Pulmonary vein cellular electrophysiology and atrial fibrillation: Does basic research help us understand clinical pulmonary-vein arrhythmogenesis?

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Arguably the most important discovery in the clinical electrophysiology of atrial fibrillation (AF) has been the recognition, largely through the work of Haissaguerre's group,[1] of the enormous importance of pulmonary vein (PV) myocardial sleeves in AF initiation. Numerous clinical investigators have confirmed the value of PV focal-source ablation and/or PV-left atrial disconnection in the management of AF, particularly of the paroxysmal variety.

Because of the substantial clinical importance of PV activity in AF, basic investigators have made great efforts to understand what specific properties of the PVs make them susceptible to ectopic impulse formation. In this issue of *Heart Rhythm*, Miyauchi et al[2] provide a novel contribution by showing that heterogeneous PV repolarization properties are associated with a propensity to early-after depolarization (EAD) and triggered-activity initiation by isoproterenol and rapid pacing. The mechanism(s) of this phenomenon is (are) not elucidated, but heterogeneous ion-current distribution and differential action-potential restitution are suggested by the investigators as potential contributors. Whether the abnormal activity is due to local reentry, to Ca^{2+}-induced triggered activity as has been suggested by previous investigators,[3] or to Ca^{2+}-current reactivation as for classical EADs[4] remains unknown.

These observations add an additional candidate mechanism for the basis of PV arrhythmia vulnerability, along with marked tissue anisotropy,[5] Ca^{2+}-handling abnormalities,[3] arrhythmogenic responses to local autonomic activity,[6] and peculiarities of PV ion-channel distribution.[7] However, these observations pose challenges to clinical and basic investigators alike. If normal PVs, as assessed in all of these studies, are so good at generating ectopic activity, why don't we all have paroxysmal AF, or at least frequent atrial ectopic activity? What is it about the PVs that make them such good arrhythmia generators in AF patients? Is there an underlying PV predisposition to arrhythmogenesis that requires only a specific additional insult to unmask (the "multiple-hit" theory)? If so, what is the insult that moves PV arrhythmogenesis from latent to manifest? Or is there some specific pathology to which clinically arrhythmogenic PVs are susceptible that simply never occurs in normal PVs? Although studies in normal experimental animals and their tissues give useful insights into basic differences between PV myocardial sleeves and atria, they may not reveal the path to clinical arrhythmogenesis. Until we understand the crucial mechanistic factor(s) that differentiate clinically normal from arrhythmogenic PVs, we will not understand the role of PVs in AF.

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