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EDITORIAL COMMENT

Sorting Out the Significance of Nonpulmonary Vein Triggers*

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Nonpulmonary vein (PV) foci have been reported as possible initiating triggers in patients undergoing catheter ablation of atrial fibrillation (AF) (1-8). In selected patients with reproducible non-PV triggers as the only trigger for AF, their effective ablation has resulted in good AF control during follow-up (1,2,4). In addition, previous observational studies have reported that the outcome, when identified non-PV triggers are ablated successfully coincident with PV isolation, approximated the outcome of those patients in whom non-PV triggers were not identified and only PV were isolated (1,2,5,7,8). Moreover, in 2 recent reports, the outcome, in patients with non-PV triggers that are unable to be localized and successfully ablated, was poor, with 68% and 65.7% reported AF recurrence rates (8,9). Thus, non-PV triggers resulting in AF initiation appear to be clinically relevant and appropriate targets for ablation.

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The paper by Hojo et al. (10) published in this issue of *JACC: Clinical Electrophysiology* is a retrospective observational study focusing on non-PV triggers. The study offers a unique perspective because patients were routinely brought back to the electrophysiology lab with or without AF recurrence at 6 months. After PV isolation, patients underwent a non-PV provocation protocol that included 4 μg/min of isoproterenol infusion followed by a bolus infusion of 40 mg of adenosine triphosphate. Of note, non-PV triggers were identified in 20 patients (9.3%) during the first procedure and new non-PV triggers were identified in 50 patients (25%) at the 6-month redo procedure. Thus, the overall prevalence of non-PV triggers initiating AF was 32.4%. In addition to identifying more triggers at the time of the repeat procedure, the investigators also noted that the length of time with AF history prior to the first procedure and AF recurrence after the first procedure identified patients more likely to have new non-PV triggers. Of importance, new non-PV triggers strongly correlated with AF recurrence after the repeat procedure (31% vs. 12.3%). Of note, Takigawa et al. (9) also recently reported that the presence of non-PV foci were common with the second procedure (45.9%). They and other investigators have also noted that non-PV triggers at the time of repeat procedure are a harbinger for recurrences even if targeted for ablation, supporting the current report (9,11).

The effort to provoke, localize, and ablate non-PV triggers has not been uniformly embraced by the electrophysiologic community despite the multitude of important observational reports regarding non-PV triggers (12). It is important to try to identify gaps in knowledge and discrepancies in data presented, which may serve as reasons for not embracing non-PV trigger identification and ablation as part of the AF ablation routine.

PROVOCATION OF NON-PV TRIGGERS

Many reports have suggested the importance of high-dose isoproterenol (up to 20 to 30 μg/min) for trigger initiation (4-7,9). High doses of isoproterenol must be accompanied by vasopressor support. Cardioversion of spontaneous or induced AF without and during infusion of 3 to 6 μg/min of isoproterenol has also been described as a technique for provoking non-PV

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triggers (2,5,7). Of note, in the Hojo et al. (10) report, 46.2% of triggers noted at the second procedure were induced using low-dose isoproterenol infusion (4 μg/min), whereas 54% of triggers required an adenosine triphosphate bolus added to the isoproterenol infusion. Other studies have not identified a dramatic increase in trigger initiation when adenosine has been added to high-dose isoproterenol infusion (5). The best protocol for identifying non-PV triggers needs to be determined.

DEFINITION OF NON-PV TRIGGERS

Even the precise definition of what characterizes a non-PV trigger remains controversial. Although most reports have required the initiation of AF by the non-PV triggers, more recently the importance of frequent non-PV firing in the form of isolated atrial premature depolarizations (APD) has been suggested (5,6). Elayi et al. (5) found that patients in whom frequent APD were identified without definitive AF initiation but not targeted for ablation had frequent AF recurrences. The same group reported that targeting frequent APD that originate from the coronary sinus and left atrial appendage may improve outcome (6).

DIFFERENCES IN PREVALENCE AND ANATOMIC DISTRIBUTION OF NON-PV TRIGGERS

Of note, in the report by Hojo et al. (10), 32% of patients demonstrated non-PV triggers and the distribution of non-PV triggers favored the superior vena cava (SVC), including 52% of triggers in the first ablation and 35.4% of triggers noted at the time of the redo procedure. In contrast, Santangeli et al. (7) recently reported an equal prevalence of non-PV triggers of 11% in patients with paroxysmal and persistent AF and with only 14% of non-PV triggers originating from the SVC. As noted, Elayi et al. (5) have identified frequent and repetitive APD from the coronary sinus and left atrial appendage in most patients with persistent AF. Differences in the anatomic distribution of non-PV triggers beg the question of whether the prevalence and anatomic distribution are based on protocol-specific differences for initiation, the definition of the non-PV trigger used, or patient-specific differences, such as ethnicity of the study population (2,5,7,9,10). Certainly there appears to be a higher incidence of triggers from the SVC with adenosine administration (13). These observed differences need to be explained. An increase in non-PV triggers from the posterior wall of the left atrium, mitral annular region, and left atrial appendage in more persistent forms of AF suggests a possible link of the non-PV triggers to the anatomic substrate for AF that also needs to be better defined (5,7).

CHALLENGES IN LOCALIZATION OF NON-PV TRIGGERS AND ENDPOINTS FOR ABLATION

Localization of non-PV AF triggers can be challenging particularly when only the first “triggering” beat is the target. Mapping typically starts with a careful analysis of both the timing and specific intra-atrial activation pattern on multipolar electrode catheters placed in the posterior right atrium extending into the SVC and the proximal CS (7). Occasionally the surface P-wave, if separated from the QRS complex and T-wave, may also help regionalize (2,7). Moving the circular or other multipolar mapping and/or ablation catheters around the atria and repeatedly reinitiating AF is typically required for precise localization for many non-PV trigger sites. The process of precise localization can be quite difficult and frequently the site of origin of the non-PV trigger may only be regionalized. The process may be confounded by a multiplicity of triggers from the same or different regions. Schmitt et al. (14), in 2002, emphasized the importance of biatrial multisite mapping using a 64-electrode basket catheter for identifying non-PV triggers. Efforts to further characterize the AF substrate have resurrected the interest in multipolar mapping. Basket multipolar or body surface multipolar electrocardiographic mapping may facilitate the more precise localization of non-PV triggers, and their effectiveness is under active investigation. Because of the difficulty in precise localization, isolation of structures (left atrial appendage, SVC) or regions (posterior wall) may be preferred. The study by Hojo et al. (10) suggests that although arduous, a positive acute outcome with elimination of the trigger and a negative response to repeat provocative maneuvers can be nearly uniformly achieved.

Hojo et al. (10) add to an important body of information on non-PV triggers. As with many good investigative efforts, the study raises some questions. Why were so many new non-PV triggers evident at the 6-month study compared with the first procedure? Are recurrences in patients with new non-PV triggers during the second procedure due to difficulty in localization and long-term elimination or are the new triggers a marker for the development of additional triggers during subsequent follow-up? Long-term follow-up and repeat studies with recurrences are required to address this issue. More work is also needed to resolve some of the profound discrepancies

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in reported results on non-PV triggers, identify the most effective and reliable provocative maneuvers, improve localization tools and techniques, and confirm the clinical importance of non-PV triggers' identification and ablation on long-term AF control. The roadmap of missing information has been defined.

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