VIEWPOINT

The role of the autonomic system in rate-dependent repolarization changes

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Cardiac autonomic effects include modulation of sinus pacemaker rate and of ion fluxes in the working myocardium (atria and ventricles). On the other hand, many of the ionic currents determining action potential duration (APD), including those subject to direct autonomic modulation, are also intrinsically rate dependent. Therefore, autonomic modulation of repolarization can be unambiguously defined only if its rate dependency is considered. A systematic analysis of autonomic modulation of APD rate dependency requires controlling heart rate over a broad range of values while exposing the working myocardium to neural stimulation (or receptor agonists). This is difficult to achieve in humans; therefore, studies in animal species with human-like repolarization (guinea pig, rabbit, cat, dog, pig) would be pivotal for this purpose. Unfortunately, the literature available claims that even the sign of autonomic modulation of repolarization (i.e., APD shortening vs. prolongation) is inconsistent among these species, thus questioning the possibility of generalizing results. Differences are often explained by species specificity of I_{Ks}, an important repolarizing current under autonomic modulation. Herein we critically review such literature and come to the tentative conclusion that autonomic modulation of repolarization might depend on action potential contour, rather than reflecting species specificity of individual current components. Moreover, we propose that under physiological conditions, autonomic modulation may serve to stabilize repolarization at its rate-determined course, rather than independently acting to change it.

Single cell studies

Guinea pig action potential has a pronounced plateau phase; therefore, it is often studied to evaluate modulation of repolarization. In guinea pig ventricular myocytes, β-adrenergic receptor (βAR) stimulation by isoproterenol selectively prolongs APD at long cycle lengths (CLs), thus increasing the steepness of the steady-state APD/CL relationship (Figure 1A). An analysis of the underlying ionic mechanisms by the action potential clamp (AP-clamp) technique showed that this is readily explained by the rate-dependent behavior of isoproterenol-induced membrane current, which mainly includes I_{Ks}, I_{CaL}, and currents activated by Ca^{2+} influx.[1] In particular, the I_{Ks} component of isoproterenol-induced current was enhanced at shorter CLs, consistent with the well-described I_{Ks} behavior in this species.

Opposite of what occurs in guinea pig, in canine ventricular myocytes isoproterenol shortens APD at long CLs, thus decreasing the steepness of the steady-state APD/CL relationship[2] (Figure 1B). In this preparation, isoproterenol effect on I_{Ks} rate dependency was studied by a pseudo AP-clamp technique in which the same action potential waveform, acquired at a long CL, was applied with different diastolic intervals.[2] Under this condition, isoproterenol-stimulated I_{Ks} increased at shorter CLs, a pattern qualitatively similar to that observed in guinea pig myocytes and thus seemingly unsuitable to explain the opposite APD response. This contradiction was explained by rate dependency of the *relative* contribution of I_{Ks} to net membrane current,[2] an argument difficult to reconcile with the linear dependency of repolarization velocity on the *absolute* value of net membrane current.[3,4] In our opinion, a better mechanistic interpretation of the difference between guinea pig and dog response patterns is suggested by prediction of I_{Ks} rate dependency in the 2 species provided by numerical action potential models.[5] In in-silico experiments, I_{Ks} rate dependency was found to be opposite between the 2 species (direct in guinea pig and inverse in dog) because of the peculiar spike-and-dome contour of the canine action potential. Such contour, which supports faster I_{Ks} activation, is minimized at short CLs because of incomplete I_{to} recovery, thus providing a mechanism of inverse rate dependency.[5] Although adrenergic modulation was not directly addressed by this modeling study, the reported species differences in I_{Ks} rate dependency is suitable to account for the opposite APD modulation by isoproterenol between guinea pig and dog myocytes. Notably, according to this interpretation, I_{to} expression, rather than intrinsic I_{Ks} properties, would be the primary factor accounting

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ABBREVIATIONS **AP** = action potential; **APD** = action potential duration; **βAR** = beta-adrenergic receptors; **CL** = cycle length; **MAP** = monophasic action potential; **QT** = electrocardiographic QT interval; **QTc** = rate-corrected QT interval; **RRD** = repolarization rate-dependency (Heart Rhythm 2010;7:1700–1703)

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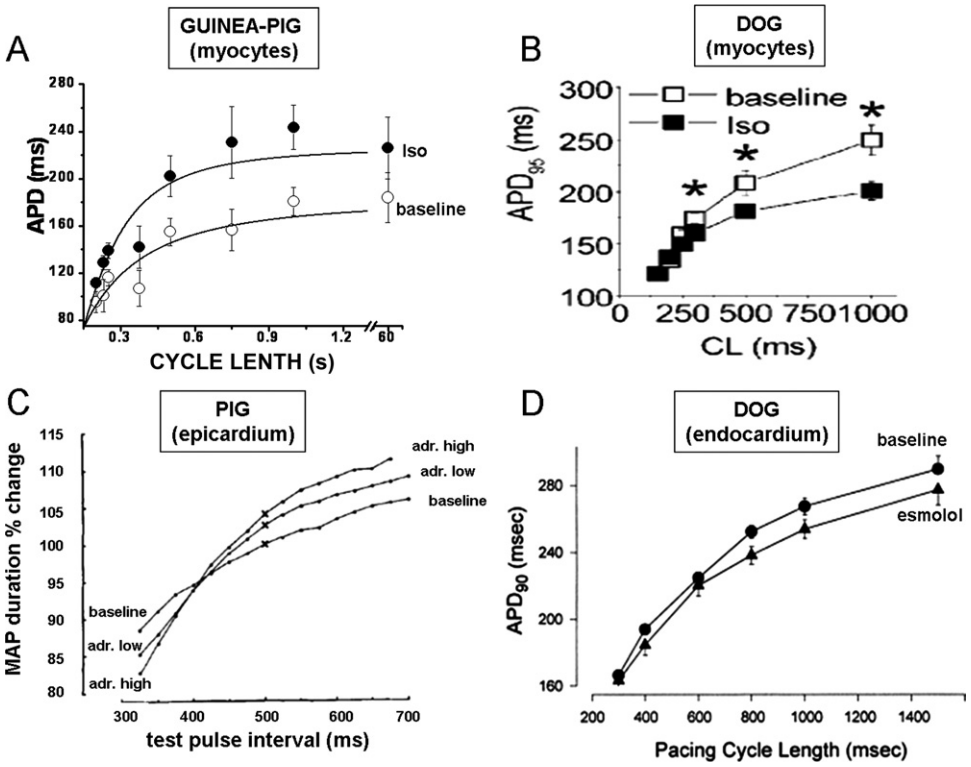

Figure 1 **A:** Effect of βAR stimulation on steady-state APD/CL relationship in guinea pig myocytes (modified with permission from Rocchetti et al[1]). **B:** Effect of βAR stimulation on steady-state APD/CL relationship in dog myocytes (modified with permission from Stengl et al[2]). **C:** Effect of βAR stimulation on APD restitution in pig epicardium (modified with permission from Taggart et al[15]). **D:** Effect of βAR blockade (esmolol) on APD steady-state APD/CL in dog endocardium (modified with permission from Peralta et al[12]). Iso = isoproterenol; adr = adrenaline (low and high dose). βAR = beta-adrenergic receptors; APD = action potential duration; CL = cycle length.

for the difference. I_{to}, almost absent in the guinea pig, is nonuniformly expressed across the canine ventricular wall. This suggests that even within the same species, autonomic modulation of APD rate dependency may change sign between subendocardial and subepicardial layers.

Different I_{Ks} gating properties are often claimed to be primarily responsible for species difference in modulation of APD rate dependency. A common view is that in guinea pig, only diastolic deactivation of I_{Ks} is slow enough to promote accumulation of the channel open state within diastolic intervals in the physiological range. However, the I_{Ks} deactivation rate has been seldom measured at diastolic potentials, and according to our own measurements (τ = 43 ms at −80 mV, 36.5°C),[6] it is too fast to afford sizable open-state accumulation even in guinea pig myocytes. If this is the case, what is the mechanism of I_{Ks} rate dependency? AP clamp experiments showed that I_{Ks} open-state accumulation is indeed very small in guinea pig myocytes;[7] rate-dependent acceleration of time-dependent I_{Ks} onset was observed instead and was markedly enhanced by βAR stimulation.[6] Thus, the major contribution to rate-dependent I_{Ks} enhancement in the guinea pig may be provided by accumulation of channels in a nonconducting state proximal to the open one, which may outlast current deactivation.[7,8] This mechanism makes I_{Ks} rate dependency theoretically compatible with fast deactivation kinetics, and its existence in larger mammals has not been investigated thus far. Although the above considerations may question species specificity of I_{Ks} kinetics, many reports converge to indicate that constitutive I_{Ks} density is very low in dogs and humans. Thus, some degree of βAR stimulation may be required to support baseline I_{Ks} expression during canine (e.g., Biliczki et al[9]) and human (e.g., Iost et al[10]) repolarization in the heart in situ.

In vivo studies

Irrespective of the underlying mechanism, the single-cell studies discussed previously support a sharp distinction between the guinea pig and dog in autonomic modulation of APD rate dependency. The picture becomes more confused if in vivo measurements are considered. A potential source of confusion is that analysis of APD rate dependency at steady state is often replaced by APD restitution analysis in in-vivo studies. However, "restitution portrait" analysis has recently shown that when simultaneously measured, the parameters describing steady-state rate dependency and restitution are linked by strong direct proportionality.[11] Therefore, for the purpose of the following discussion, it is safe to assume that modulation should change the 2 types of measurements in the same direction (see also Peralta et al[12]).

In anesthetized cats with left ventricular endocardial monophasic action potential (MAP) recordings, manipulation of ventricular neural output (by unilateral sympathetic denervations, βAR-blockade, vagotomy) modulated APD rate dependency consistently with the dog pattern (i.e., the steepness of the steady-state APD/CL relationship was decreased by sympathetic activation or vagotomy).[13,14] However, catecholamines infusion increased restitution steepness in the epicardium of anesthetized pigs (left ventricular MAP recordings)[15] (Figure 1C) and human endocardium (right ventricular MAP recordings).[16] In both cases, the modulation sign was surprisingly consistent with the guinea pig pattern. In the endocardium of dogs (left ventricle)[12]