Electrical Restitution Hysteresis
Good Memory or Delayed Response?

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The action potential duration (APD) of ventricular myocytes depends on the length of the preceding diastolic interval (DI) in a relationship termed “electrical restitution.” The APD shortens with decreasing cycle length and thus with decreasing DI. The teleological advantage of this phenomenon is that it provides increased time for excitation-contraction coupling at long cycle lengths while preserving diastolic time for coronary perfusion and ventricular filling at short cycle lengths.

Restitution of the APD may also lead to rich behavior in beat-to-beat APD fluctuations. At a fixed cycle length, a perturbation in action potential that shortens the APD results in concomitant shortening of the DI. The APD restitution relationship dictates that a prolonged DI will lead to lengthening of the APD. Thus, the initial perturbation results in alternation in APD between values that are shorter or longer than the steady-state APD. Whether the APD oscillations grow or decay depends on whether the slope of the restitution curve in the region near the steady state is greater than or less than unity. In the case of growing APD alternans, regions of myocardium may develop sufficiently long APD on some beats as to be rendered refractory to activation on the subsequent beat. This results in wavebreak and the substrate for reentry and fibrillation.

But there is further complexity in electrical restitution in that the shape and duration of the action potential depend on more than just the DI of the preceding beat. The APD observed at any given DI is not unique and depends on the history of activation sequence leading up to that beat. In this issue of Circulation Research, Wu and Patwardhan report on APD restitution in canine isolated ventricular tissue preparations using oscillatory sequences of DI. These investigators made use of a system they previously developed to provide explicit control over DI by starting a timer when the action potential achieved 90% repolarization and stimulating the tissue when the elapsed time reached the prescribed DI for that beat. They utilized sequences in which DI varied linearly, sinusoidally, and randomly.

Wu and Patwardhan found that the relationship between APD and preceding DI followed a hysteresis loop rather than a fixed unimodal curve when DI varied sinusoidally. For a given DI, APD was consistently lower when DI was on the rising limb than when DI was falling. When DI varied randomly, the plot of APD versus preceding DI consisted of points that largely filled the interior of a hysteresis loop. When DI varied linearly (following a triangular wave), the APD-versus-DI curve followed a hysteresis loop similar to that observed during sinusoidally varying DI, although with a somewhat shallower set of slopes. These findings are consistent with those of Elharrar and Surawicz, who showed two decades ago that the restitution curve is shifted higher for sequences with long cycle lengths than that found for sequences with shorter cycle lengths. Of note, both the ascending and descending limbs of the hysteresis loops obtained by Wu and Patwardhan curved monotonically, without evidence of supernormal APDs, as has been observed by others. This may reflect the fact that most of the data were collected at DIs longer than that at which supernormality is typically observed. The authors demonstrate by graphical simulation that the presence of hysteresis in APD restitution has the effect of dampening fluctuations in APD, thus stabilizing the substrate against “runaway” oscillations, even if part of the restitution curve has slope greater than unity, consistent with the findings of others.

The elegant experiments performed by these investigators beg the question of what is the mechanism that underlies hysteresis in APD restitution. The phenomenon is often characterized as a manifestation of cardiac memory. Memory is an attractive description for APD restitution hysteresis, because the APD is longer than that predicted by a simple unimodal restitution curve if the previous APD is long and shorter than that predicted if the previous APD is short, as if the tissue remembers. The short-term influence of activation history on APD should not be confused, however, with changes in T-wave shape or polarity lasting days to weeks after altered activation sequence (eg, cessation of ventricular pacing), an effect also termed “cardiac memory.”

Several investigators have studied APD memory by measuring the dependence of $APD_{n+1}$ on $APD_n$ (where the subscript refers to the beat number) and with mathematical models in which $APD_{n+1}$ depends explicitly on $APD_n$. A simple example of a memory effect is demonstrated in the Figure. Panel A shows a unimodal restitution curve, in which APD depends on the preceding DI according to the equation

$$APD_{n+1} = \alpha - \beta e^{-D_n/\tau},$$

where $\alpha$ is the asymptotic value of APD at long DIs, $\beta$ is the maximum negative change in APD, $\tau$ is the time constant of the exponential decay, and $D_n$ is the preceding DI.
a model similar to that used by Watanabe and Koller. In these simulations, \( \alpha = 290 \) ms, \( \beta = 90 \) ms, and \( \tau = 200 \) ms. Panel B shows the development of hysteresis when APD memory is added. Here, memory is introduced by setting

\[
\text{APD}_{n+1} = \alpha - \beta \cdot \text{exp} \left( - \frac{3}{4} \sum_{i=0}^{3} \text{DI}_{n-i} / \tau \right).
\]

In this case, the APD depends on the DIs of previous beats but not on the previous APD. In this case, hysteresis in APD restitution can be explained without invoking novel feed-forward mechanisms that link the inward currents of one beat to the next. Rather, modified kinetics of the ionic mechanisms that govern unimodal APD restitution would be sufficient to achieve hysteresis and the appearance of "memory." This would occur, for example, if \( I_{\text{Kr}} \) and \( I_{\text{Ks}} \) were themselves slow to respond to changing DI. Import-
tantly, however, nonlinear behavior must be present as well, to explain asymmetry in the hysteresis loop and different delay times between DI and APD peaks and nadirs, as observed by Wu and Patwardhan.\(^{10}\)

Identification of the mechanism that underlies APD restitution hysteresis is more than just an academic exercise. Since hysteresis in the restitution curve serves to dampen APD oscillations and potentially prevent malignant arrhythmias, it would be useful to discover strategies to augment this phenomenon. Flattening the restitution curve has been shown to be potentially antifibrillatory,\(^ {23}\) although this remains controversial.\(^ {21}\) Establishing the mechanistic underpinnings of restitution hysteresis will hopefully provide a new target for antiarrhythmic therapy.

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**References**


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