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EDITORIAL

Restitution slope is determined by the steady state action potential duration: law and disorder

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This editorial refers to 'Restitution slope is principally determined by steady-state action potential duration' by M.J. Shattock *et al.*, pp. 817–828.

In this issue of Cardiovascular Research, Michael Shattock and co-authors publish data that support the statement that the maximum slope of the ventricular restitution curve is determined by the steady state action potential.[1] Restitution, the relation between action potential duration (APD) and the preceding diastolic interval, is an important characteristic of myocardium because it allows shortening of the APD with increasing heart rates. The maximum slope of the restitution relation is important for arrhythmogenesis. A sudden change from a slow to a fast heart rate induces beat by beat variation in APD (alternation). It has been suggested that if the maximum slope of the restitution relation exceeds 1 this alternation does not die out but causes wave break and ventricular fibrillation.[2] In hearts of patients undergoing cardiac surgery, restitution has been measured at multiple sites.[3] The maximum slope regionally exceeded 1 in these patients at risk for arrhythmias.[3] Also in models of classical reentry a steep restitution slope (although not necessarily with a slope >1) facilitates arrhythmia based on reentry.[4,5]

It is generally accepted that the dV/dt_{max} of the upstroke of the action potential is the equivalent of the maximum net inward current.[6] Likewise, the dV/dt_{min} of the cardiac action potential is the equivalent of the maximum net outward current that causes repolarization. The concept that the maximum slope of the ventricular restitution curve is determined by the steady state action potential is directly derived from previous work by the authors in which they have demonstrated that the duration of the cardiac action potential depends on the repolarizing rate.[7] The idea is summarized in the figure (compiled and modified from Winter *et al.* [7] and Shattock *et al.*[1]). Winter *et al.*[7] have previously demonstrated that a similar change between the slopes of the repolarization rates (depicted in the figure as angle α) results in a much larger difference in APD when the initial action potential is long than when the initial action potential is short (*Figure 1A*). This dependence is simply caused by the morphology of the action potential. Therefore, the relation between net repolarizing current (the slope of the repolarization rate of the action potential) and the APD is non-linear (*Figure 1B*). If the same increase in repolarizing current is applied to the starting points *1* and *3* (figure, arrows) a larger decrease in APD occurs when the action potential is long, than when it is short (*Figure 1C*). This is valid for any basic cycle length (S1 stimulation).

Shattock *et al.* take this message a step further, by extrapolating their findings to the restitution curve. Following the same reasoning as in Winter *et al.*,[7] the authors now demonstrate that the maximum slope of the restitution curve, and indeed the restitution curve as a whole, is determined by the maximum APD of the restitution curve (the steady state APD). The figure (*Figure 1D*) schematically shows the last action potential of a train of S1 stimuli, followed by premature action potentials (after a S2 stimulus) with a short and long (steady state) diastolic interval. From the article of Shattock *et al.* in this issue of Cardiovascular Research it is now clear that the restitution curves belonging to a long steady state APD and that of a short steady state APD by necessity converge. This implies that if APD differences exist between the two restitution curves at long diastolic intervals (long cycle lengths), they tend to disappear at short diastolic intervals (short cycle lengths) and, therefore, that the slope of the restitution curve is steeper in the red (with the longer steady state APD) than in the green curve (with the shorter steady state APD).

A scientific law is a statement that is based on multiple experimental observations that points to a causal relation between the components of the statement and that has general applicability in more or less equal conditions. Based on such a statement, predictions can be formulated and tested. The idea presented in the article by Shattock *et al.* shares characteristics with those of a biological law. The traditional response of a scientist to a statement that claims general applicability is to find the exception that proves the statement wrong. Our system of peer review is intended to challenge the ideas of authors to the extreme, in order to test and improve the scientific quality of a article. The peers thereby are incited to play the role of the ultimate skeptic, that of the 'devil's advocate'. It is only natural that the reviewers question the claim of general applicability and demand demonstration of the validity of the alleged law under all possible conditions. The article of Shattock *et al.* carries all signs inflicted by the skeptic's peer review process. Despite these multiple and apparently disordered challenges of their idea, the authors have succeeded to write the story in a coherent manner. Their statement is tested under a plethora of conditions pertinent to normal heart function as well as to pathological heart function, involving pharmacological challenges with drugs that either prolong or shorten APD, but also with

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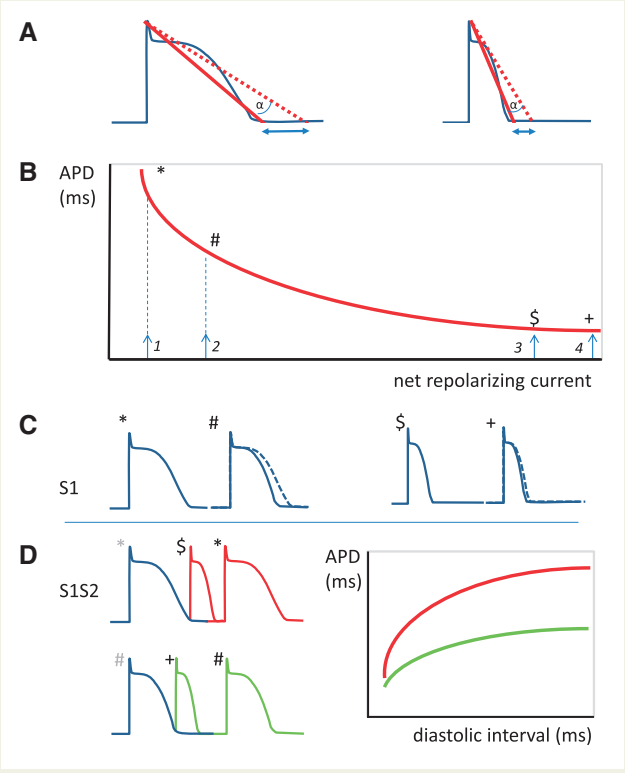

Figure 1 Schematic representation of the relation between repolarization rate, APD and restitution slope. (*A*) Two schematic action potentials are shown. Superimposed red drawn lines indicate the averaged repolarization rate (the net repolarizing current). A change in repolarization rate (from the drawn to the dotted red lines) with the same angle α induces a larger increase in APD in the long than in the short action potential (two-headed arrows) (modified from Winter *et al.*[7]). (*B*) Schematic representation of the relation depicted in (*A*). A similar change in net repolarizing current (from arrow 1 to 2, and from arrow *3* to *4*) causes a larger decrease of (APD) in the starting condition * (a long APD) than in $(a short action potential). (modified from Shattock *et al.*[1]). (*C*) Schematic action potentials during various, regular pacing rates (S1) with decreasing cycle lengths marked in (*B*) (*,#,$,+). Superimposed dotted lines represent action potentials * and $, respectively, for comparison. (*D*) Left: The last action potential of a train of S1 stimuli, followed by premature action potentials (after stimulus S2) with a variable diastolic interval. The action potentials marked * (red) and # (green) follow after a long diastolic interval and have the same duration as the corresponding last S1 action potential (they have reached a steady state), those marked # and + follow a short diastolic interval (compare with *B* and *C*). The difference between the APD of + and # is much smaller than that between $ and *. Thus, the restitution curves converge (*D*, right) and the slopes of the restitution curves depend on the APD at a long diastolic interval (steady state). Compiled and modified from Winter *et al.*[7] and Shattock *et al.*[1] Note that the X- and Y-axes of the second panel are interchanged in comparison to figure 1C in Ref. 1. APD, action potential duration; S1, stimulus 1 (basic cycle length); S2, stimulus 2 (premature stimulus).

drugs that do not affect APD. Heart rate is changed (as a method to induce short term memory). Sympathetic and parasympathetic stimulation is performed (pharmacologically and neurally), and current is injected into myocytes. Transaortic constriction is employed to induce heart failure and hypertrophy. Furthermore, two different species are employed. Tests are applied on isolated perfused hearts and on isolated myocytes and with two different pacing protocols to generate restitution data (dynamic restitution, S1S2 restitution). Under all the tested conditions the relation between steady-state APD and restitution slope holds. Normalization of the restitution curve relative to the steady-state APD (APD_{ss}) renders the same restitution slope under all tested conditions.

The authors demonstrate that the mathematical dependence of APD on the other factors in Equation (1) in their article (the time constant, the minimum diastolic interval or the normalized minimum diastolic interval) is absent and therefore that APD is only determined by APD_{ss}.[1] The implications of this relation are important. First, the relation not only is valid for the restitution slope, but also for the entire restitution curve. This implies that we now have a method to correct APD for diastolic interval (or the QT interval on the ECG for heart rate). The traditional Bazett formula is based on an empirical relation between QT and RR-intervals of multiple individuals.[8] We can replace it by a method that is accurate and that can be individualized (probably by defining the time constant of restitution in each individual). Second, we can understand that the hope for a drug with class III action with use-dependent characteristics is vain. If we prolong (pharmacologically, genetically or otherwise) the APD_{ss} the restitution slope will be steeper and the 'dreamed' (antiarrhythmic) increase of APD at shorter cycle lengths will be less than anticipated (*Figure 1D*). Third, because APD depends on the net repolarizing current (*Figure 1B*),[1] and APD can be used as a surrogate measure of this current, it allows quantification of what is called repolarization reserve (the ability of a myocyte to repolarize when one of the repolarizing currents is blocked).[9] A caveat is that multiple ion currents contribute to the plateau phase of the action potential and thus may complicate the picture.

Reentry is dependent on the refractory period[10] and APD is often equated with the refractory period. This is true in most healthy myocardium, but not when post repolarization refractoriness is present. In that case the refractory period extends beyond the duration of repolarization. This occurs in acute myocardial ischemia or after the application of some pharmacological drugs, especially at short coupling intervals.[11] Thus, caution should be used when extrapolating the statement on APD by Shattock *et al.* to the refractory period and reentry.

It is not often that one encounters a new law in biology. Shattock *et al.*[1] describe what can be conceived as a law in cardiac electrophysiology.

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