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Chasing with ranolazine pulmonary vein afterpotentials before it's too late

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By 1876, Brunton and Frayer had already observed the “independent pulsation” of the pulmonary veins (PV) in experimental animals by showing their continued pulsation long after the atria had ceased to beat.¹ However, it was Favaro who in 1910 first coined the term “pulmonary myocardium” (*il miocardio pulmonare*) by demonstrating atrial myocardial continuity (sleeve) between the atria and the thoracic veins.² In 1972 Spach, Barr, and Jewett demonstrated the propagation of excitation wave from the atria to the thoracic veins in humans and dogs.³ The PV myocardial sleeve is now established to be an important atrial anatomical site for triggering many of the human paroxysmal atrial tachycardia/fibrillations (AT/AF) of diverse etiologies.⁴ Not unexpectedly, the goals of recent experimental AF studies focused on identifying the cellular mechanisms by which the PV sleeve triggers AF and on assessing the influence of different classes of drugs on these trigger mechanisms. To accomplish these goals, different animal models were used that scaled up from isolated single pulmonary myocytes,⁵ isolated-superfused blocks of pulmonary veins,^{6,7} isolated coronary-perfused whole hearts,⁸⁻¹⁰ and in *in-situ* open-chest beating hearts.^{11,12}

In this issue of *Heart Rhythm*, Sicouri et al¹³ using isolated-superfused bits of canine PV (mainly left superior) report that ranolazine reduces PV myocyte action potential maximum upstroke velocity (V_{max}) (surrogate of I_{Na}), and promotes post-repolarization refractoriness causing intra-PV conduction block. Most interestingly, these authors found that ranolazine, the late sodium current (I_{Na}) inhibitor, suppressed PV afterpotentials in the form of EADs & DADs induced by increasing the autonomic influences (Ach + Iso) and elevating the Ca_i^{2+} concentrations by rapid pacing + elevated Ca_o^{+2} . The importance of intra-PV conduction block as a potential for triggering AF could not be determined in these studies that used isolated bits (1.5 by 2 cm) of PV tissues with severed atrial connections. However, the importance of ranolazine induced intra-PV conduction block in terminating PV reentry shown to occur transiently in the distal canine PV¹⁴ remains to be determined. Our sequential microelectrode “mapping” studies on PV in the isolated coronary-perfused whole rat hearts showed that a progressive rapid left atrial pacing resulted in the conversion of 1:1 capture to 2:1 capture in the distal PV myocardial cells (adventitial side of the vein) at a time when the left atrium, the proximal and mid PV myocardial cells maintained 1:1 capture.⁸ The intra-PV conduction block observed during the rapid atrial pacing, however, did not result in atrial ectopy.⁸ Interestingly, Miyauchi et al found that EADs and EAD-mediated

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triggered activity (induced by Iso and rapid pacing) propagated to the atria, causing rapid repetitive atrial activity.⁸ We further have shown that atrial tachycardia initiated by the late phase EAD-mediated triggered activity in or near the PV-left atrial junction could promote sustained AF in atria with increased interstitial fibrosis.¹⁵ The study of Sicouri et al demonstrating suppression of EADs and DADs by ranolazine may have significant therapeutic benefit against paroxysmal AF episodes triggered in the PV by either EADs or DADs. Ranolazine, by blocking the late I_{Na} , may suppress the EADs by eliminating the state of reduced repolarization reserve caused by the persistent I_{Na} during the repolarization. We think of EAD generation as an emergent property at the cellular scale.¹⁶ This indicates that the EAD is not caused by any single ionic current, instead it results from the dynamic interaction of multiple mechanisms that brings about a reduction in repolarization reserve (late I_{Na}), reactivation of L-type calcium current (I_{Ca-L})¹⁷ and activation of the sodium-calcium exchanger (forward mode)⁶ that control the EAD. Alteration in any one of these modules may disrupt the genesis of EAD. Most interestingly, EADs may be linked to DAD genesis in that during the EAD the L-type calcium channels remain open for longer durations, allowing more calcium to enter the cell causing greater loading of the SR. Calcium overloaded SRs are prone to release their calcium via a voltage independent mechanism during diastole causing the DADs.¹⁸ Suppression of EADs by ranolazine could therefore also suppress the DADs, as both mechanisms can coexist.¹⁹ Ranolazine may also terminate EAD- and DAD-mediated triggered activity in the ventricles so to suppress VF initiated by triggered activity. Assessing these potential antiarrhythmic benefits of ranolazine in intact hearts is clearly worth the time and effort.

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