Is Dispersion of Refractoriness the Key to Reentry Vulnerability in Myocardial Ischemia? Insights From Simulations.

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It is commonly known that reentrant arrhythmias, such as certain types of tachycardias and – most importantly - fibrillation, are life-threatening if they occur in the ventricles, and can become chronic (increasing mortality and morbidity) if they take place in the atria. Reentrant-type arrhythmias in heart tissue are normally initiated by the unidirectional block of the electrical wavefront traveling through the myocardium. Well-known experimental observations have shown that different myocardial zones with different degrees of electrical excitability must co-exist adjacent to each other in order for a reentry to occur. According to the classical theory, spatial dispersion of refractoriness (i.e. different values of effective refractory period [ERP] in neighboring zones) is the key to unidirectional block, because a wavefront can be blocked when entering a region with large ERP, surround it via short-ERP tissue, and retrogradely invade the large-ERP zone when its ERP has finished, giving rise to a reentrant pattern.

Although dispersion of refractoriness is thought to be the key factor in determining myocardial vulnerability to reentry, recent simulation work from our group has shown that this may not always be the case. In this work, we simulate reentrant activity during acute myocardial ischemia (a condition which is known to severely increase vulnerability to ventricular tachycardia and fibrillation) in a 2D virtual myocardium, and we show that dispersion of refractoriness is not correlated to reentry vulnerability. Instead, the "safety factor for propagation" (SF), a parameter that quantifies the source-sink relationship in conduction, is the index that should be looked at to explain reentrant arrhythmia generation.

For this purpose, we have used a second generation ionic current and action potential model (the Luo-Rudy model in its 2000 version) to simulate the electrical activity of myocardial cells. A 5.5x5.5 cm inhomogeneous and anisotropic 2D tissue was used in the simulations, and a central ischemic zone (CZ), surrounded by an electrophysiological border zone (BZ), was placed in the center of the tissue, using experimental data to reproduce conditions of hypoxia, hyperkalemia and acidosis as previously published by our group. Reentry was initiated by adequately timing two consecutive stimuli (S1-S2) delivered at one of the tissue borders. The Vulnerable Window (VW) for reentry was defined as the set of S1-S2 coupling intervals which gave rise to at least one complete reentry cycle, and its time-evolution during the first 10 minutes of acute ischemia was determined. Simultaneously, the ERP of all the cells of the virtual tissue was estimated using an h*j-based method previously published by our group, and the "actual" ERP of different selected zones was calculated using the classical protocol. The SF was also computed in all cells of the tissue using an extended and modified version of

the SF defined by Shaw and Rudy, which was made computationally effective for 2D calculations.

Our results are consistent with experimental studies and show that vulnerability to ventricular arrhythmias has a unimodal behavior in the acute phase of ischemia. In the early stages of ischemia (prior to minute 6.5), our simulations show no reentry. For further minutes of ischemia, the width of the VW widens and reaches a maximum value of 58 ms for minute 8. Finally the VW diminishes again (and eventually vanishes) as ischemic conditions become more severe.

Patterns of activation and maps of ERP in the different stages of ischemia show that dispersion in refractoriness is a necessary condition for the tissue to nest reentry. In the eighth minute of ischemia, the ERP map is drastically more abrupt than in early stages (minute 4) where no reentry is found. However, as ischemia progresses, the values of the maximum difference between the measured ERP in the different zones of the tissue (an indicator of dispersion in refractoriness) increase from 84 ms at minute 6.5 to 214 ms at minute 8.75. However, this monotonous increase is not coupled to the VW time-course, as it does not present such a unimodal behavior. Indeed, the correlation coefficient between dispersion of refractoriness and the VW yields only 0.03.

These results suggest that although dispersion of refractoriness is necessary for reentry to occur, its spatial dispersion degree does not correlate with vulnerability. When further analyzing the role of refractoriness in the reentry initiation process, we find a clear relationship between dispersion of refractoriness and reentry initiation in 57% of the reentries. However, in the other 43%, conduction block occurs in myocardial zones that have already recovered from refractoriness. Thus, other ionic factors such as axial currents must be involved in the modulation of the vulnerability to reentry.

To further investigate the role of axial currents in the genesis of reentry, we mapped the SF in the tissue during the initiation phase of reentry. Our results show, on the one hand, that the three main components of ischemia (hyperkalemia, acidosis and hypoxia) tend to reduce the SF, though in a very different manner. Hypoxia, in particular, does not reduce the SF significantly but anticipates the occurrence of block when combined with hyperkalemia. On the other hand, the SF value reaches values below 1 in our simulations at the sites where unidirectional block (the reentry precursor) occurs, indicating that source-sink mismatches (rather than refractoriness) is the ultimate cause of conduction block.

In conclusion, the SF approach provides new insight in the mechanisms responsible for reentry in ischemia, as unidirectional block takes place as a result of source-sink relationship reduction, which is intimately related to axial currents, rather than dispersion of refractoriness. The effects of the main components of ischemia on the SF shed light on their role in ischemic reentry generation.