Catheter Ablation for Paroxysmal Atrial Fibrillation
Triggers and Thoughts Provoked by Adenosine*

Gregory F. Michaud, MD, Saurabh Kumar, BSc(Med)/MBBS, PhD

It has been 15 years since the mechanism of paroxysmal atrial fibrillation (AF) was attributed to triggering foci, largely within pulmonary veins (PVs) (1); since then, catheter ablation procedures for AF have risen exponentially with isolation of PV electrical activity from the left atrium (LA) forming the cornerstone of most ablation strategies (2). However, procedural success rates appear to have reached an efficacy “ceiling” with ~50% of patients experiencing recurrences at 1 year off antiarrhythmic drugs, even at experienced centers (3). Incomplete efficacy is likely due to our inability to create durable transmural lesions with subsequent recovery of electrical conduction responsible for both intermediate and long-term AF recurrence following PV isolation (4–6). Much work has recently focused on elucidating the triggering and sustaining mechanisms for AF beyond the PVs, with appreciation that the existence of organized re-entrant circuits (rotors) or focal impulses are not necessarily constrained to the PVs, are biaxially distributed (even in paroxysmal AF), and can be targeted with focal ablation in an attempt to improve outcomes (7).

In the context of such discussion, it is timely that Kuroi et al. (8), in this issue of JACC: Clinical Electrophysiology, report their attempt at improving ablation outcomes in 464 consecutive patients with paroxysmal AF who, firstly, underwent circumferential PV isolation using the double-circular mapping catheter technique, followed by systematic provocation with high-dose adenosine (30 mg intravenous) injection and concomitant isoproterenol infusion. The purpose was to identify and eliminate dormant PV conduction and triggered AF from non-PV foci. The salient findings were that:

1. Acute PV conduction recovery was present in 30% of patients during the first procedure, and 85% of patients had spontaneous PV conduction recovery discovered at a re-do procedure;
2. Non-PV foci were uncovered in 4.3% of patients during their first and in 6.9% of patients during their second procedure; these were localized to either atria (62%) or to the superior vena cava (SVC) (38%). All foci were successfully ablated in the first procedure; however, 3 of 8 foci (38%) were not successfully ablated during the second procedure, all of which were non-SVC origin;
3. One-year single and multiple procedure success rates off antiarrhythmic medications were 55% and ~67%, respectively. Notably, identification and elimination of non-PV foci did not enhance single-procedure success, but paradoxically, conferred worse outcomes predominantly driven by an ~4-fold higher risk of AF recurrence in patients with triggering foci from atrial sites. By contrast, elimination of SVC triggers via SVC isolation yielded similar outcomes to patients without any triggers beyond the PVs.

In an attempt to identify nontransmural lesions, adenosine is often used to hyperpolarize damaged cells such that they transiently regain electrical excitability (9); isoproterenol provides no incremental benefit for this purpose (10). In the present study
(8), a high rate of PV conduction recovery (30%) was observed after initial PV isolation, reflecting an inability to reliably produce transmural lesions with the common endpoint of acute PV isolation. Despite a systematic effort to ablate sites of dormant PV conduction recovery, it is notable that procedural efficacy rates did not improve on those reported in the published literature (5). This may be partially explained from a practical standpoint, because the use of adenosine provides a fleeting moment to identify the site of dormant conduction (4). Although this approach can improve AF-free survival as reported in the ADVICE (Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination) trial (11), it may also identify patients with more incomplete transmural encirclement and a greater likelihood of AF recurrence not overcome by additional ablation (12). It remains to be seen whether elimination of dormant conduction provoked by adenosine offers any sustained benefit (11), but it is clear that PV conduction recovery remains the single most important factor hampering the success of PV isolation procedures for paroxysmal AF (6,13).

Adenosine was also used in this study to provoke AF triggers by engaging a number of putative mechanisms described in the literature, including action potential shortening (14); hyperpolarizing atrial cells, thereby enhancing excitability, rotor frequency, and stability (15); sympathoexcitatory effects (16); and effects on ganglionic plexi at anatomic sites such as the SVC-aortic region that can encourage uncovering of SVC triggers (17). Isoproterenol may also identify non-PV triggers (18), and it is not clear whether the combination of the 2 agents is necessary or whether isoproterenol alone at higher doses is sufficient. This may be important when one considers that isoproterenol may allow more accurate assessment of triggers that might occur repeatedly, but this study was not designed to provide that answer or determine whether the agents would have identified distinctly different triggers.

Previously published reports have identified non-PV triggers initiating AF in up to one-third of unselected patients with paroxysmal AF with origin from various sites such as posterior LA, SVC, the inferior vena cava, crista terminalis, fossa ovalis, coronary sinus, Eustachian ridge, ligament of Marshall, and adjacent to the atrioventricular valve annuli (13). The SVC is a well-appreciated trigger for AF, and outcomes after SVC isolation in addition to PV isolation are favorable (19), consistent with the present report (8). This is not surprising because isolation of the SVC musculature is a straightforward endpoint. However, one of the most intriguing findings in this study was that the majority of non-PV foci were from atrial...
sites and that the presence of atrial triggering sites independently conferred a poor prognosis. This observation may reflect a more generalized atrial susceptibility to provocation, or perhaps the transient nature of the triggers did not allow accurate identification of discrete sites. Data derived from mapping of focal impulses and rotors in patients with paroxysmal AF that show that non-PV triggering sources often lie at atrial sites (right or left), remote from regions likely to be encompassed during traditional PV isolation (20). It is intriguing to consider whether the use of high-density mapping catheters and novel mapping technologies during sustained AF (seen in approximately 50% after adenosine provocation) would have allowed these triggering atrial sites to be successfully ablated.

As in previous studies, non-PV triggers were observed in a small percentage of patients in this nonrandomized study by Kuroi et al. (8), but the results highlight key contemporary challenges in the catheter ablation of paroxysmal AF (Figure 1). Although conscious efforts to improve lesion transmurality by meticulously achieving pre-set goals of biophysical parameters for every lesion are likely to provide the greatest improvement in single-procedure efficacy (21–23), one must be cognizant of the important contribution of non-PV triggers and high-dose adenosine injection during isoproterenol infusion provides another tool to provoke them.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Gregory F. Michaud, Cardiac Arrhythmia Service, Cardiovascular Division, Brigham and Women’s Hospital, Boston, Massachusetts 02115. E-mail: gfvmichaud@partners.org.

REFERENCES


KEY WORDS adenosine, atrial fibrillation, catheter ablation, dormant conduction, isoproterenol, pulmonary veins, pulmonary vein isolation, rotors, substrate, transmural lesions, triggers