Delayed rectifier currents and stability of ventricular repolarization. The case of Brugada's syndrome.

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In cardiac muscle the shape of the action potential has a pivotal role in maintaining normal excitation and in modulating its coupling to contraction. Repolarization contour varies among different regions of the heart (conduction system vs. working myocardium, endocardium vs. epicardium, etc.) with a well-defined pattern, suitable to maintain the correct relationship between activation times and local refractory periods. If this pattern is grossly altered abnormal excitation may occur; thus, "stability" of repolarization at any given site may be crucial to maintain physiological activation of the muscle. Brugada's and long QT syndromes (LQTS) are examples of arrhythmogenesis resulting from local repolarization instability.

Delayed rectifier currents (I_{Kr} and I_{Ks}) are important contributors to the repolarization process; while they are directly involved in the pathogenesis of LQTS, little is known on their significance in Brugada's syndrome. Here we will discuss the different roles for I_{Kr} and I_{Ks} in determining repolarization stability and speculate on their impact on repolarization abnormalities thought to underlie Brugada's syndrome. We will pursue this aim by using numerical models of I_{Kr} and I_{Ks}, developed and validated by experimental observations in the guinea-pig (1;2). The gating parameters have been modified here to reproduce the slower kinetics peculiar of canine currents (3;4), this with the purpose of applying the model to epicardial action potentials with the "spike and dome" morphology relevant to the pathogenesis of Brugada's syndrome. Since the available information on the voltage-dependency of I_{Kr} and I_{Ks} kinetics in canine myocytes is only partial, the simulations should be considered only in qualitative terms.

As a consequence of the steep voltage-dependency of ionic conductances, a reciprocal relation exists between membrane current (I_m) and potential (V_m). This implies that any (primary) change in V_m, will feed-back on I_m , whose changes will in turn cause V_m to vary further. Such a circular process continues until a new stable repolarization contour is achieved. Hence, the steady-sate (observed) effect of a perturbation will depend on its features as well as on those of the I_m-V_m feed-back cycle. Depending on the kinetic properties of the specific conductance(s) involved, the membrane current-potential feed-back can be either positive or negative. A feed-back is defined as "positive" if it tends to amplify the initial perturbation. Conversely, a "negative" feed-back would buffer the changes induced by the same perturbation. The magnitude of the amplification/buffering process will be referred to as the "gain" of the feed-back circuit.

During the plateau phase of repolarization, I_{Kr} conductance is mainly determined by the time course of membrane potential, increasing more steeply as repolarization is accelerated (1;4) (FIG 1a and b); this can be explained as follows.

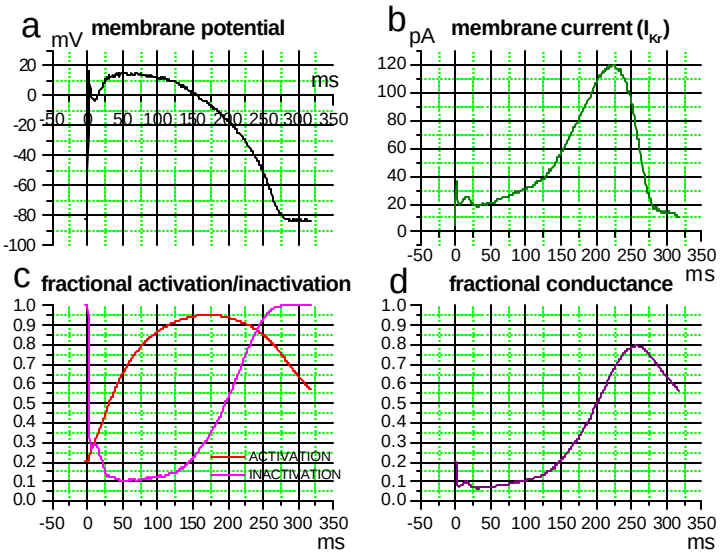

Figure 1: Predicted time course of I_{Kr}: membrane current (b), activation and inactivation gating variables (b) and fractional conductance (c) during the action potential shown in (a). I_{Kr} *residual activation* (see text) set at 20% of maximal. I_{Kr} amplitude was computed by assuming a maximal conductance of 3 nS.

At positive potentials (phase 1, initial phase 2) I_{Kr} activates and immediately inactivates (5), thus resulting in low fractional conductance (FIG 1c and d). During most of the action potential (up to 225 ms in the figure) I_{Kr} deactivation is slow as compared to the rate of membrane potential changes; thus the activation gate remains partly open. Conversely, inactivation gate reopening (recovery) is practically instantaneous; thus, the increase in I_{Kr} conductance closely follows the course of membrane potential (FIG 1d). Since such an increase in conductance outweights the decrease in electromotive force, I_{Kr} amplitude progressively increase along the plateau phase (FIG 1b). To summarize, a faster repolarization rate leads to a faster increase in I_{Kr} availability. Since I_{Kr} is a repolarizing current, this may generate a positive feed-back loop between I_{Kr} and V_m. Moreover, the gain of the feed-back loop may increase whenever repolarization rate becomes faster as compared to I_{Kr} deactivation rate (1). This arrangement has the following implications: 1) I_{Kr} may amplify the effects on repolarization of changes in other conductances. This may be useful to boost repolarization, once this has been initiated by other currents, but may also render it more vulnerable to perturbations (e.g. the transient outward or inward currents); 2) if repolarization is initially slow I_{Kr} will be poorly recruited; this may contribute to explain why a long action potential is generally easier to prolong than a shorter one.

In canine and human myocytes, the activation gating of I_{Kr}, appear to be slower than in guinea pig (3;4;6). Deactivation may not complete during the diastolic interval , thus causing a proportion of channels to be already in the activated state when the action potential ensues. However, this can increase I_{Kr} only moderately; indeed, during the plateau phase I_{Kr} activation may be close to saturation anyway, independently of this phenomenon (FIG1c, red curve).

The increase in I_{Ks} conductance upon membrane depolarization is not restrained by inactivation and it is considerably slower than the one of I_{Kr} (FIG 2) (4)

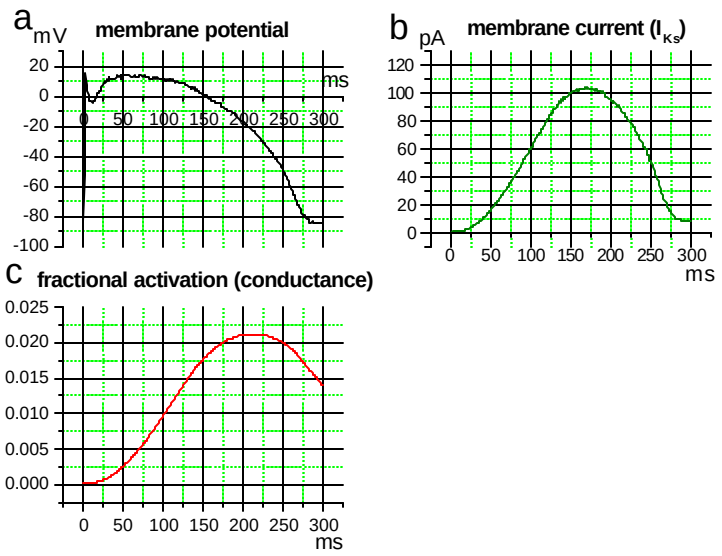

Figure 2: Predicted time course of I_{Ks}: membrane current (b), activation gating variable, corresponding to fractional conductance (c) during the action potential shown in (a). Gating parameters from ref. (2), I_{Ks} amplitude was computed by assuming a maximal conductance of 60 nS.

These two features are sufficient to account for a dependency of I_{Ks} from the action potential contour very different from that of I_{Kr}. Due to slow kinetics, the proportion of total I_{Ks} which is activated during the action potential is very small (FIG 2c) and may considerably increase if depolarization is prolonged. Moreover, as membrane potential repolarizes, I_{Ks} activation slows and the electromotive force decreases; thus, opposite to I_{Kr}, I_{Ks} is diminished by a faster repolarization. I_{Ks} deactivation may also fail to complete at short diastolic intervals (e.g. in the guinea pig) (7).Unlike I_{Kr} (see above), the resulting "accumulation" of the proportion of channels in the activated state may lead to a large increase in I_{Ks} flowing throughout repolarization. Thus, shorter cycle length or prolonged action potential duration may cause I_{Ks} to increase considerably (1). All such features concur to the genesis of a negative feed-back loop between I_{Ks} and V_m and suggests that this current may be ideal to buffer changes in the course of repolarization. In particular, sensitivity of I_{Ks} to β-adrenergic stimulation makes this current pivotal in controlling repolarization during sympathetic activation, when a concomitant large increase in plateau inward current (I_{CaL} and I_{NaCa}) has to be offset.

In summary, the kinetic properties of I_{Ks} and I_{Kr} suggest different roles for these currents in repolarization. While the former may act as a buffer to make repolarization course resistant to perturbations, the latter may support autoregenerative repolarization. While both actions may be important to stabilize the action potential contour under physiological conditions, I_{Kr} positive feed-back regulation may also amplify the effect of abnormalities in other currents. This view may help to interpret features of the phenotype of channel mutations determining LQTS; the case of Brugada's syndrome will be discussed below.

Albeit Brugada's syndrome is primarily the result of mutations leading to loss of Na^+ channel function, its phenotype seems more related to repolarization than to conduction abnormality. According to the present interpretation (8), depressed I_{Na} would leave I_{to} unopposed; phase-1 notch would be deepened and the action potential dome delayed, ultimately leading to premature repolarization in epicardial myocytes. A strong disparity in repolarization course would thus be generated between these cells and endocardial ones, which express I_{to} to a minor extent. The ECG pattern of Brugada's syndrome and, possibly, arrhythmogenesis would be accounted for by such a disparity.

An enhanced phase-1 notch, the initiating mechanism of Brugada's syndrome, can be viewed as a perturbation of the repolarization course. It may be worthwhile considering how, during the action potential, the

function of otherwise "normal" I_{Kr} and I_{Ks} channels might be affected by such a perturbation. Figure 3 illustrates how enhancement of the phase 1 notch (panel a) would change the course of I_{Kr} (panel b) in a canine epicardial myocyte.

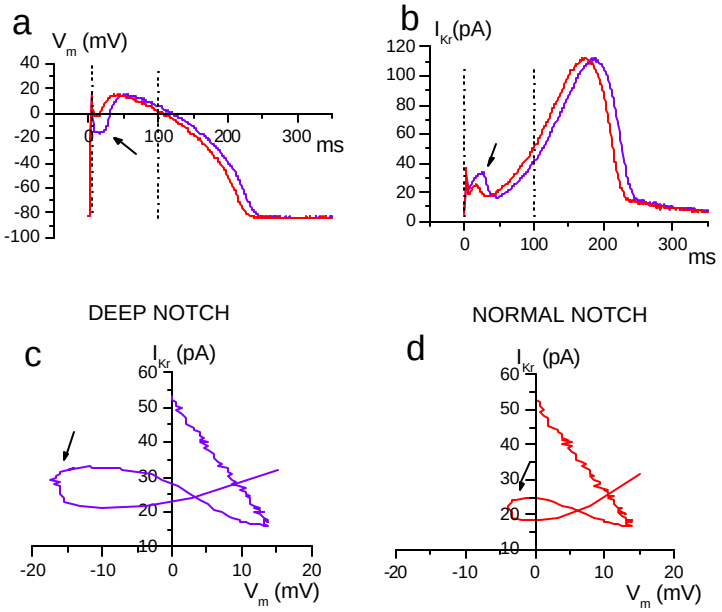

Figure 3. Predicted effect of phase 1 notch on I_{Kr} : (a) action potentials with normal (red line) and enhanced (blue line) phase-1 notch . (b) predicted time course of I_{Kr} during the two action potential waveforms (color codes as in (a)); (c,d) dynamic current/voltage relations obtained by plotting I_{Kr} as a function of V_m for enhanced and normal phase-1 notch; only the section of the trace enclosed by the dotted lines of panels (a) and (b) is shown for clarity. Arrows mark the points corresponding to the secondary depolarization ("dome") in all panels. I_{Kr} *residual activation* (see text) set at 20% of maximal.

The current flowing during the notch reflects fast recovery of channels activated and quickly inactivated during fast depolarization (FIG 1c); thus, a deeper notch recovers more current. This is best appreciated from the I/V relations (FIG 3 c and d) showing that a deeper notch is associated with a larger I_{Kr} conductance (more current flowing at the same potential). The amount of recoverable current also depends on the degree of channel activation; at the time of phase–1 notch, channels which failed to deactivate during the previous diastolic interval (residual activation) can provide a significant contribution to it. The excess current provided by I_{Kr} would tend to deepen the notch further in an autoregenerative fashion, eventually leading to premature repolarization. Since shorter diastolic intervals are associated with larger residual activation, I_{Kr} flowing during the notch would be enhanced by faster heart rate. This might contribute to the rate-dependent facilitation of the abnormalities associated with Brugada's syndrome.

The predicted response of I_{Ks} to enhancement of the phase-1 notch is shown in fig 4.

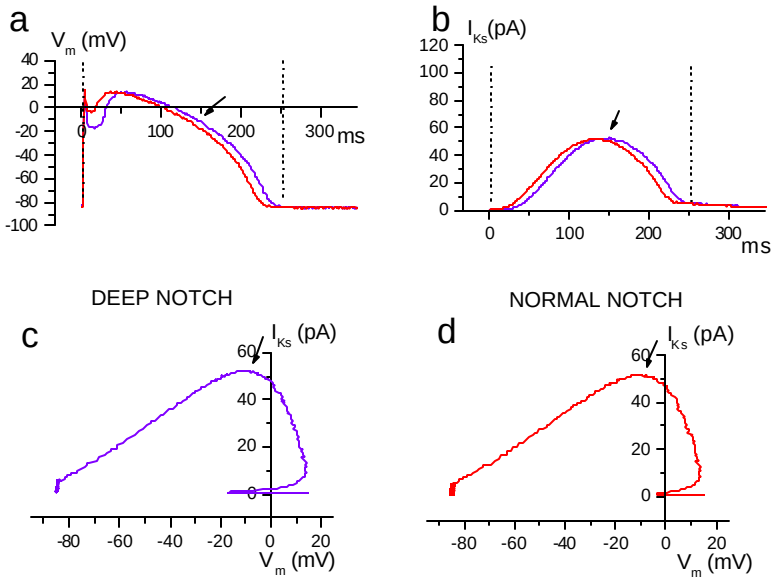

Figure 4. Predicted effect of phase 1 notch on I_{Ks} : (a) action potentials with normal (red line) and enhanced (blue line) phase-1 notch . (b) predicted time course of I_{Ks} during the two action potential waveforms (color codes as in (a)); (c,d) dynamic current/voltage relations obtained by plotting I_{Kr} (b) as a function of V_m (a) for enhanced (c) and normal (d) phase 1 notch. Arrows mark the points corresponding to peak I_{Ks} in all panels.

At the time of the notch I_{Ks} activation is negligible (FIG 2c); thus this current may neither modulate this phase, nor contribute to premature repolarization.. On the other hand, action potential prolongation, resulting from a delayed dome, may increase I_{Ks} conductance throughout the following phases of repolarization. This would tend to offset the impact of the delayed dome on the overall action potential duration. Thus, consistently with what discussed earlier, the properties of I_{Ks} are such as to minimize the impact of the I_{Na} defect on the course of repolarization.

In quantitative terms, the currents provided by I_{Kr} and I_{Ks} are small as compared to others which prevail during early repolarization (i.e. I_{Na}, I_{CaL}, I_{to}). Nonetheless, premature repolarization is an "all-or-none" phenomenon, whose threshold is finely set by the balance of all active conductances. Thus, even the small changes predicted from the kinetic properties described here may be of pathophysiological relevance. Should blockade of delayed rectifier currents be considered as a mean to prevent the abnormalities peculiar of Brugada's syndrome, I_{Kr} should be viewed as the most promising target, at least based on theoretical considerations as those offered by the present discussion.

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