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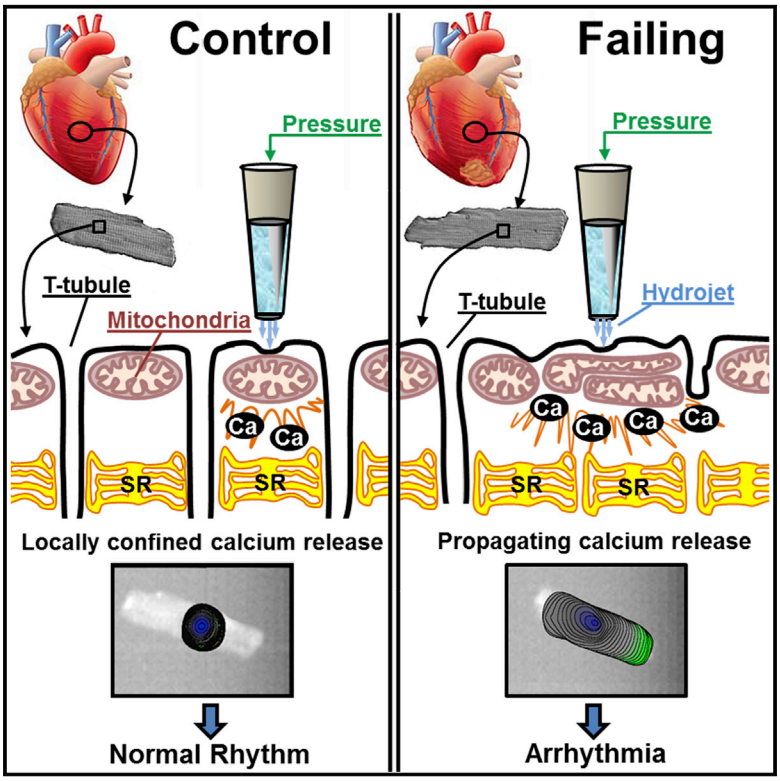
Microtubule-Dependent Mitochondria Alignment Regulates Calcium Release in Response to Nanomechanical Stimulus in Heart Myocytes

Graphical Abstract



Highlights

- Nanomechanical pressure application changes mechanosensitivity in failing heart cells
- Microtubular network disorganization mediates the change in mechanosensitivity
- Mitochondria are displaced from their original location and trigger calcium release
- Uncoupling the mitochondrial proton gradient completely abolishes the phenomena

Authors

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In Brief

Miragoli et al. show that failing heart cells have altered sensitivity to nanomechanical stimuli mediated by changes in the alignment of microtubules. The microtubule network disorganization leads to displacement of mitochondria and alterations in calcium release.

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Microtubule-Dependent Mitochondria Alignment Regulates Calcium Release in Response to Nanomechanical Stimulus in Heart Myocytes

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SUMMARY

Arrhythmogenesis during heart failure is a major clinical problem. Regional electrical gradients produce arrhythmias, and cellular ionic transmembrane gradients are its originators. We investigated whether the nanoscale mechanosensitive properties of cardiomyocytes from failing hearts have a bearing upon the initiation of abnormal electrical activity. Hydrojets through a nanopipette indent specific locations on the sarcolemma and initiate intracellular calcium release in both healthy and heart failure cardiomyocytes, as well as in human failing cardiomyocytes. In healthy cells, calcium is locally confined, whereas in failing cardiomyocytes, calcium propagates. Heart failure progressively stiffens the membrane and displaces sub-sarcolemmal mitochondria. Colchicine in healthy cells mimics the failing condition by stiffening the cells, disrupting microtubules, shifting mitochondria, and causing calcium release. Uncoupling the mitochondrial proton gradient abolished calcium initiation in both failing and colchicine-treated cells. We propose the disruption of microtubule-dependent mitochondrial mechanosensor microdomains as a mechanism for abnormal calcium release in failing heart.

INTRODUCTION

Pump failure and sudden cardiac death remain a major clinical problem despite conventional therapies. Altered mechanosensitivity initiates electrical instability and arrhythmia in heart failure (Kiseleva et al., 2000). Whereas pro-arrhythmic mechano-electric transduction has been extensively investigated in intact hearts in situ, isolated hearts, and in isolated cellular preparations, the initial subcellular mechanisms required for signal transduction and its initiation remain elusive (Lammerding et al., 2004). Recent attention has focused upon different sarcomeric components (Kim et al., 1999), and in addition to force generation, several sarcomeric proteins were found to provide mechanosensing and/or signaling functions (Borg et al., 2000; Knöll et al., 2002). Mutations in these sarcomeric or Z-disk complex proteins cause abnormal intracellular Ca^{2+} responses (Knöll et al., 2002).

During heart failure, the cytoskeletal scaffold remodels, and this may also disturb the normal regulation of mechanosensation (Janmey and Miller, 2011). Loss of appropriate mechanical feedback control may contribute to the development of heart failure. The structural remodeling that occurs during heart failure involves the cell membrane (loss of T-tubules; Lyon et al., 2009), intercalated disks (Ferreira-Cornwell et al., 2002), and sub-membrane microdomains involving ryanodine receptors (RyRs) and the sarcoplasmic reticulum (Dobrev and Wehrens, 2014). Importantly, mitochondria change their subcellular location (Piquereau et al., 2013; Rosca et al., 2013) and the inter-fibrillar mitochondria alignment is altered early following myocardial infarction (Dague et al., 2014). Regular alignment of mitochondria and the dyad plays a pivotal role in the homeostasis of excitation-contraction coupling (Chen et al., 2012; Kohlhaas and Maack, 2013; Lu et al., 2013) and intracellular calcium handling (Belmonte and Morad, 2008b). However, little is known about the possible role of mitochondria remodeling in mechanoelectric transduction-induced arrhythmia. This reflects the inability of many conventional technologies to selectively and mechanically activate or investigate mitochondrial involvement within a single sarcolemmal microdomain. Here, we have employed scanning ion conductance microscopy (SICM) and surface