Cardiac myosin-binding protein C reduces cardiac power output via drag forces and myosin binding inhibition

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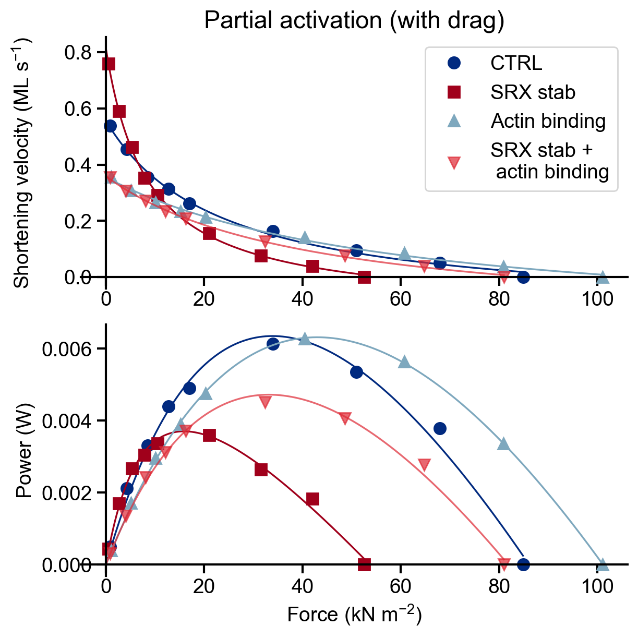
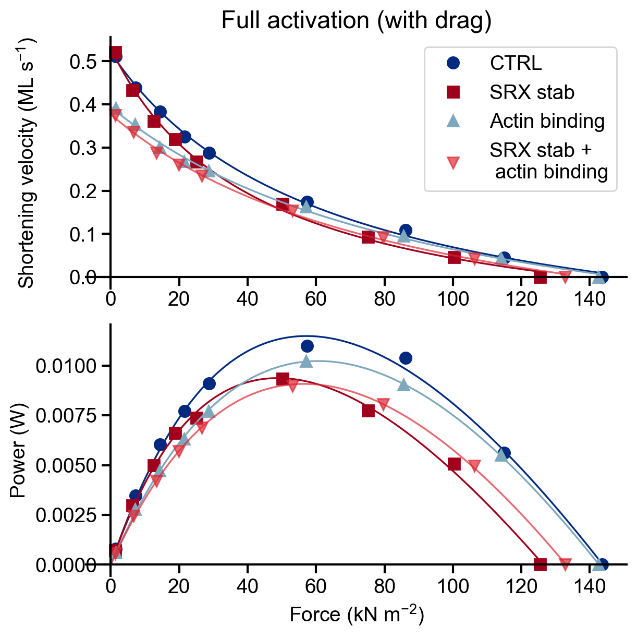
Cardiac myosin-binding protein C (cMyBP-C) is an essential regulator of cardiac function. Mutations in cMyBP-C are one of the major causes of hypertrophi*c* cardiomyopathy, the most common inherited form of heart disease. Despite its significance in cardiac health, surprisingly little is known about how cMyBP-C mediates its functional effects. Computational modelling tools may provide new quantitative insights into the cMyBP-C regulatory role.

Numerical simulations were performed using FiberSim, a spatially-explicit model of myofilament-level contraction. Loaded shortening protocols were implemented to test two hypotheses on cMyBP-C interaction with myofilaments. The first mechanism (M1) is the cMyBP-C stabilization of the super-relaxed state (SRX) of myosin dimers. This myosin state is associated with a low ATPase activity and an absence of interaction with actin. The other mechanism (M2) is cMyBP-C binding to actin. Bound cMyBP-Cs act as “non-force-generating” crossbridges and compete with the myosin heads for actin binding sites.

At full activation (pCa 4.5), both M1 and M2 lead to a decreased maximal power output (Pmax) compared to a situation where no cMyBP-C molecules are present (control case). At partial activation (pCa = 5.7), M2 leads to improved power outputs at high loads, and to similar Pmax compared to the control case. Removing the “dragging” effect of cMyBP-C (by setting the actin link stiffness to zero) lead to increased shortening velocities and increased power outputs for M2 compared to the control case (at partial activation).

At both full and partial activation levels, M1 and M2 combined lead to decreased Pmax. These results confirm the experimental evidence that cMyBPC acts to limit power output. Our simulations suggest that both the inhibition of myosin binding by stabilization of the SRX (M1), and drag forces due to bound cMyBPCs (M2) are responsible for the decreased power outputs.

FIGURES



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