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Is Isolation of Arrhythmogenic Pulmonary Veins Sufficient for the Long-term Efficacy of Atrial Fibrillation Ablation?

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Introduction

Atrial fibrillation (AF) is the commonest cardiac rhythm disorder, affecting about 5% of elderly patients.[1] Despite the wide spread prevalence of AF, treatment options for the condition up until recently, were limited. Antiarrhythmic drug therapy which for a long time had been and to some extent still is the cornerstone for treating these patients, has shown a disappointing (≤ 40%) efficacy for long-term maintenance of sinus rhythm.[2] The seminal observations by Haissaguerre and colleagues demonstrating AF initiation from electrical depolarizations in the pulmonary veins (PV) and cure of AF in these patients by radiofrequency ablation (RFA) of the PV focus, has led to the emergence of percutaneous catheter based AF ablation.[3] Since its original description in 1998, the AF ablation procedure has evolved considerably.[4-7] This evolution was the result of several short comings of the original technique (focal ablation) including the inability to expeditiously target multiple evanescent PV foci effectively and the long term consequences of delivering RF energy within the PVs i.e., occurrence of vein stenosis.[8-12] Thus an alternative approach was developed where instead of ablating individual foci within the veins, RF lesions are delivered around the circumference of the PV ostium in order to interrupt PV-left atrial (LA) electrical connections and thus achieve PV isolation (PVI).[8] Compared with focal AF ablation, PVI has shown a significant enhancement in long term arrhythmia control while dramatically reducing the occurrence of PV stenosis.[11, 13] both of which are welcome developments. A potential reason for the enhanced success of PVI may be that the triggers of AF are clustered in close proximity to the vein ostia. However, an alternative explanation for the enhanced success of PVI is that the procedure inadvertently targets LA tissue (around PV os) and so results in modification of the underlying substrate. This hypothesis has been supported by the observation that anatomically guided circumferential PV ostial ablation without necessarily achieving true PVI (entry / exit block) is equally efficacious in achieving long term AF control.[5,6] In fact, this observation has led to the development of an anatomically guided incremental ablation strategy which attempts to substantially modify the AF substrate by extensive LA ablation.[14-16] However, such an approach has not consistently demonstrated a significant improvement in long term AF control rates as compared with PVI alone, which would suggest that PVs may be critical to the initiation and / or maintenance of AF.[18,19] The purpose of this editorial is to provide the readers with a concise overview on the arrhythmogenic potential of PVs and to discuss how best we can identify and target such veins and whether that translates into long term control of AF.

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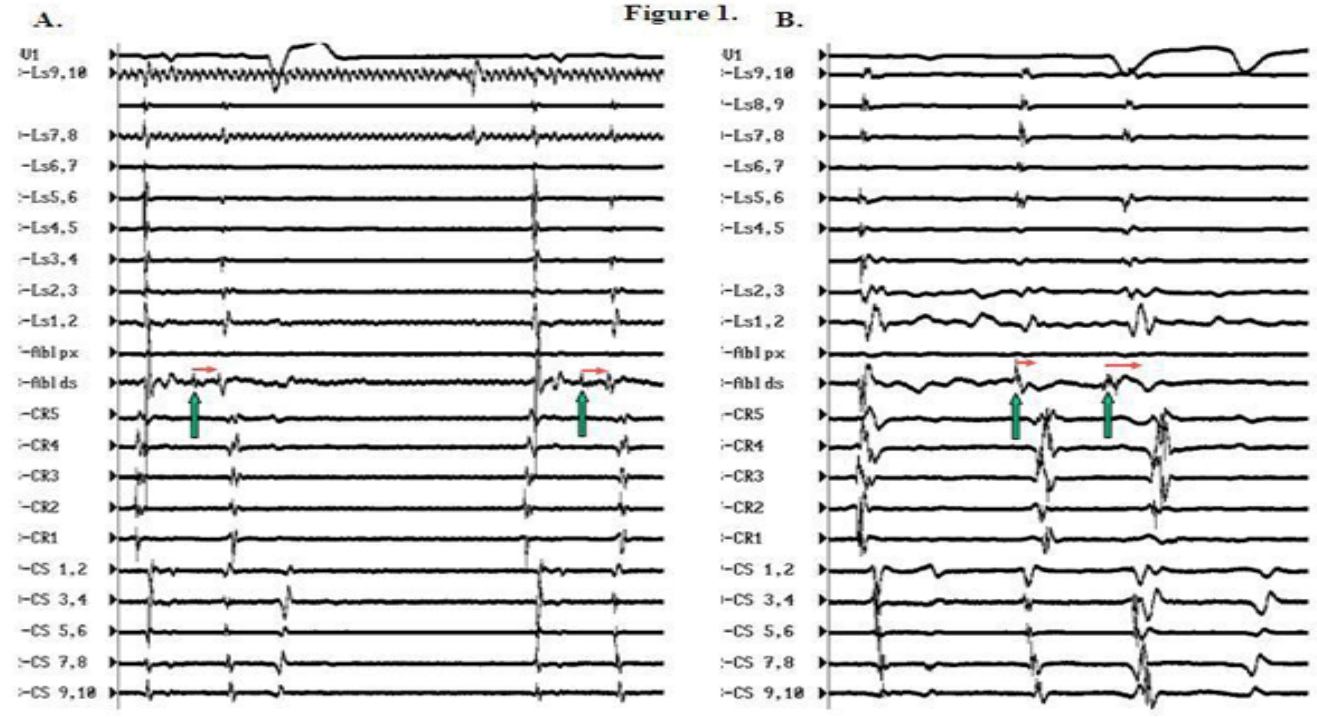
Are the Pulmonary Veins Arrhythmogenic by Design?

Both anatomical and electrical abnormalities can result in cardiac tissue arrhythmogenecity.[20-23] Anisotropy which, can be defined as lack of shared regional directionality amongst muscle fibers, is commonly observed in the right atrium along the crista terminalis, in the cavo-tricuspid isthmus region, near the coronary sinus ostium / eustachian ridge area, and these locations have frequently been identified as sites of atrial premature complexes and / or atrial tachycardias.[24-26] Data from autopsied human hearts has also shown marked tissue anisotropy in the form of complex looping posterior LA musculature encircling individual PV ostia and extending distally along the PV walls where it interdigitates with thevein musculature.[27] Such anisotropy may result in variable conduction velocities and unidirectional blocks that could potentiate wave front fractionation and AF initiation. Cardiac tissue arrhythmogenecity can also be an electrical phenomenon, due to alterations in the action potential profile of individual myocardial cells and / or cell groups resulting in abnormalities of impulse formation and / or conduction.[21-23] The PVs have been shown, both in animal models and human studies to have shorter refractory periods as compared with the rest of the LA.[28, 29] Also, within the confines of the PVs, interdigitating LA musculature that is relatively isolated from the main LA syncitium, may manifest a different resting membrane potential which in turn can alter its action potential characteristics thus promoting arrhythmogenecity. Developmentally too, in the mouse model, cells constituting PV tissue have demonstrated properties akin to the AV node.[30] In support of the latter hypothesis, in some patients undergoing AF ablation where frequent spontaneous PV depolarizations have been identified, using a combination of circular mapping and a quadripolar ablation catheter, we have noted decremental conduction across the PVs such that the more closely coupled PV depolarizations manifest a longer exit time out of the vein. In these patients, isoproterenol infusion appears to facilitate PV conduction [Figure 1].

Figure 1: **Panel A** shows pulmonary vein depolarization (PVD; green arrows) recorded on the distal pole of ablation catheter (Abl ds) positioned in the left inferior (LI) PV with constant exit time out of the vein (interrupted line to generate atrial premature complexes (APCs). **Panel B** shows PVD response to isoproterenol infusion which causes increased frequency and the first PVD demonstrates shorter exit time compared with the second more closely coupled PVD that takes longer to exit out of the vein. Such behavior is consistent with facilitated and decremental conduction. From top to bottom the tracings are arranged as follows: ECG lead V1, Lasso (Ls; poles 9,10 to 1,2) positioned in the right superior PV, proximal (px) and distal (ds) poles of ablation catheter positioned in LIPV, decapolar catheter positioned in the posterior right atrium (CR5 – CR1) and decapoler catheter positioned in the coronary sinus (CS1,2 – CS 9,10)



Mechanisms Underlying PV Triggers of AF

Despite ample proof of the arrhythmogenic potential of PVs, there remains lack of consensus on the mechanism(s) that underlie PV triggers of AF. In an acetylcholine mediated, pacing induced model of AF in isolated sheep hearts, using optical and electrical mapping techniques, dominant and highest frequencies during AF were observed in the PV / posterior LA, and micro reentry mediated wave fronts were proposed as "drivers" for AF maintenance in the model.[28, 31] Consistent with this observation, during ongoing AF in human subjects, rapid electrical activity has been infrequently recorded from within the PVs which has also been attributed to micro-reentry.[3, 6, 8] However, such sustained fast and organized electrical activity or PV tachycardia during AF is rarely observed.

More frequently, AF is seen to initiate by atrial premature complexes (APCs) resulting from isolated PV depolarizations,[3, 8] and these too are hard to characterize mechanistically [Figure 2]. On the other hand, sustained PV depolarizations or "firing" which can be defined as repetitive, discrete, multiphasic electrical activity recorded from catheters at/or distal to PV os [Figure 3, Panels A], that does not correlate in timing with other cardiac events (P, QRS and T waves) and persists at baseline for ≥ 5 minutes is an uncommon finding but when observed, it provides us a unique opportunity to explore mechanisms underlying PV arrhythmogenecity. In a series of 210 patients undergoing AF ablation at our center, using a combination of a decapolar circular mapping and quadripolar ablation catheters either simultaneously or separately we were able to identify sustained firing (PVF) in 15 subjects (7.1%; age 55±9 years; 14 males). Sustained PVF was observed in 16 veins including 6 right superior (RS), 4 left superior (LS), 1 right inferior (RI) and 5 left inferior (LI) PVs [20]. The relationship of sustained PVF to native sinus rhythm complexes showed a bigeminal pattern in the majority (n=11; 69%; Figure 3; Panel A), trigeminal pattern in 3 cases (19%; Figure 3; Panels B) and a variable pattern in 2 cases (13%). Once sustained PVF was confirmed, pacing was performed from coronary sinus and/or poste-

Figure 2: From top to bottom are ECG lead V1, 10 bipolar recordings of circular mapping (Lasso) catheter located at LIPV Os, recordings from distal and proximal bipoles of ablation catheter located in LSPV and 5 bipolar recordings from catheters positioned in coronary sinus (CS) and right atrium (RA). Initial two beats represent sinus rhythm with delayed conduction within LIPV (arrow heads). The 3rd beat is an atrial premature complex (APC) which degenerates into AF. Note earliest electrical depolarization in the distal bipole of the ablation catheter (star) preceding APC. Similar electrical activity is noticed in the distal bipole of the ablation catheter after the 1st sinus beat (open arrow). This may represent localized "depolarization" within the LSPV that fails to propagate within or exit the vein.

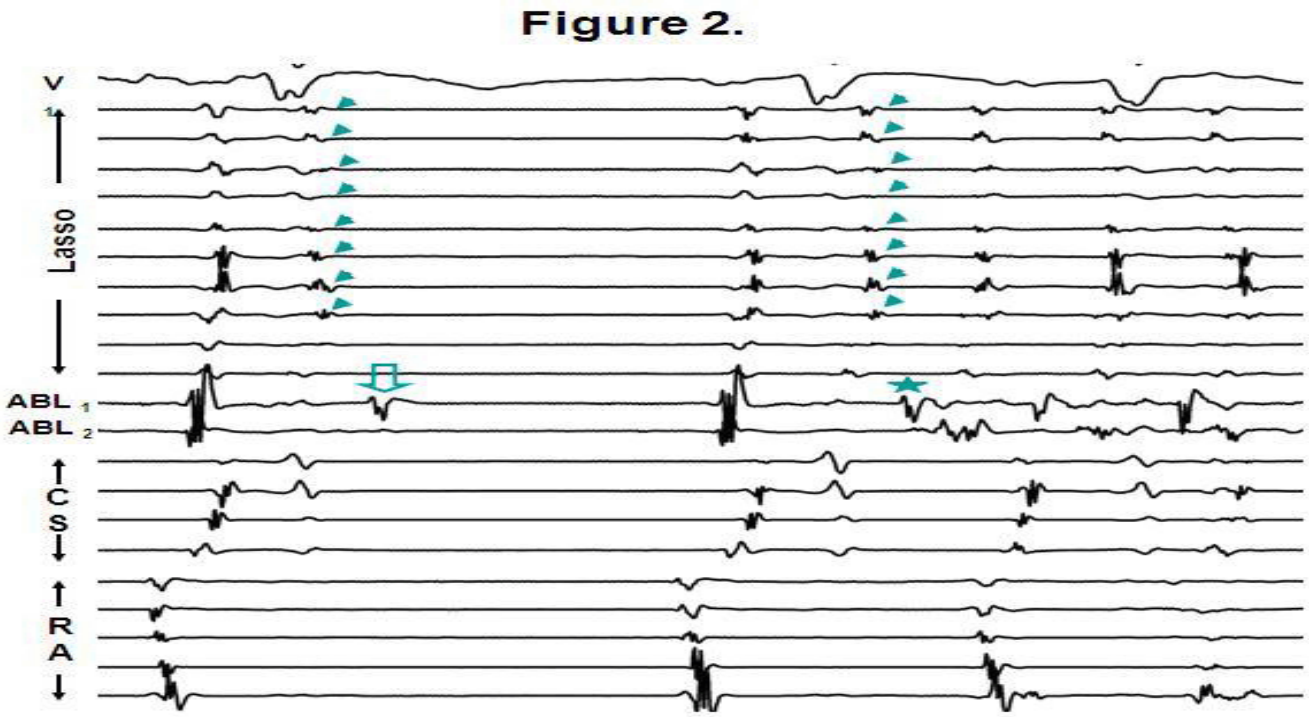


Figure 3, Panel A: Illustrates the commonest pattern of sustained pulmonic vein firing (PVF) observed in our study. From top to bottom, the arrangement of tracings are: surface lead V1 , recordings from decapolar circular mapping catheter (Lasso) positioned at os of left superior pulmonic vein, distal bipole of ablation catheter positioned just beyond os of right superior pulmonary vein (RSPV), and recordings (distal to proximal) from decapolar catheters along the posterior right atrium (Ct) and in the coronary sinus (CS) respectively. Discrete multiphasic electrograms (Egm) representing spontaneous PVF are seen on the bipole of ablation catheter (arrow heads) that do not correspond in timing with P, QRS, or T waves. Since PVF occurs after each sinus beat, we define this pattern as bigeminal. Please note that PVF in this case does not exit out of the RSPV.

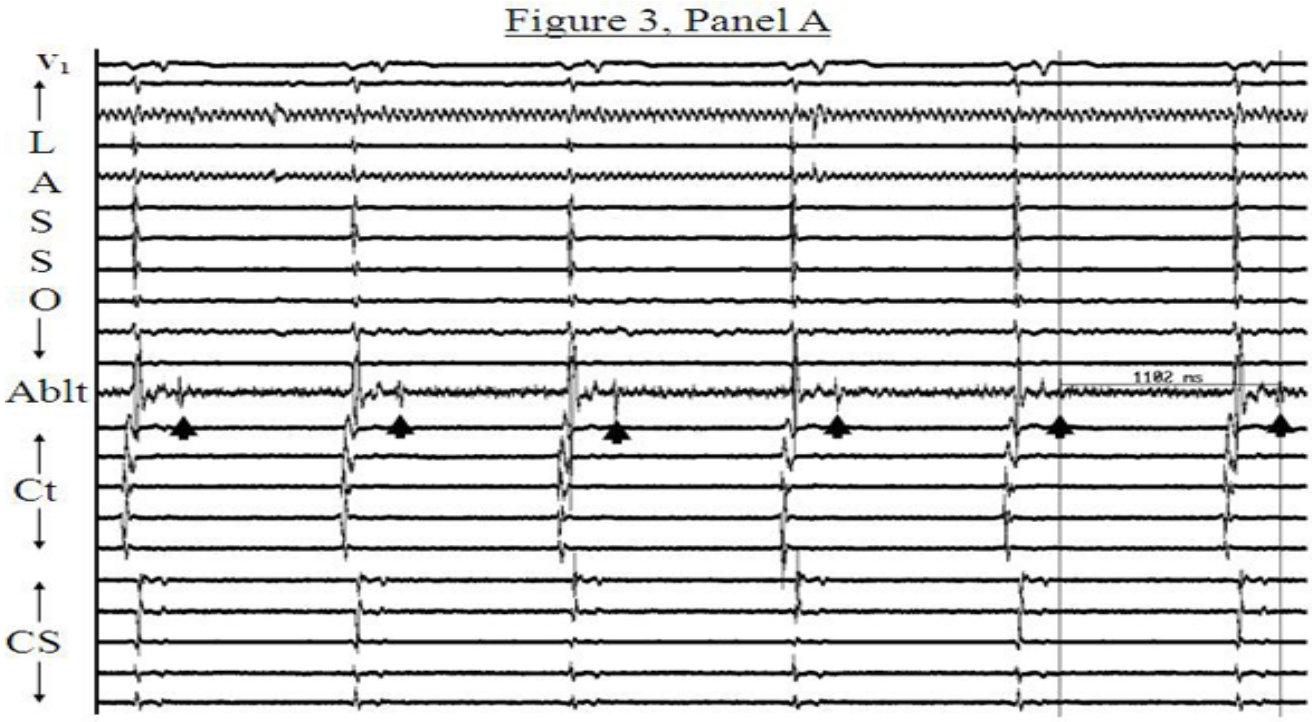
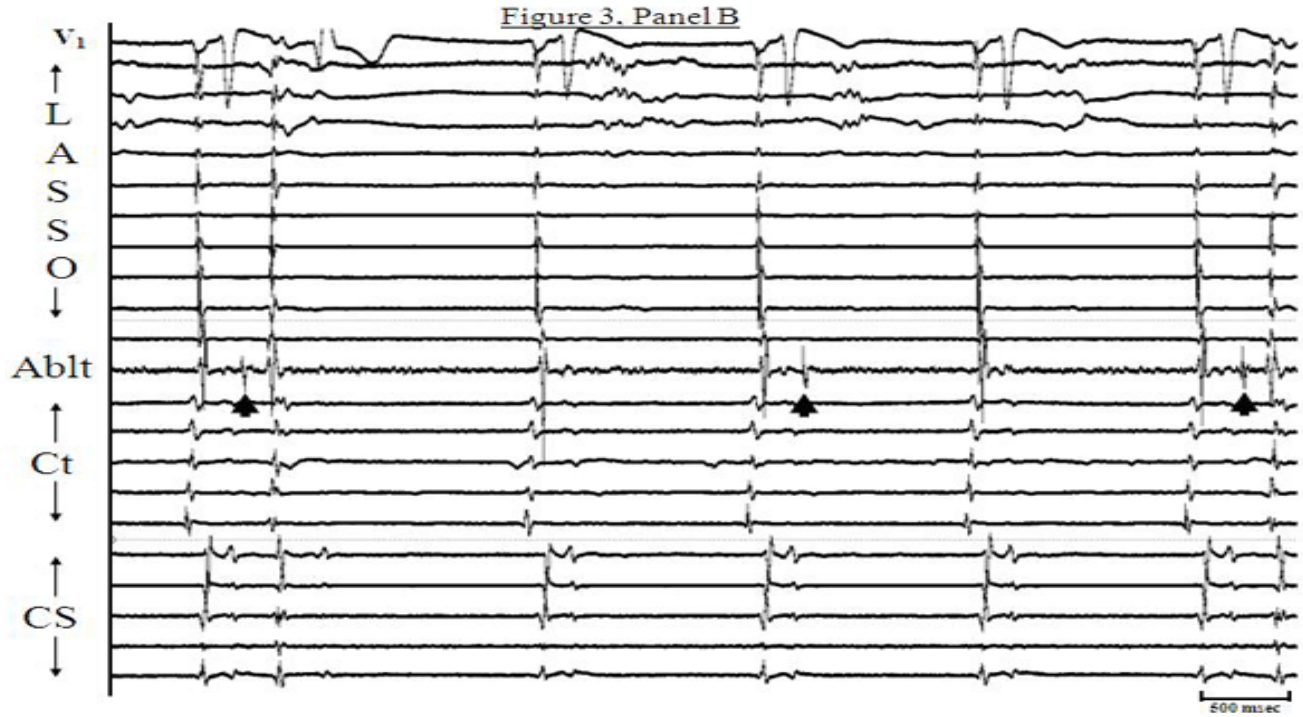


Figure 3, Panel B : Illustrates another pattern of sustained pulmonic vein firing (PVF). The arrangement of tracings are identical to Panel A. Discrete multiphasic electrograms (Egm) representing spontaneous PVF are seen on the bipole of ablation catheter (arrow heads) and do not correspond in timing with P, QRS, or T waves. In this case, PVF occurs after every two sinus beat, and so the pattern is trigeminal. It can be appreciated from the figure that the 1st and last PVF exit out of the vein, generating atrial premature complexes (APCs) with expected alteration of intracardiac activation patterns and surface P wave morphology.



rior right atrium at different cycle lengths (900 to 400ms; duration: 30 – 60 sec) following which, if PVF persisted, then in random order, isoproterenol and adenosine were administered and carotid sinus massage (CSM) was performed. PVF response was classified as: suppressed (complete quiescence during the maneuver; Figure 4, Panels A and B), augmented (increase in frequency of PVF / AF initiation; Figure 5, Panels A and B) and "no effect" [Figure 6]. In 13 pts (81%), PVF was suppressed during overdrive pacing with early recurrence (≤5seconds) post pacing regardless of the pacing cycle length in 11pts (85%). PVF was augmented by isoproterenol in the majority (88%), showed mixed response to adenosine (augmented-40%, suppressed-20 % and no effect-40%) and CSM appeared to have no effect on PVF. These observations suggest that PVF is unlikely due to sustained reentry and is more likely a result of triggered activity and / or abnormal automaticity.[20] Our observations on the mechanisms underlying PV triggers have been corroborated by the work of other investigators.[32] Based on these observations, we have developed a standardized stimulation protocol to elicit PV triggers for AF. Our stimulation protocol consists of 1) isoproterenol infusion (starting at 3-5 mcg and incrementing by 3-5 mcg every 3 minutes till a maximum of 20 mcg) and, 2) cardioversion of AF induced by LA or RA pacing (15-beat runs at amplitude of 10mA and pulse width of 2msec; decrementing by 10 msec from 250 msec to 180 msec and / or failure to capture with and without isoproterenol infusion).[33] We define arrhythmogenic PVs as veins that are documented to initiate AF and / or atrial premature complexes based on direct intracardiac recordings and / or activation sequences of multiploar catheters located in the posterior RA and coronary sinus mimicking PV pace maps.[12]

Is Isolation of Arrhythmogenic PVs Sufficient for the Long-Term Efficacy of AF Ablation?

Since its original description in 1998,[3] atrial fibrillation (AF) ablation procedure has undergone several modifications. Many operators performing AF ablation utilize an anatomical approach that involves creation of circumferential radiofrequency ablation (RFA) lesions encircling ipsilateral pulmo-

Figure 4, Panel A: Illustrates response of sustained pulmonic vein firing (PVF) to overdrive pacing. The arrangement of tracings are similar to figure 1 and decapolar circular mapping catheter (Lasso) is positioned at os of right superior pulmonic vein (RSPV). Following both the initial sinus beats, discrete multiphasic electrograms (Egm) representing spontaneous pulmonic vein PVF (open boxes) are seen on multiple bipoles of Lasso catheter and result in atrial premature complexes. Pacing is initiated from distal most bipole of CS catheter(interrupted line) and capture of both atria is achieved with the second pacing drive (arrow head). Almost immediately with capture of overdrive pacing no further PVF is seen for the rest of the recording. Such early PVF suppression (within 5 seconds) in response to overdrive pacing was observed in the majority of cases in our study.

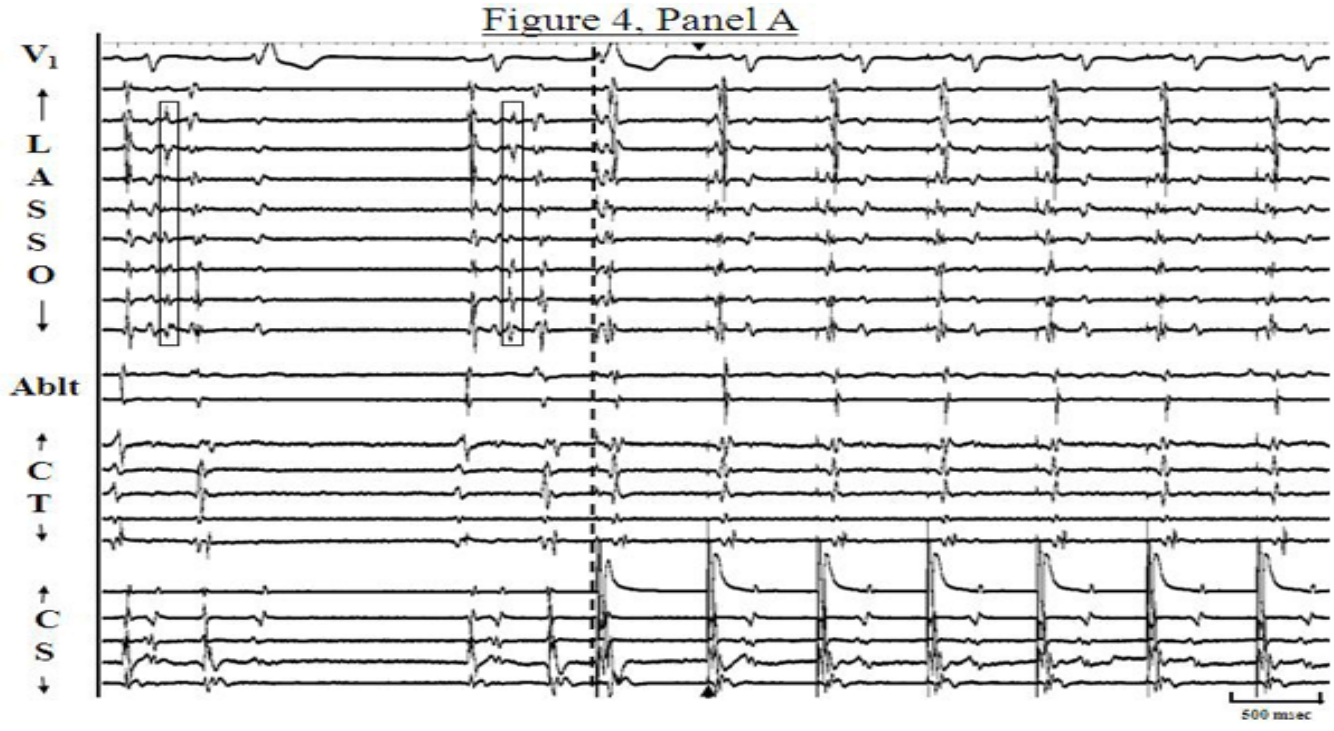
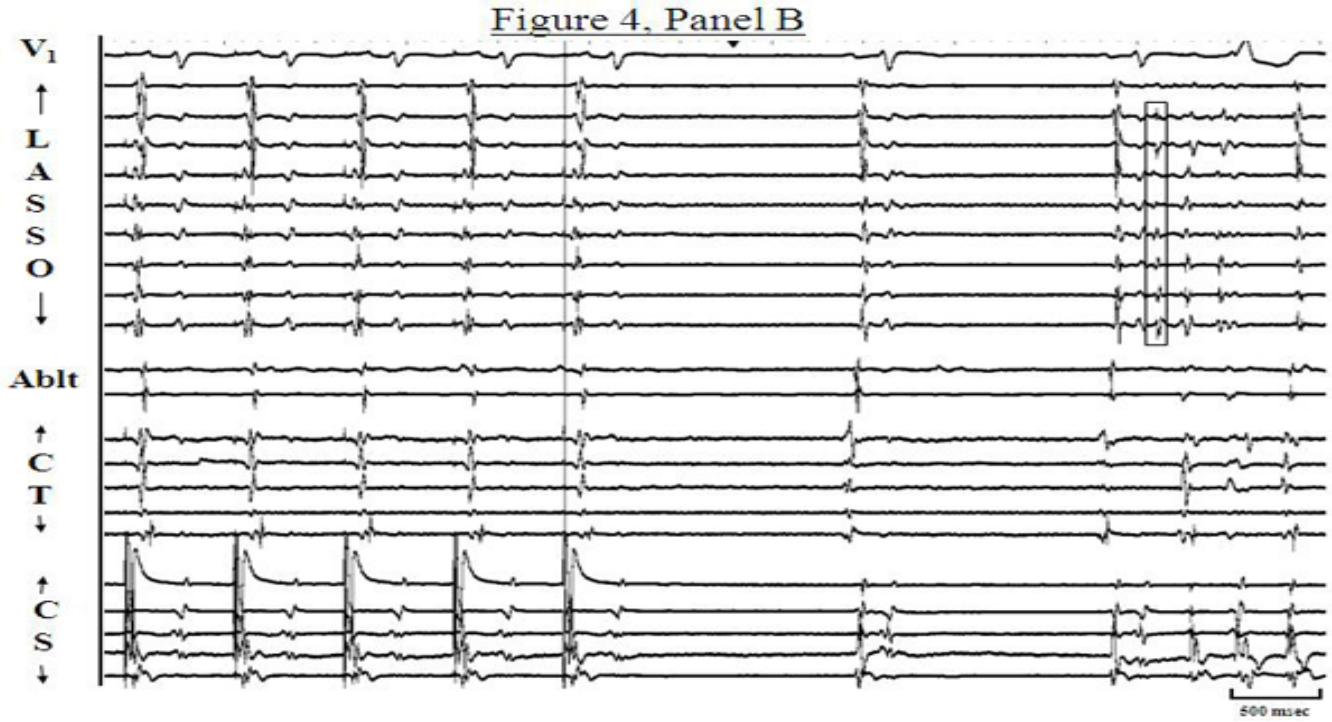


Figure 4, Panel B: Is the continuation of the example in Figure 1, Panel A (with identical arrangement of tracings) and represents termination of the 60-second pacing drive from the distal CS bipole (cycle length 600 msec). Recurrence of PVF post pacing (open box) is seen after the 2nd sinus beat and occurs within 5 seconds of pacing drive termination (early recurrence). This pattern of early PVF recurrence post pacing was a commonly observed response in our study.



nary veins (PVs) with or without additional left atrial (LA) linear lesions.[4-7, 14, 17, 18] Practitioners of this approach do not seek proof of PV "arrhythmogenecity" and may not consistently document isolation of the targeted veins. While this strategy has shown good AF control rates, it involves extensive LA ablation.[15, 17, 18] An alternative approach is to target only the arrhythmogenic PVs. This latter technique has not gained wide acceptance because PV triggers of AF can be evanescent and there is no established protocol which has been consistently shown to reproducibly elicit them. The advantage of this approach may be the ability to achieve AF control by limiting ablations to only the arrhythmogenic veins. We conducted a prospective, randomized study to, 1) assess the ability of our stimulation protocol to consistently identify arrhythmogenic PVs and, 2) compare the efficacy of isolating thus identified arrhythmogenic PVs versus empiric isolation of all PVs on long term control of AF.[34,35] The primary endpoint was the efficacy of either strategy in achieving long-term control of AF which, was defined as complete freedom and / or >90% reduction in AF burden either off or on previously ineffective antiarrhythmic drugs (AAD) at 1 year after a single ablation procedure. All patients with drug refractory AF undergoing their first ablation procedure were eligible to participate. Thus over a 20-month period 105 subjects were enrolled: 53 subjects to the all vein arm and 52 subjects to the arrhythmogenic vein arm. Using the stimulation protocol, PV triggers were reproducibly identified in all but one patient randomized to the arrhythmogenic PV arm based on which mean of 2.9±0.9 veins were isolated per patient in this arm [≤2 veins were isolated in 15 patients (29%), 3 veins were isolated in 21 patients (40%) and 4 veins were isolated in 16 patients (31%)]. Total procedure and fluoroscopy times (secondary end-points) showed a trend towards being longer in the all PV (327±97 minutes and 97±36 minutes, respectively) as compared with the arrhythmogenic PV arm (317±88 minutes and 85±33 minutes, p=0.57 and 0.14, respectively). As expected, time taken to elicit triggers was longer in the arrhythmogenic as compared to the all PV arm (50±23 minutes Vs 31±14 minutes; p<0.05). Other parameters to assess acute outcomes including PV isolation time, number of lesions delivered per vein and acute PV reconnection rates were comparable between the two groups (Table 1). Of the 105 subjects enrolled, 103 (98%) completed the one year follow-up visit. Long-term control of AF after a single ablation procedure (primary

Figure 5, Panel A: IIllustrates sustained pulmonic vein firing (PVF) at baseline seen as discrete multiphasic electrograms (Egm) on multiple poles of Lasso catheter (open boxes) positioned at os of left inferior pulmonary vein (LIPV). The arrangement of tracings areas in previous figures. PVF in this case does not exit out of the LIPV.

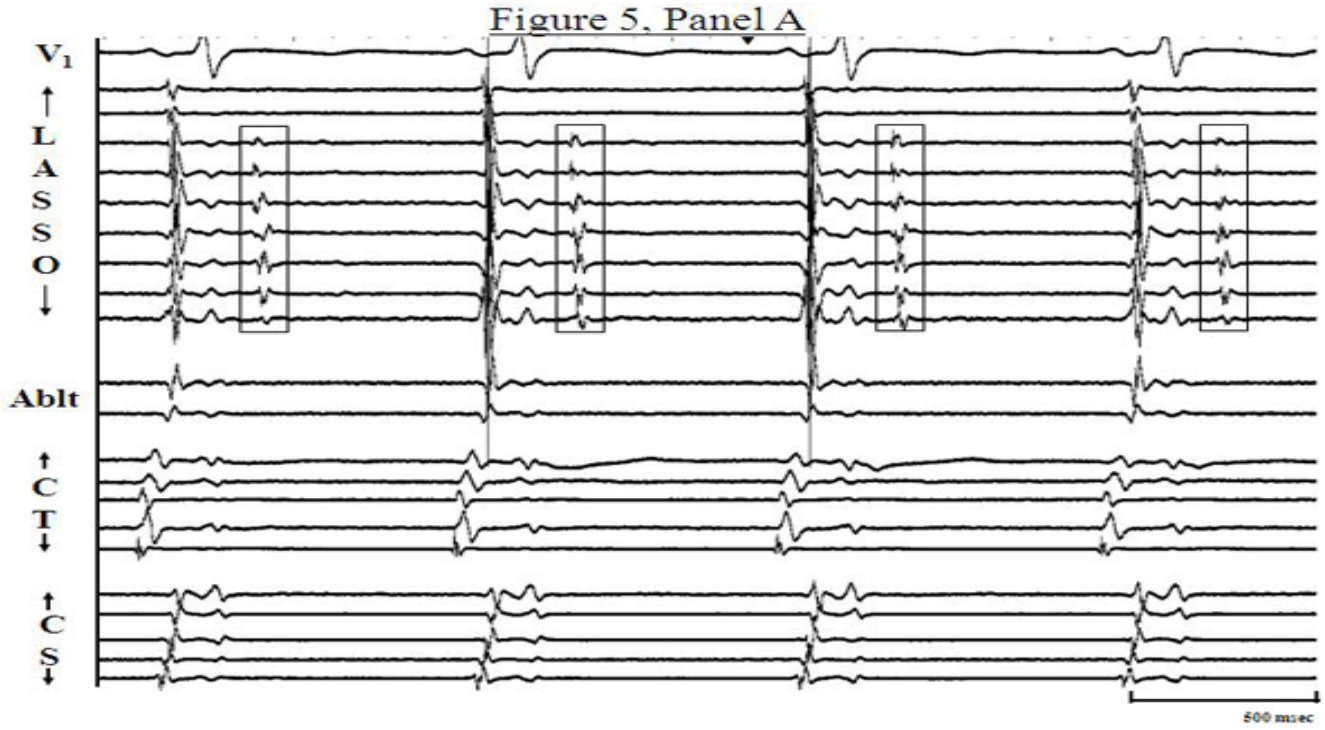
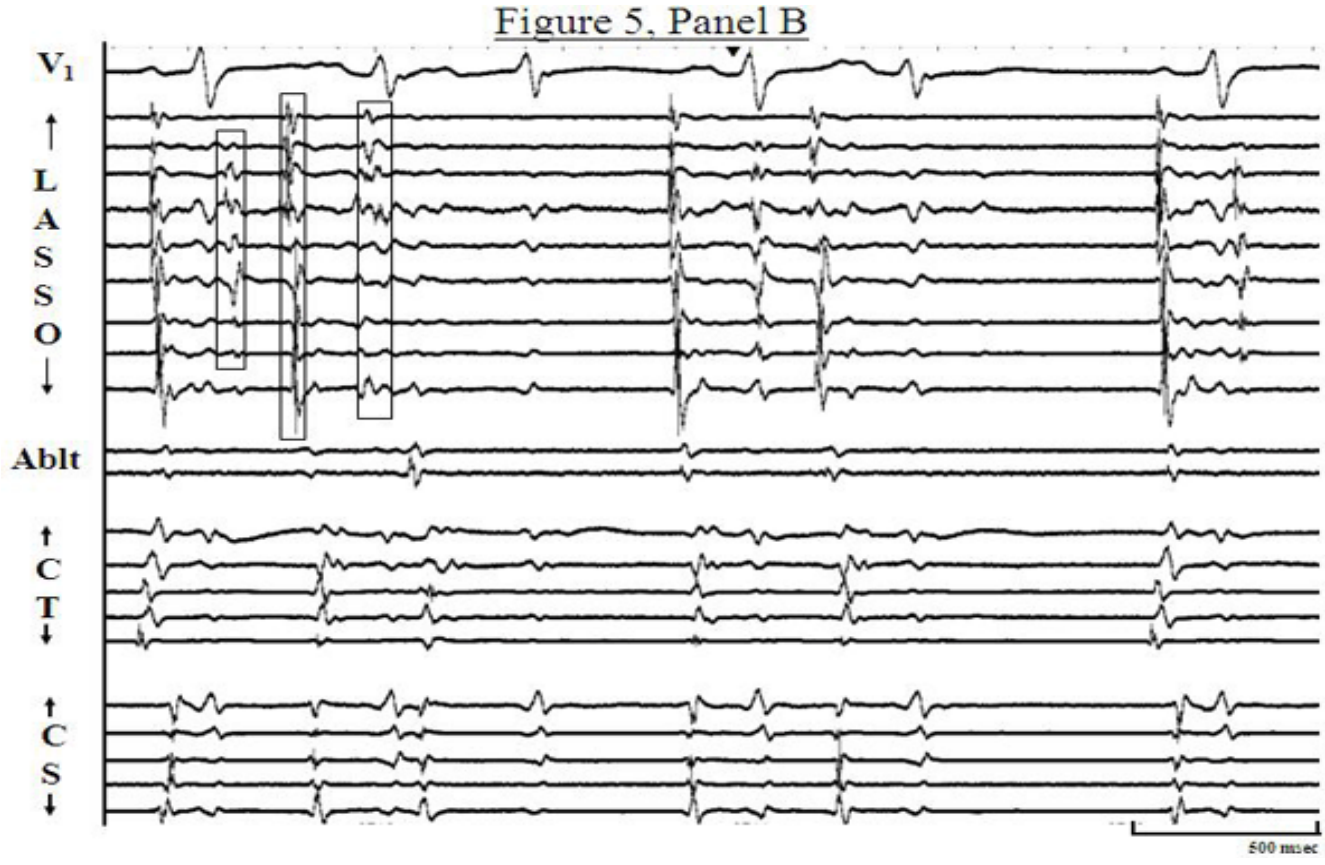


Figure 5, Panel B: This figure represents pulmonic vein firing (PVF) in the same patient as in Panel A. In response to isoproterenol, there is increase in the heart rate. Also evident is an increase in the frequency of PVF (multiple discrete electrograms on several bipoles of Lasso catheter – open boxes) with and without conduction out of the vein resulting in atrial premature complexes. This constitutes augmentation of sustained PVF in response to isoproterenol.



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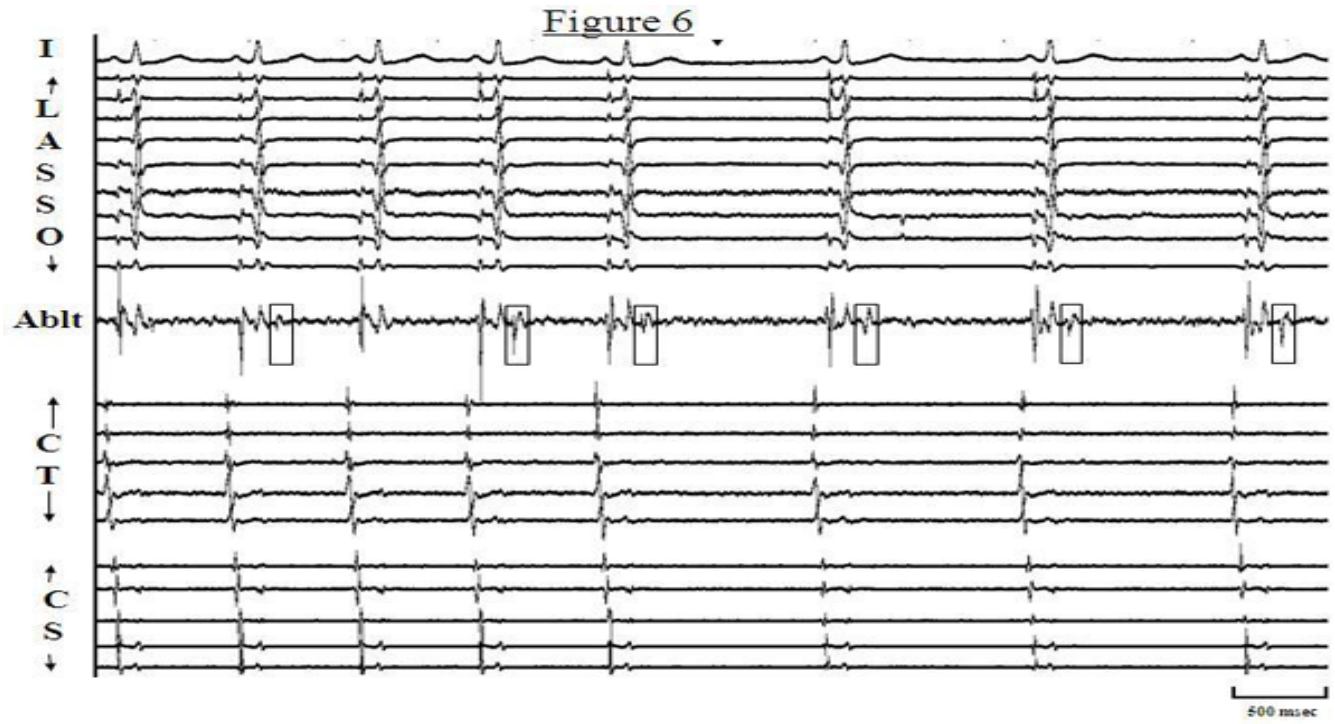

end-point) was achieved in 75 patients (73%) and was not different between patients randomized to undergo isolation of all versus arrhythmogenic veins [38 patients (75%) versus 37 patients (71%), respectively; OR 1.18; 95% CI 0.50, 2.83; p = 0.70; Table 2]. The secondary end point of freedom from AF at 1 year off AADs after a single procedure was achieved in 61 patients (59%) and was also not different between patients randomized to undergo isolation of all versus arrhythmogenic veins [30 patients (59%) versus 31 patients (61%), respectively; OR 1.03; 95% CI 0.47, 2.27; p = 0.935; Table 3]. Furthermore, long-term AF control and freedom from AF off AAD at 1 year after a single ablation procedure were comparable in patients who had all 4 veins isolated (72% and 58% respectively) versus those who had ≤3 veins isolated (75% and 61% respectively; p = 0.715 and 0.775 respectively). Serious adverse events were observed in 2 subjects (small right subcortical thromboembolic stroke and LA-esophageal fistula) who were both randomized to undergo isolation of all veins. Thus our study showed that in a mixed population of patients with predominantly paroxysmal AF, isolation of arrhythmogenic veins identified using a comprehensive stimulation protocol was as efficacious as empiric isolation of all veins in achieving long-term arrhythmia control after a single ablation procedure.[35]

Challenges to Identifying and Targeting Arrhythmogenic Pulmonary Veins

Although our randomized study supports the utility of a standardized stimulation protocol in successfully identifying arrhythmogenic PVs, there are several limitations inherent to this approach:

1. Performing the stimulation protocol can be tedious and timeconsuming.

2. Because the mechanisms underlying abnormalities of impulse formation, especially triggered activity can be evanescent, inability to demonstrate arrhythmogenicity does not necessarily exclude PV triggers of AF.

3. Mechanisms underlying PV triggers may not be consistent amongst the veins. Therefore after the initially identified arrhythmogenic PVs have been successfully isolated, repeat stimulation may be required to identify additional veins.

4. Since only a limited number of catheters are

Table 1 Comparison of acute outcomes between patients randomized to isolation of all versus arrhythmogenic veins. PV – Pulmonary vein; * p < 0.05

	All Veins (n = 53)	Arrhythmogenic Veins (n = 52)
Veins Isolated / Patient	4	2.9 ± 0.9
Procedure Time (minutes)	327 ± 93	317 ± 88
Total Fluoroscopy Time (minutes)	97 ± 36	85 ± 33
Time for Isolation of Veins (minutes)	50 ± 30	40 ± 23
Time to Elicit Triggers (minutes)	31 ± 14	50 ± 23*
Number of Lesions / Vein	17 ± 9	20 ± 10
Acute PV Reconnect	49 / 185 (26%)	39 / 129 (30%)

deployed in the LA, inability to sample all veins simultaneously may potentially preclude identification of an arrhythmogenic vein due to lack of direct recordings. To overcome this limitation, we have developed a methodology for using activation patterns of multipolar catheters in locations distant from the PVs which can help in localizing the culprit vein.[36,37] However, this may not be as definitive as direct catheter recordings of AF triggers from within the veins.

5. Despite our ability to successfully identify and isolate arrhythmogenic veins, in patients demonstrating arrhythmia recurrences subsequently, up to 40% of previously targeted PVs have been documented to reconnect in one or more segments.[38,39] Whether this is a limitation of the currently used energy sources or a reflection of the unique regenerative potential of PV musculature, remains to be answered. Nevertheless, in patients experiencing arrhythmia recurrences post AF ablation, on the repeat procedure in our experience, reisolating

Table 2 Unadjusted odds ratios for various factors vis-à-vis endpoint of freedom from AF at 1 year off AADs after single ablation procedure. Co-morbidities include hypertension, chronic pulmonary disease (obstructive or restrictive), diabetes and sleep apnea. AF – atrial fibrillation, AADs – antiarrhythmic drugs, CI – confidence interval

Predictor / Covariate	Freedom from AF at 1 year off AADs	Odds Ratio	95% C.I.	P-value
Ablation Strategy		1.03	(0.47, 2.27)	0.935
All Veins	30 (59%)			
Arrhythmogenic Veins	31 (60%)			
Gender		1.42	(0.54, 3.73)	0.476
Male	50 (61%)			
Female	11 (52%)			
Paroxysmal AF		2.53	(1.04, 6.10)	0.042
Yes	49 (65%)			
No	12 (43%)			
Number of Veins Isolated				0.816
≤ 2 Veins	10 / 15 (67%)	1.45	(0.46, 4.61)	0.527
≤ 3 Veins	22 / 36 (61%)	1.13	(0.49, 2.58)	0.775
4 Veins	39 / 67 (58%)	ref. group	ref. group	ref. group
Co-Morbidities		1.38	(0.56, 3.36)	0.481
Yes	31 (53%)			
No	30 (67%)			
Early AF Recurrence		0.04	(0.01, 0.20)	<0.001
Yes	2 (10%)			
No	57 (72%)			

Table 3 Unadjusted odds ratios for various factors vis-à-vis endpoint of long term AF control at 1 year after single ablation procedure. Co-morbidities include hypertension, chronic pulmonary disease (obstructive or restrictive), diabetes and sleep apnea. AF – atrial fibrillation, CI – confidence interval

Predictor / Covariate	Long-Term AF Control	Odds Ratio	95% C.I.	P-value
Ablation Strategy		1.18	(0.50, 2.83)	0.702
All Veins	38 (75%)			
Arrhythmogenic Veins	37 (71%)			
Gender		1.45	(0.52, 4.08)	0.479
Male	61 (74%)			
Female	14 (67%)			
Paroxysmal AF		2.76	(1.09, 7.01)	0.032
Yes	59 (79%)			
No	16 (57%)			
Number of Veins Isolated				Overall 0.919
≤ 2 Veins	11 / 15 (73%)	1.03	(0.30, 3.57)	0.961
≤ 3 Veins	27 / 36 (75%)	1.18	(0.47, 2.99)	0.715
4 Veins	48 / 67 (72%)	ref. group	ref. group	ref. group
Co-Morbidities		1.28	(0.53, 3.11)	0.582
Yes	41 (71%)			
No	34 (76%)			
Early AF Recurrence		0.14	(0.05, 0.42)	<0.001
Yes	8 (40%)			
No	65 (82%)			

the reconnected veins alone can achieve long-term AF control rates of ≥90%.[38] Thus, research efforts towards developing alternative energy sources that can achieve more lasting PV isolation may be worthwhile. Similarly, strategies that can better identify dormant PV conduction (adenosine infusion, etc) during the initial or redo ablation procedure may also be useful.[40,41]

Conclusions

From the above narrative, one may conclude that the PVs are arrhythmogenic by design. In our experience, PV triggers of AF can be reproducibly identified using a standardized stimulation protocol and targeting thus identified arrhythmogenic PVs alone can be sufficient in achieving long term arrhythmia control in the majority of patients with AF. If done correctly, the advantage of this limited approach to AF ablation is the potential for reducing procedure complications that may be associated with more extensive AF ablation strategies.

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