Published in final edited form as:

J Cardiovasc Electrophysiol. 2014 February ; 25(2): 119–121. doi:10.1111/jce.12310.

What Tissue Does Circumferential PV Isolation Actually Modulate?

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Editorial Comment

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice and a major cause of disabling cardiovascular symptoms, stroke, and even death¹. Recent trials employing drugs to maintain sinus rhythm² or to limit ventricular rate³ have been disappointing, and have thus reinvigorated attempts to improve ablation for AF. Despite remarkable success in some patients, the overall results for AF ablation are suboptimal both for paroxysmal AF⁴⁻⁶ and persistent AF, particularly after a single procedure⁷. Further work is clearly needed before we can declare victory over this obstinate arrhythmia.

Ablation of AF is still substantially hampered by our incomplete mechanistic understanding of the arrhythmia. A reasonable mechanistic formulation is that AF, like other arrhythmias, requires 1) a trigger that induces AF and 2) a substrate that supports the maintenance of sustained AF. The mechanisms that actually induce triggers are less well studied, but may include abnormalities of the cardiac autonomic nervous system (CANS)⁸, atrial stretch⁹, genetic¹⁰ or other factors. Our understanding of AF triggers advanced enormously in 1998, when Haïssaguerre et al. reported on 45 patients with paroxysmal AF whose episodes occurred frequently enough for repetitive AF onset to be observed in the laboratory¹¹. In this population, episodes of AF were often triggered by bursts of premature atrial depolarizations from the pulmonary veins (PV), where radiofrequency ablation eliminated AF short-term in 62% of patients. This work laid the foundation for the strategy of eliminating triggers using pulmonary vein isolation (PVI), which has gained wide acceptance as therapy for AF^{12,13}.

Many questions still remain on how PVI is successful, since it remains very difficult to identify which patients will enjoy long-term procedural response. PVI may simply destroy site(s) of triggering beats or prevent their conduction into the left atrium. However, much evidence suggests that the mechanism of success of PVI is more complex, since the correlation between AF recurrence and PV reconnection is increasingly unclear. While patients with recurrent AF often have reconnection of at least one PV^{14,15}, many patients

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do not have AF recurrence despite reconnected PVs^{16–18} suggesting that another mechanism explained successful ablation. In addition, AF may recur even with isolated PVs^{16–18}, by definition proving the relevance of AF triggers outside the PVs. To make AF ablation more uniformly successful, it may be helpful to identify these non-PV actions of PVI. Broadly speaking, this includes triggering mechanisms outside the PVs^{19–21} or abnormal atrial substrates that enable AF to sustain once initiated²².

Into this background step Jiang et al., the authors of a thought-provoking study reported in this issue of the *Journal*²³. The paper addresses whether the PV firing that can trigger AF may in fact result from “upstream” mechanisms in the left atrium outside the PVs that are inadvertently targeted by PVI. The authors studied 109 patients with drug-refractory paroxysmal AF. Prior to ablation, with catheters placed in the coronary sinus and pulmonary veins, patients were given adenosine triphosphate and isoproterenol (ATP+Isuprel) intravenously in an attempt to induce AF. This protocol triggered AF in 58% of patients (47 out of 82), and in most cases the trigger lay in the PVs (37 out of 43, 93%). After a circumferential PVI procedure (CPVI) the authors re-challenged patients with this same regimen and found that AF could still be triggered in 34% of patients (16 out of 47) – but that the trigger now almost always arose outside the PVs (14 out of 16 cases, 86%), at sites including the coronary sinus ostium, superior vena cava, and anterior and posterior left atrial walls. Furthermore, 17 of the still inducible patients were subjected to vigorous atrial pacing from inside the encircling lines with and without administration of ATP+isuprel, in order to mimic PV firing. Notably, AF was induced in only 1 patient (6%).

We congratulate the authors on this important and novel work that substantially advances our understanding of the impact of PV ablation on AF triggers. First, these results reaffirm that PV firing can trigger AF induction and demonstrate that PV isolation reduced AF induction by 66% with $P < 0.01$. After the procedure, rapid pacing to mimic PV firing from inside the CPVI lesions rarely induced AF, a testament to the completeness of the electrical isolation that was achieved.

However, a second more notable result was that CPVI not only eliminated electrical conduction from PVs to the atria, but also eliminated PV triggers themselves, at least those induced by ATP+isuprel. Although this is frequently observed in clinical practice, few studies have addressed why this may occur. The authors conclude that ablation did not target the actual site of PV triggers, since CPVI was performed 5–10 mm outside the PV ostia, but postulate instead that ablation targeted the cardiac autonomic nervous system (CANS). To further support this hypothesis, the authors note that in 2 patients PV triggers persisting after ablation were eliminated by ablating outside CPVI lines in areas where the ganglionated plexi of the CANS typically lie. The authors conclude that PV firing may be secondary to an ‘upstream’ abnormality within the CANS. These results, and substantial prior data^{8,24}, are consistent with this intriguing hypothesis. However, one major caveat is that localizing human atrial ganglionated plexi is not trivial. Ganglionated plexi are small (5–200 neurons) and widely distributed, and their location is quite variable between different hearts²⁵. Although they can be functionally identified by vagal responses to high frequency stimulation²⁶ or ablation²⁷, neither is a sensitive marker²⁸ and neither was described in this study. A minor concern is that trigger sites could possibly have been damaged by CPVI

lesions a few millimeters away. Thus, while a CANS-based mechanism for the efficacy of CPVI in this study is plausible, corroborative studies are required to prove that ganglionated plexi were in fact ablated. The authors' induction protocol of ATP+Isuprel was designed to stimulate sympathetic and parasympathetic limbs of the autonomic nervous system, and might be a useful tool in acutely assessing the success of ablation or in predicting the risk of long-term recurrence. The induction rate of AF (58%) was lower than that reported by using isoproterenol (87%) alone or rapid atrial pacing (93%) alone²⁹. Although this same protocol was applied before and after CPVI, more aggressive pacing may have uncovered inducible AF in a higher proportion of patients.

An important third finding in this study is that after CPVI AF triggers were commonly inducible from non-PV sites. This hierarchy reaffirms the need to identify non-PV triggers in each patient if AF trigger elimination is the goal²¹. However, localization of AF triggers is an imprecise science. Because of the transient nature of most triggers and limited number of available clinical catheters, it is very difficult to locate precisely an identified trigger. Perhaps for this reason, the reported incidence of non-PV triggers for paroxysmal AF ranges from 2% using clinical catheters¹¹ to 4% when sampling both atria globally using basket or non-contact catheters¹⁶.

Another important facet of this study is the relationship of PV ablation to AF-maintaining substrates. The rate of AF induction by PV pacing after CPVI in this study was only 6% (1/17), likely because pacing was performed from within effective lines of block. One limitation of trigger-based ablation is that other triggers can still induce AF, and in other studies coronary sinus or left atrial appendage pacing (mimicking tachycardias from these locations) initiated AF in 40–60% of patients after PVI^{23,31}. A viable clinical alternative to ablating every identifiable trigger, which may be very difficult, is to ablate patient-specific AF substrates^{32,33}. In the present study, AF terminated during CPVI in some patients, suggesting ablation of AF-sustaining substrates rather than triggers. Work from our laboratory has shown that targeted elimination of patient-specific rotors or focal sources³⁴ can eliminate AF acutely and on follow up, presumably by preventing sustained AF if PVs reconnect or other triggers emerge. Additional work shows that PVI, linear lesions or other empirical ablation lesions, if effective, may operate by inadvertently ablating stable rotors³⁵. Accordingly, substrate-guided ablation is gaining increasing attention²² as an alternative to the lengthy patient-specific trigger identification and elimination that is likely required to fully exploit the trigger hypothesis.

In summary, Jiang et al. substantially advance our understanding of AF triggers by showing that CPVI not only isolates but suppresses PV triggers, perhaps by ablating sites representing the cardiac autonomic nervous system, and that this may unmask non-PV triggers. These data emphasize that any ablation approach to eliminate triggers cannot stop with PV isolation, but must rigorously map and ablate non-PV triggers after vigorous induction methods. An alternative requiring a formal comparison is modification of the atrial substrate in such a way that would make AF non-sustainable regardless of whether triggers recur or not. Tailoring the ablation procedure away from an anatomical approach towards patient-tailored physiology will ultimately offer the best chance for a durable solution.

Acknowledgments

This work was supported by grants to Dr. Narayan from the NIH (HL103800).

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