Editorial

Procedural End Points in Pulmonary Vein Antrum Isolation

Are We There Yet?

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If you have ever been on a long car trip with a small child, you have almost certainly encountered the age-old question, “Are we there yet?” Although a careful review of the literature reveals surprisingly little in the way of rigorous studies on this matter, strong anecdotal evidence suggests that the longer or more arduous the journey and the more desirable the destination, the more likely it is this question will be asked. In our quest to develop a cure for atrial fibrillation (AF) with our catheters, electrophysiologists have found ourselves asking the very same question. This is no surprise, because the journey has been difficult, with long, technically demanding procedures, and the destination, the cure of a disease with often profound symptoms and morbidity that affects millions, is coveted. In the world of pulmonary vein antrum isolation (PVAI), what we are really asking is whether our lesions will provide our patients with a lasting cure of their AF: “Are we there yet?”

Unfortunately, the answer to this question has not come easily. AF is notoriously sporadic. Just because a patient’s AF is gone one moment does not mean it will not return the next. No imaging or serological testing can yet identify or rule out the heart’s propensity to develop this arrhythmia. Instead, we must hunt for surrogates to tell us whether or not we have adequately diminished the ability of a patient’s heart to develop AF. Here again, though, the questions and their answers are difficult to illuminate. Ablation strategies aimed at curing AF have sought to either eliminate the triggers of AF by isolating them from the rest of the atrial myocardium or to alter the atrium in such a way that reentrant wave fronts of AF can no longer be maintained, also referred to as substrate modification. The answer to whether the ablation has been successful relies on which goal one seeks to obtain: the isolation of triggers, modification of the substrate, or both.

Fortunately, some clarity has been developing in this confusing picture. Substrate modification, it seems, is not by itself adequate to achieve a durable cure from AF. Techniques solely aimed at substrate modification without any attempt to isolate common triggers of AF have been associated with high rates of recurrence and have since been abandoned.1,2 Purely anatomic PVAI techniques have been demonstrated to electrically isolate the pulmonary veins (PVs) in only a minority of cases.3,4 Its proponents attributed successful elimination of AF by this technique to substrate modification and the elimination of the ability of the atria to maintain AF. This strategy, however, has been associated with higher rates of recurrence of AF when medications are stopped and unacceptably high rates of development of other atrial tachyarrhythmias.4–7

Electrical isolation of AF triggers, on the other hand, does appear to be associated with a high rate of cure from AF. Purely anatomic techniques of PVAI have been found to be inferior to techniques that rigorously confirm complete electrical isolation.4,6 When only 1 or 2 PVs are isolated, AF recurrence has often been attributed to triggers found later in the nonisolated PVs.8 Additional isolation of common non-PV triggers, such as the superior vena cava, has been shown to improve the rate of cure, which also supports the importance of isolation.9–11 Further evidence for the importance of electrical isolation of triggers in the cure of AF comes from a growing body of data demonstrating that the majority of patients with recurrent AF after PVAI have recovery of conduction in 1 or more PVs.8,12–14 The most convincing evidence for the crucial role of electrical isolation of AF triggers in the cure of AF comes from a few recent trials that have taken patients who have been cured of AF after PVAI and brought them back to the electrophysiology laboratory to reexamine their PV conduction. These studies have shown a dramatic difference in persistent PV isolation between patients cured of AF and those with recurrences.12,13

Commonly used end points in PVAI reflect the growing understanding that isolation of AF triggers is critical to the cure of AF. Elimination or dissociation of PV potentials is indicative of PV entrance block and has become the primary end point used in PVAI. We believe that the use of a circular mapping catheter with tightly spaced electrodes is critical for the assessment of electrical gaps in the lines of isolation and cannot be replaced by point-by-point interrogation of the PVs and their ostia with the ablation catheter. Demonstration of exit block by pacing just within the PV ostium has also been proposed as a possible end point for PVAI.15 Although Gerstenfeld et al19 reported that only a fraction of PVs demonstrating entrance block also showed exit block, our experience has been that entrance block and exit block go hand in hand, and demonstration of exit block is not routinely used for all PVs. Demonstration of exit block may, however, be useful by itself or in conjunction with differential pacing in the left atrium and left atrial appendage when ablation or

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far-field electrograms obscure whether entrance block has truly been obtained.

The inclusion of other isolation end points may improve outcomes. Our technique includes electrical isolation of the superior vena cava at the superior vena caval–right atrial junction unless precluded by close proximity of the phrenic nerve to this site. AF triggers have been found in the superior vena cava in approximately 6% to 10% of patients, and the additional isolation of the superior vena cava has been shown to mildly improve rates of cure of AF after PVAI.10,11

One downfall of these end points is that they may not predict long-term durability of PV isolation. Local edema may mask gaps in isolation lesions. These gaps may then recover conduction as the edema resolves, allowing recovery of conduction into and out of the PV. In patients with recurrence of AF after PVAI, recovery of PV conduction is almost universal. As previously mentioned, recurrence of PV conduction is frequently seen in patients undergoing repeat ablation for recurrence of AF. Early recovery of PV conduction is thought to be common, and reexamination of the PVs with a circular mapping catheter at least 20 minutes after isolation of the last PV may detect conduction recovery in up to 11% of PVs.15 Limited data have also suggested that administration of adenosine and isoproterenol may be useful in uncovering persistent PV conduction. Although data supporting the role of these medications in PVAI are currently insufficient, studies investigating their use are ongoing.

So, if durable electrical isolation of the PVs and other common AF triggers is our best surrogate for cure of AF, how do our common end points fare in providing this result? Prior studies that examined patients cured of AF have shown recovery of PV conduction in these patients to be infrequent. Ouyang et al12 examined patients without recurrence of AF after PVAI and found 100% of the PVs remained isolated in these patients. We have previously reported our data from a multicenter study that included patients cured of AF after PVAI (group 1), patients with AF recurrence after PVAI who were maintained in sinus rhythm with antiarrhythmic drugs and a minimum of 2.5 years of follow-up after the ablation procedure. Ouyang et al12 included predominantly patients with paroxysmal AF (88%), and our findings were reported on a mixed population that included 42% with paroxysmal AF, 22% with persistent AF, and 35% with permanent AF. It is possible that durability of isolation differs in this highly select population.

Another possible explanation for the disparity between this and prior studies may relate to differences in monitoring for postprocedural arrhythmias. It is possible that patients with asymptomatic recurrences of AF were miscategorized as being cured. Postablation rhythm monitoring included only 24-hour Holter monitoring at 1, 3, 6, 9, and 12 months and then every 6 months thereafter. Weekly transtelephonic monitoring was not initiated until 2 years after ablation.16 Early initiation of frequent transtelephonic monitoring immediately after the blanking period, as done by ourselves13 and Ouyang et al,12 would have improved this surveillance and may have altered the categorization of patients included in the group thought to be cured of AF.

Although the rates of persistent electrogram abatement, dissociated PV potentials, and exit block are reported, associations among these end points are not described. Although it may be reasonable to suspect that all indicators of PV isolation go hand in hand, studies have demonstrated that at the time of ablation, many PVs with entrance block may still have PV-A conduction.15 We are not told by the authors of the present study whether associations were found between sustained exit block, electrogram abatement, and entrance block. Additionally, we are not provided with the number of PVs in each group with recovery of all 3 end points. It is possible, for instance, that patients with recurrent AF after PV isolation are more likely to have PVs with complete recovery of all end points.

Finally, our study13 and that by Ouyang and colleagues12 reported A-PV conduction times in recovered PVs. We reported dramatically increased A-PV conduction times in patients cured of AF, with statistically significant differences in conduction increases between the AF cure group and both the group with sinus rhythm while taking antiarrhythmic drugs and the group with refractory AF (P<0.001).13 Ouyang et al12 reported a mildly increased A-PV delay in patients with AF recurrence that was comparable to patients we described with recurrence of AF. Unfortunately, A-PV conduction times before ablation and at the time of follow-up are
not reported in the present study by Pratola and colleagues, and they may well provide the best explanation for their findings. Our data suggest that markedly prolonged A-PV conduction times are sufficient to create a functional block that prevents AF triggers from initiating AF. In spite of recovered electrograms, PV potentials, and exit conduction, A-PV conduction times may have been markedly increased in the AF cure group compared with those with recurrent AF. We would argue that these conduction times hold the key to explaining the findings of the present study.

We have come a long way in our journey to develop a durable cure for AF. Cure rates after a single procedure approach 75% to 80% at some centers. Improvements in catheters have reduced radiofrequency delivery times, and electroanatomic mapping systems have reduced fluoroscopic and total procedure times. Balloon catheters, alternative ablative energy sources, and remote catheter manipulation may further decrease technical demands and procedure times of PVAI. Electrical isolation of AF triggers, as evidenced by PV potential elimination or dissociation, remains our best procedural end point. Differential pacing maneuvers may help guide when isolation has been achieved. Additional maneuvers such as administration of adenosine and isoproterenol may eventually prove to be helpful in establishing the durability of isolation.

Are we there yet? We’ve come a long way, but keep your seat belts on. We still have a long journey ahead.

Disclosures
Dr Natale serves on the Speaker’s Bureau for and receives honoraria from Medtronic, St Jude, and Boston Scientific. Dr Callahan reports no conflicts.

References

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