Published in final edited form as:

Heart Rhythm. 2009 June ; 6(6): 823–824. doi:10.1016/j.hrthm.2009.03.021.

Turning On/Off the Dome in Phase 2 Reentry: The Switching Wave Hypothesis

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Knowledge that most cases of ventricular tachycardia and fibrillation (VT/VF) depend on either anatomic or functional reentry for their maintenance leads to the search for new mechanisms of abnormal impulse generation and propagation that may result in such complex self-sustained patterns of activation. The normal cardiac wavefront may undergo functional block upon interacting with another wavefront generated by a variety of ectopic mechanisms, including automaticity, early or delayed after-depolarizations, reflection, and the so called “phase 2 reentry” (P2R). P2R refers to a particular type of ectopic discharge in which re-excitation is generated at the interface between cells exhibiting a spike-and-dome action potential morphology and cells lacking such a dome and whose action potential duration is abnormally abbreviated. It has been demonstrated that under such heterogeneous conditions electrotonically mediated re-excitation can be triggered during the dome phase (phase 2) and spread, either retrogradely or anterogradely. The P2R wave in itself is not predicted to sustain fibrillation but it runs the risk of interacting with other waves to precipitate rotors and fibrillation, as suggested for example for VT/VF in the setting of Brugada syndrome¹ and of ischemia², both of which are notorious for generating heterogeneity.

At the cellular level, the presence or absence of a spike and dome configuration of the action potential depends on the balance of membrane currents that are active during the rapid early repolarization phase (phase 1), mainly the transient outward current (I_{to}), the sodium current (I_{Na}), and the current that dominates the beginning of the dome phase; i.e., the L-type calcium current ($I_{Ca,L}$). Hence, the complex spike and dome morphology that has been observed under various conditions has been attributed by investigators to the non-linear nature of the interplay between the transmembrane voltage and its ionic currents, primarily I_{to} and $I_{Ca,L}$.³ In this issue of *Heart Rhythm*, Maoz et al⁴ present an elegant numerical study postulating that the contribution of the unstable dependence of the action potential dome on I_{to} to P2R goes beyond the I_{to} intrinsic heterogeneity. Rather, these investigators demonstrate that the probability for a heterogeneous dome-shaped action potential resulting in a P2R increases in relation to the high sensitivity of the action potential morphology to I_{to} . At the single cell level they reproduced the exquisite sensitivity of the action potential to the I_{to} conductance (G_{to}), in such a way that a G_{to} reduction of just 10-20% (from 1.3 to 1.1 mS/ μ F) abruptly changed the action potential morphology from loss-of-dome to spike-and-

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dome with about a 3 fold prolongation. Interestingly, an unstable regime of G_{to} over a considerably wide range of values (from 1.25 to 1.65 mS/ μ F) was found to generate repetitive switching sequences between the two morphologies in response to a rhythmic pacing at 1 Hz, suggesting a temporal scale that is relevant to the normal heart rate. When propagation of action potentials was studied along a cable with G_{to} in the switching regime, the P2R occurrence increased compared with a cable with G_{to} outside that regime. Somewhat surprisingly, spatial G_{to} heterogeneity was not critical for the P2R as even a homogeneous cable was not spared from P2R induced by intermittent heterogeneity in dome-shaped action potential when the G_{to} was set within its switching regime.

The study by Maoz et al enhances our understanding of the mechanisms leading to P2R. The demonstration that heterogeneities in dome morphology that lead to P2R may be functionally induced by waves traveling in the medium challenges the role of the intrinsic heterogeneity and provokes a number of relevant questions. For example, it would be very important to assess the relative contribution to P2R of intrinsic versus functional heterogeneities under more realistic conditions as the functional heterogeneity hypothesis would render P2R relevant to heart conditions without heterogeneity. In the present study, it is very likely that the pacing and geometry of the model had an indirect effect on the dynamics found to lead or not to P2R. Thus understanding the mechanism by which a local injection of current at the pacing site causes the breaking up of the homogeneity at some particular distance along the uniform cable seems critical. It would then be of interest to assess the effect of altered distribution of electrotonic currents as present in the whole heart on the formation of that heterogeneity. In this regard, one should wonder whether a modification of the liminal length hypothesis is applicable to the understanding of heterogeneity formation in the sense that, for re-excitation to propagate, more than a critical number of cells along the simulated cable must be depolarized simultaneously. In addition, one may speculate that decreasing the input resistance and increase in the space constant of the medium, either by increasing intercellular coupling⁵ or reducing membrane conductance, would be unfavorable for the formation of P2R, as it will tend to reduce functional gradients. Yet another question that is provoked by the study of Maoz et al⁴ relates to whether the P2R periodicity induced by the switching is related in any way to action potential duration and conduction velocity restitution. Establishing the mechanistic link between those hypotheses as triggers of VF may be an important step towards clinically-relevant understanding and possible application.⁶ Although it still remains to be seen to what extent and under what conditions the mechanism proposed by Maoz et al contributes to P2R, their paper is already important in elucidating the behavior of ectopic cardiac excitability and encouraging further research. Reading through their paper we are again reminded that cardiac activity as a multivariate non-linear system, although deterministic, is very hard to predict.

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