In Silico Assessment of Cardio-protection by Therapeutic Hypothermia

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1. Background

Hypothermia is known to impact multiple physiological mechanisms that include neurologic and cardiovascular systems. Therapeutic hypothermia (TH), as a mild reduction of body core temperature, has become the standard cardioprotective treatment for several patient groups, including those affected by ischemia. Patients undergoing long term treatments such as dialysis experience global ischemia in addition to the presence of localized myocardial stunning [1], which together may promote persistent ventricular fibrillation. Fibrillation avoidance or reduction of initiation risk using non-pharmacological TH may be beneficial to critically ill patients.

Basic science experimental studies have shown that hypothermia prolongs cardiomyocyte action potential [2] and reduces cardiac conduction velocity. However, the clinical effectiveness of TH on arrythmia abrogation remain debated. In this study, a multi-scale computational cardiology approach was used to illuminate the effects of TH on cardiomyocytes and tissue.

2. Methods

A multi-scale cardiomyocyte to 3D human ventricle wedge workflow was implemented to *in silico* model the effects of ischemia and TH. Our newly developed cardiac simulator, the Virtual Cardiac Physiology Laboratory, was used in this study.

2.1 Cell model: The cardiomyocyte model of human ventricle cell electrophysiology by ten Tusscher-Panfilov [3] capable of simulating transmural action potentials was adapted in this study. Ischemia was simulated by inclusion of the ATP sensitive potassium current, I_{KATP}, as well as other well-known alterations [4]. The experimentally known temperature dependence of ion channel kinetics, Q_{10}, was ascertained from the literature [5]. Specifically, a Q_{10} of 2 was applied to both the hERG and sodium channels' kinetics. TH was defined as a reduction of temperature to 33°C in the cell models. Validation was performed by qualitatively comparing the simulated action potential features to experimental data [2, 5]. Numerical solutions for the cell models were obtained using implicit backward differences with a time step of $\Delta t = 0.1$ ms.

2.2 1D and 2D electrically homogeneous models: 1D models were constructed to quantify conduction velocity under above mentioned pathophysiological conditions at various pacing cycle lengths. Electrically homogeneous 2D models permitted quantification re-entrant wave life spans.

2.3 3D human ventricle wedge model: The 3D electrically heterogeneous and spatially anisotropic wedge (20 mm x 20 mm x 8 mm) representing the left ventricle free wall was constructed. The wall thickness was taken to be 8 mm and divided into 1:2:3 proportion transmural slices representing the endocardial, mid-myocardial, and epicardial layers respectively. Each layer was assigned the respective cell model variant. Further, transmural fibre orientation anisotropy was also implemented. To simulate a stunned region within the wedge, an

ellipsoidal region predominantly within the mid-myocardium where I_{KATP} was further increased were randomly placed. The model was stimulated at the endocardial surface to simulate Purkinje-myocardial junctions. The 3D model was validated by qualitatively reproducing physiological ECG from lead 6 (V6) in the absence of ischemia or stunned regions. Electrical propagations in the spatial models were modelled using anisotropic mono-domain equations, which were discretized using implicit finite differences at a space step of $\Delta x = 0.1$ mm.

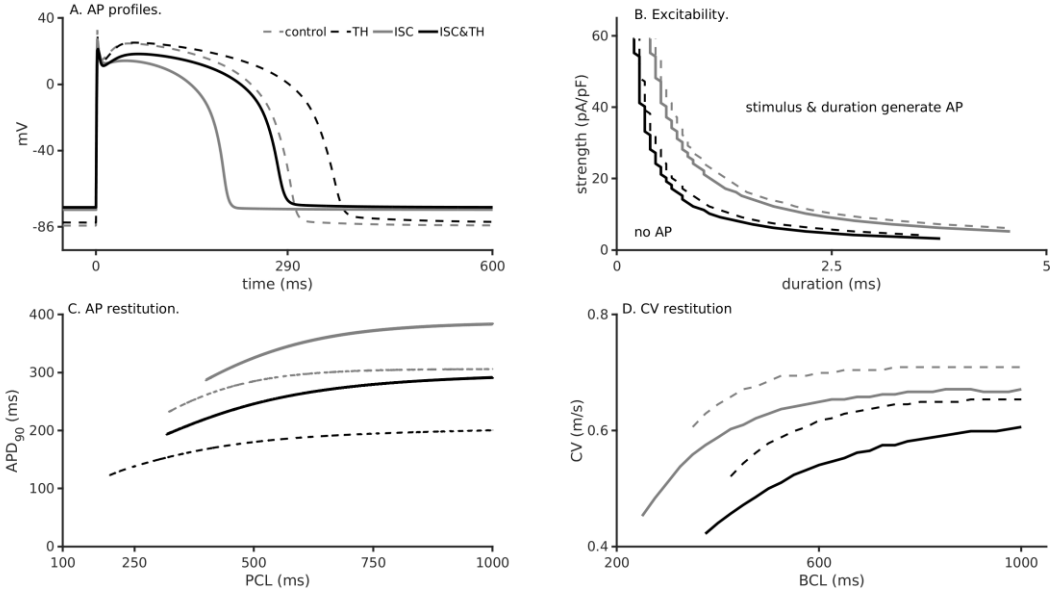

Figure 1. Cell and 1D simulations. A: AP profiles under control (dashed gray), TH (dashed black), ischemic (solid gray), and TH under ischemia (solid black). B: Strength-duration curves to estimate excitability. C: AP restitution showing cell model ability to sustain high pacing rates. D: CV restitution showing 1D tissue model ability to sustain high pacing rates.

3. Results

3.2.1 Cell model behaviour: TH partially restored the ischemia abbreviated action potential duration (APD_{90}) (Figure 1A). The strength duration curves show that both ischemia and TH reduced the rheobase current and chronaxie time (Figure 1B), which indicates increased excitability under the two conditions. APD_{90} restitution (Figure 1C) showed that ischemic cardiomyocytes permit excitation at high arrhythmic pacing rates, and thus possess pro-arrhythmic attributes. The propensity to sustain high pacing rates was reduced due to TH. In 1D tissue, it was found that both ischemia and TH reduced conduction velocity (Figure 1D). Ischemic 1D strands were capable of permitting propagations at high pacing rates, whereas TH treated tissues were resistant to high pacing rate stimuli.

Similar results regarding action potentials, restitution, dispersion, and excitability were obtained in the mid-myocardial and endocardial cell and 1D models.

3.2.2 2D spiral wave dynamics: 2D sheets electrically homogeneous and spatially isotropic sheets representing epicardial, midmyocardial, and endocardial layers were used in 2D simulations.

Spiral waves, initiated using the phase distribution method, were permitted to evolve under control, TH, ischemia, or TH treated ischemic conditions. Under control as well as TH

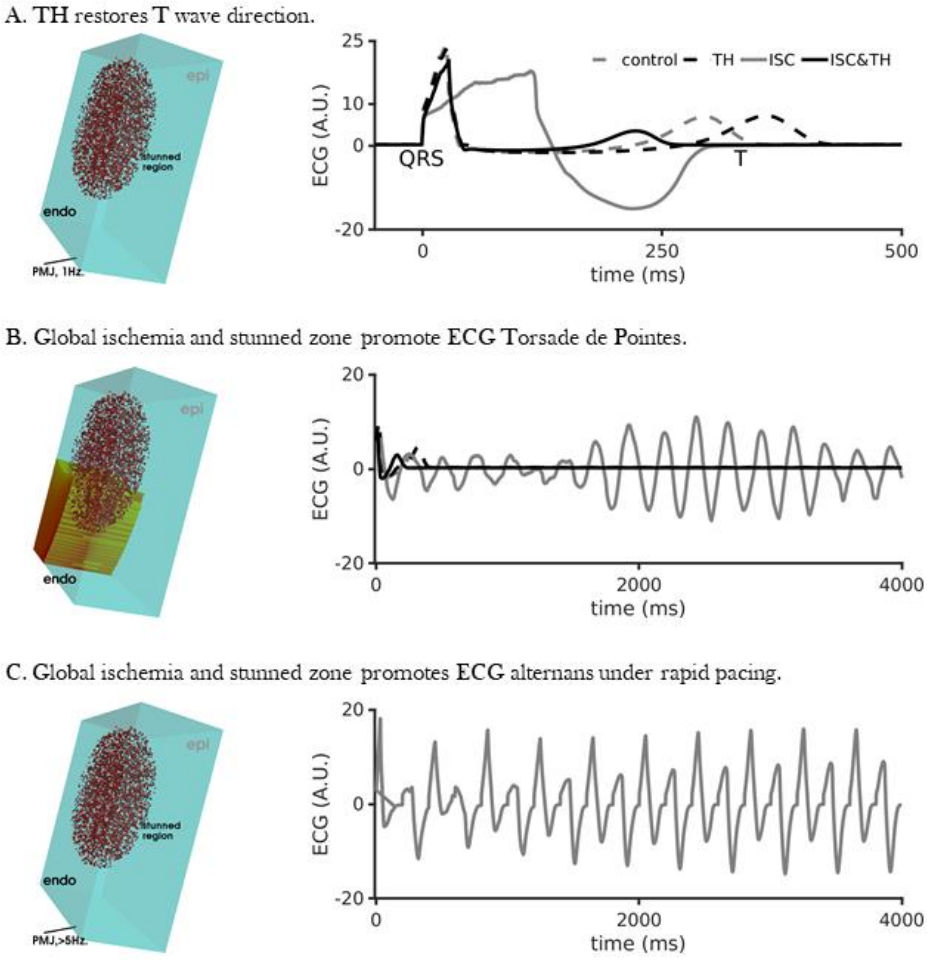

Figure 2. Association between global ischemia, stunned myocardium, and ECG. Left columns show the ventricular wedge with embedded stunned region. A: Physiological pacing at a PCL = 850 ms was applied in one corner of the endocardial surface as shown. Simulated ECG under control (dashed gray), TH (dashed black), ischemic (solid gray), and TH under ischemic (solid black) conditions is shown. B: Effect of scroll waves on ECG. Left panel illustrates the initial scroll wave which was permitted to evolve for 4000 ms duration. The persistent ECG with a changing amplitude (solid gray, ischemic) can be seen in the figures. Under other conditions, scroll waves self-terminated or meandered out of the wedge. C: Rapid pacing at a PCL = 170 ms under ischemic conditions induced ECG alternans.

conditions, the spiral waves self-terminated rapidly due to large spiral wave tip meander. Under ischemic conditions, persistent ventricular fibrillation was observed. The single induced spiral wave degenerated into multiple re-entrant waves which persisted for the duration of the simulation. Upon simulating TH conditions in the ischemic sheets, the lifespans of the induced spiral wave tachycardia abbreviated significantly. Further, fewer daughter wavelets were observed. *3.3.3 3D wedge simulations:* The human ventricle wedge with a stunned central region was used to simulate a pseudo ECG representing the ventricular part of the bio-signal. TH prolonged the

QT interval (Figure 2A), and ischemia altered the ECG considerably. Upon simulating TH under ischemic conditions, an upright T wave was restored. Scroll waves that were induced transmurally in the 3D wedge persisted only under ischemic conditions (Figure 2B), which showed features of Torsade de Pointes in the ECG. Under global ischemic conditions, ECG alternans were observed (Figure 3C). Persistent erratic propagations could be induced only under ischemic conditions in the presence of a stunned region.

4. Conclusions, Discussion, and Limitations

4.1 Conclusions and discussion: Our findings agree with extant experimental data (see e.g. [2]), and extend it to a functional 3D human ventricle wedge model capable of simulating ECG. The findings suggest that the benefit due to TH surpasses its marginal side effects. It is evident that TH reduces conduction velocity and excitability threshold, both of which may be though to be pro-arrhythmic. However, TH increases action potential duration which increases the propagation's wavelength, thus causing re-entry to self-annihilate or meander out of the wedge. Stunned regions consisting of acutely ischemic cardiomyocytes form localized sinks thus damping electrical waves propagating towards the central of the stunned regions and provide border zone that promotes complex propagations that potentially lead to persistent fibrillation. Importantly, the effects of ischemia, TH therapy, and myocardial stunning appear to have distinct ECG features, thus providing a non-invasive biomarker for arrhythmia risk assessment.

4.2 Limitations: The effectiveness of TH to reduce risk of arrythmia caused by non-ischemic factors is being tested. The effects of TH on conductances, steady state gating values, and intracellular dynamics has yet to be incorporated into the model. Further, uncertainty quantification in the cell and 3D models will be performed to explore intra-cardiac variability. Simulation of ion channel dynamics using Markov models may provide further capabilities to incorporate the effects of temperature.

References

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