A new era of atrial fibrillation (AF) treatment began in 1997–1998 with the discovery that triggers within the pulmonary veins initiate AF and reports that elimination of these triggers is successful in treating AF in its paroxysmal form. However, in patients with persistent AF, the success rate of exclusive pulmonary vein isolation is substantially lower. To improve the outcome of persistent AF ablation, different ablation strategies have been explored, but to date the optimal strategy has not been defined. Although some groups argue that limited ablation, including pulmonary vein isolation and, if present, ablation of nonpulmonary vein triggers, is sufficient for persistent AF ablation, other groups, including ours, favor more extensive, substrate-based ablation in addition to pulmonary vein isolation.

In this review, we will discuss the rationale for a substrate-based ablation strategy to treat persistent AF and show why elimination of triggers is not sufficient in most patients with persistent AF.

Response by Roten et al on p 1232

Definition of Triggers and Substrate in Persistent AF

In a simple model, an electric impulse in AF can form because of abnormalities in impulse generation (triggers) or can result from abnormal impulse propagation (reentry). By a strict definition, a trigger is a focal source of new impulse generation. The mechanism by which a new impulse can form is either abnormal automaticity or triggered activity. Trigger-ablation protocols target these sources of new impulse generation.

Abnormal impulse propagation, on the other hand, depends on altered substrate properties causing nonuniform or slowed conduction. This in turn causes multiple forms of wave reentry thought to be responsible for AF perpetuation: random reentry (multiple wavelets), macro- and microreentry, or functional reentry (rotors). Substrate-based ablation strategies aim to abate abnormal impulse propagation and interrupt any form of atrial reentry.

Trigger Ablation in Persistent AF

Triggers of paroxysmal AF are mainly located in the pulmonary veins. In persistent AF, if triggers are specifically searched before ablation, most of them are also situated in the pulmonary veins. Results from pharmacological and electrophysiological studies in animals and humans have yielded conflicting results regarding the mechanism of pulmonary vein firing. There is evidence for enhanced automaticity and triggered activity, as well as microreentry to all be involved in impulse generation within the pulmonary veins. However, because initiation of a reentrant circuit is dependent on a premature stimulation, either triggered activity or enhanced automaticity is likely involved in pulmonary vein firing and probably all mechanisms work in combination.
the pulmonary veins, focal discharges initiating AF have been witnessed from within the superior vena cava, the vein of Marshall, and the coronary sinus.\textsuperscript{17–20} These triggers probably act through similar mechanisms as in the pulmonary veins.

Trigger-ablation protocols of persistent AF generally involve repeat cardioversion and isoproterenol infusion or burst pacing to awaken the triggers.\textsuperscript{1,8,11} Once a trigger is identified, it has to be mapped and ablated. This can be very challenging, especially when multiple triggers are present. In a recent study, Inoue et al\textsuperscript{10} were able to ablate only 30\% of nonpulmonary vein triggers because of the difficulties in localizing them. Furthermore, the ability of trigger-ablation protocols to identify all relevant triggers remains questionable. For example, in early studies involving paroxysmal AF patients, only pulmonary veins harboring triggers were isolated. During repeat procedures and using the same protocol, 1 study reported that 32\% of the triggers were located in pulmonary veins in which no trigger was found during the index procedure.\textsuperscript{21} We can speculate that nonpulmonary vein triggers will not behave differently. Finally, in up to 91\% of persistent AF patients no extrapulmonary vein triggers are detected.\textsuperscript{10,22,23} To the best of our knowledge, the only study that directly compared trigger elimination with substrate ablation is the RASTA study. In this study, Dixit et al\textsuperscript{24} compared 3 ablation strategies in 156 patients: (1) circumferential pulmonary vein isolation plus ablation of nonpulmonary vein triggers (standard approach); (2) standard approach plus empirical ablation at common nonpulmonary vein trigger sites; and (3) standard approach plus complex fractionated atrial electrogram (CFAE) ablation. Single procedure success in group 3 was significantly worse than in the 2 other groups, whereas arrhythmia-free outcome off antiarrhythmic drugs after repeat procedures in 37\% of patients was not different between the groups (53\%, 62\%, and 51\%, respectively; \(P=0.49\)). Interestingly, in group 2 the duration of nonpulmonary vein ablation was significantly higher compared with group 3 (59 versus 38 minutes). Furthermore, the rate of AF termination during ablation was only 6\% in group 3, which is exceptionally low for a study involving CFAE ablation. And finally, the authors themselves questioned their determination to accurately isolate the pulmonary veins in group 3. These limitations severely impair the validity of the study regarding the benefit of trigger ablation in persistent AF. Besides, empirical ablation at presumed trigger sites as performed in the RASTA study (group 2) would probably be labeled substrate ablation by most operators.

Inoue et al\textsuperscript{10} observed reproducible, immediate recurrences of AF after cardioversion at the beginning of the procedure in 27\% of 263 persistent AF patients. Importantly, triggers reinitiating AF were located within the pulmonary veins in 22\% of patients and outside in 9\% with some patients having multiple triggers. After elimination of all pulmonary vein triggers and 30\% of nonpulmonary vein triggers, patients in whom all triggers had been ablated had significantly better arrhythmia-free outcome than the patients in whom triggers were found but could not be ablated. This study reinforces the idea that in persistent AF triggers are infrequent, mainly located in the pulmonary veins and of course should be ablated if present.

In a retrospective study, Lin et al\textsuperscript{25} reported on antral pulmonary vein isolation and additional nonpulmonary vein trigger ablation in 130 patients with long-standing persistent AF. They elicited 40 nonpulmonary vein triggers in 19\% of patients either during the initial or repeat procedure. Only 50\% of the patients remained in sinus rhythm off antiarrhythmic drugs after a mean follow-up of 39 months and repeat procedures in 28\% of patients. Unfortunately, this study had no control group of additional substrate ablation.

In the studies mentioned above, nonpulmonary vein triggers were identified only in a limited proportion of patients and were successfully eliminated in an even smaller proportion. Therefore, a trigger-ablation strategy is limited to exclusive pulmonary vein isolation in most persistent AF patients. However, there is now abundant evidence that exclusive pulmonary vein isolation in persistent AF has a low success rate, and this therefore questions the rationale of a strategy targeting only the triggers in persistent AF.\textsuperscript{4,5,25}

To date, 3 studies randomized persistent AF patients to either circumferential or segmental pulmonary vein isolation.\textsuperscript{26–28} These studies consistently found better arrhythmia-free outcome with circumferential pulmonary vein isolation. Triggers in persistent AF are mainly located within the pulmonary veins or the carina zones, and nonpulmonary vein triggers do not cluster in the antral region of the veins.\textsuperscript{8,11} Furthermore, circumferential pulmonary vein ablation targets a region of important substrate in persistent AF.\textsuperscript{29} Therefore, the superiority of

| Table. Pros and Cons of Trigger Ablation and Substrate Ablation Using the Stepwise Approach |
|-----------------------------------------------|-----------------------------------------------|
| Trigger ablation                             | Limited ablation                              |
|                                               | Atrial tachycardia rare                       | Repeat cardioversions necessary               |
|                                               |                                               | Reliability of trigger induction uncertain    |
|                                               |                                               | Mapping and ablation of nonpulmonary vein triggers difficult |
|                                               |                                               | Most triggers confined to pulmonary veins     |
|                                               |                                               | Multiple triggers may be present              |
|                                               |                                               | Low success rate                             |
|                                               |                                               | Extensive ablation                           |
|                                               |                                               | Atrial tachycardia frequent                  |
| Substrate ablation (stepwise approach)        | High success rate                             |
|                                               | AF organization and termination by ablation predictive for success |
|                                               | Allows for tailored ablation                  |

\textsuperscript{1225}
CFAE Ablation

In 2004, Nademanee et al. described a technique of CFAE ablation without pulmonary vein isolation and reported a high arrhythmia-free success rate. However, other groups were not able to replicate this success rate with exclusive CFAE ablation. Several studies then investigated the incremental benefit of CFAE ablation when added to pulmonary vein isolation. In patients with persistent AF, most studies, as well as 3 meta-analysis, found that addition of CFAE ablation to pulmonary vein isolation improved arrhythmia-free outcome. Brooks et al. systematically reviewed the literature with regard to the impact of different ablation strategies on the outcome of persistent AF ablation. In this indirect comparison of available data, success rate of CFAE ablation when added to pulmonary vein isolation was superior to exclusive pulmonary vein isolation (Figure 1). Therefore, available clinical evidence clearly suggests that additional CFAE ablation after pulmonary vein isolation has an impact on the substrate of AF and translates into better arrhythmia-free outcome.

Several limits of CFAE ablation need to be mentioned, and these probably are responsible for the heterogeneous results of studies investigating CFAE ablation. Most importantly, CFAE definition is not uniform. The standard definition of CFAE usually involves both time domain and frequency domain, and interpretation remains somewhat subjective. Second, sites with CFAE are not necessarily important for AF perpetuation. A multitude of mechanisms can be responsible for CFAE formation. Multicomponent atrial electrograms show a stereotypical distribution to anatomic areas of tissue heterogeneity or anatomic junctures, and fractionation usually occurs after shortening of AF cycle length. It is well described that shortening of AF cycle length results in slow conduction, functional conduction block, and fibrillatory conduction at sites of tissue anisotropy. Furthermore, CFAE sites usually display distinct electrograms of normal voltage in sinus rhythm, suggesting absence of structural scar. These observations suggest that remote activation of adjacent structures and local, atrial structural complexity are the main mechanism of multicomponent CFAE formation. Therefore, multicomponent atrial electrograms are a passive phenomenon and not sites of a focal, triggering source. Nevertheless, the complex structures underlying multicomponent CFAE formation may be important for promotion of different kind of reentry. This could explain why Takahashi et al found that ablation at sites showing electrograms with a high percentage of continuous electric activity or a temporal activation gradient was associated with slowing of AF cycle length or AF termination. Similarly, another group also reported that AF cycle length prolongation was more likely during ablation of sites with more fractionated atrial electrograms.

High-dominant frequency sites are also preferred ablation targets and correspond to the frequency domain definition of CFAE. These sites display an important frequency gradient toward surrounding atrial tissue and are mainly located within the pulmonary veins in paroxysmal AF and throughout both atria in persistent AF. Electrogram fractionation preferentially occurs around these sites as a result of the dynamic interaction between shortening of cycle length and atrial anatomy. In a sheep model, these sites have been demonstrated to correspond to functional reentry (rotors). Very recently, one group claimed to have revealed for the first time sustained, localized rotors in human AF by computational mapping. Such discovery could open the door to tailored substrate ablation once...
these sources can be identified during the ablation procedure and selectively targeted.

The mechanism by which CFAE ablation improves arrhythmia-free outcome in persistent AF remains incompletely understood. As mentioned above, sites harboring important drivers like functional reentry may be modified by CFAE ablation. Extensive CFAE ablation may also decrease tissue anisotropy by microscar formation and reduce the tissue available for any kind of reentry. Finally, both CFAE ablation and circumferential pulmonary vein ablation target sites where ganglionated plexi and their axons are located. Some groups specifically advocate ablation of the cardiac autonomic nervous system because of its role in initiation and maintenance of AF.

Linear Ablation

In 1991, Dr James Cox introduced the Cox-maze procedure. The procedure aims to compartmentalize both atria by a set of surgical, linear lesions, including isolation of the pulmonary veins. The hypothesis is that multiple reentrant wavelets are responsible for AF perpetuation and that reducing their number by compartmentalization of the atria will terminate AF. Long-term arrhythmia-free outcome of the Cox-maze procedure is very high and impressively proves that simple substrate modification by linear lesions can suppress persistent AF.

Given the high success rate of the Cox-maze procedure, linear ablation was also introduced in the electrophysiology laboratory. Three studies randomized patients with persistent AF to pulmonary vein isolation without additional ablation versus additional linear ablation. In all 3 studies, arrhythmia-free outcome in the linear ablation group was significantly improved. In the systematic review by Brooks et al mentioned above, success rates of pulmonary vein antrum isolation plus linear ablation or ablation of a box lesion also were higher than after exclusive pulmonary vein isolation (Figure 1). Only 1 study randomized patients to linear ablation versus CFAE ablation, both added to pulmonary vein isolation, and found similar arrhythmia-free outcome after single and multiple procedures. Finally, it has to be mentioned that ablation of lines has its own downsides. It can be impossible to achieve complete block across an ablated line and conduction can recover. Both incomplete linear ablation and conduction recovery are proarrhythmogenic and are associated with a high rate of recurrent atrial tachycardia. These technical limitations probably account for the lower efficacy of linear ablation compared with the cut-and-sew Cox-maze procedure and the necessity of repeat procedures.

Stepwise Ablation

The stepwise AF ablation approach was introduced by the Bordeaux group in 2005. It combines pulmonary vein isolation with both CFAE ablation and linear ablation. During the procedure, AF cycle length is monitored in both appendages and usually prolongs gradually during stepwise ablation (Figure 2). Stepwise ablation is continued until AF terminates to either sinus rhythm or atrial tachycardia, which thereafter is ablated as well. If AF does not terminate after all steps have been accomplished, cardioversion is performed. With this strategy, termination of AF is achieved in up to 87% of patients. With the stepwise approach, all steps contribute to prolongation of AF cycle length. However, it is rare that AF already terminates after pulmonary vein isolation. For example, in a study by O’Neill et al AF was terminated in 85% of 150 patients. The step during which termination occurred was pulmonary vein isolation in 11%, CFAE ablation in 68%, and linear ablation in another 21% of patients.

Arrhythmia-free outcome after repeat ablation as necessary is excellent with the stepwise ablation approach. In the above-mentioned literature review by Brooks et al this strategy achieved highest success rate of all ablation strategies (Figure 1). Importantly, if the stepwise ablation strategy
is used, termination of AF during the index procedure is predictive of arrhythmia-free outcome.70–72,74,75 Gradual prolongation of AF cycle length during substrate ablation up to AF termination and the predictive value of AF termination for arrhythmia-free outcome both indicate that the atrial substrate plays an important role in AF perpetuation and that substrate modification by ablation is important. Patients in whom AF is terminated by ablation during the index procedure tend to have atrial tachycardias in case of arrhythmia recurrence, whereas patients in whom termination is not achieved mostly recur in form of AF.71 This further strengthens the concept that substrate modification is necessary in the majority of patients with persistent AF to organize and finally control AF. Importantly, with the stepwise ablation strategy substrate ablation is tailored to the patients’ need, as no additional ablation is performed once AF has terminated. Therefore, only a minority of patients in whom AF terminates after pulmonary vein isolation, ie, patients with very active pulmonary veins responsible for AF maintenance, will have no further substrate ablation. The pros and cons of substrate ablation with a stepwise ablation strategy are summarized in the Table. Finally, it has to be mentioned as a limitation that to date no randomized clinical trial has compared the stepwise ablation strategy with either exclusive pulmonary vein isolation or a trigger-ablation strategy.

### Trigger Disease Versus Substrate Disease

Most evidence links paroxysmal AF to pulmonary vein triggers.1–4 As disease progresses, AF episodes tend to become more frequent and longer in duration. We arbitrarily define AF as persistent as soon as the majority of episodes last >7 days.76 This definition, although useful in daily clinical practice, completely lacks any pathophysiological basis. Everyone involved in AF ablation will have witnessed cases in whom persistent AF terminated after pulmonary vein isolation and thereafter does not terminate despite extensive substrate ablation, with the need of cardioversion at the end of the procedure.

Instead of asking whether trigger elimination is sufficient for persistent AF ablation, we should therefore better ask whether AF in a particular patient is a disease of triggers or substrate. Inoue et al10 in their study provided us with a nice scheme on these 2 mechanisms that possibly can sustain persistent AF (Figure 3). Some cases of persistent AF will have a disease of triggers that are sufficiently active to sustain AF. These will mainly be cases in whom the duration of continuous AF is rather short, probably lasting a couple of months up to 1 year, although there certainly are exceptions. Other clues that persistent AF is a disease of triggers are repetitive bursts of very short cycle length within 1 or several pulmonary veins, AF termination after pulmonary vein isolation, or the observation of repeat termination of AF with immediate recurrence after 1 beat of sinus rhythm. The number of patients with persistent AF having a disease of triggers and in whom pulmonary vein isolation will be sufficient depends on the rate of persistent and long-standing persistent patients included in a study. In any case, these patients will only form a minority of persistent AF patients.10,22,24 Successful ablation in these patients will face the same challenges as in the gold model for a disease of triggers: paroxysmal AF. Pulmonary vein reconduction after ablation will determine the success rate and the necessity of repeat procedures, whereas only a minority of them will have nonpulmonary vein triggers that have to be addressed for a successful outcome.

However, in the majority of persistent AF patients a mechanically and electrically remodeled atrial substrate is responsible for AF perpetuation. In these patients, additional substrate ablation is necessary after pulmonary vein isolation to control AF. Issues that have to be addressed in these patients are optimized tools allowing for complete and durable linear ablation, as well as better understanding of the mechanisms responsible for AF perpetuation and their manifestation on intracardiac electrograms to allow tailored substrate ablation.
Conclusions

Triggers in persistent AF are mainly located in the pulmonary veins, and nonpulmonary vein triggers are rare and difficult to ablate. If a trigger-ablation strategy is sufficient for persistent AF, segmental pulmonary vein isolation should be successful. However, available clinical data clearly show that additional substrate ablation, including circumferential instead of segmental pulmonary vein isolation, CFAE, and linear ablation, increases arrhythmia-free outcome in patients with persistent AF. Persistent AF is maintained by a very active pulmonary vein triggers in only a minority of patients, and in these patients pulmonary vein isolation is indeed sufficient. But in the vast majority of persistent AF patients, additional substrate ablation is necessary to achieve satisfying arrhythmia-free outcome.

Disclosures

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References


**Key Words:** atrial fibrillation • catheter ablation
Response to Laurent Roten, MD, Nicolas Derval, MD, and Pierre Jaïs, MD
Sanjay Dixit, MD, David Lin, MD, David S. Frankel, MD, and Francis E. Marchlinski, MD

Roten et al have questioned the validity of our approach of antral pulmonary vein isolation (PVI) and nonpulmonary vein (PV) trigger ablation for persistent atrial fibrillation (AF). In doing so, they ignore the irrefutable evidence that antral PVI is highly effective in targeting the most common and frequently identified source of AF triggers. They also choose to ignore other benefits of antral PVI, including modification of ganglionated plexi or eliminating hinge points for potential rotor cores in proximity to PVs. Furthermore, they fail to acknowledge the cumulative data that clearly show that persistent PVI is difficult to achieve over the long term, and in patients experiencing AF recurrence, PV reconnection is the rule. Furthermore, in these patients using standard stimulation protocol AF triggers can be reproducibly elicited from reconnected veins and other non-PV locations. Roten et al claim that the latter (non-PV trigger sources) are difficult to identify and target. We completely disagree with this contention because in our experience non-PV trigger sources can be successfully eliminated with relative ease using a methodical protocol for induction and mapping.

The step-wise ablation approach advocated by Roten et al uses CFE and linear ablation beyond PVI. Both CFE ablation and line creation have flaws, which the authors themselves acknowledge. Why combining these 2 flawed strategies should improve ablation outcomes in patients with persistent AF remains scientifically unanswered. Proponents of step-wise ablation approach argue that with each added step beyond PV isolation, AF slows and then eventually terminates. However, review of the data from centers reporting this technique reveals that AF termination to sinus rhythm is rare. In the majority, AF transitions into organized atrial tachyarrhythmias that require additional ablation, despite which eventually half these patients have to be electrically cardioverted. Over the long term, >60% of patients undergoing this procedure require ≥1 repeat ablation for arrhythmia recurrences. Thus, the single procedure efficacy of step-wise ablation in patients with persistent AF is <40%, and ≥2 additional ablation attempts are required to achieve intermediate-term success in 80% of patients. These results are not superior to the outcomes that we have achieved using antral PVI and ablation of non-PV triggers. Investigators favoring extensive ablation strategies argue that recurrent arrhythmias in their series are predominantly atrial tachycardias and not AF. Although this may be true, recurrent organized atrial tachyarrhythmias are typically more symptomatic than AF and ablating these can be just as invasive as targeting reconnected PVs and non-PV triggers. Other concerns with extensive ablation strategies include risk of collateral damage to surrounding structures (circumflex artery, phrenic nerve, etc), as well as their long-term impact on atrial transport function.

We do agree with Roten et al that the 7-day cutoff used to differentiate between paroxysmal and persistent AF in the current guidelines does not adequately reflect the mechanism underlying these 2 forms of AF. We also agree that the ablation strategy should be targeted to the underlying arrhythmia mechanism. However, in contrast to Roten et al, we remain unconvinced of the need for extensive substrate modification in patients with persistent AF. We remain proponents of ablation techniques that are based on proven physiological principles rather than empiricism. The latter in our opinion is a moving target that advocates extensive ablation based on anecdotal evidence while ignoring the proarrhythmia and potentially serious risk of this approach. If in the future additional targets outside the PV antrum and non-PV trigger locations are scientifically validated, we will endorse their ablation in the hope of moving the EP community to a uniform approach for improving long-term ablation outcomes in patients with persistent AF.
Catheter Ablation for Persistent Atrial Fibrillation: Elimination of Triggers Is Not Sufficient

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