved for patients without PV reconnection. Extensive ablation may come with the costs of altering atrial contractile properties, increasing the risk for procedural complications, and placing the patient at risk for iatrogenic atrial flutter(s) if bidirectional block is not achieved across linear lesions.<sup>37</sup> Ultimately, the critical question is how important the PVs are in driving a given patient's arrhythmia. Comparing the cycle length of PV triggers to the cycle length in the coronary sinus during AF may provide some indication as to the role of the PVs in supporting a patient's arrhythmia.<sup>38</sup> Pulmonary vein electrogram frequency tends to be much higher than the coronary sinus early in the disease process (suggesting PV isolation will result in a high likelihood of arrhythmia control), whereas the PV electrogram frequency is often lower than the coronary sinus as the disease process becomes more advanced (suggesting non-PV sources may be of increased importance and PV isolation alone may not result in optimal outcome).

There are no randomized controlled trials evaluating the efficacy of substrate modification techniques in patients with recurrent AF. The available data for non-PV based ablation come from patients undergoing de novo ablation procedures. Substrate modification techniques such as left atrial linear ablation, focal impulse or rotor modulation, ablation of complex fractionated atrial electrograms (CFAEs), and ganglionated plexi modification have been evaluated primarily in patients undergoing initial ablation for persistent and longstanding persistent AF. Extrapolation of these results to patients undergoing repeat ablation should be done with caution. Electrical isolation of the LA posterior wall has been evaluated primarily in patients with persistent AF with mixed results.<sup>39,40</sup> Ablation of areas with complex fractionated activity (CFAEs) have been investigated in patients with paroxysmal and persistent AF. Nademanee et al. targeted CFAEs defined as sites with low-amplitude potentials and continuous electrical activity or cycle length < 120 ms and reported a success rate of 91% at 1-year follow-up.<sup>41</sup> A more recent study evaluated adjunctive ablation of CFAE sites (identified with an automated mapping system) versus ablation of sites with continuous electrical activity.<sup>42</sup> At 1-year follow-up, freedom from arrhythmia, although modest, was higher with CFAE ablation compared with ablation of sites with continuous electrical activity (50 vs 28%). Adjunctive CFAE ablation has not been uniformly demonstrated to improve outcomes as one study randomly assigned 156 patients to PVI plus ablation of inducible non-PV triggers versus one of two additional strategies: PVI + empiric ablation of common non-

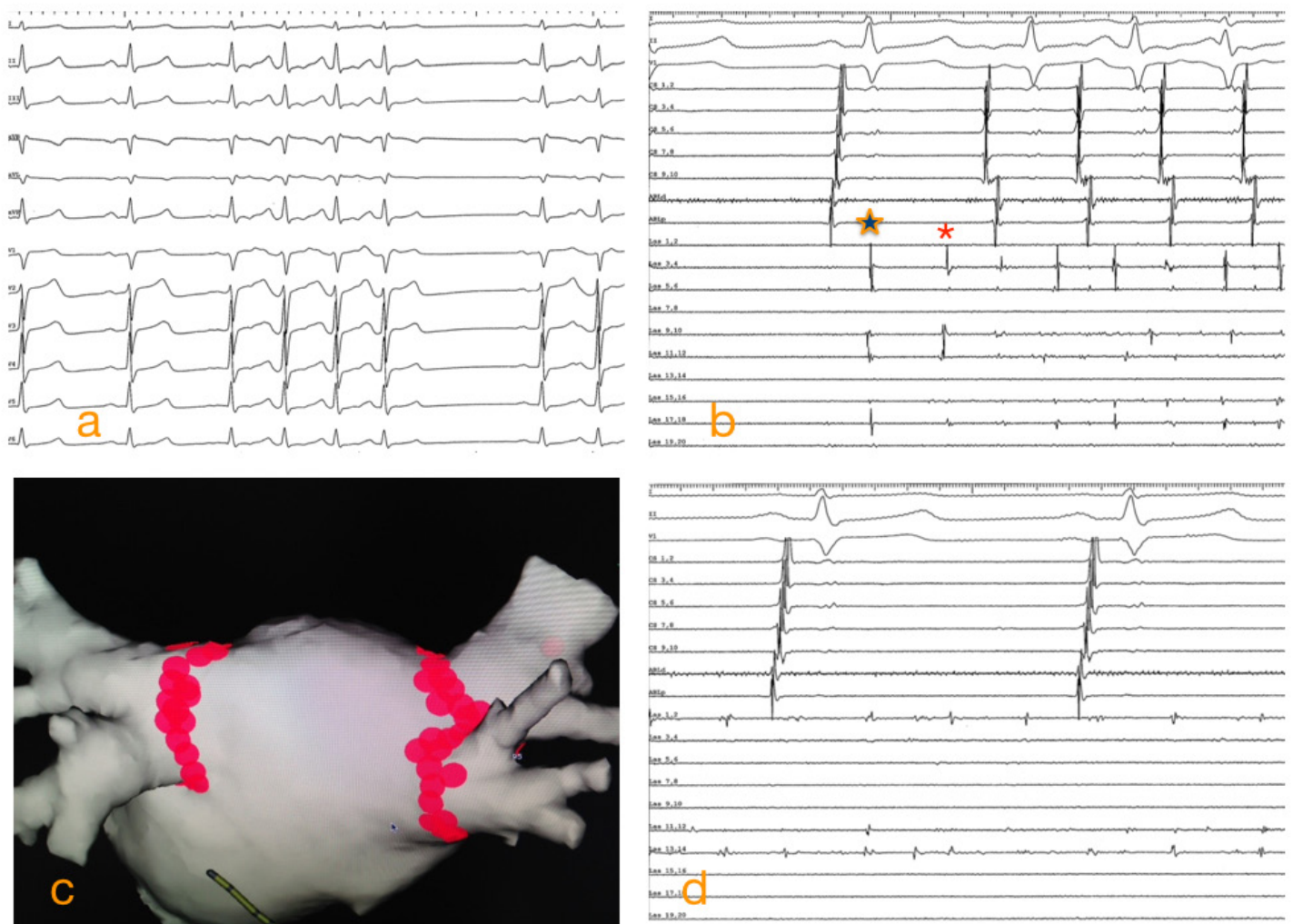


Figure 3:

**Illustrative case of a 47 year-old man undergoing repeat catheter ablation for atrial fibrillation. Paroxysmal AF had been diagnosed 2 years prior, and the patient underwent catheter ablation approximately 12 months earlier at another institution. He was AF free for nearly 9 months but then began having recurrent symptoms with paroxysmal AF documented. a) baseline rhythm at the start of the procedure under general anesthesia; frequent short bursts of AF noted; b) displayed are 3 surface ECG leads and intracardiac recordings from a decapolar catheter in the coronary sinus (labeled cs 9,10 through cs 1,2) and a circular mapping catheter (labeled Las 19,20 through Las 1,2) placed in the right superior pulmonary vein; note the delayed pulmonary vein potential (star) and initiation of AF triggered by spontaneous firing from the RSPV (asterisk); the other 3 PVs remained electrically isolated from the prior procedure; c) electroanatomic map with a posterior view of the left atrium; the RSPV was re-isolated using RF ablation and additional tags were placed at sites around the remaining pulmonary veins where there was bipolar volt-age < 0.2 mV and no pace capture; 4) the circular mapping catheter in the right superior pulmonary vein demonstrates AF in the RSPV with exit block while the atria remain in sinus rhythm**

PV AF trigger sites or PVI + ablation of left atrial CFAE sites.<sup>43</sup> Ablation of CFAE sites did not result in improved arrhythmia control at 1-year follow-up. In addition, a more recent randomized trial (STAR AF II) further assessed the role of adjunctive CFAE and linear ablation among patients with persistent atrial fibrillation.<sup>44</sup> At 18 months follow-up, 59% of PVI only patients were free from recurrent arrhythmia as opposed to 49% of patients who underwent PVI + CFAE ablation and 46% of patients who underwent PVI + empiric linear ablation.

The autonomic nervous system may play a role in initiating and maintaining AF through several mechanisms: facilitating spontaneous premature atrial depolarizations; shortening of atrial and PV effective refractory periods; and increasing heterogeneity of refractoriness. Consequently, a number of authors have investigated the role of adjunctive ganglionated plexus (GP) ablation. A randomized trial involving 67 patients with paroxysmal AF assigned to PVI versus PVI plus GP ablation showed improved outcomes at 10 month

follow-up (45.5 vs 73.5%).<sup>45</sup> This is an area of active investigation and additional data involving a larger number of patients is needed to determine if GP ablation truly improves outcomes.

Recent studies have reported the presence of stable reentrant circuits ("rotors") within the atria of AF patients which may provide an additional target during AF ablation.<sup>46-48</sup> The CON-FIRM trial reported initial experience in 92 patients treated either with FIRM-guided ablation with PVI versus PVI alone.<sup>49</sup> FIRM ablation was associated with slowing or termination of AF in 86% of patients, and over follow-up 82% of FIRM patients remained free of AF compared with 45% in the PVI-only group. More recently, two additional studies evaluated the efficacy of FIRM ablation on early and long-term outcomes and reported less optimistic results. One study reported 6-month outcomes among 29 patients (20 persistent, 9 longstanding persistent) undergoing FIRM-identified rotor ablation alone.<sup>50</sup> Single-procedure freedom from atrial tachyarrhythmias without anti-arrhythmic drugs was 17%. The other study reported

**Table 1: Risk factors for atrial fibrillation recurrence after ablation**

Age	Increased risk of recurrence with advancing age
AF duration and type	(Longstanding persistent > persistent > paroxysmal)
Cardiac structural changes	Left atrial dilatation; left ventricular function; hypertrophic cardiomyopathy; valvular heart disease
Clinical features	Hypertension; obesity; obstructive sleep apnea/sleep disordered breathing; metabolic syndrome; thyroid disease

outcomes among 43 patients (56% paroxysmal) who underwent FIRM ablation and PVI.<sup>51</sup> At 18 month follow-up only 21% of patients were free from arrhythmia off antiarrhythmic drugs.

Additional studies have evaluated the benefit of assessing for low-voltage areas at the time of ablation and performing additional substrate modification of these sites. A study involving 178 patients (65% persistent) found low voltage abnormalities in 35% and 10% of persistent and paroxysmal patients, respectively.<sup>52</sup> Low voltage areas were defined as sites with  $\geq 3$  adjacent points with bipolar voltage < 0.5 mV. Catheter ablation of low voltage areas in addition to PVI resulted in 12-month arrhythmia freedom of 70% compared with 27% among 26 patients with low voltage abnormalities who did not undergo further substrate modification. Another study assessed outcomes among 85 patients who underwent PVI and ablation of low voltage areas associated with either fractionated or discrete rapid local activity within or along the border zones of low voltage areas compared with 42 “control” patients with persistent AF who underwent PVI alone.<sup>53</sup> Arrhythmia freedom at 13 months was 69% among patients who underwent ablation of low voltage areas compared with 47% in the PVI-alone control group.

Substrate modification techniques (i.e., linear ablation; targeting of CFAEs or low voltage areas) have yielded conflicting results among patients undergoing de novo ablation and have not been studied and are of unclear benefit in patients undergoing repeat AF ablation. Given that the majority of studies investigating non-PV based ablation have shown little to no improvement over PVI alone (e.g., STAR AF II), it is hard to advocate for extensive atrial ablation. The majority of evidence suggests repeat PVI (if the PVs have reconnected) and ablation of non-PV triggers seems to be the most effective strategy. If the PVs have not reconnected, it seems reasonable to perform a comprehensive EP study to assess for inducible atrial flutter(s) or atrial tachycardia(s) and reserve substrate modification for patients in whom the PVs have not reconnected and other arrhythmias are not inducible. If linear ablation is performed it is imperative that bidirectional block be confirmed to avoid creating the substrate for iatrogenic atrial arrhythmias.

#### Repeat AF Ablation: Cryoablation Versus Radiofrequency?

When patients have recurrent AF after ablation is a certain energy delivery system preferred for repeat PVI? If cryoablation was used in the index procedure, should radiofrequency (RF) be employed in a subsequent procedure or vice versa? There is limited data addressing this subject but one interesting study is worth mention. Pokushalov et al. randomly assigned 80 patients with recurrent paroxysmal AF after a first PVI using radiofrequency ablation to repeat PVI with either cryoablation or RF.<sup>54</sup> Study participants had implantable loop recorders to monitor for recurrence. At 1-year follow-up more patients randomized to repeat ablation with RF (58%) were AF-free compared with those who underwent cryoablation (43%). This finding suggests repeat PVI with RF, as opposed to cryoablation, results in improved outcomes although this study is small and the

results should be validated in a larger number of patients.

#### Pre-Procedural And Intra-Procedural Imaging To Guide Ablation

Ideally pre-procedural imaging could be used to identify sites of PV reconnection or provide clues to the mechanism of recurrent arrhythmia to guide repeat ablation. Late gadolinium-enhanced (LGE) MRI has been used to identify gaps in lesion sets which may be targeted acutely or with repeat ablation.<sup>55-57</sup> One study involving 15 patients undergoing repeat ablation for AF found pre-ablation late gadolinium-enhanced MRI accurately identified gaps in areas of prior ablation resulted in shorter procedure times by allowing more targeted ablation.<sup>58</sup> In addition, as previously mentioned there is some evidence suggesting improved outcomes if areas of low voltage are targeted in addition to PVI. If this is validated in subsequent studies and found beneficial in patients undergoing repeat ablation, LGE-MRI may be useful for pre-procedure planning by helping identify abnormal substrate which could be targeted for ablation.

A critical step forward may be noninvasive imaging of electrical activation to identify the processes essential to maintaining an individual's arrhythmia. Identification of focal drivers or rotational activities prior to entering the electrophysiology laboratory may facilitate a tailored ablation strategy more likely to be successful than empirically applying the same lesion sets to each patient regardless of arrhythmia mechanism. Medtronic, Inc. and CardioInsight's ECVUETM is a noninvasive system which captures body surface electrical data to create and visualize epicardial 3D electroanatomic maps. The system has proven successful in mapping and ablation of persistent AF in a multicenter study.<sup>59</sup> In the study, 118 persistent AF patients underwent pre-ablation body surface mapping with data used to guide ablation of AF drivers. Acute success (AF termination) was achieved in 64% with driver-based ablation alone. At mean 6 months' follow-up, 83% of patients were AF free including recurrent atrial tachycardia in 38%. Although additional work needs to be done to validate the accuracy of noninvasive electrical mapping, the concepts and available data are intriguing. Noninvasive electrical mapping may become a valuable pre-ablation tool for both de novo and repeat AF ablation procedures by potentially identifying areas critical to a patient's AF mechanism(s) prior to entry into the EP laboratory.

#### Ancillary Interventions To Minimize AF Recurrence

In addition to procedural interventions to treat AF, one should also screen for and modify any comorbid conditions which may increase the likelihood of AF recurrence (table 1). Specifically, it is prudent to address obesity; sleep-disordered breathing/obstructive sleep apnea; hypertension; smoking and alcohol consumption. Obesity is a clearly defined risk factor for AF.<sup>60</sup> It increases the risk of hypertension, metabolic syndrome/diabetes mellitus, and obstructive sleep apnea (OSA), all of which have also been associated with development of atrial fibrillation. Weight reduction has been shown to reduce AF symptom burden and severity.<sup>61</sup> Obstructive sleep apnea independently increases the risk of incident atrial fibrillation and increases the risk of recurrent AF after ablation.<sup>62,63</sup> OSA promotes atrial structural and electrical remodeling including atrial enlargement and low-voltage areas with conduction abnormalities.<sup>64</sup> Treatment of OSA with continuous positive airway pressure (CPAP) improves arrhythmia-free survival post-catheter ablation.<sup>63</sup> A recent study demonstrated aggressive risk factor modification including weight reduction (initial goal to reduce body weight by 10% followed by target BMI < 25 kg/m<sup>2</sup>); blood pressure management with target

< 130/80 mmHg; aggressive lipid and glycemic control; treatment of obstructive sleep apnea if the apnea-hypopnea index (AHI) was > 30/hour; and abstinence from smoking and alcohol significantly improved arrhythmia-free survival.<sup>65</sup> Additional research is needed to define optimal targets for management of AF risk factors, but it is clear that treatment of comorbid conditions optimizes AF control.

### Conclusions

Recurrent AF after catheter ablation occurs in at least 20 to 40% of patients. Repeat ablation is primarily considered for those with symptomatic AF recurrences (often drug-refractory) occurring at least 3 months or more post-ablation. Pulmonary vein reconnection is almost universally encountered, and repeat isolation of electrically connected pulmonary veins should be the primary ablation strategy. Beyond repeat PVI and possible ablation of non-PV triggers, there is little to no evidence that additional substrate modification improves outcomes. If substrate modification and linear lesions are created, however, it is imperative to confirm bidirectional conduction block to avoid creating substrate for iatrogenic atrial arrhythmias. In addition to repeat ablation, it is critical to treat the “whole” patient by addressing comorbid conditions which increase arrhythmia risk post-ablation. Specifically, obesity, hypertension, and sleep-disordered breathing should be targeted and modified to increase the likelihood of success.

### References

- Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJG, Damiano RJ, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iedaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-Up, Definitions, Endpoints, and Research Trial Design. *Europace* 2012; 14: 528 - 606.
- Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A randomized controlled trial of circumferential pulmonary vein isolation versus anti-arrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF study. *J Am Coll Cardiol* 2006; 48 (11): 2340 - 2347.
- Wazni O, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themis-toclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005; 293 (21): 2634 - 2640.
- Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clementy J, Haissaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008; 118 (24): 2498 - 2505.
- Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F, Bates ER, Lehmann MH, Vicedomini G, Augello G, Agricola E, Sala S, Santinelli V, Morady F. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med* 2006; 354 (9): 934 - 941.
- Packer D, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front STOP-AF pivotal trial. *J Am Coll Cardiol* 2010; 55: E3015 - E3016.
- Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawat-tanakul S, Punlee K, Kangkagate C. A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. *J Med Assoc Thai*. 2003; 86 (Suppl 1): S8 - S16.
- Noheria A, Kumar A, Wylie JV, Jr., Josephson ME. Catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation: a systematic review. *Arch Intern Med* 2008; 168 (6): 581 - 586.
- Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Franco Vitale D. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation for the Cure of Atrial Fibrillation Study). *Eur Heart J* 2006; 27 (2): 216 - 221.
- Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010; 303 (4): 333 - 340.
- Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol* 2009; 2 (6): 626 - 633.
- Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2009; 2 (4): 349 - 361.
- Kobza R, Hindricks G, Tanner H, Schirdewahn P, Dorszewski A, Piorkowski C, Gerds-Li JH, Kottkamp H. Late recurrent arrhythmias after ablation of atrial fibrillation: incidence, mechanisms, and treatment. *Heart Rhythm* 2004; 1 (6): 676 - 683.
- Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J, Gunther J, Potenza D, Martin DO, Cummings J, Burkhardt JD, Saliba W, Schweikert RA, Natale A. Re-sponse of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation* 2005; 112 (5): 627 - 635.
- Callans DJ, Gerstenfeld EP, Dixit S, Zado E, Vanderhoff M, Ren JF, Marchlinski FE. Efficacy of repeat pulmonary vein isolation procedures in patients with recurrent atrial fibrillation. *J Cardiovasc Electrophysiol* 2004; 15 (9): 1050 - 1055.
- Gerstenfeld EP, Callans DJ, Dixit S, Zado E, Marchlinski FE. Incidence and location of focal atrial fibrillation triggers in patients undergoing repeat pulmonary vein isolation: implications for ablation strategies. *J Cardiovasc Electrophysiol* 2003; 14 (7): 685 - 690.
- Nanthakumar K, Plumb VJ, Epstein AE, Veenhuyzen GD, Link D, Kay GN. Resumption of electrical conduction in previously isolated pulmonary veins: rationale for a different strategy? *Circulation* 2004; 109 (10): 1226 - 1229.
- Hussein AA, Saliba WI, Martin DO, Bhargava M, Sherman M, Magnelli-Reyes C, Chamsi-Pasha M, John S, Williams-Adrews M, Baranowski B, Dresing T, Callahan T, Kanj M, Tchou P, Lindsay BD, Natale A, Wazni O. Natural history and long-term outcomes of ablated atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011; 4: 271 - 278.
- Tzou WS, Marchlinski FE, Zado ES, Lin D, Dixit S, Callans DJ, Cooper JM, Bala R, Garcia F, Hutchinson MD, Riley MP, Verdino R, Gerstenfeld EP. Long-term outcome after successful catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; 3: 237 - 242.
- Lin D, Santangeli P, Zado ES, Bala R, Hutchinson MD, Riley MP, Frankel DS, Garcia F, Dixit S, Callans DJ, Marchlinski FE. Electrophysiologic findings and long-term outcomes in patients undergoing third or more catheter ablation procedures for atrial fibrillation. *J Cardiovasc Electrophysiol* 2015; 26: 371 - 377.
- Bhargava M, Di Biase L, Mohanty P, Prasad S, Martin DO, Williams-Adrews

- M, Wazni OM, Burkhardt JD, Cummings JE, Khaykin Y, Verma A, Hao S, Beheiry S, Hongo R, Rossillo A, Raviele A, Bonso A, Themistoclakis S, Stewart K, Saliba WI, Schweikert RA, Natale A. Im-pact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: Results from a multicenter study. *Heart Rhythm* 2009; 6: 1403 - 1412.
22. Di Biase L, Conti S, Mohanty P, Bai R, Sanchez J, Walton D, John A, Santangeli P, Elayi CS, Beheiry S, Gallinghouse GJ, Mohanty S, Horton R, Bailey S, Burkhardt JD, Natale A. General anesthesia reduces the prevalence of pulmonary vein reconnection during repeat ablation when compared with conscious sedation: results from a randomized study. *Heart Rhythm* 2011; 8: 368 - 372.
  23. Hutchinson MD, Garcia FC, Mandel JE, Elkassabany N, Zado ES, Riley MP, Cooper JM, Bala R, Frankel DS, Lin D, Supple GE, Dixit S, Gerstenfeld EP, Callans DJ, Marchlinski FE. Efforts to enhance catheter stability improve atrial fibrillation outcome. *Heart Rhythm* 2013; 10 (3): 347 - 353.
  24. Piorkowski C, Eitel C, Rolf S, Bode K, Sommer P, Gaspar T, Kircher S, Wetzel U, Parwani AS, Boldt LH, Mende M, Bollmann A, Husser D, Dagues N, Esato M, Arya A, Haverkamp W, Hindricks D. Steerable versus nonsteerable sheath technology in atrial fibrillation ablation. *Circulation Arrhythm Electrophysiol* 2011; 4: 157 - 165.
  25. Sciarra L, Golia P, Natalizia A, De Ruvo E, Dottori S, Scara A, Borrelli A, De Luca L, Rebec-chi M, Fagagnini A, Bandini A, Guarracini F, Galvani M, Calo L. Which is the best catheter to perform atrial fibrillation ablation? A comparison between standard ThermoCool, Smart-Touch, and Surround Flow catheters. *J Interv Card Electrophysiol* 2014; 39: 193 - 200.
  26. Park CI, Lehrmann H, Keyl C, Weber R, Schiebeling J, Allgeier J, Schurr P, Shah A, Neu-mann FJ, Arentz T, Jadidi AS. Mechanisms of pulmonary vein reconnection after radiofre-quency ablation of atrial fibrillation: the deterministic role of contact force and interlesion dis-tance. *J Cardiovasc Electrophysiol* 2014; 25: 701 - 708.
  27. Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, Kantipudi C, Mansour MC, Melby DP, Packer DL, Nakagawa H, Zhang B, Stagg RB, Boo LM, Marchlinski FE. Paroxysmal AF catheter ablation with a contact force sensing catheter. *J Am Coll Cardiol* 2014; 64 (7): 647 - 656.
  28. Kuhne M, Suter Y, Altmann D, Ammann P, Schaer B, Osswald S, Sticherling C. Cryobal-loon versus radiofrequency catheter ablation of paroxysmal atrial fibrillation: biomarkers of myocardial injury, recurrence rates, and pulmonary vein reconnection patterns. *Heart Rhythm* 2010; 7 (12): 1770 - 1776.
  29. Chen S, Meng W, Sheng He D, Chen G, Zhang F, Yan Y, Zhu-Ge Y, Liu S. Blocking the pulmonary vein to left atrium conduction in addition to the entrance block enhances clinical efficacy in atrial fibrillation ablation. *Pacing Clin Electrophysiol* 2012; 35: 524 - 531.
  30. Nakamura K, Naito S, Kaseno K, Tsukada N, Sasaki T, Hayano M, Nishiuchi S, Fuke E, Miki Y, Sakamoto T, Nakamura K, Kumagai K, Kataoka A, Takaoka H, Kobayashi Y, Funabashi N, Oshima S. Optimal observation time after completion of circumferential pul-monary vein isolation for atrial fibrillation to prevent chronic pulmonary vein reconnections. *Int J Cardiol* 2013; 168: 5300 - 5310.
  31. Steven D, Sultan A, Reddy V, Luker J, Altenburg M, Hoffmann B, Rostock T, Servatius H, Stevenson WG, Willems S, Michaud GF. Benefit of pulmonary vein isolation guided by loss of pace capture on the ablation line: results from a prospective 2-center randomized trial. *J Am Coll Cardiol* 2013; 62: 44 - 50.
  32. Cheung JW, Lin FS, Ip JE, Bender SR, Siddiqi FK, Liu CF, Thomas G, Markowitz SM, Ler-man BB. Adenosine-induced pulmonary vein ectopy as a predictor of recurrent atrial fibrilla-tion after pulmonary vein isolation. *Circ Arrhythm Electrophysiol* 2013; 6: 1066 - 1073.
  33. McLellan AJA, Kumar S, Smith C, Morton JB, Kalman JM, Kistler PM. The role of adeno-sine following pulmonary vein isolation in patients undergoing catheter ablation for atrial fibril-lation: a systematic review. *J Cardiovasc Electrophysiol* 2013; 24 (7): 742 - 751.
  34. Macle L, Khairy P, Weerasooriya R, Novak P, Verma A, Willems S, Arentz T, Deisendorfer I, Veenhuyzen G, Scavee C, Jais P, Puererfellner H, Levesque S, Andrade JG, Rivard L, Guerra PG, Dubuc P, Thibault B, Talajic M, Roy D, Nattel S. Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicenter randomised superiority trial. *Lancet* 2015; 386 (9994): 672 - 679.
  35. Mainigi SK, Sauer WH, Cooper JM, Dixit S, Gerstenfeld EP, Callans DJ, Russo AM, Verdino RJ, Lin D, Zado ES, Marchlinski FE. Incidence and predictors of very late recurrence of atrial fibrillation after ablation. *J Cardiovasc Electrophysiol* 2007; 18: 69 -74.
  36. Takigawa M, Takahashi A, Kuwahara T, Okubo K, Takahashi Y, Nakashima E, Watari Y, Yamao K, Nakajima J, Takagi K, Kimura S, Hikita H, Hirao K, Isobe M. Impact of non-pulmonary vein foci on the outcome of the second session of catheter ablation for paroxys-mal atrial fibrillation. *J Cardiovasc Electrophysiol* 2015; 26: 739 - 746.
  37. Sawhney N, Anousheh R, Chen W, and G Feld. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; 3: 243 - 248.
  38. Bunch TJ and MJ Cutler. Is pulmonary vein isolation still the cornerstone in atrial fibrillation ablation? *J Thoracic Dis* 2015; 7 (2): 132 - 141.
  39. Oral H, Chugh A, Good E, Iqbal P, Elmouchi D, Tschopp DR, Reich SS, Bogun F, Pelosi F, Morady F. Randomized comparison of encircling and nonencircling left atrial ablation for chronic atrial fibrillation. *Heart Rhythm* 2005; 2: 1165 - 1172.
  40. Bai R, Di Biase L, Mohanty P, Trivedi C, Dello Russo A, Themistoclakis S, Casella M, San-tarelli P, Fassini G, Santangeli P, Mohanty S, Rossillo A, Pelargonio G, Horton R, Sanchez J, Gallinghouse J, Burkhardt JD, Ma CS, Tondo C, Natale A. Proven isolation of the pulmo-nary vein antrum with or without left atrial posterior wall isolation in patients with persistent atrial fibrillation. *Heart Rhythm* 2016; 13 (1): 132 - 140.
  41. Nademane K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: map-ping of the electrophysiologic substrate. *J Am Coll Cardiol* 2004; 43: 2044 - 2053.
  42. Verma A, Sanders P, Champagne J, Macle L, Nair GM, Calkins H, Wilber DJ. Selective complex fractionated atrial electrograms targeting for atrial fibrillation study (SELECT AF): a multicenter, randomized trial. *Circ Arrhythm Electrophysiol* 2014; 7: 55 - 62.
  43. Dixit S, Marchlinski FE, Lin D, Callans DJ, Bala R, Riley MP, Garcia FC, Hutchinson MD, Ratcliffe SJ, Cooper JM, Verdino RJ, Patel VV, Zado ES, Cash NR, Killian T, Tomson TT, Gerstenfeld EP. Randomized ablation strategies for the treatment of persistent atrial fibrilla-tion: RASTA Study. *Circ Arrhythm Electrophysiol* 2012; 5 (2): 287 - 294.
  44. Verma A, Jiang C-Y, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P. Approaches to catheter ablation for persistent atrial fibrillation (STAR AF II). *N Engl J Med* 2015; 372: 1812 - 1822.
  45. Katritsis DG, Giazitzoglou E, Zografos T, Pokushalov E, Po SS, Camm AJ. Rapid pulmo-nary vein isolation combined with autonomic ganglia modification: a randomized study. *Heart Rhythm* 2011; 8: 672 - 678.
  46. Skanes AC, Mandapati R, Berenfeld O, Davidenko MJ, Jalife J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. *Circulation* 1998; 98: 1236 - 1248.
  47. Ryu K, Shroff SC, Sahadevan J, Martovitz NL, Khrestian CM, Stambler BS. Mapping of atrial activation during sustained atrial fibrillation in dogs with rapid ventricular pacing induced heart failure: evidence for a role of driver regions. *J Cardiovasc Electrophysiol* 2005; 16: 1348 - 1358.

48. Shivkumar K, Ellenbogen KA, Hummel JD, Miller JM, Steinberg JS. Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: first multicenter experience of focal impulse and rotor modulation (FIRM) ablation. *J Cardio-vasc Electrophysiol* 2012; 23: 1277 – 1285.
49. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardi-ol* 2012; 60: 628 – 636.
50. Gianni C, Mohanty S, Di Biase L, Metz T, Trivedi C, Gokoglan Y, Gunes MF, Bai R, Al-Ahmad A, Burkhardt JD, Gallinghouse GJ, Horton RP, Hranitzky PM, Sanchez JE, Halbfab P, Muller P, Schade A, Deneke T, Tomassoni GF, Natale A. Acute and early outcomes of focal impulse and rotor modulation (FIRM)-guided rotors-only ablation in patients with non-paroxysmal atrial fibrillation. *Heart Rhythm* 2016; 13: 830 – 835.
51. Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J, Mandapati R, Ellenbogen KA, Shivkumar K. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: a multicenter experience. *Heart Rhythm* 2016; 13: 636 – 641.
52. Rolf S, Kircher S, Arya A, Eitel C, Sommer P, Richter S, Gaspar T, Bollman A, Altmann D, Piedra C, Hindricks G, Piorkowski C. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014; 7: 825 – 833.
53. Jadidi AS, Lehrmann H, Keyl C, Sorrel J, Markstein V, Minners J, Park C, Denis A, Jais P, Hocini M, Potocnik C, Allgeier J, Hochholzer W, Herrera-Sidloky C, Kim S, El Omri Y, Neumann FJ, Weber R, Haissaguerre M, Arentz T. Ablation of persistent atrial fibrillation target-ing low-voltage areas with selective activation characteristics. *Circ Arrhythm Electrophysiol* 2016; 9: e002962
54. Pokushalov E, Romanov A, Artyomenko S, Baranova V, Losik D, Bairamova S, Karaskov A, Mittal S, Steinberg JS. Cryoballoon versus radiofrequency for pulmonary vein re-isolation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation. *J Cardio-vasc Electrophysiol* 2013; 24: 274 – 279.
55. Ranjan R, Kato R, Zviman MM, Dickfeld TM, Roguin A, Berger RD, Tomaselli GF, Halperin HR. Gaps in the ablation line as a potential cause of recovery from electrical isolation and their visualization using MRI. *Circ Arrhythm Electrophysiol* 2011; 4: 279 – 286.
56. Ranjan R, Kholmovski EG, Blauer J, Vijayakumar S, Volland NA, Salama ME, Parker DL, MacLeod R, Marrouche NF. Identification and acute targeting of gaps in atrial ablation lesion sets using a real time MRI system. *Circ Arrhythm Electrophysiol* 2012; 5 (6): 1130 – 1135.
57. Vergara GR and NF Marrouche. Tailored management of atrial fibrillation using a LGE-MRI based model: from the clinic to the electrophysiology laboratory. *J Cardiovasc Electrophysiol* 2011; 22 (4): 481 – 487.
58. Bisbal F, Guiu E, Cabanas-Grandio P, Berruezo A, Prat-Gonzalez S, Vidal B, Garrido C, An-dreu D, Fernandez-Armenta J, Tolosana JM, Arbelo E, de Caralt TM, Perea RJ, Brugada J, Mont L. CMR-guided approach to localize and ablate gaps in repeat AF ablation procedure. *JACC: Cardiovascular Imaging* 2014; 7 (7): 653 – 663.
59. Knecht S, Sohal M, Arentz T, Jadidi A, Rostock T, Deisendorfer IV, Cauchemez B, Albenque JP, Neumann T, Ernst S, Packer D, Tavernier R, Duytschaever M. Noninvasive mapping prior to ablation for persistent atrial fibrillation: The AFACART multicenter study (PO 06-52). *Heart Rhythm* 2015; 12: S508.