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LATENT ATRIAL FIBRILLATION TRIGGERS ORIGINATING IN ACCESSORY PATHWAYS

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In Wolff-Parkinson-White (WPW) syndrome,¹ atrial and ventricular myocardium are connected via one or more accessory pathways that allow electrical propagation across the normally insulated annulus fibrosus.² These accessory atrio-ventricular (AV) connections are believed to arise from residual tissue remaining from incomplete segmentation of the cardiac tube into atrial and ventricular chambers during development. Clinically, preexcitation syndromes are not associated with other structural heart disease in a majority of affected individuals.^{3, 4} However, the presence of preexcitation exposes some patients to rapidly conducted atrial tachyarrhythmias, and carries a small risk of sudden cardiac death.⁵

One of the most common arrhythmias in this setting is preexcited atrial fibrillation (AF),^{6, 7} which may occur in the absence of structural heart disease or the usual electrophysiologic substrate for AF.^{4, 8} The mechanism responsible for AF initiation in patients with accessory pathways is not completely understood. Successful surgical or catheter ablation of accessory pathways has been shown to reduce recurrence of AF,^{7, 9} suggesting that accessory pathways themselves may play a role in arrhythmogenesis. However, AF still occurs in some patients with WPW syndrome following successful ablation,^{3, 6, 10, 11} suggesting that intrinsic atrial properties may also play a role.

The Present Study

In this issue of *Heart Rhythm*, Schwieler *et al*¹² provide mechanistic insights into the relationship between accessory pathways and initiation of atrial fibrillation. They begin with an assessment of risk factors associated with AF in over 500 patients with preexcitation. Their examination of clinical records confirms that AF is more common in older males with manifest (compared to concealed) accessory pathways. The authors' ranking of these criteria suggests that male gender, manifest preexcitation and age (in that order) are most likely to be associated with AF occurrence in patients with accessory pathways. Atrial conduction times, P-wave duration or dispersion values were not shown to correlate with AF history. However, conflicting results in previous studies^{3, 13} suggest that AF recurrence may arise from atrial vulnerability to profibrillatory factors that are independent of the accessory pathway.

To computationally probe for possible mechanisms of reentry in the presence of accessory AV pathways, Schwieler *et al*¹² couple mathematical models of atrial and ventricular action potentials in 2-dimensional spaces joined by a small accessory pathway. Two configurations

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for accessory pathways are examined: (i) a linear passive element bridging the gap (measuring 2×6 mm) between excitable atrial and ventricular tissue, and (ii) a bifurcated accessory pathway with one fast and one slow branch connecting the atrial and ventricular regions.

In both scenarios, stimulation of atrial tissue produces antegrade wave propagation across accessory pathways, leading to retrograde waves propagating back through the atrial regions. Interactions between the resulting retrograde atrial waves and subsequent, well-timed and -placed stimuli are sufficient to induce wavebreak and trigger spiral waves that are believed to initiate fibrillation. In the case of the linear accessory pathway, the retrograde atrial wave is generated by reflection within the accessory pathway. In the case of the bifurcated accessory pathway, the retrograde wave results from microreentry progressing from the slow to fast branch of the accessory pathway. Retrograde reentry through the fast branch of the accessory pathway becomes feasible following unidirectional block at the junction of the fast accessory branch and the ventricular interface, resulting from source/sink mismatch.

The major conclusion of Schwieler *et al*¹²— that accessory AV pathways can potentially provide a substrate that generates latent triggers for AF initiation via either wave reflection or microreentry — sheds some light on the link between preexcitation and AF. This mechanism can operate independently of AV nodal function as well as in the absence of multiple accessory pathways. Such a mechanism is consistent with the clinical observations of minimal AF recurrence following successful ablation of accessory pathways.^{7, 9}

The Role of Computational Studies

Although computational studies are very elegant, there are major caveats to keep in mind when extrapolating these insights to a clinical context. These simulations were conceptualized in 2-dimensional compartments representing atrium, ventricle and accessory pathway. Real accessory pathways, as well as atrial and ventricular tissues, are three-dimensional structures with distinct heterogeneous compositions and variable geometries that have been simplified in the present study. Location and proximity of accessory pathways to the AV node or neighboring accessory pathways may play a role in initiation of AF or other arrhythmias such as AV reciprocating tachycardia. Even in the absence of AV nodal influences, it remains to be seen whether retrograde wavefronts originating from accessory pathways are as vulnerable to wavebreak induction and spiral wave initiation *in vivo* as they are *in silico*, where ideally shaped extrastimuli can be optimally timed and positioned. Nonetheless, the present findings strengthen the hypothesis that accessory pathways can act as sources for reflected and reentrant waves.

If reflected waves traveling in the retrograde direction can trigger spiral wave formation and fibrillation in the atria, this raises the possibility that, under appropriate conditions, a similar phenomenon might be possible on the ventricular side of the accessory pathway. Such reflected wave activity would require a particularly configured accessory pathway (i.e. requisite conduction delay, geometry, passive electrotonic element), but could potentially trigger similar fibrillatory episodes in the ventricles. Reflected ventricular waves penetrating retrogradely through tissue might provide an alternative mechanism to rapidly conducted AF for the rare WPW-related ventricular fibrillation¹⁴.

Tissue excitability: potential molecular clues

Another aspect of cellular electrophysiology in this condition related to data in familial WPW syndromes that show an association with missense mutations in the *PRKAG2* gene which encodes the $\gamma 2$ regulatory subunit of AMP-activated protein kinase.^{15, 16} Adenosine monophosphate-activated protein kinase (AMPK) regulates several cellular metabolic functions including ATP utilization, fatty acid oxidation, and creatine kinase activity. Recently,

transgenic mouse studies have shown that AMPK mutations can lead to structural disruptions in the annulus fibrosus, contributing to accessory pathway formation,¹⁷ as a result of glycogen handling abnormalities.¹⁸ Furthermore, AMPK is implicated in Na current (I_{Na}) regulation. Constitutively active AMPK mutations have been shown to prolong action potential durations in ventricular myocytes by slowing I_{Na} inactivation and causing a hyperpolarizing (leftward) shift in I_{Na} activation.¹⁹ While the impact of AMPK-dependent I_{Na} modifications on AF initiation in WPW syndrome have not yet been fully elucidated, it is interesting to note that Schwieler *et al*¹² enhance tissue excitability in both atrial and ventricular mathematical action potential models by employing a significant hyperpolarizing shift in I_{Na} activation.

In summary, the mechanisms for AF predisposition in WPW syndrome remain elusive. It is likely that AF propensity in WPW syndrome is multifactorial, involving the presence of an accessory pathway as well as atrial vulnerability that may be reflected in the gender and age biases towards AF. The study by Schwieler *et al* provides a useful examination of the role of the accessory pathway as a source for potential AF triggers.

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