Sinoatrial Node Cell Response to Isoprenaline Stimulation and Hypocalcemia

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Abstract

Aims: *The purpose of this study is to assess the effects of autonomic modulation and hypocalcemia on the pacemaking rate in a human sinoatrial node (SAN) cell model. The clinical relevance is to bring a better understanding of the increased risk of sudden cardiac death in chronic kidney disease patients who regularly undergo hemodialysis.* **Methods:** *The Fabbri et al. (2017) SAN model was used to compute the gradual response on isoprenaline concentration (*$[\mathrm{ISO}]$*) between 0 and 1.5* μM *with extracellular calcium concentrations (*$[\mathrm{Ca}^{+2}]_\mathrm{o}$*) in the range from 1.2 to 2.2 mM. The pacing capacity of the model was evaluated by assessing the pacing rate (in beats per minute (BPM)).* **Results:** *Low* $[\mathrm{Ca}^{+2}]_\mathrm{o}$ *led to decreased pacing rate: at* $[\mathrm{Ca}^{+2}]_\mathrm{o} = 1.4$ *mM, the rate without extra autonomous stimulation was only 50 BPM compared to the 74 BPM at the default* $[\mathrm{Ca}^{+2}]_\mathrm{o} = 1.8$ *mM. This effect was counteracted by autonomous modulation. The* $[\mathrm{ISO}]$ *necessary to restore the baseline pacing rate was 0.5* μM *and 1* μM *when* $[\mathrm{Ca}^{+2}]_\mathrm{o}$ *was reduced to 1.6 mM and 1.4 mM, respectively.* **Conclusions:** *Isoprenaline stimulation can conserve the pacing capacity during hypocalcemia. However, extremely high* $[\mathrm{ISO}]$ *may lead to saturation and a non-linear response, which the current model does not take into account.*

1. Introduction

A natural pacing system controls the activity of the heart. An electric impulse starts in the cells of a small oval region in the upper back wall of the right atrium, called sinoatrial node (SAN) and propagates through the rest of the cardiac tissue. This sequence repeats in regular intervals. The study of the SAN can guide our understanding of the mechanisms underlying serious diseases such as pronounced bradycardia in chronic kidney disease (CKD) patients. It has been reported that CKD patients die from cardiac arrest 14 times more often than patients with cardiovascular disease and normal kidney function [1]. This is likely linked to altered ionic concentrations in the blood caused by the kidney failure and hemodialysis [2] although the exact mechanisms are not fully understood.

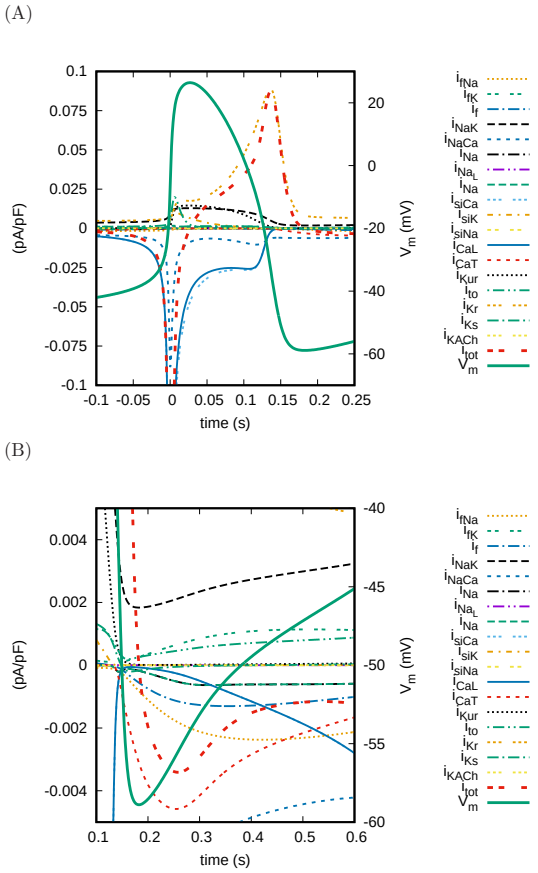

Figure 1. Simulated action potential (green line, right axes) and the currents of the SAN cellular model (left axes) at default $[\mathrm{Ca}^{+2}]_\mathrm{o} = 1.8$ mM and $[\mathrm{ISO}] = 0.0\,\mu$M. Panel (A) shows the complete view and panel (B) shows the detail of the diastolic depolarization phase.

The transmembrane voltage ($\mathrm{V_m}$) time course of SAN cells can be divided into a diastolic part and the actual action potential (AP). The total membrane current (the balance of influx and outflux from the cell) is 0 at the lowest diastolic potential (Fig. 1). After that, the negative total current $\mathrm{i_{tot}}$ (influx) causes increasing $\mathrm{V_m}$ and the cell slowly depolarizes until a threshold that allows an abrupt increase of $\mathrm{i_{NaCa}}$, $\mathrm{i_{CaL}}$ and $\mathrm{i_{siCa}}$ currents. After this AP

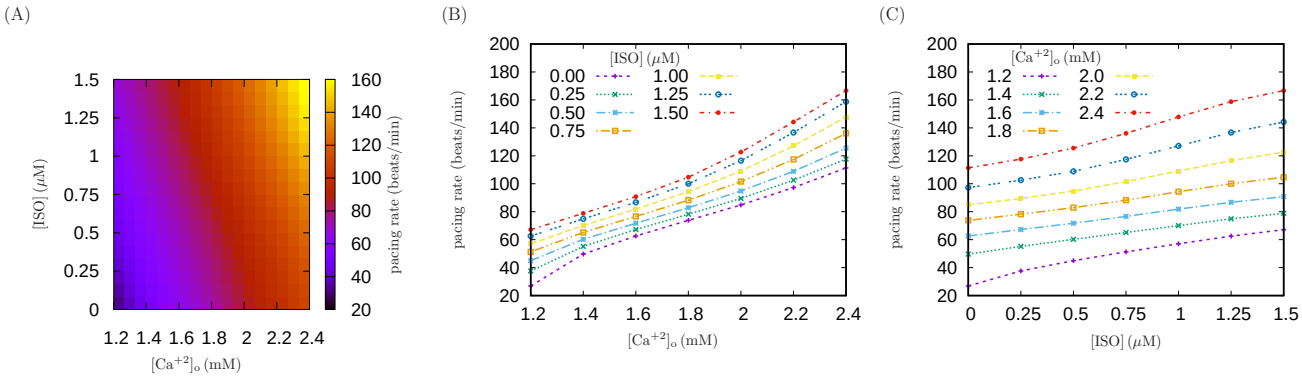

Figure 2. Pacing rate dependence on (A) both $[Ca^{+2}]_o$ and [ISO]; (B) $[Ca^{+2}]_o$; (C) [ISO].

upstroke, the high voltage is counteracted by outflux currents: mainly i_{Kr} but also by i_{NaK} and i_{Kur} until reaching the diastolic potential again and entering the next cycle.

The autonomous nervous systems controls the spontaneous pacing of the sinus node to maintain homeostasis. Isoprenaline is a β-adrenoceptor agonist mediating sympathetic stimulation increasing the pacing rate.

In this study, we investigate the effects of altered $[Ca^{+2}]_o$ and [ISO] in a computational model of human SAN cells.

2. Methods

The model definition by Fabbri *et al.* [3] was obtained from the CellML [4] repository. With the original implementation of the model, it was possible to simulate the sinoatrial node either without any influence of isoprenaline or under exposure to $[ISO] = 1\,\mu M$. We altered the model to introduce a linear dependence on isoprenaline based on the effects described by Fabbri *et al.* for the concentration of $1\,\mu M$. Isoprenaline stimulation affects the currents i_f, i_{NaK}, i_{CaL}, i_{Ks} and the SERCA pump P_{up} [5].

The model was solved with the forward Euler integration scheme with a module developed as part of BeatBox [6]. The code of the simulator with the implementation of modified model is available online [7]. Simulations were performed for 30 seconds after which a limit cycle was reached. The simulated [ISO] were between $0.0\,\mu M$ and $1.5\,\mu M$ in steps of $0.25\,\mu M$ and $[Ca^{+2}]_o$ from 1.0 mM to 2.5 mM in steps of 0.2 mM. To compute beats per minute, we used the average cycle length (CL) computed from the last 5 APs.

3. Results

There was no automaticity (no APs present) for $[Ca^{+2}]_o = 0.8$ mM unless [ISO] was to set to values above $1.65\,\mu M$. At $[ISO] = 1.65\,\mu M$ only two APs were observed after which the automatic activity ceased. At $[ISO] = 1.75\,\mu M$ the simulations presented four APs and for values $[ISO] \geq 1.8$, sustained automaticity was restored. For $[Ca^{+2}]_o = 1.0$ mM and $[ISO] \geq 0.5\,\mu M$ only one AP was present; for $[ISO] \geq 0.7\,\mu M$, two APs were present and starting from $[ISO] \geq 0.75\,\mu M$, sustained automaticity was restored.

Figure 2 shows the rate dependence on $[Ca^{+2}]_o$. The behaviour is nearly linearly dependent on both $[Ca^{+2}]_o$ and [ISO]. Figure 3 shows the last two APs of the 30 s of simulation. The different [ISO] in the simulated range had only minor effects on the morphology of the AP (panel (A)) and modulated the CL between 0.6 and 0.9 s with lower CL at higher [ISO]. On the other hand, the range of simulated $[Ca^{+2}]_o$ had a more notable effect both on the morphology of the AP as well as the CL, which was around 0.6 s for $[Ca^{+2}]_o = 2.4$ mM and up to 2.3 s for $[Ca^{+2}]_o = 1.2$ mM. Thus, increasing $[Ca^{+2}]_o$ caused a reduction of the CL in the model. Figure 4 shows the transmembrane voltage (right axes) and currents affected by isoprenaline at the extrema of simulated concentrations during the penultimate AP (concentrations in the corners of Figure 2(A)). Another aspect that can be observed in Figure 3 (panels (C), (D)) from the diastolic phase is a qualitatively different influence on the AP onset. Larger $[Ca^{+2}]_o$ caused steeper diastolic depolarization both in the early and late phases. On the other hand, larger [ISO] did not cause noticeably steeper diastolic depolarization but mediated its effect primarily by a less negative maximum diastolic potential.

Although, the mechanism of action of $[Ca^{+2}]_o$ and [ISO] is different, the decreasing $[Ca^{+2}]_o$ can be largely compensated in terms of pacing rate by increasing [ISO] in the model.

4. Discussion

The model suggests that the bradycardia caused by the depletion of extracellular calcium, which potentially happens in CKD patients [2], can be compensated by in-

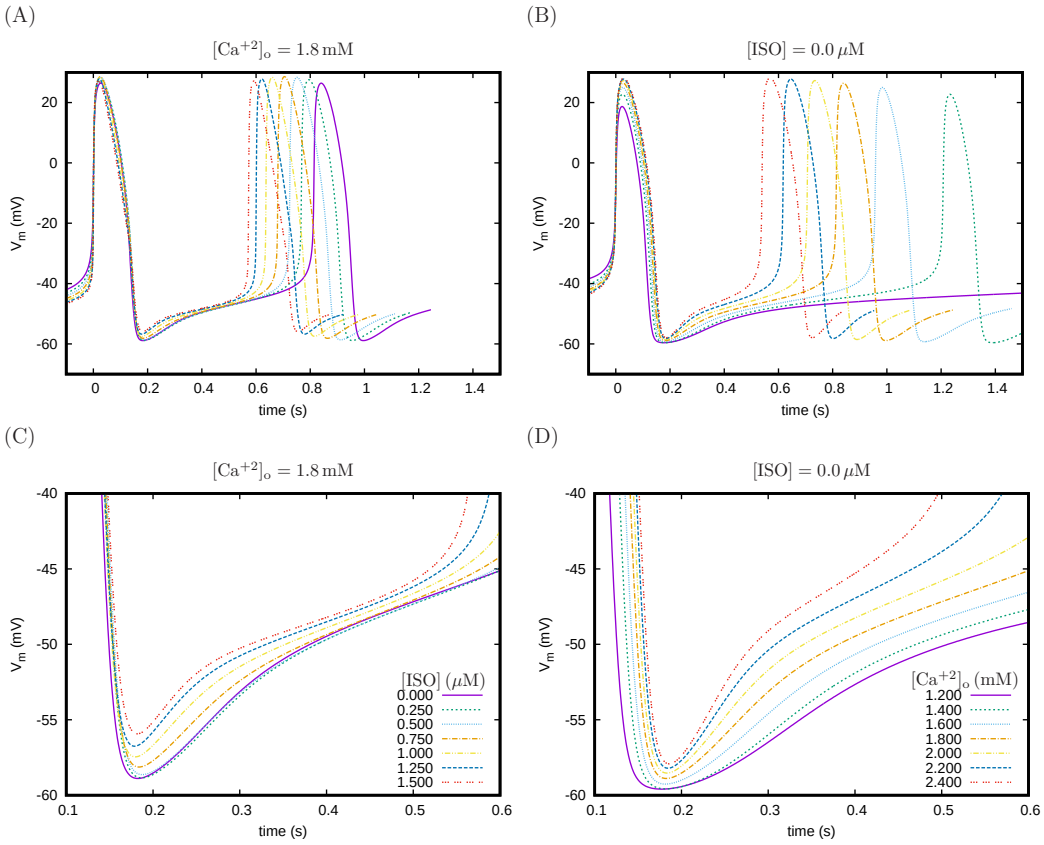

Figure 3. Simulated action potentials (top row – (A), (B)) and a detail of the diastolic phase (bottom row – (C), (D)); at basal $[Ca^{+2}]_o = 1.8\,mM$ (first column – (A), (C)) and different $[ISO]$ (lines); at $[ISO] = 0\,\mu M$ (second column – (B), (D)) and different $[Ca^{+2}]_o$ (lines). The legend in the panels in the bottom row applies to the corresponding panels above.

creased sympathetic stimulation to a certain extent.

However, the simplified linear dependence on $[ISO]$ might be far from the reality. The isoprenaline binding pathways were described mathematically in the past for example by Behar *et al.* [8]. The implementation of these pathways into the human SAN model would be an appealing direction of further work.

The nearly linear dependence of pacing rate on $[ISO]$ is not a direct consequence of the introduced linear dependence of model variables on $[ISO]$ as the nonlinear cellular model we are dealing with might yield non-linear and even non-intuitive responses.

The differential equations of sodium and potassium concentrations as was introduced in [2] may also be relevant to uncover further important factors in the pathogenesis of hypocalcemia-induced bradycardia. However, the parameter identification by fitting the model to the experimental results has to take isoprenaline stimulation into account.

Besides automaticity on the cellular level, the excitation also needs to be captured by the surrounding myocardium to initiate a heart beat in vivo [9]. The combined effect of hypocalcemia and sympathetic stimulation on the pace-and-drive capacity of the human SAN remains to be studied. Beyond monodomain simulations on the tissue level, cell-by-cell models might be helpful to elucidate relevant mechanisms [10].

In conclusion, this study shows interrelation between altered $[Ca^{+2}]_o$ potentially linked to sudden cardiac death frequently occurring in CKD patients and its possible mitigation by β-adrenergic isoprenaline stimulation.

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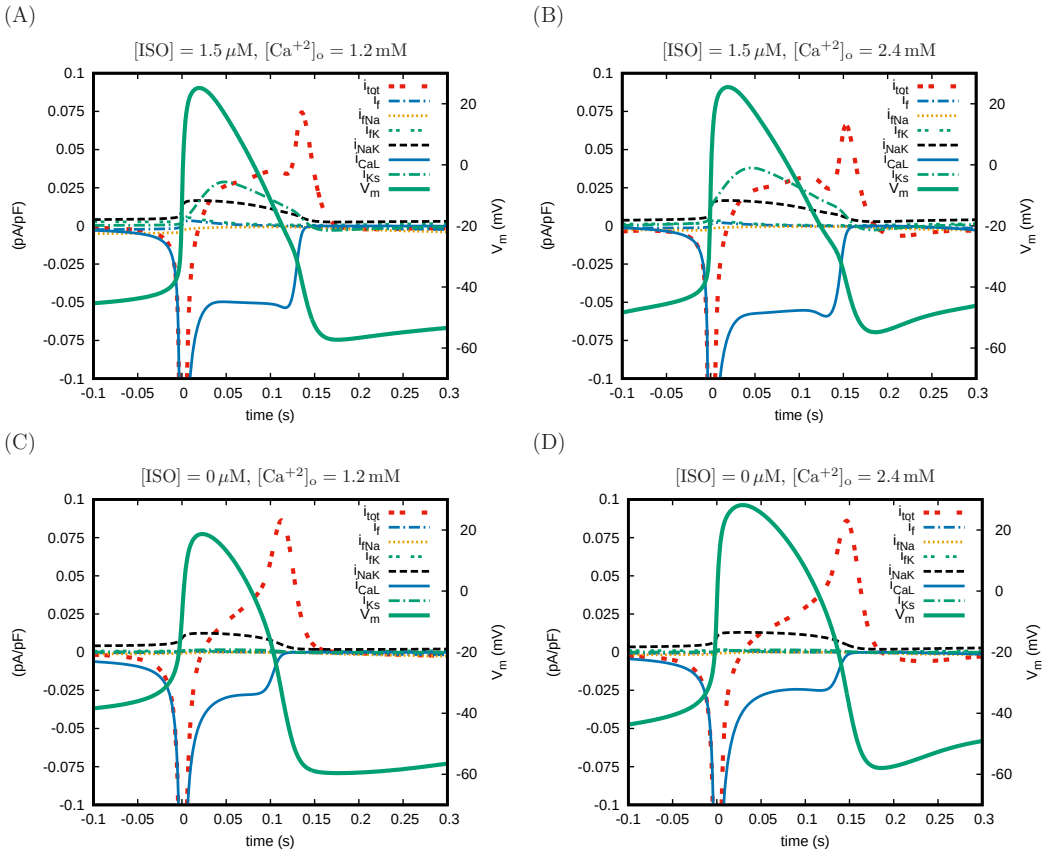

Figure 4. Currents affected by isoprenaline (left axis), and transmembrane voltage V_m (right axis) at extreme $[Ca^{+2}]_o$ and [ISO]. Lowest $[Ca^{+2}]_o$ (1.2 mM): first column – (A), (C); highest $[Ca^{+2}]_o$ (2.4 mM): second column – (B), (D); highest [ISO] (1.5 μM): first row – (A), (B); lowest [ISO] (0 μM): second row – (C), (D). The concentrations are shown in the plot titles.

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