JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 5, NO. 11, 2019

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Clarifying the Definition of Non–Pulmonary Vein Triggers of Atrial Fibrillation*

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Non-pulmonary vein (PV) foci have been shown to initiate atrial fibrillation (AF) at the time of AF catheter ablation (1-5). The reported incidence of non-PV triggers initiating AF varies dramatically from 5% to 69% (1-5). Provocative maneuvers to elicit these triggers include the infusion of high-dose isoproterenol, the administration of adenosine or adenosine triphosphate or both isoproterenol and adenosine or adenosine triphosphate, and cardioversion of spontaneous or induced AF with or without the infusion of low- to intermediate-dose isoproterenol (1-9). Initiation of non-PV triggers appears to be influenced by the stimulation techniques used to provoke, underlying cardiac structural abnormalities, the presence of persistent vein isolation, and patient sex, but does not appear to vary based on the paroxysmal versus persistent nature of the arrhythmia (1-6). Of note, a shift from more frequent right to more frequent left atrial origin for non-PV AF triggers does appears to be favored by men, the presence of more structural abnormalities, and the chronicity of AF (2). Although there are no randomized prospective studies that have assessed whether ablation of non-PV triggers alters clinical outcome, there are 2 sets of observational data that indicate that non-PV AF triggers are clinically relevant and appropriate targets for ablation. First, when non-PV AF triggers are ablated successfully coincident with PV isolation, AF recurrence rates appear similar to those noted in patients who had non-PV triggers for AF were not identified and only PV isolation was performed (1,3,9). Second, and in contrast, patients with non-PV triggers for AF that are not able to be localized and successfully ablated have higher AF recurrence rates (3,9).

The definition of non-PV foci or "triggers" has been typically restricted to those that cause nonsustained or more typically sustained AF (1-5). A few investigators have broadened the definition to include premature atrial contractions (PACs) with a requirement for a specific frequency of PACs (typically >10/min) to target the PACs for ablation (5-8). Thus, it is controversial whether PACs that do not result in AF need to be targeted to optimize outcome and prevent AF recurrences.

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In this issue of *JACC: Clinical Electrophysiology*, Nakamaru et al. (5) report a retrospective observational study that includes 536 patients with the goal of determining whether PACs provoked with high-dose isoproterenol, but not causing AF, have clinical significance. Patients with non-PV AF initiation (n = 26, ~5%) were excluded from the follow-up analysis. Three groups of patients were identified: patients with no PACs induced (n = 424, 79%), patients with a low level of PACs induced (<10 PACs/min) (n = 47, 9%), and patients with frequent PACs (≥10 PACs/min) (n = 65, 12%). The PACs were not targeted for ablation, although they were mapped and localized. The origin of

*Editorials published in *JACC: Clinical Electrophysiology* reflect the views of the authors and do not necessarily represent the views of *JACC: Clinical Electrophysiology* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2019.08.004

reproducible PACs was determined by positioning the mapping catheter in the superior vena cava, the right atrial free wall, the coronary sinus ostium, the interatrial septum, the left atrial posterior wall and the left atrial anterior wall in the vicinity of the left atrial appendage. The catheter was described to have been manipulated with great care to not mechanically induce beats. When PACs diminished after repositioning of the catheter, they were considered as induced by a mechanical stimulus of the catheter. The most frequent origin of non-PV PACs was the right atrial free wall (n = 53, 47%), followed by the intra-atrial septum, the left posterior wall, the superior vena cava, and the coronary sinus, with, of note, only rare PACs from the left atrial appendage (n = 2, 2%). During an average follow-up of 670 days, there was no significant difference in the AF recurrence rate among patients with frequent non-PV PACs (35%), rare non-PV PACs (26%), and no non-PV PACs (n = 424, 34%). Of importance, in a subgroup of patients who returned for a repeat procedure, the sites of non-PV PACs during the first procedure were frequently different from those of the non-PV AF-triggers during the second procedure and approximately one-half of these patients with non-PV PACs during the first procedure did not have them during the second procedure, suggesting the lack of reproducibility and therefore clinical significance of the observed PACs over time in most patients.

The study by Nakamaru et al. (5) offers a unique perspective that directly challenges some of the observations and assumptions previously made related to the need to target PACs that do not initiate AF. Electrophysiologists accept that not all ventricular premature contractions (PVCs) are worrisome and predispose to ventricular fibrillation. Right ventricular outflow tract PVCs are typically benign and in the absence of symptoms or signs of depressed left ventricular function, patients can be wisely reassured. In fact, PVCs have been reported commonly with isoproterenol infusion administered at the time of AF ablation procedures and are appropriately not routinely treated (10). Targeting PACs that are neither clearly causing symptoms nor associated with a suspected cardiomyopathy or associated with AF initiation may also provide no clinical benefit and just add to the length and possibly the risk of the AF ablation procedure. What makes the PAC particularly arrhythmogenic still needs to be deciphered, but in the absence of initiating AF at the time of provocative maneuvers, a cautious approach is recommended. It will be interesting to determine if the arrhythmogenicity of PACs is based on the spontaneity of event, coupling interval, anatomic site of origin, or other factors. The beneficial effect of empirically targeting frequent non-PV trigger sites as performed in the RASTA (Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation) trial suggests that site of origin may be a critical factor (11).

The uncommon origin of PACs from the left atrial appendage note by Nakamaru et al. (5) even with approximately one-third of their patients having persistent AF is consistent with other reports (1–5,12). The study results are at variance with reports that indicate more frequent PACs from the left atrial appendage that also suggest the need for appendage isolation to eliminate these PACs to improve AF outcome (6). The antiarrhythmic effects associated with left atrial appendage isolation may not be related to PAC elimination unless the PACs are documented to actually trigger AF. If there is an additional antiarrhythmic benefit from left atrial appendage isolation, as suggested by the BELIEF (Bevacizumab and ErLotinib in EGFR Mut+ NSCLC) trial, it is probably via another mechanism that needs to be determined (13).

In summary, Nakamaru et al. (5) add to an important body of information on non-PV triggers. Their study provides convincing evidence that: 1) provoked PACs alone may not serve as an appropriate target for elimination during an AF ablation procedure; 2) the left atrial appendage appears to represent an uncommon source of non-PV triggers and probably should not be targeted for isolation with the goal of eliminating PACs. Whether there is a beneficial debulking effect, autonomic alteration, or, as yet to be identified, antiarrhythmic benefit, needs to be established with certainty before left atrial appendage isolation becomes a routine versus selective approach for more persistent forms of AF. More work is also needed to resolve some of the profound discrepancies in other reported results on non-PV triggers: the most effective and reliable provocative maneuvers need to be defined, localization tools and techniques need to be improved (14), and the clinical importance of non-PV triggers' identification and ablation on long-term AF control with a randomized prospective study design needs to be considered. The puzzle still has a few missing pieces, but we are getting closer to getting a clearer view of the definition and importance of non-PV triggers in AF pathogenesis and management.

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JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 5, NO. 11, 2019
NOVEMBER 2019:1328–30

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KEY WORDS atrial fibrillation, catheter ablation, non-pulmonary vein, premature atrial contractions