Cardiac myosin filaments are directly regulated by calcium

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Calcium (Ca2+) signaling coordinates many different intracellular processes in plant, animal, and human physiology. Muscle contraction is one of those biological processes regulated by Ca2+ and is propelled by the sliding of actin-containing thin filaments along myosin-containing thick filaments in the sarcomere. Classically, striated muscle contraction is initiated by Ca2+-dependent structural changes in regulatory proteins on actin-containing thin filaments, which allow binding of myosin motors to generate force. The dynamic switching between the resting off states and the active on states of myosin is also critical in regulating muscle contractility. However, the molecular switch on the myosin-containing thick filament that drives this process is not understood. Here we decoupled Ca2+-mediated thin filament-based regulation from thick filament-based regulation, using a small-molecule thin filament inhibitor. Here we show that cardiac thick filaments are directly Ca2+-regulated. We find that Ca2+ progressively moves the myosin heads from ordered off states close to the thick filament backbone to disordered on states closer to the thin filaments in the absence of active force. This Ca2+-dependent structural shift of myosin is accompanied by a biochemically defined transition from the inactive super-relaxed state(s) to the active disordered relaxed state(s). Furthermore, we find that this Ca2+-mediated molecular switching is an intrinsic property of cardiac myosin but only when assembled into thick filaments. This novel concept of Ca2+ as a regulatory modulator of the thick filament provides a fresh perspective on nature's two orthogonal mechanisms to regulate muscle contraction via the thin and the thick filament and potentially have a wide-reaching impact on muscle biology and its therapeutic potential in different cardiac and skeletal pathologies.