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EDITORIAL COMMENT

Important Differences Exist Between Atrial Fibrillation and Atrial Flutter in Atrial Remodeling*

Hugh Calkins, MD

From a clinical perspective, atrial fibrillation (AF) and atrial flutter (AFL) share many similarities. They both are rapid upper chamber arrhythmias. They both cause a range of symptoms including palpitations, fatigue, and exercise intolerance. They both can cause a rate-related cardiomyopathy. They both increase stroke risk. They both can be treated with rate or rhythm control. They both respond to cardioversion. And, both respond to antiarrhythmic therapy or catheter ablation. These 2 rapid atrial arrhythmias are intertwined by the observation that without antecedent AF, AFL will rarely develop (1,2). This explains why one-third of patients effectively treated with ablation of the cavatricuspid isthmus developed clinically manifest AF at 15-month follow-up (3). But, we cannot forget the important differences between AF and AFL. AFL is harder to rate control and easier to ablate. The stroke risk in patients with AFL is less than those with AF. And, AFL results in a regular rhythm, whereas AF is irregular. In contrast to the well-defined clinical features of AF compared with AFL, remarkably little is known about the relative impact of AF and AFL on atrial remodeling.

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It is with this background that we consider the results of the study by Guichard et al. (4) in this issue of the *Journal*, which uses an animal model of atrial flutter to compare atrial remodeling caused by AF with that caused by AFL. An intercaval radiofrequency lesion created a substrate for sustained isthmus dependent AFL in 3 of the 4 cohorts. All dogs had an atrioventricular node ablation and ventricular pacemaker implanted and were paced at 80 beats/min. A total of 24 dogs were divided into 4 cohorts and were intensively studied 3 weeks later. One cohort of 6 dogs were in AFL. A second cohort of 6 dogs were in sustained AF and did not have an intercaval line created. A third cohort of 6 dogs had the intercaval line created for AFL but were in sustained AF. And, a final group of 6 dogs had the intercaval line created but remained in sinus rhythm for the duration of the study. At the termination of the 3-week study period, each dog underwent extensive evaluation to determine the relative degrees of structural and electrical remodeling, including an echocardiogram and a terminal open-chest electrophysiology study. The results of this study revealed that the effective refractory period was reduced similarly in each of the 3 AF and AFL groups as compared with the sinus rhythm control group. Each AF and AFL group also demonstrated an increase in AF vulnerability to AF induced with extra stimuli. But, the duration of induced AF was greater in the 2 AF cohorts but not the AFL group. The induced AF with an intercaval line had shorter CLs (cycle lengths) and substantial irregularity as compared with the AFL group. The left atrial volume increased in the 2 AF groups but not the AFL group. Another difference was that the 2 AF groups showed significant conduction delay on optical mapping and fibrosis and collagen-gene upregulation compared with the AFL group. A transcriptomic analysis revealed dysregulation of inflammatory and extracellular-matrix signaling pathways with AF but not AFL.

This study is a real tour de force contribution by a world-class team of basic electrophysiologists. As

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From the Johns Hopkins Hospital, Baltimore, Maryland. Dr. Calkins is a consultant and/or has received honoraria from Medtronic, Abbott Medical, Biosense, Boston Scientific, Ablacon, and Atricure.

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with the clinical features of AF and AFL reviewed in the previous text, some aspects of atrial remodeling in AF and AFL are similar and others differ. Not surprisingly, both AFL and AF shorten the effective refractory period and increase vulnerability to AF induced with atrial extrastimuli. But, what is a bit surprising and new, is the ways in which atrial remodeling differs with these 2 common arrhythmias. AF increases left atrial size but AFL does not. AF results in atrial conduction slowing, fibrosis, and collagen-gene up-regulation but AFL does not. And, AF results in dysregulation of inflammatory and extracellular-matrix pathways, but AFL does not.

This is by all measures an elegant and detailed study. But, should clinicians care? Is this information only of importance to basic scientists? I think not. From a clinical perspective these data explain why AF duration predicts the outcomes of AF ablation. The longer a patient is in AF the worse the outcome of AF ablation as the atria enlarge and become more fibrotic. But, this relationship has never been reported for AFL patients, and this study gives us scientific insight as to why this is the case. These data also help us to understand the belief that patients with AFL have lower stroke risk than AF patients. If AFL does not cause the same degree of left atrial dilation, enlargement, fibrosis, and inflammation, it only follows that stroke risk should be reduced.

At the end of the day I believe this an important study. We are grateful to the authors for the considerable time and effort put forth to make this publication possible.

ADDRESS FOR CORRESPONDENCE: Dr. Hugh Calkins, Johns Hopkins Hospital, Sheikh Zayed Tower 7125R, 1800 Orleans Street, Baltimore, Maryland 21287-6568. E-mail: hcalkins@jhmi.edu. Twitter: @HopkinsMedicine.

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