Predicting the Effect of Ischemia-Reperfusion Injury on Cardiomyocytes

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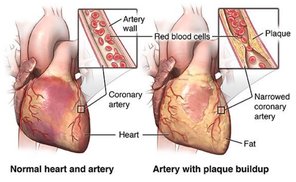
Abstract

A cardiac ischemia-reperfusion (IR) injury (heart attack) can be the cause of up to 50% of the damage to the heart for an individual who has suffered from a heart attack. We update the 2004 Kyoto model with a new metabolism model to explore how calcium overload impacts the cardiomyocyte energetics and contractility. The model simulates excitation, contraction, and metabolism of the heart and allows us to run the system such that it mimics calcium overload. We perturb selected parameters and initial conditions individually in an effort to gain perspective of how the parameter affects the model by quantifying how much the perturbation impacts the system; the technique is called local sensitivity analysis. We then tested several hypotheses linking oxidative stress to myocyte function believed to occur in IR injury. To do this, we added free radical signaling mechanisms to the ECC and calcium handling processes in the model. We found that oxidative-induced modifications of the ryanodine receptor significantly altered electrophysiological and mechanical behavior closely mimicking what was observed in other studies. Oxidative stress dependent effects are then added to explore the damage caused by this addition.

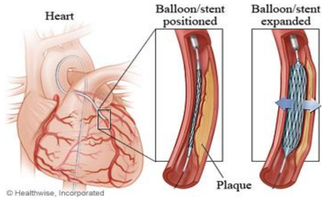
Introduction

- Heart attacks are a direct result of clogged arteries (ischemia) which starve the heart of vital metabolites causing it to stop beating
- Paradoxically, reperfusion leads to calcium overload and oxidative stress which damages the myocardial tissue
- To elucidate the molecular mechanisms responsible, a computational model was developed and analyzed from two prior models

Heart Attack



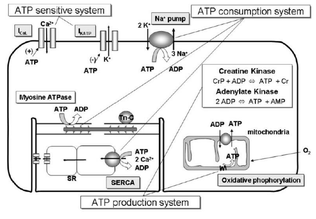
Reperfusion



Model

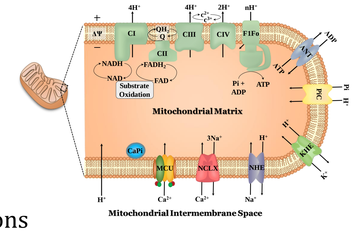
Cardiomyocyte model:

- Electrophysiology
  - Major ion channels and pumps
- Calcium handling
  - L-type calcium channels, ryanodine receptors and SERCA pumps
- Contraction
  - Cross-bridge dynamics



Mitochondrial model:

- Oxidative phosphorylation (ATP)
- Calcium effects on metabolism
- Free radical generation

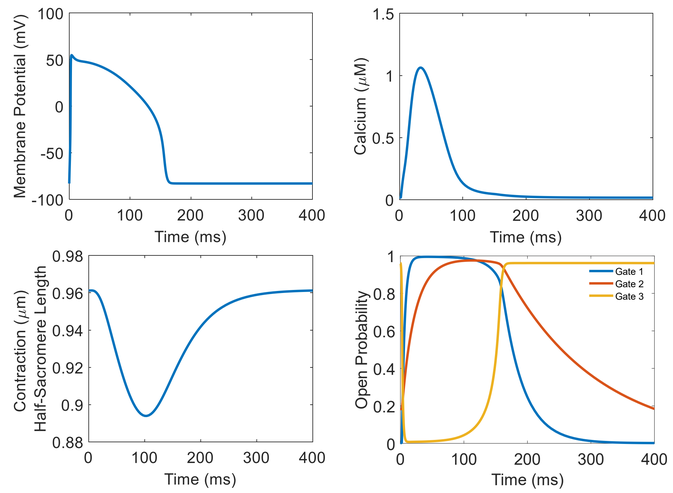


The two models interact through cations and metabolites

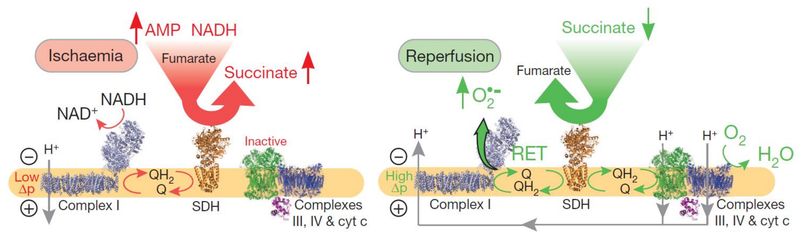
- 76 state variables
- Over 100 parameters

Baseline

Below are simulations of the cardiomyocyte and metabolism model. Simulations were run until the model reached a pseudo-steady state.



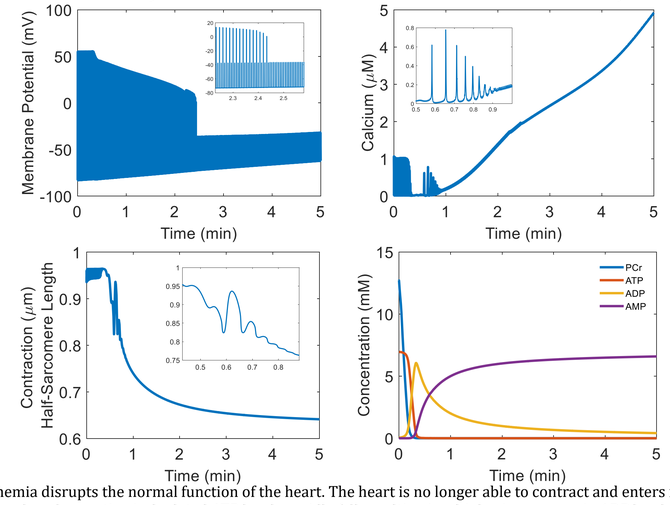
These figures are select state variables and show the model operating under normal conditions during a single action potential. The membrane potential shows the voltage of the cytosolic membrane. The depolarization causes calcium to be released from internal stores. Calcium release activates cross-bridge cycling and triggers contraction of the heart. The final figure displays the inward-rectifier potassium channel gating dynamics. This channel is responsible for repolarization.



During ischemia, succinate accumulates in the myocardial tissue. Upon reperfusion, the excess succinate leads to a substantial increase in mitochondrial free radical production. These free radicals then contribute to tissue injury by several possible mechanisms. We test one computationally.

Ischemia

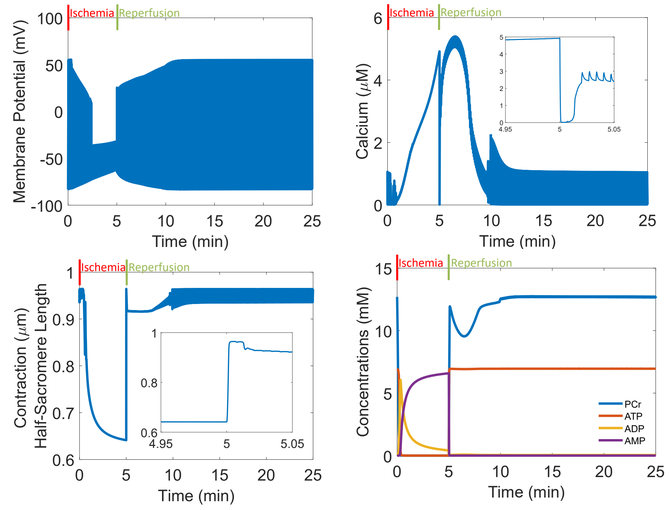
To simulate ischemia, the oxygen concentration was set to zero. As a result, mitochondrial metabolism is disrupted and ATP is depleted. This leads to arrythmias, calcium overload, and contractile dysfunction.



Ischemia disrupts the normal function of the heart. The heart is no longer able to contract and enters rigor. Once phosphocreatine is depleted ATP levels rapidly fall resulting in a biphasic response in ADP levels and a rise in AMP levels. This causes the energy-dependent pumps responsible for ionic balance to fail causing weakened action potential and loss of calcium homeostasis.

Reperfusion

Reperfusion provides the heart with oxygen again and allows beating to restart. The results from simulating this are below.

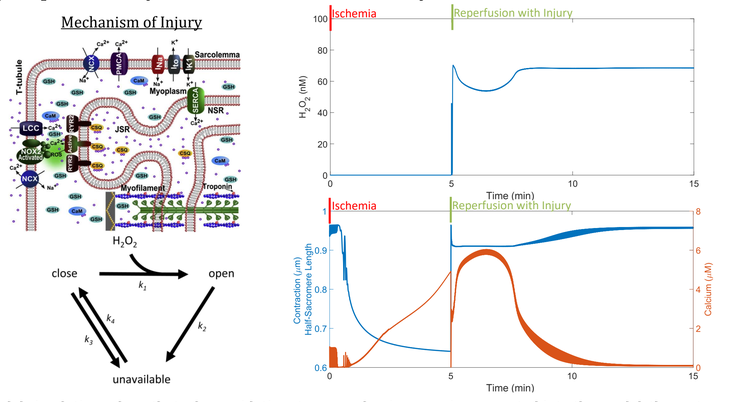


When oxygen is reintroduced to the ischemic tissue, mitochondrial metabolism is activated and restores cytosolic ATP levels. This allows for the pumps responsible for ionic homeostasis to reset the system. This process takes approximately 10 minutes after the onset of reperfusion.

Interestingly, the system cannot reset if the duration of ischemia is too long.

Injury

Adding the effects of oxidative stress impacts the ryanodine receptor open probability and causes contractile dysfunction.



Model simulations show that when oxidative stress mechanisms are incorporated into the model, the system does not recover. This is because ryanodine receptor channel gating is altered causing a depletion of calcium from internal stores. This also decreases cell shortening and leads to weaker contractions.

Conclusions and Next Steps

- Ischemia causes severe disruption in ion and metabolite levels
- Reperfusion in the absence of oxidative stress allows the system to recover; however, only when the duration of ischemia is short
- When oxidative stress mechanisms are included, the system cannot recover after five minutes of ischemia
- Need to add glycolysis, which contributes to cytosolic acidification and affects ion channel gating and metabolism
- Also need to include fatty acid metabolism, which constitutes up to 50% of energy during rest and is severely comprised by calcium overload

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