Overall cardiac function. Our data suggest that the progression from hypertensive heart failure (HF) develops. The goal of this study was to measure the relationship between junctional SR from trigger Ca entry and the increase in orozomalbism (ischémia)-induced heart failure. We found that the levels of CSQ protein did not change significantly as a result of either of these two treatments. CSQ recovered from control dog heart tissue was, however, fundamentally different from that present in normal dogs. CSQ undergoes both co-translational addition of an N-linked glycan as well as an unusual co-translational phosphorylation of its C-terminus. In control heart tissue, CSQ exhibited its characteristic polymorphic pattern of post-translational deamannosylation and dephosphorylation. Failing hearts, however, was marked by large percentages of CSQ molecules (20-40% of total levels) with Mannose 2-6 Gal linked, reflecting more newly synthesized protein in rough ER. In addition, there was a significant "retrograde shift" in the average glycan processing of CSQ glycans, with longer-lived CSQ molecules replaced with shorter-lived. Such changes indicate a major degradation and biosynthesis (increased turnover) phenotype for CSQ, perhaps representing changes needed to support increased hypertrophic growth. Two phenotypes are also evident using a SDS gel-based analysis. Taken together with our recent findings that CSQ is synthesized around myonuclei and phosphorylated on its C-terminus during its biosynthesis, we propose that qualitative alterations in CSQ metabolism occur in hypertrophic heart. In this proposed model, increased CSQ synthesis leads to increased CSQ in perinuclear cisternae, while increased CSQ degradation prevents buildup of protein in junctional SR cisternae.

T-Tubule Remodeling Causes Ca\(^{2+}\) Cycling Defects during the Progression to Heart Failure in the Intact Spontaneously Hypertensive Rat Heart

James E. Kelly, Satvik Ramakrishna, Daniel Schuster, Nimi Chirayil, J. Andrew Wasserstrom

T-tubule disorganization is a major feature of the phenotype is accelerated protein synthesis, but changes are complex, involving increases in protein translation capacity, efficiency, and turnover. We purified calsequestrin (CSQ), a major protein component of the Ca\(^{2+}\) release protein complex, from frozen heart samples of sham control mongrel dogs, or dogs subjected to either tachycardia-induced or microembolism (ischémia)-induced heart failure. We found that the levels of CSQ protein did not change significantly as a result of either of these two treatments. CSQ recovered from control dog heart tissue was, however, fundamentally different from that present in normal dogs. CSQ undergoes both co-translational addition of an N-linked glycan as well as an unusual co-translational phosphorylation of its C-terminus. In control heart tissue, CSQ exhibited its characteristic polymorphic pattern of post-translational deamannosylation and dephosphorylation. Failing hearts, however, was marked by large percentages of CSQ molecules (20-40% of total levels) with Mannose 2-6 Gal linked, reflecting more newly synthesized protein in rough ER. In addition, there was a significant "retrograde shift" in the average glycan processing of CSQ glycans, with longer-lived CSQ molecules replaced with shorter-lived. Such changes indicate a major degradation and biosynthesis (increased turnover) phenotype for CSQ, perhaps representing changes needed to support increased hypertrophic growth. Two phenotypes are also evident using a SDS gel-based analysis. Taken together with our recent findings that CSQ is synthesized around myonuclei and phosphorylated on its C-terminus during its biosynthesis, we propose that qualitative alterations in CSQ metabolism occur in hypertrophic heart. In this proposed model, increased CSQ synthesis leads to increased CSQ in perinuclear cisternae, while increased CSQ degradation prevents buildup of protein in junctional SR cisternae.

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**Stereoselectivity of Propafenone RyR2 Channel Block and Prevention of Ventricular Arrhythmia In Vivo**

Michelle Faggione, Hyun Seok Hwang, Bjorn C. Knollmann

Backgr: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by an unusual physical stress-induced arrhythmias in carriers of mutations in either cardiac ryanode receptor (RyR2) or cardiac calsequestrin (Casq2). These mutations cause spontaneous premature sarcoplasmic reticulum Ca\(^{2+}\) release, which activates the Na\(^+\)/Ca\(^{2+}\) exchange leading to delayed afterdepolarization with an increased risk of ventricular arrhythmias. As reported elsewhere, we found that the enantiomers of the class-I antiarrhythmic drug propafenone are stereoselective blockers of single RyR2 channels expressed in bilayers. Here we studied the efficacy of propafenone and its R and S enantiomers on spontaneous Ca\(^{2+}\) release in myocytes and in vivo in a CPVT mouse model.

RESULTS: Consistent with its higher potency of RyR2 channel block in bilayers, R-propafenone was more potent than S-propafenone in reducing the rate of isoproterenol-stimulated Ca\(^{2+}\) waves (IC50=1.1±0.47mM and 6.2±0.41mM respectively) in intact myocytes isolated from Casq2-/- mice. We then tested the effects of an intraperitoneal injection of either racemic propafenone or its enantiomers in vivo in Casq2-/- mice using a treadmill exercise test. A dose of 5mg/kg of racemic mixture of propafenone protected the mice from CPVT during exercise compared to the vehicle but not during the hours following the test. Consistently with our in vitro results, we then observed that 5mg/kg of R-propafenone significantly prevented CPVTs, both during exercise and in the follow-up hours, whereas the same dose of 5mg/kg of S-propafenone was not effective. A dose of 20 mg/kg of S-propafenone were required in order to obtain the same protection as R-propafenone.

CONCLUSIONS: Our results suggest that compared to S-propafenone, R-propafenone, has a higher potency in blocking RyR2 channels and spontaneous Ca\(^{2+}\) waves, which resulted in a significantly better protection from stress-induced CPVT in vivo. Supported by NIH-R01-HL08635.

**SYMPOSIUM 9: Cell and Tissue Mechanics and Modeling-AFM and Rheology, Small to Tissue Scale**

992-Symp

**Cytokinesis Through Biochemical-Mechanical Feedback Loops**

Douglas N. Robinson

Cytokinesis, the division of a mother cell into two daughter cells, is an essential cellular process with significant developmental and medical implications. Fundamentally mechanical, this geometrically simple cell shape change encompasses nearly all cellular processes. Particularly featured are cytoskeletal mechanics, molecular motor mechanochemistry, fluid dynamics, and cellular physiology, all of which are carried out by genetically encoded biomolecules. Furthermore, our work is revealing that cytokinesis is an integrated control system characterized by mechanical and biochemical feedback loops. I will present our current thinking of how these processes and features contribute to the physical aspects of cytokinesis.