Regulation of mitochondrial energy supply and implications on cardiac cellular function: a simulation study

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Background

Cardiac myocytes utilize energy stored in the ATP hydrolysis potential (ΔGATP) to fund force development and cellular ion homeostasis. Energy arises from hydrolysis of adenosine triphosphate (ATP), forming the end-products adenosine diphosphate (ADP) and inorganic phosphate (Pi). Mitochondria maintain cytosolic ΔGATP by resynthesizing ATP from ADP and Pi via oxidative phosphorylation in response to changing cellular energy demand. The mechanisms responsible for this regulation remain unclear.

We developed a mathematical model of cardiac cellular excitation-contraction and mitochondrial energetics to distinguish among three proposed regulatory pathways: 1) Ca^{2+} regulation of dehydrogenase flux (Ca-DH), 2) Pi regulation of dehydrogenase flux (Pi-DH) and 3) Pi regulation of Complex III (Pi-CIII), in matching energy supply to energy demand. The model was interrogated to assess the effects of impaired mitochondrial function on cellular electrophysiology, ion homeostasis and force production

Model description

Steady-state model of **Na/K pump** [1].

Steady-state model of the **SERCA pump** [2].

Dynamic model of **Cross-bridge kinetics** [3].

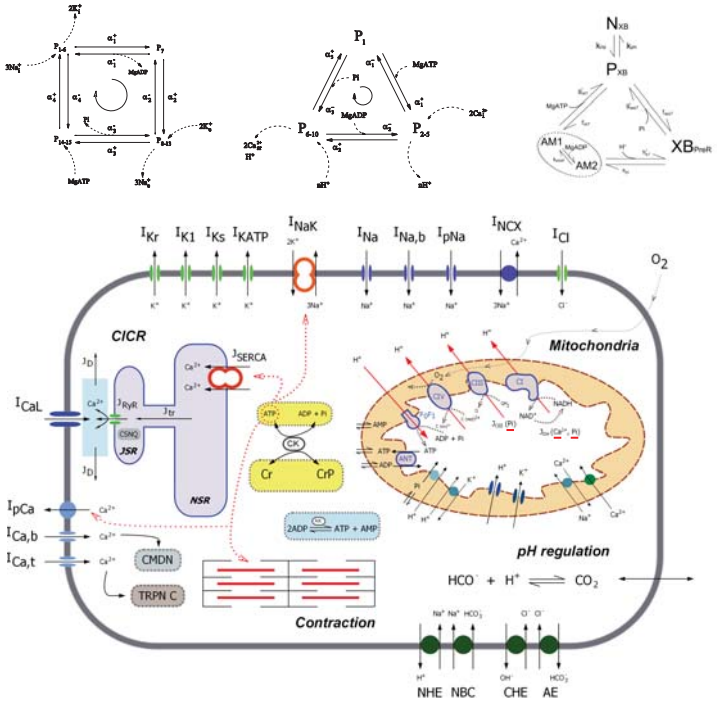

Fig 1 A schematic of the cell model. The electrophysiology model is based on the Crampin and Smith [4] which includes membrane transporters to capture pH regulation. The energy demand processes [1,2,3] are coupled to a model of mitochondrial oxidative phosphorylation [5,6] through the cytosolic metabolites (MgATP, MgADP and Pi) and intracellular [Ca^{2+}], [Na^+], [K^+] and [H^+]. The three mechanisms of mitochondrial regulation investigated here are underlined in red inside the mitochondrion.

Conclusions

The heart can transition from a low to a high work state with little observable change in the concentration of cytosolic metabolites.

The mechanism(s) by which cardiac mitochondria is regulated in response to changes in energy demand is not fully understood.

Our model predicts that, under physiological conditions, regulation of mitochondrial function occurs within the respiratory chain and can be mediated by inorganic phosphate.

The increase in cytosolic Ca^{2+} and Na^+ as a result of an increase in cellular work demand is initiated by the inhibition of changing metabolite concentrations (rising MgADP and Pi) on the kinetics of the Na/K pump.

This effect is mitigated by the activation of Pi-CIII regulation.

Results

The effectiveness of the three regulatory mechanisms are tested by systematically activating each one, while increasing the pacing frequency to simulate an increase in work demand. An increase in frequency, with all three mechanisms active, leads to a small depolarisation in the membrane potential, a rise in cytosolic Ca^{2+} and a rise in force production (Fig. 2; left panel).

When each of the three regulatory mechanism are systematically activated, we see that their effect on the cytosolic metabolite concentrations can be separated into distinct groups: with or without Pi-CIII feedback (Fig. 2, middle panel). In the absence of Pi-CIII regulation, the metabolite concentrations deviate to a greater extent when energy demand is increased.

The simulations also predict that NADH concentration is not a good predictor of mitochondrial ATP production rate (Fig. 2; right panel). This is because ATP production is not limited by the supply of NADH but by the availability of ADP and Pi and by the activation of complex III by Pi.

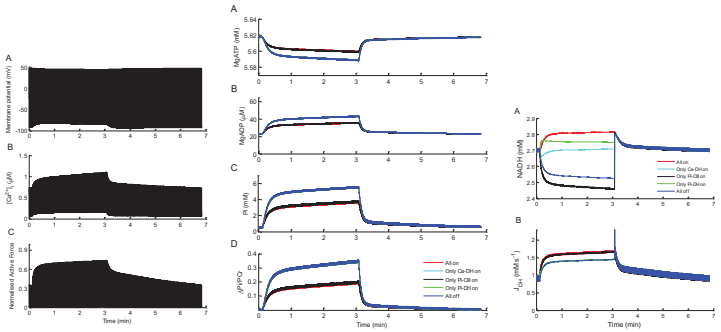

Fig. 2 The effect of increasing stimulus frequency from 0.25Hz at t = 0 to 2 Hz at t = 3 min on: membrane potential, cytosolic Ca^{2+} and force production where all regulatory mechanisms are active (left-hand panel); cytosolic metabolite concentrations (middle panel); mitochondrial NADH concentration and dehydrogenase flux (right-hand panel).

Given that Pi-CIII is the primary regulator of mitochondrial ATP production, its effects on cellular function was tested under a length-change protocol to increase energy demand. The simulations indicate that in the absence of Pi-CIII regulation, the metabolite concentrations increase dramatically (Fig. 3; left panel). This leads to inhibition of the Na/K pump (Fig. 3; middle panel, B), caused by the rise in MgADP and Pi, which elevates cytosolic [Ca^{2+}] and [Na^+] and depresses [K^+] (Fig. 3; right panel). The rise in diastolic [Ca^{2+}] increases the diastolic force, leading to incomplete relaxation (Fig. 3; middle panel, D).

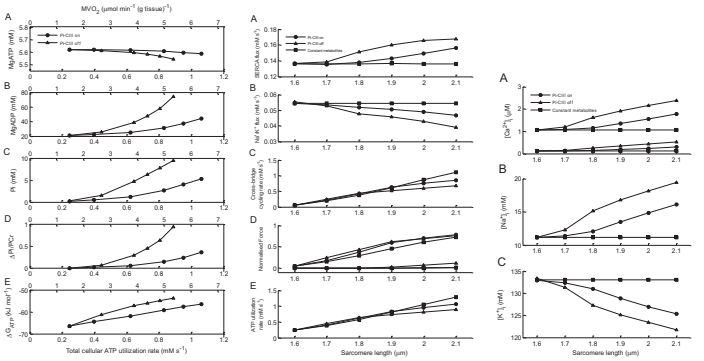

Fig. 3 The effect of increasing cellular energy demand (by increasing sarcomere length) on cytosolic metabolite concentrations (left-hand panel); increasing sarcomere length on SERCA cycle flux, Na/K cycle flux, cross-bridge cycle flux, normalised force and total ATP utilization (middle panel); increasing sarcomere length on cytosolic Ca^{2+}, Na^+ and K^+ concentrations (right-hand panel). Simulations are performed with the Pi-CIII regulation either activated or inactivated.

References

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Acknowledgements

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