Is the Elimination of Triggers Sufficient? Current Controversies in Catheter Ablation of Persistent Atrial Fibrillation

Catheter Ablation for Persistent Atrial Fibrillation

Antral Pulmonary Vein Isolation and Elimination of Nonpulmonary Vein Triggers Are Sufficient

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Since its original description in 1998, the technique of catheter-based atrial fibrillation (AF) ablation has undergone several modifications. Currently, many operators use an anatomic approach consisting of circumferential lesions encircling individual or ipsilateral pulmonary veins (PVs) with additional empirical left atrial (LA) ablation (lines), whereas others perform a more PV-specific approach using entrance/exit block to validate isolation, deferring any additional non-PV lesions unless clinically indicated.2–7 Despite these differences in technique, the outcome data for AF patients undergoing ablation seem remarkably consistent between centers, with overall single procedure efficacy of ≥70% in achieving long-term arrhythmia control for patients with paroxysmal AF but significantly lower success rates for patients with persistent or long-standing persistent AF. These observations imply that the mechanisms underlying persistent/long-standing persistent AF may be different from paroxysmal AF. It has been posited that once in the persistent stage, the underlying substrate rather than triggers alone maintains this arrhythmia. Although this hypothesis remains to be proven, it has nevertheless resulted in the development of adjunctive substrate modification strategies for patients with more established forms of AF.8–11 Among the various substrate modification strategies currently being used, complex fractionated electrogram (CFE) ablation is the most popular. This technique was originally described by Nademanee et al,8 where by targeting CFEs exclusively these investigators were able to achieve long-term arrhythmia control after a single procedure in up to 70% of patients with persistent AF. However, subsequent attempts by other investigators have not yielded comparable results.12,13 Despite this inconsistency, many centers are targeting CFEs as a part of the ablation strategy in this group of patients. Contrary to this practice and regardless of the type of AF, our group at the Hospital of the University of Pennsylvania has consistently used an approach comprising pulmonary vein isolation (PVI) with additional targeting of non-PV trigger sites of AF that are identified by a standard stimulation protocol.14–24 Using this methodology, we have reported outcomes in patients with persistent and long-standing persistent AF, which are comparable with the results achieved by more extensive ablation strategies, including CFE ablation. The purpose of this review is to offer the readers our perspective on the importance of PVs in more established forms of AF and why targeting them (together with documented non-PV trigger sites) remains our preferred ablation strategy for this group of patients.

Response by Roten et al on p 1223

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
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(Circ Arrhythm Electrophysiol. 2012;5:1216-1223.)
Role of PV Triggers in Paroxysmal and Persistent AF

The observations made by Haïssaguerre et al1 on PV triggers of AF generated tremendous interest in understanding the mechanisms underlying these triggers. To that end, several studies have characterized the anatomy and electrophysiological properties of PVs.25–31 It has been consistently shown in both animal models and autopsied human hearts that PVs have a complex anatomy, especially where they merge into the LA.26–28 Finger-like projections of atrial musculature of varying lengths typically extend epicardially into the PVs.28,29 This results in a complex arrangement of anisotropic excitable myocardial tissue in relative isolation from the rest of the atrial syncytium, which can promote abnormalities of impulse formation (triggered activity, abnormal automaticity) and propagation (reentry).22,32 Both these mechanisms have been implicated in PV triggers. In their seminal study, Haïssaguerre et al attributed PV arrhythmogenicity to triggered automaticity. Other investigators have hypothesized microreentry as the potential mechanism underlying these triggers.27 Our own experience using a combination of pharmacological maneuvers and pacing interventions suggests that the mechanism underlying PV triggers can be both abnormal automaticity and afterdepolarization-mediated triggered activity.24 Based on these observations, we have developed a stimulation protocol for reproducibly eliciting PV and non-PV triggers. We tested the validity of our stimulation protocol in a prospective study where 103 subjects were randomized on a 1:1 basis to undergo isolation of all PVs (51 patients) versus arrhythmogenic PVs only (52 patients).3 Arrhythmogenic veins were identified using a protocol that consisted of (1) isoproterenol infusion (starting at 3 μg and incrementing every 2–3 minutes to 6, 12, and 20 μg), and (2) cardioversion of AF induced by LA or right atrial pacing (15-beat drive train at an amplitude of 10 mA and pulse width of 2 ms; decrementing by 10 ms from 250 ms to 180 ms and failure to capture with 5-second pause between drives). The primary study end point was long-term AF control (freedom or >90% reduction in AF burden off or on previously ineffective antiarrhythmic drugs at 1 year after a single ablation procedure) that was found to be similar in patients randomized to all versus arrhythmogenic PV arms (38 patients [75%] versus 37 patients [71%], respectively; odds ratio [OR], 1.18; 95% CI, 0.50–2.83; P=0.70). In the arrhythmogenic PV arm, our stimulation protocol identified AF triggers in ≤2 veins in 29% patients, 3 veins in 40% patients, and 4 veins in 31% patients, and this distribution was not different in subjects with paroxysmal versus persistent AF (30% of participating subjects). These observations suggest that PV arrhythmogenicity was the predominant mechanism underlying both paroxysmal and persistent forms of AF in our series, and it strongly supports the specificity of our protocol for identifying true arrhythmogenic veins. In fact, in our AF ablation experience of over a decade,5,14–24 despite the evolving population (older subjects with persistent/long-standing persistent AF manifesting more comorbidities and larger atria),18 the distribution of PV and non-PV triggers for AF has remained relatively similar between our early and more current experience. Importantly, over this extended time frame, using the aforementioned stimulation protocol we have been able to reproducibly identify PV triggers in 55% and non-PV triggers in 20% of the patients with persistent and long persistent AF, which is comparable with what we have found in patients with paroxysmal AF (PV triggers in 70%, non-PV triggers in 18%).36 Furthermore, in both groups of patients (paroxysmal and persistent AF) who have undergone repeat ablation (for arrhythmia recurrences), reconnection of ≥1 previously isolated veins has been observed in all (≥99%), and reisolating these (with ablation of documented non-PV triggers in a minority) has translated into long-term arrhythmia control rates of >80% in patients with persistent and long-standing persistent AF.37,38 These observations suggest that PVs play an important role in the etiopathogenesis of persistent and long-standing persistent AF.

Single Procedure Efficacy of Ablation in Patients With Persistent AF: Is More Better?

In the previously mentioned prospective randomized study, where we compared efficacy of isolating all versus arrhythmogenic PVs among the covariates analyzed to assess their impact on single procedure efficacy, the presence of persistent AF and early recurrence of AF (within 6 weeks of initial ablation) were the only variables associated with late AF recurrence.2 Late AF recurrence was more likely to occur in patients with persistent AF (43% versus 21% for patients with paroxysmal AF; OR, 2.76; 95% CI, 1.09–7.01; P=0.032) and those experiencing early recurrence of AF (60% versus 18% not experiencing early recurrence of AF; OR, 0.14; 95% CI, 0.05–0.42; P<0.001). In our subsequent larger observational experience involving >1700 patients, we have found similar higher long-term AF recurrence after the initial ablation procedure in patients with persistent AF. However, in these patients after the second ablation attempt (targeting reconnected PVs mostly), long-term AF control rates comparable with the paroxysmal AF group (79% versus 86%, respectively; P=NS) were achieved.37,38 Thus, in our experience, compared with the paroxysmal AF group, more patients with persistent/long-standing persistent AF needed repeat procedures (31% versus 21%; P<0.05) to achieve comparable long-term outcomes. This is consistent with the observations of other investigators who have reported similar lower single procedure efficacy rates in persistent AF patients.10,13,39,40 Thus, there is a concerted effort to modify the current approach to enhance single procedure efficacy of ablation in patients with persistent and long-standing persistent AF. To this end, many investigators have pursued strategies that are targeted toward the underlying substrate. These include empirical linear lesions across potential reentrant channels, targeting of CFEs, ablating ganglionated plexi or AF nests, and so on.5,13,41–43 CFE ablation, which was first described by Nademanee et al,5 is currently the most popular substrate modification strategy. In their seminal observations, these investigators were able to achieve long-term arrhythmia control after a single procedure in up to 70% patients with
persistent AF by targeting CFEs exclusively. However, comparable results have not been achieved by other investigators.12,13,42 A potential explanation for this discrepancy may have been inconsistency in subjective interpretation of CFE signals which can be operator-dependent. To overcome this limitation, automated computerized algorithms have been developed, which can more objectively identify CFEs. The accuracy and reproducibility of these algorithms have been previously validated.13,44–46 Studies have also assessed the efficacy of the computerized algorithm-guided CFE ablation on long-term AF control. However, the limitations of these studies include small sample size, short follow-up duration, combination of CFE ablation with other substrate-modifying strategies, heterogeneous AF type, and so on.8–13,42,45,46 To overcome these limitations, we designed a prospective randomized study to assess the efficacy of CFE ablation for enhancing single procedure efficacy beyond PVI in an exclusive group of patients with persistent and long-standing persistent AF.47 We also sought to compare this approach with a new ablation strategy of empirically targeting common non-PV trigger sites of AF. The latter strategy was based on our center’s experience of documenting certain common anatomic regions that typically harbor non-PV AF triggers.48 We hypothesized that additional lesions beyond PVI, whether at CFE locations or non-PV AF trigger sites, should enhance the single procedure efficacy of AF ablation in patients with persistent AF. Over a 32-month period (October 2006 to June 2009), 156 patients with persistent (n=117; 75%) or long-standing persistent AF (n=39; 25%) participated in the study. Fifty-five subjects were randomized to the standard approach (PVI+ablation of documented non-PV triggers identified by a standard stimulation protocol; arm 1), 50 subjects to standard approach+empirical ablation at common non-PV trigger sites (arm 2), and 51 subjects to standard approach+LA CFE ablation (arm 3). The average age of the population was 58±9 years (men=136; 87%), and the mean AF duration was 47±50 months. It required a mean of 152±64 minutes to achieve PVI, and this was comparable in the 3 groups (P=0.367). Acute PV reconnection was observed in 54 patients, and this was equally distributed in the 3 study arms (P=0.243). In arm 2, non-PV locations were targeted by a mean of 33±10 lesions over 59±24 minutes. In arm 3, a median of 3 LA CFE locations (appendage region, anterior wall, roof, septum, and the mitral annular region) were targeted with a mean of 22±9 lesions over 38±21 minutes. AF termination to sinus rhythm and organized atrial tachyarrhythmias were infrequently observed in our study (n=5,3%) and were not significantly different in the 3 arms (4% in arm 1, 0 in arm 2, and 6% in arm 3; P=0.238). Freedom from atrial arrhythmias at 1 year after a single ablation procedure (primary study end point) was achieved in 71 patients (46%), and this was significantly worse in arm 3 (29%) compared with arm 1 (49%; P=0.040) and arm 2 (58%; P=0.004). Arrhythmia control at 1 year after single ablation procedure (secondary study end point) was achieved in 92 patients (59%), and this too was significantly worse in arm 3 (43%) compared with arm 1 (64%; P=0.036) and arm 2 (70%; P=0.003). Comparing outcomes between arm 1 and arm 2, the latter (standard strategy+empirical ablation at common non-PV trigger sites) did show 22% higher odds of achieving freedom from atrial arrhythmias and 33% higher odds of achieving arrhythmia control at 1 year compared with the standard ablation strategy. These, however, were not statistically significant, but this may be because our study was not powered to find such ORs between groups. Early occurrence of atrial arrhythmias (OR, 4.5; 95% CI, 2.0–10.0; P<0.001) and randomization to arm 3 (OR, 4.2; 95% CI, 1.5–12.0; P=0.007) were the only independent predictors of lack of freedom from AF at 1 year after a single ablation procedure.47 These data suggest that in patients with persistent or long-standing persistent AF additional substrate modification beyond PVI and ablation of documented non-PV trigger sites, especially LA CFE ablation does not improve single procedure efficacy. Of note, 57 patients from this series (37%) underwent ≥1 repeat ablation for arrhythmia recurrence beyond the initial 6 weeks after the first procedure. Fifteen patients (27%) were originally randomized to arm 1, 17 patients (34%) were randomized to arm 2, and 25 patients (49%) were randomized to arm 3 (P=0.061). At least 1 PV demonstrated reconnection in all patients, and ≥3 PVs were reconnected in the majority (75.9%). Reisolating these veins without additional empirical lesions and CFE ablation resulted in long-term (follow-up duration: 22±9 months [19±9 months from the last ablation]) arrhythmia control in 126 patients (81%; arm 1, 80%; arm 2, 82%; arm 3, 80%; P=0.96).47 These observations suggest that in the persistent and long-standing persistent AF population, durable PVI (with ablation of documented non-PV triggers) and not additional substrate modification may be of primary importance in improving procedure efficacy. In a recent observational analysis of 130 patients from our center, all with long-standing persistent AF who underwent antral PVI with additional ablation of documented non-PV trigger sites (our standard ablation approach), over a mean follow-up of 39 months with ≥1 ablation, 52% of patients maintained sinus rhythm off antiarrhythmic drug therapy and an additional 20% of subjects were in sinus rhythm on antiarrhythmic drugs.38 Similar to our prior observations, in this group of patients, at the time of repeat ablation (28%) for arrhythmia recurrences, previously targeted veins had reconnected in all, and reisolating them alone in the majority translated into long-term arrhythmia control rates of 72%, which is comparable with what has been reported by investigators who have used more extensive substrate-modifying strategies. Thus, similar to our experience in the persistent AF group, durable PVI also seems to be critical for improving ablation outcome in patients with long-standing persistent AF.

Additional Benefits of Antral PV Isolation

Pulmonary vein isolation was developed to isolate PV triggers of AF from the rest of the atria without targeting the actual trigger site within the vein.2–5 Although this still remains the primary purpose of the approach, evolution in the technique (antral PV ablation) has resulted in deployment of lesions over
A wider area, which not uncommonly includes the LA posterior wall, posterior septum, and portions of the roof, as a result, more LA tissue is now being targeted during antral PVI than what was accomplished with segmental PVI. The obvious benefit of this extended ablation strategy is that it incorporates sites in the posterior wall, septal region, and the LA roof, which have often been shown to be the source of non-PV triggers of AF. This may be one reason why antral PVI has shown better long-term outcomes than segmental PVI. It has also been noted that when ablating near the roof bordering the superior veins (both left and right) as well as the septum adjoining the right veins, significant bradycardia can occur. Yet another benefit of this extended ablation strategy is that it incorporates more LA tissue during antral PVI than what was accomplished with segmental PVI. The obvious result, more LA tissue is now being targeted during antral PVI and these lesions may also alter the cardiac autonomic input. Such autonomic alterations have been observed in the process of achieving PVI, these lesions may also alter the underlying AF substrate. It has also been noted that when ablating near the roof bordering the superior veins (both left and right) as well as the septum adjoining the right veins, significant bradycardia can occur. The likely reason for this phenomenon is that the antral PVI lesion set can extend to LA regions that are in proximity to ganglionated plexi (anterior LA roof, inferoposterior LA, LA appendage ridge area, anterior location near septum). Thus, in the process of achieving PVI, these lesions may also alter the cardiac autonomic input. Such autonomic alterations have been shown to be beneficial in achieving long-term AF control beyond PVI. Yet another benefit of antral PVI may be inadvertent substrate modification. In a prospective study, we compared CFE maps acquired before and after antral PVI in 22 patients with persistent AF. At baseline, CFE was noted over 47% of the LA surface. However, after antral PVI, the CFE distribution diminished significantly (to 23%; \( P < 0.01 \)), and this attenuation was noted both in the PV region (50% versus 6%; \( P < 0.01 \)) and in the non-PV regions (61% versus 39%; \( P < 0.01 \)). In this study, antral PVI was also associated with an increase in the AF cycle length (144 ms pre-PVI versus 214 ms post-PVI; \( P < 0.01 \)). Consistent with these observations, circumferential PV ablation has been shown by other investigators to alter spectral characteristics of AF and attenuate the distribution of LA dominant frequencies. The mechanism underlying this observation may be PVI-induced alteration in AF propagation and modification of the underlying AF substrate. It has also been noted that in patients with persistent AF undergoing PVI alone, subsequent arrhythmia recurrences are usually paroxysmal. This suggests a beneficial effect of PVI on atrial remodeling. It, however, remains unclear whether this remodeling is because of successful isolation of triggers or modification of the underlying substrate. One explanation for alteration in the nature of AF after antral PVI may pertain to LA compartmentalization. Prior work on Langendorff-perfused whole animal heart models has demonstrated that spatiotemporally stable LA rotors underlie most AF episodes and these rotors require elbow room to persist. It has recently been proposed that rotors may also underlie human AF. If rotors in human AF are similar to what has been observed in animal models, then antral PVI by reducing the LA real estate could potentially reduce duration of rotors, which could account for change in the nature of AF recurrence (from persistent to paroxysmal). This may also explain why empirical ablation at common non-PV trigger sites further improved outcomes beyond PVI as observed in our randomized study assessing efficacy of different ablation strategies in an exclusive group of patients with persistent and long-standing persistent AF. It has been recently shown that electric rotors and focal impulse sources can be clinically mapped and ablated to terminate AF in patients. Some of the locations where these sources were found (septum near mitral annular region) seem to be in vicinity of common non-PV trigger sites. This may be another reason why targeting these locations empirically yielded better outcomes than PVI alone in our series. However, we cannot comment on whether targeting these locations without performing PVI would have been as effective. An alternative explanation for change in nature of AF after PVI is that the latter reverses progression of unfavorable atrial electric remodeling (maladaptation of atrial refractory periods which has been posited to be the mechanism underlying, AF begets AF). However, in the event that the arrhythmogenic veins reconnect after initial ablation, PV triggers of AF can reestablish. Our observations on nearly universal PV reconnectivity seen during repeat ablation suggest that this indeed may be the case. Initially, as the PV triggers reestablish, AF recurrences may be paroxysmal in patients with previously persistent or long-standing persistent AF. However, because the underlying atrial remodeling may not have completely reversed, if the reestablished PV triggers are not interrupted, AF may rapidly progress in these electrically primed atria to the persistent state. Thus, one possible way to enhance long-term AF control in patients with persistent and long-standing persistent AF may be to intervene early in the event of arrhythmia recurrence after the initial procedure. However, a potential downside to early intervention is that some veins may artificially appear disconnected as a result of edema from the recent prior ablation procedure.

Achieving Persistent PV Isolation

The above narrative suggests that in persistent and long-standing persistent AF patients, there is a cause-effect relationship between reestablishment of PV reconnectivity and arrhythmia recurrences. Thus, achieving lasting PVI may be the key to improving efficacy of the AF ablation procedure in this group of patients. To that end, \( \geq 1 \) of the following steps, in our opinion, may be helpful:

1. Achieving exit block in addition to entry block: this can be accomplished by pacing around the circumference of the ablated PV ostia. We have previously shown that despite achieving entry block, PV exit can still be seen in up to \( \approx 20\% \) of the veins.
2. Excluding acute PV reconnection: this can be achieved by reassessing the targeted veins for entry/exit block \( \geq 20 \) minutes after achieving initial PVI. We have found that PV reconnection can occur acutely in up to \( 41\% \) of veins.
3. Assessing for dormant PV conduction after achieving PVI: this can be provoked by intravenous adenosine which has been shown to unmask dormant PV conduction in both animal models and humans.
4. Targeting the carina region during PVI: we have found PV carina to be a frequent source of AF triggers, as well as the region where reconnection most frequently occurs. However, meticulous effort should be made to identify and avoid ablating recessed carina because this may enhance the subsequent risk of PV stenosis.

5. Creating more effective radiofrequency (RF) lesions: this may be facilitated by using steerable sheath (to optimize catheter-tissue interface) and high-frequency jet ventilation (to minimize movement). We have shown that incorporating these 2 modalities can decrease procedure duration and enhance long-term outcomes in patients undergoing AF ablation.

6. Alternative energy sources/ablation platforms: there continues to be tremendous interest within the electrophysiology community for alternative energy sources and delivery platforms that may achieve lasting PVI more efficiently than point-by-point RF lesion creation. However, at the present time, none of the alternatives (cryothermy, laser, high-frequency ultrasound, unipolar RF energy, etc) has shown significant benefits over conventional bipolar RF ablation.

**Conclusion**

Compared with paroxysmal AF, the single procedure efficacy of catheter-based RF ablation remains lower in patients with persistent and long-standing persistent AF. Although the reasons for this discrepancy remain unclear, many investigators are using extensive substrate-modifying strategies in patients with more established forms of AF. Contrary to this practice, our group continues to use a more limited ablation strategy targeting PVs with additional ablation of only documented non-PV triggers in all patients undergoing AF ablation at our center. Using this approach, we have shown long-term outcomes in patients with persistent and long-standing persistent AF that are comparable with the results achieved by more extensive ablation strategies with a lower incidence of iatrogenic LA flutters. We have also consistently found that in patients with persistent and long-standing persistent AF who experience arrhythmia recurrences after initial ablation, previously isolated veins are universally reconnected, and targeting these alone in the majority translates into subsequent improved outcomes. These observations suggest that durable PVI may be the key to improving single procedure efficacy of the ablation procedure in patients with persistent and long-standing persistent AF. Only after durable PVI is achieved on a routine basis, we will be able to decipher what else needs to be ablated beyond provoked non-PV triggers initiating AF. Even as the quest for the Holy Grail to unmask the mechanism underlying AF perpetuation continues, we are convinced that the approach to identify best lesion set beyond PVI by targeting new locations outside the PV antral region without a consistently reproducible end point has not been a compelling strategy. Hence, we as group remain focused on techniques to achieve durable PVI and reproducibly provoke reliable non-PV triggers that warrant targeting.

**Sources of Funding**

This work was supported by the F. Harlan Batrus Research Fund and the Susan and Murray Bloom Research Fund.

**Disclosures**

None.

**References**


Response to Sanjay Dixit, MD, David Lin, MD, David S. Frankel, MD, and Francis E. Marchlinski, MD

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Dixit et al have provided us with an elaborate review on the rationale, methods, and results of a trigger-ablation strategy for persistent atrial fibrillation (AF) ablation. They conclude that ablation of triggers is sufficient for persistent AF. We agree that if triggers are present in persistent AF, these should be ablated. Most triggers in paroxysmal or persistent AF are located in the pulmonary veins, and we also agree that every possible effort should be made to achieve persistent pulmonary vein isolation.

However, there are some flaws in their rationale, and important limitations of the trigger-ablation strategy are not mentioned. For example, they state that the percentage of patients in whom they identified pulmonary vein and nonpulmonary vein triggers and number of veins harboring a trigger were not different in paroxysmal and persistent AF. They conclude that this suggests pulmonary vein arrhythmogenicity as the predominant mechanism underlying both forms of AF. However, if trigger ablation suffices, the success rate also should be the same for both forms. We all know that this is not the case, and in our opinion the rationale mentioned above suggests the opposite: pulmonary vein arrhythmogenicity may indeed be present in persistent AF, but other factors are responsible for AF maintenance.

Even with the most sophisticated trigger-ablation protocols, no triggers can be awaken in a considerable proportion of patients with paroxysmal or persistent AF. But on the contrary, no one would conclude from this that pulmonary vein arrhythmogenicity is not important. The opposing group also has reported that during repeat procedures one third of triggers were found in pulmonary veins in whom initially no triggers were found, raising questions on the sensitivity of trigger-ablation protocols.

The only randomized controlled trial comparing a trigger-ablation strategy to pulmonary vein isolation and additional substrate ablation is the Randomized Ablation Strategies for the Treatment of persistent Atrial fibrillation (RASTA) study. As we have already pointed out, the significance of this single-center study is impaired by severe limitations that we do not want to iteritate here. The other study by Lin et al mentioned by the opposing group was observational and no definite conclusion can be drawn by indirect comparisons.

Dixit et al also argue for antral instead of ostial pulmonary vein isolation and object that this region might be an important site of nonpulmonary vein triggers. Given the fact that nonpulmonary vein triggers are rarely identified in persistent AF, it is much more probable that the superiority of antral ablation is the result of concomitant substrate modification.

Studies analyzing the benefit of additional substrate ablation after pulmonary vein isolation compared with pulmonary vein isolation alone are not consistently in favor of additional substrate ablation, but many are. Multiple reasons might account for these inconsistencies, among which different ablation protocols, patient selection, mode of follow-up, and operator skills might be the most important ones. Clearly, further understanding of the mechanisms responsible for AF maintenance is required to allow for tailored substrate ablation. With noninvasive ECG imaging and computational mapping as used in the Conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation (CONFIRM) trial, such tools are on the verge. And these might help to clarify whether persistent AF is mainly a disease of triggers or substrate, rendering the current debate obsolete.
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Circ Arrhythm Electrophysiol. 2012;5:1216-1223
doi: 10.1161/CIRCEP.111.970343

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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