Cardiac Mechanoelectric Feedback: A Role for Caveolae?

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Mechanical stretch of cardiac muscle affects myocyte electrophysiology is potentially arrhythmogenic. We investigated the effects of stretch *in vitro* and in the intact heart on action potential conduction. Using optical mapping to measure in isolated mouse hearts and in micropatterned mouse cardiomyocyte we found that conduction velocity decreased rapidly and reversibly with volume loading and stretch. This slowing was not altered by stretch-activated channel inhibition, but was abrogated when caveolae were disrupted by genetic deletion of caveolin-3 or chemical depletion of membrane cholesterol. Electron microscopy showed that stretch in wild-type mouse hearts, causes recruitment of caveolae to the sarcolemma. Stretch significantly increases membrane capacitance, electrical time constant and lipid recruitment to the bilayer in wildtype mice. To investigate these mechanisms further we have used computational models of normal and cav-3 mutant myocytes as well as coupled electromechanical models.

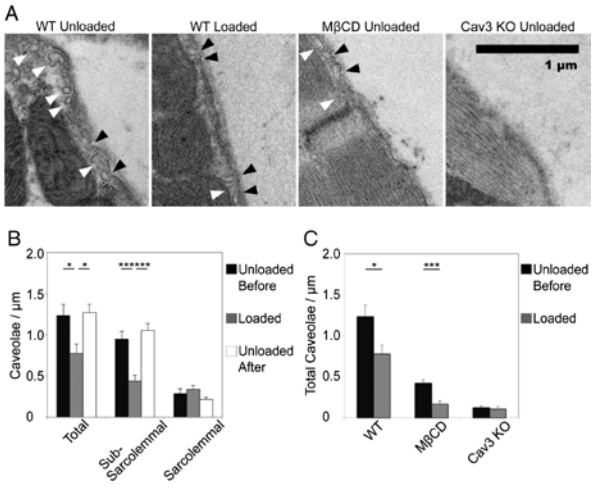

Figure. Stretch reversibly recruits sarcolemmal caveolae (white arrows). (A) Pressure loading alters caveolar density and localization in WT hearts by EM (scale: 1 μm). Caveolae integrate into the sarcolemma (black arrows) when the ventricle is loaded. (B) Caveolar recruitment from sub-sarcolemmal region during loading in WT hearts ($P < 0.001$), (C) Total caveolar density is reduced by loading. In MβCD-treated hearts and Cav3 KO hearts, caveolae are reduced or absent ($P < 0.001$).