Sensitivity of the Human Ventricular BPS2020 Action Potential Model to the *In Silico* Mechanisms of Ischemia

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Abstract

Myocardial acute ischemia is due to a reduced or suppressed blood supply to the heart. It heavily impacts the electrical and mechanical functionality of cardiomyocytes (CMs), up to cell necrosis. We evaluate the effects of the three main consequences of acute ischemia (hypoxia, acidosis, and hyperkalemia) on the recent Bartolucci-Passini-Severi (BPS2020) model of human adult ventricular CM. We run a sensitivity analysis considering different ischemia severity, mechanisms, and formulations of the ATP-sensitive K^+ current (I_{KATP}), initially not included in BPS2020. We further compare our results with other in silico and in vitro data and evaluate the BPS2020 capability to simulate alternans in ischemia. Hyperkalemia remarkably depolarized the resting membrane potential and reduced the maximum upstroke velocity. Acidosis slightly shortened the action potential (AP) duration. Hypoxia mainly reduced the AP duration and its peak. Our results agree with simulations performed with other in silico models. Finally, the full ischemia model produced alternans at fast pacing. Our sensitivity analysis demonstrates that the BPS2020 model correctly recapitulates the acute ischemia effects, and it is suitable for more advanced simulations.

1. Introduction

Acute myocardial ischemia results from a reduced or suppressed blood supply to the heart, e.g., consequent to the occlusion of a blood vessel. Cardiomyocytes (CMs) experience a reduction of oxygen availability and metabolic alterations that impact their electrical and mechanical functionality, the extent of which is related to the severity and duration of the reduced perfusion. *In silico* simulations of the major ischemia consequences on the CM electrophysiology are nowadays well consolidated [1–5]. They have been applied to different scales: single cell, tissue, and whole heart levels, also simulating the alterations in the ECG.

Our goal is to evaluate i) the effects of the three main consequences of acute ischemia (hypoxia, acidosis, and hyperkalemia) on the recent Bartolucci-Passini-Severi (BPS2020) model [6] of the human adult ventricular action potential (AP), ii) its capability to simulate ischemia at the cell level and iii) how it compares with other *in vitro* and *in silico* studies.

2. Methods

We simulated two levels of acute ischemia severity: i) after 5 minutes (Severity 1) and ii) after 10 min (Severity 2). We followed a well-established framework as in [1–5] to simulate the three acute ischemia mechanisms.

Hyperkalemia was simulated by simply increasing the extracellular K^+ concentration (K_o) to 6.25 and 9 mM, as in [4]. As in [1,2], acidosis was simulated by reducing the maximum conductances of the fast Na^+ current (I_{Na}) and the L-Type Ca^{2+} current (I_{CaL}) by f_{inhib} = 12.5% and 25%. In addition, we applied the same changes to the late Na^+ current (I_{NaL}) since BPS2020 has a separate formulation for such current. Finally, we added the ATP-sensitive K^+ current (I_{KATP}) to BPS2020. We tested two formulations: the former by Ledezma *et al.* [4] the latter by Kazbanov *et al.* [7]. For the I_{KATP} formulations, we refer to the original publications. Ledezma I_{KATP} has a maximum conductance G_{KATP} = 0.064 mS/µF, which was rescaled by f_{KATP} = 0.1 and 0.2 according to the severity level. Likewise, Kazbanov G_{KATP} = 155 mS/µF was rescaled by f_{KATP} = 0.00275 and 0.0055. Fig. 1 shows the IV curves for the two severity levels (K_o = 6.25 and 9 mM, respectively).

In addition to adding I_{KATP}, we considered that hypoxia affects also other ATP-sensitive transports. Changes to the Na^+/K^+ pump (I_{NaK}) were simulated via MgATP reduction and MgADP increase, in addition to the progressive reduction of the Ca^{2+} sarcolemma pump (I_{pCa}) and the SERCA pump (J_{up}) maximum currents (scaled by f_{pCa} and f_{up}).

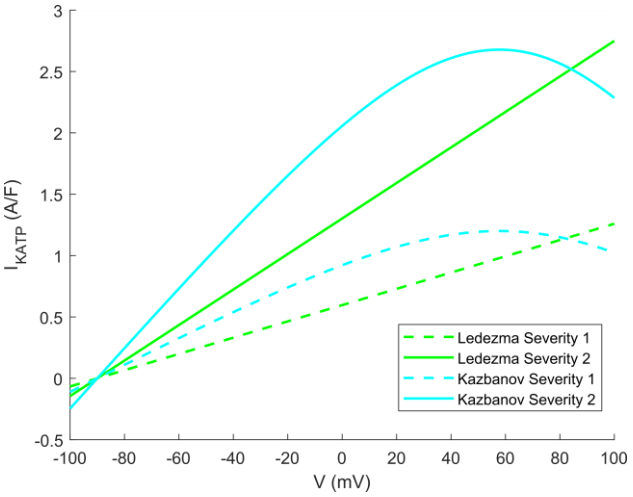

Figure 1. Current-voltage curves for the two considered models of the ATP-sensitive K^+ current (I_{KATP}).

Table 1. Full list of parameters with references. MgATP and MgADP were scaled according to the values reported in [8] at 10 min (Severity 2): (4.49/6.51=0.69 and 520.4/44.5=11.7). Scaling factors at 5 min (Severity 1) were obtained by linear interpolation between values at 40 s and 10 min from Michailova *et al*. The same scaling values were used for f_{pCa} and f_{up} as in [8].

Parameter	Control	Sev 1	Sev 2
K_o (mM) [4]	5.4	6.25	9
f_{inhib} [4]	1	0.875	0.75
f_{KATP} Ledezma [4]	0	0.1	0.2
f_{KATP} Kazbanov [7]	0	0.00275	0.0055
MgATP (mM) [8]	9.8	9.8×0.75	9.8×0.69
MgADP (mM) [8]	0.05	0.05×7.12	0.05×11.7
f_{pCa} [8]	1	0.75	0.69
f_{up} [8]	1	0.75	0.69

We used scaling coefficients computed from [8] at Severity 2, equivalent to 10 min since ischemia onset, and linearly rescaled for Severity 1, considering 5 min after onset. Table 1 reports the full list of parameters and scaling factors. We assessed the effects of hyperkalemia, acidosis, hypoxia and their combination in terms of the action potential (AP) biomarkers: AP duration at 90% of repolarization (APD_{90}), triangulation factor (Tri_{90-40}), maximum upstroke velocity (dV/dt_{max}), peak voltage (V_{peak}), resting potential (RMP) and the diastolic and systolic Ca^{2+} concentration in the cytosol (Ca_{iDiast}, Ca_{iSyst}).

3. Results

3.1. Dissecting acute ischemia mechanisms

Fig. 2 and 3 show how the acute ischemia mechanisms, isolated and together, affect the BPS2020 model. As expected, hyperkalemia main effects are the RMP depolarization (+4% and +16%) due to the K_o increase, and the decrease of dV/dt_{max} (-21% and -61%) due to the limited I_{Na} availability, again a consequence of the greater K_o. As we simulated acidosis as smaller I_{Na} and I_{CaL}, we obtained once again dV/dt_{max} reduction (-9% and -18%) and APD_{90} shortening (-2% and -4%). Hypoxia results are consistent across the two I_{KATP} formulations, with the Kazbanov one returning greater biomarker changes. The most remarkable effects are a smaller APD_{90} (-13% and -26% for Ledezma I_{KATP} and -21% and -37% for Kazbanov) and V_{peak} (-15% and -21% for Ledezma I_{KATP} and -17% and -23% for Kazbanov) due to I_{KATP}, which activates already during the upstroke. Also, the weaker J_{up} affects the cytosolic Ca^{2+} concentrations, in particular the diastolic Ca_{iDiast} (~+15% for Ledezma I_{KATP} and ~+20 for Kazbanov). All together, these three mechanisms result in the very short and depolarized cyan APs in Fig. 3.

3.2. Comparison with other *in silico* and *in vitro* data

The same effects on the AP biomarkers were observed in literature, using different *in silico* models. Weiss *et al.* [1] used the TenTusscher 2006 (TT06) model [9] combined with the I_{KATP} formulation by Ferrero et al. [10]. They reported, for 5 and 10 min after ischemia onset, qualitatively similar changes in RMP (+14% and +24%), V_{peak} (-42% and -58%) and APD_{90} (-14% and -25%). Ledezma *et al.* [4] observed similar AP biomarker changes on mild and severe ischemia *in silico* populations developed using the TT06 and the O'Hara-Rudy [11] models as baselines. Fig. 4 details these APD_{90} changes also with respect to *in vitro* data recorded on samples from CMs from human (after 3 min), guinea pig (after 10/15 min), and cat (after 10/15 min), and summarized in [3].

3.3. Alternans development in acute ischemic conditions

Finally, we tested the ability of the BPS2020 model to develop alternans in acute ischemia and high pacing rate, as done in [12]. We challenged the BPS2020 in Severity 2 conditions by pacing it with cycle length 300 ms. We obtained that, regardless of the I_{KATP} formulation, a 2:1 alternans pattern emerges, as shown in Fig. 5.

4. Discussion and conclusions

In this work, we showed the effects of the isolated and combined consequences of ischemia on the BPS2020 model, assessing its sensitivity and how it compares with previous *in silico* studies and a limited set of *in vitro* data.

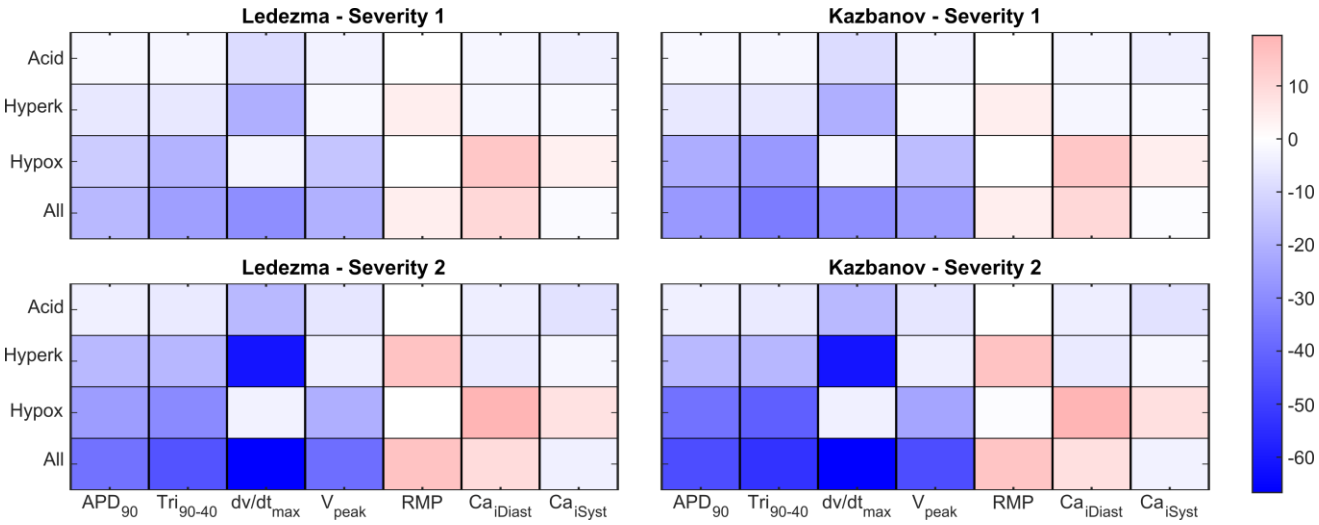

Figure 2. Sensitivity maps for each of the acute ischemia mechanisms: acidosis (Acid), hyperkalemia (Hyperk), and hypoxia (Hypox). The last row in each panel considers the combination of the three mechanisms. The first two lines are equal in each panel for the same severity level since they do not depend on the implementation of the ATP-sensitive K^+ current.

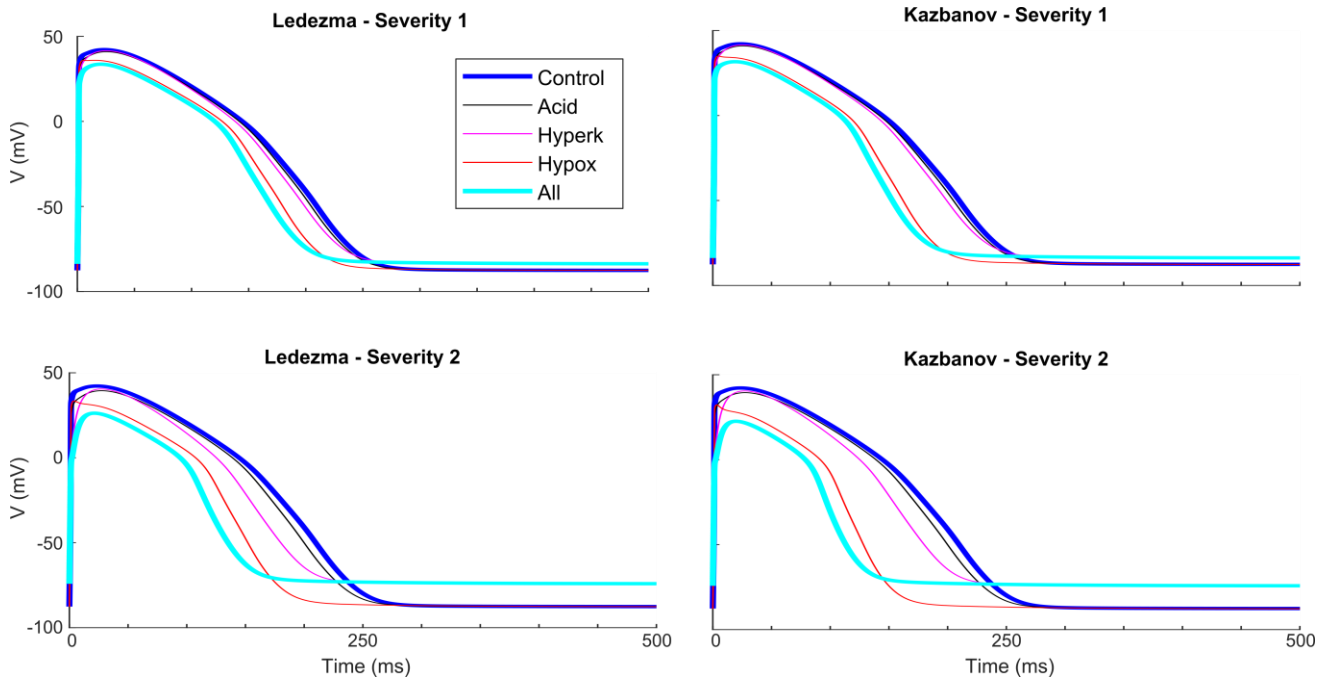

Figure 3. Action potential traces simulated by the BPS2020 model for each of the acute ischemia mechanisms: acidosis (Acid), hyperkalemia (Hyperk), and hypoxia (Hypox). The cyan trace All includes the combination of the three mechanisms. The blue, black, and purple traces are equal in each panel for the same severity level since they do not depend on the implementation of the ATP-sensitive K^+ current.

To do so, we used a well-assessed framework that identifies the main effects on the CM electrophysiology for each ischemia component. Our work presents a very common limitation in this kind of cellular studies: we were not able to simulate the dynamics of metabolites profoundly affected in ischemic conditions (e.g., the production of ATP in the cell, etc.) since the BPS2020 model, as most electrophysiological CM models, does not

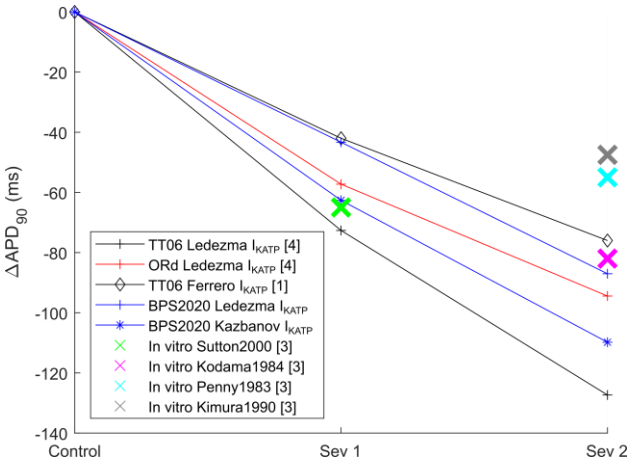

Figure 4. Comparison of acute ischemia effects with *in vitro* data and in other *in silico* studies where the authors used the TenTusscher2006 (TT06) [9] and the O'Hara-Rudy (ORd) [11] models. *In vitro* data were compiled by Dutta et al. [3]: Sutton2000 (human), Kodama1984, Penny1983 (guinea-pig) and Kimura1990 (cat).

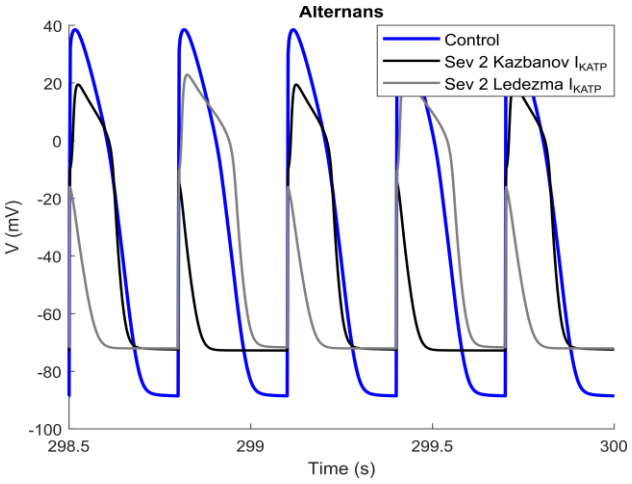

Figure 5. Occurrence of alternans at fast pacing (CL=300 ms) in ischemic conditions with both implementations of the ATP-sensitive K^+ current (I_{KATP}).

include the equations for such dynamics. Our next step will be to include a mechanical element to simulate the ischemia effects also on contractility as in [13].

Acknowledgments

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