Rate Dependence of the I_{Na}-I_{K1} Complex on Human Ventricular Conduction Velocity under Hypokalemia and Hyperkalemia Conditions

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Abstract

Conduction velocity (CV) heterogeneities are a long established pro-arrhythmic substrate in cardiac disease, including atrial fibrillation and cardiomyopathies. One mechanism for generating dispersion of electrical conduction is conduction slowing in myocardial tissue. The rate dependent interactions of the I_{Na}-I_{K1} ion channel complex on human ventricular CV are studied using an in-silico model. Two response domains of myocardial tissue are found. There exists a slow frequency of pacing domain (1 Hz), where CV is largely governed by the I_{Na} channel alone. In the fast frequency domain (3.3 Hz), I_{K1} plays a more dominant role in ventricular CV. The simulation results suggest that, under arrhythmogenic conditions, the upper limit of the CV is governed by the fast sodium to inwardly rectifying potassium channel conductivity ratio. The role of these two channels in determining the CV is further investigated under hypokalemic and hyperkalemic conditions. A marked decrease in human ventricular CV during mild hyperkalemia and a bi-phasic response during a hypokalemic episode were found. Additionally, I_{K1} is found to lose its role in governing CV under severe hypokalemic conditions, whilst I_{Na} channel conductivity is found to be crucial in all the considered scenarios.

1. Introduction

Several cardiac diseases exhibit dispersion of electrical conduction velocity (CV), including atrial fibrillation [1], Brugada Syndrome [2], hypertrophic cardiomyopathy [3] and arrhythmogenic right ventricular cardiomyopathy (ARVC) [4]. Slow and heterogeneous CV, in combination with appropriate anatomical substrates, translates into an increased risk of re-entry. Even in the absence of structural heart changes, such as in early-stage ARVC patients with ion channel remodelling but otherwise healthy hearts [4], CV abnormalities have been shown to cause sudden cardiac death in young individuals [5].

Cardiac voltage-gated sodium channels (I_{Na}) are transmembrane proteins responsible for regulating the flow of sodium ions. Loss-of-function mutations in I_{Na} channels have been implicated in lethal arrhythmias [6]. The inward rectifier current (I_{K1}) stabilises the resting membrane potential of the human action potential (AP). I_{K1} downregulation has been also experimentally linked to the creation of regional differences in cardiac excitability [7].

Emerging experimental evidence suggests that ionic channels are not regulated independently and are organised in macromolecular complexes. The I_{Na}-I_{K1} ion channels form one such complex, recently shown to control cardiac excitability and arrhythmia by Milstein *et al.* [8]. Their inter-species study concluded that an increase in functional expression of one channel reciprocally modulates the expression of the other to maximise cardiac excitability.

The extracellular potassium concentration, $[K^+]_o$, is another governing factor of myocardial CV. Elevated $[K^+]_o$ concentrations (hyperkalemia) are known to induce I_{Na} inactivation and I_{K1} opening [9], promoting longer refractoriness of myocytes. Equally, low levels of $[K^+]_o$ (hypokalemia) can lead to hyperpolarisation with an overall decrease in the resting cell potential. Both of these effects have repercussions on conduction.

This study extends to human electrophysiology the in silico study by Varghese [10], where CV modulation by the I_{Na}-I_{K1} complex was investigated using a mammalian model. Importantly, we focus on I_{Na}-I_{K1} downregulation rather than its overexpression, given the reported role of reduced function of these channels in arrhythmogenesis. We further investigate rate-dependence interactions of the I_{Na}-I_{K1} complex on human ventricular CV, as well as its modulation by $[K^+]_o$ plasma levels.

2. Methods

2.1. Human tissue electrophysiology model

At the cellular level, this study was conducted using the O'Hara-Rudy (ORd) model, as state-of-the-art and most extensively validated human cardiac electrophysiology model [11], which incorporates all main ionic channels and subcellular processes involved in the human AP.

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Tissue simulations using the bidomain equations were performed in 1D fibres (2 cm length; spatial discretisation 0.4 mm; ODE and PDE time steps of 0.025 and 0.05 ms, respectively), ensuring numerical convergence of our solver [12]. Tissue conductivities were selected as described in [13] for human transmural propagation.

2.2. Simulation protocols

The 5 leftmost nodes of the fibres were simultaneously stimulated using square waves (1 ms duration; 120 pA/pF amplitude), and fibres were paced until steady-state before CV recordings took place. Activation times (ms) were determined at the steepest upstroke of the AP at each node. The CV was subsequently calculated by a least squares linear estimate of the resulting activation curves.

To investigate the effects of I_{Na}-I_{K1} downregulation on human ventricular CV, simulations were conducted via a parameter sweep for these two channels using scaling factors in the [0.1,1] range for their respective channel conductances, G_{Na} and G_{K1} [μS/μF], where 1 represents average current density and 0.1 is equivalent to 10% of maximal current density. To evaluate if such an I_{Na}-I_{K1} interaction is rate dependent, the fibres were stimulated at different basic cycle lengths (BCLs), spanning from 200 to 1500 ms. Finally, a scaling factor was also applied to the default extracellular K^+ concentration of the ORd model ($[K^+]_o$=5.4 mM), in order to investigate confluent CV modulation by high and low $[K^+]_o$ plasma levels.

3. Results

3.1. Low frequency pacing limit

At low pacing rates equivalent to sinus rhythm (BCL > 600 ms), human ventricular CV was found to be almost entirely controlled by the I_{Na} conductance. When decreasing I_{Na} maximal channel density (smaller G_{Na} scaling factors), the CV also monotonically decreases, as illustrated in Figure 1a. On the other hand, CV varies by less than 1% within the range of G_{K1} scaling factors studied, implying a weak dependence of CV on I_{K1} in this low frequency pacing limit.

3.2. High frequency pacing limit

The high frequency pacing range is not reachable in sinus rhythm and is presented here to simulate arrhythmic scenarios. At fast pacing frequencies (BCL ≤ 300 ms), the CV was found to be dependent on I_{Na}-I_{K1} interactions. The CV exhibited a positive correlation with both G_{Na} and G_{K1} scaling factors (Fig 1b). Such a phenomenon only emerges at fast pacing BCLs, mimicking arrhythmic conditions. This suggests that once arrhythmias are initiated, the upper limit of CV of electrical wavefronts will depend on subject-specific I_{Na}-I_{K1} ionic channel balance.

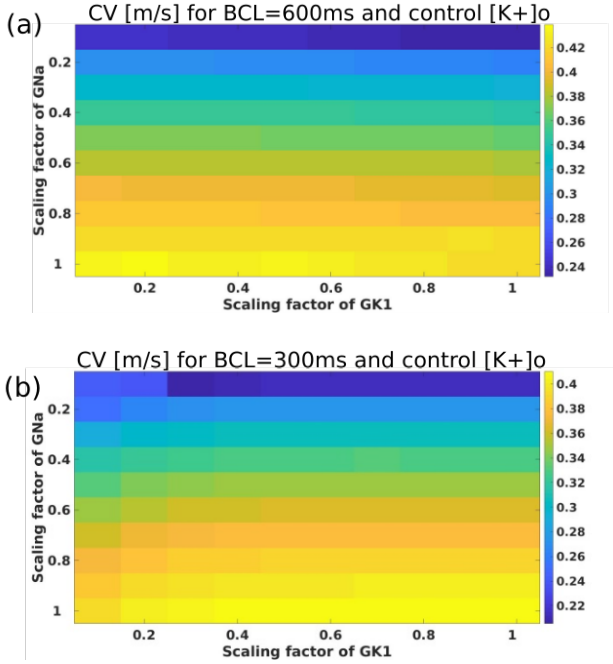

Figure 1. CV [m/s] along human 1D fibres for different scaling factors of the original conductances, G_{Na} and G_{K1}. (a) Low frequency pacing limit (BCL > 600 ms), where CV is solely governed by I_{Na} channel dynamics. (b) High frequency limit (BCL ≤ 300 ms), exhibiting a concomitant modulation of CV by both I_{Na} and I_{K1} currents.

3.3 Hyperkalemia reduces human CV

Hyperkalemia features elevated K^+ concentrations in the blood plasma. It can be shown from the Nernst equation that an increase of $[K^+]_o$ raises the ion's equilibrium potential. This is because the electrical potential opposes diffusion gradients across the cell membrane. Increasing $[K^+]_o$ results in a smaller diffusion gradient and also a less negative Nerst and resting membrane potentials. As I_{Na} recovery from inactivation is voltage dependent, a more depolarised resting membrane potential inhibits a full I_{Na} channel recovery. Furthermore, as $I_{K1} \propto \sqrt{[K]_o}$ in the ORd model, an increase in $[K^+]_o$ implies an increased maximal I_{K1} repolarising current, and hence a shortening of the AP. The same holds for the fast delayed repolarising potassium current I_{Kr}.

Simulation results confirm these mechanisms, as shown in Fig 2. Hence, I_{Na} peak availability is severely reduced and CV rapidly decreases under hyperkalemic conditions for all the studied combinations of the I_{Na}-I_{K1} complex, as captured by Fig 3 in the high frequency pacing limit (BCL

of 300 ms). The same behavior was observed for the slow frequency pacing limit (BCL > 600 ms, not shown).

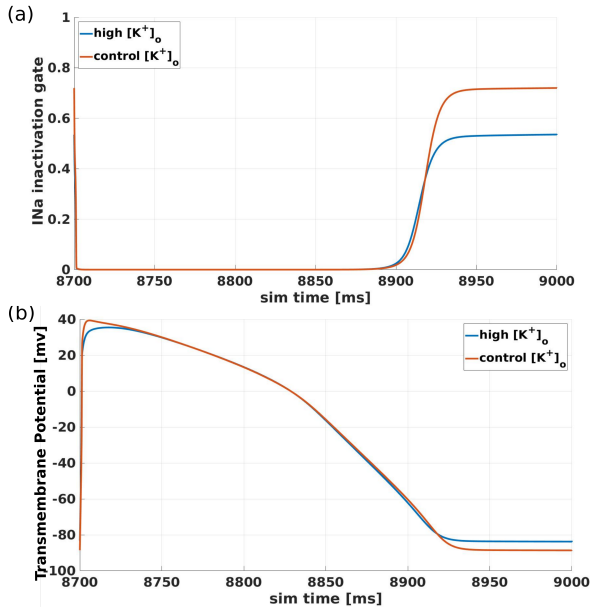

Figure 2. Cellular mechanisms underlying hyperkalemia ($[K^+]_o$ = 6.48 mM, 20% above control). (a) High $[K^+]_o$ hinders I_{Na} recovery from inactivation. (b) AP under hyperkalemic conditions, exhibiting an elevated resting membrane potential, responsible of reduced I_{Na} recovery.

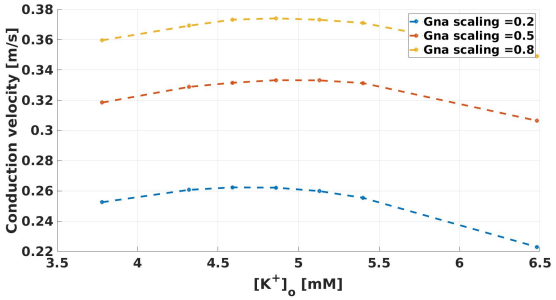

Figure 3. Human ventricular CV in 1D fibres at a BCL of 300 ms, for different $[K^+]_o$ concentrations (control given by $[K^+]_o$ = 5.4 mM). Note that a hyperkalemic scenario rapidly decreases CV for all I_{Na}-I_{K1} combinations.

3.4 Biphasic hypokalemic response of CV

Interestingly, our simulation results indicate a biphasic response of human CV to low $[K^+]_o$ (Fig 3). For mild hypokalemia, CV increases due to a larger I_{Na} availability. However, at very low $[K^+]_o$ values, the markedly lower resting membrane potential outweighs this speed up, ultimately yielding a slower CV for severe hypokalemia.

CV can be increased due to an increased I_{Na} availability via an enhanced recovery from inactivation. The low $[K^+]_o$ increases the diffusion gradient across the cell membrane, resulting in a hyperpolarization of the resting membrane potential (Fig 4a). Contrary to hyperkalemia, hypokalemia opens the voltage-dependent I_{Na} inactivation gates, once the cell has recovered (Fig 4b). In addition, the lower $[K^+]_o$ availability directly reduces the maximal densities of I_{K1} and I_{Kr} currents (Fig 4c). This, in combination with a more prominent AP upstroke and the more negative resting membrane potential, increases the repolarisation time of the ventricular myocyte, leading to a prolonged AP as experimentally confirmed in hypokalemia [14].

On the other hand, a lower resting potential implies that electrotonic currents must increase the transmembrane potential by a larger voltage difference before the I_{Na} channel is triggered in a neighboring myocyte. Hence, this slows the electrical propagation and decreases CV [14]. The same behavior was observed for the slow frequency pacing limit (BCL > 600 ms, not shown).

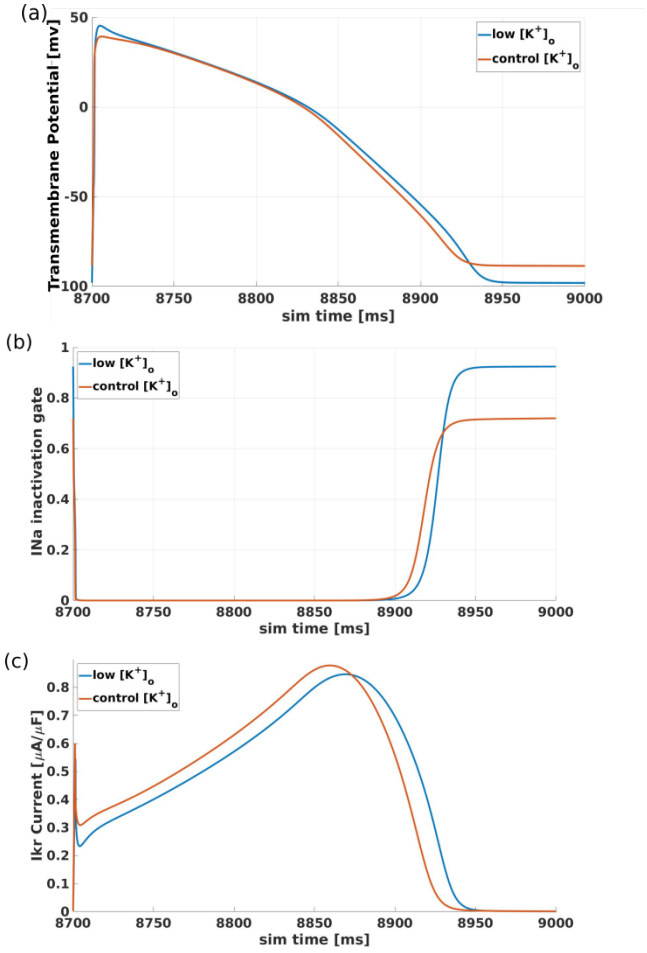

Figure 4. Cellular mechanisms underlying hypokalemia ($[K^+]_o$ = 3.78 mM, 30% below control). (a) Hypokalemic AP, exhibiting higher peak amplitude and hyperpolarised resting membrane potential. (b) Increased I_{Na} availability as a consequence of the lower resting membrane potential,

underlying the higher AP peak. (c) AP prolongation is primarily due to the decreased I_{Kr} current.

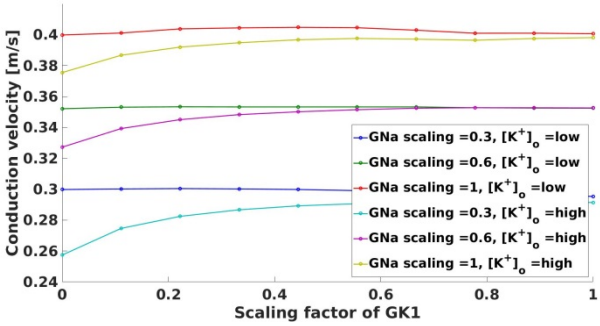

Figure 5. The dependency of CV on I_{K1} is abolished under severe hypokalemia. Here, low $[K^+]_o$ = 3.78 mM (30% reduction); high $[K^+]_o$ = 6.48 mM (20% increase).

3.5 Hypokalemia abolishes I_{K1} role on CV

Finally, I_{Na}-I_{K1} complex modulation of human CV under hypo/hyperkalemic conditions was also investigated. CV under hyperkalemia did not qualitatively change the previously described influence of the I_{Na}-I_{K1} complex on CV in control $[K^+]_o$ levels (sections 3.1 and 3.2). On the contrary, the CV dependence on I_{K1} was almost completely abolished under hypokalemia (Fig 5). This is a result of the reduced maximal I_{K1} density for low $[K^+]_o$.

4. Conclusions

In this study we have conducted a thorough in silico investigation of the impact of ion channel downregulation in the I_{Na}-I_{K1} complex on human ventricular CV, as well as its rate dependence and modulation by $[K^+]_o$ plasma levels. Our results suggest that a positive correlation between I_{K1} conductance and human ventricular CV is only present at fast pacing regimes, representative of arrhythmic scenarios (BCL ≤ 300 ms). At slower BCLs, CV was found to be solely governed by the I_{Na} channel conductance. An important novel finding is the biphasic response of human CV under hypokalemic conditions. An increase in CV is observed for mild hypokalemia due to increased I_{Na} availability, counteracted at severe episodes by the effect of a markedly hyperpolarised resting membrane potential on electrotonic currents, independent of I_{Na}-I_{K1} conductances. A final finding is that the I_{K1} dependence of CV is abolished during severe hypokalemia, due to reduced maximal I_{K1} density for low $[K^+]_o$. These findings may therefore have important implications in promoting our current understanding of I_{Na}-I_{K1} modulation of dispersion of electrical conduction under heart disease.

Acknowledgments

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