capable of detecting mechanical separation of the muscle layers, which was found to occur more frequently in w1118 than yw (0.41 ± 0.04 vs. 0.00 ± 0.02 μm separation, respectively, 1 week flies). Detection of mechanical separation between muscle layers via nanoindentation was modeled and verified in a microfabricated polydimethylsiloxane system. This first in situ mechanical analysis of a living myocardium revealed differences in cardiac mechanics due to age and suggest that aspects of the mechanical properties of the aging phenotype differ between Drosophila strains. We investigation on other laboratory Drosophila wildtype strains to assess the impact of diverse genetic backgrounds or mutations on age-related myocardial stiffening and cardiomyopathy.

1782-Pos Board B552

In Situ Mechanical Analysis of Genetic Modification and Aging on Soft, Bilayered Drosophila Myocardium

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Drosophila melanogaster is a genetically malleable organism with a short life span, making it a tractable system in which to study mechanical effects of genetic perturbation and aging on tissues, such as impaired heart function. However, Drosophila heart tube studies can be hampered by its bilayered structure: a ventral muscle layer covers the contractile cardiomyocytes. We have refined an atomic force microscopy-based analysis to measure individual mechanical components of soft composite materials. The technique was verified using bilayered polydimethylsiloxane. Its biological utility was further demonstrated by its ability to resolve stiffness changes due to cardiac-specific RNA interference to reduce cardiomyocyte myofibrillar assembly or due to aging in Drosophila myocardial layers. Female yellow-white (yw) flies experience decreased diastolic diameter with age (>20%) while cardiomyocytes stiffened more than two-fold with age (1.8 ± 0.1 vs. 3.8 ± 0.3 kPa in 1 and 5 week old flies, respectively) at cell-cell junctions. Cardiac-specific RNA-interference against myosin heavy chain severely impaired contraction and reduced stiffness after 1 week (1.0 ± 0.1 vs. 1.8 ± 0.1 kPa) without altering ventral muscle stiffness. This method provides a platform to assess the mechanics of soft biological composite systems and for the first time permits direct measurement of how genetic perturbations, aging, and disease can impact cardiac function in situ.

1783-Pos Board B553

Exploration and Suppression of Cardiac Amyloidosis Induced by Huntington's Disease-Causing Amyloid in the Drosophila Heart Model

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Accumulation of amyloids is associated with cardiomyopathy; however, the precise mechanism that leads to defective heart structure and function is unknown. Amyloid-like inclusions have been detected in patients with Huntington's disease (HD), which is caused by an expanded polyglutamine (Poly-Q) repeat in the Huntington (HTT) protein. HD patients also demonstrate a greater occurrence of cardiovascular events, presumably as a result of toxic amyloid accumulation due to global protein misfolding and/or oxidative stress. To explore cardiac defects associated with HD-causing amyloid protein, we used the UAS-Gal4 system and a cardiac-specific driver (Hand-Gal4) to express mutant HTT with short (UAS-*Httex1*-PolyQ25) and disease-causing expanded (UAS-*Httex1*-PolyQ72) Poly-Q in the *Drosophila* heart. Expression of disease causing Poly-Q in 1 and 3 week old fly hearts resulted in severe cardiac defects as evidenced by prolonged diastolic and systolic intervals, a significantly increased incidence of arrhythmias and extreme cardiac dilation that was accompanied by a significant decrease in cardiac contractility (reduced fractional shortening). Structural analysis showed myocardial cells with noticeably reduced myofibrillar content, myofibrillar disorganization and the presence of amyloid-aggregates. No such physiological and structural defects were seen upon expression of short Poly-Q under similar conditions. To take advantage of our genetic model and to further explore the mechanism underlying the PolyQ-induced cardiac defects, we co-expressed expanded Poly-Q with either the antioxidant enzyme superoxide dismutase (SOD) or a chaperone protein UNC-45. Our preliminary results suggest that cardiac dilation is reduced and cardiac performance is enhanced upon co-expression of SOD or UNC-45. Thus we have developed a novel *Drosophila* model that allows us to explore cardiac defects associated with the accumulation of HD-causing amyloid and to elucidate the mechanisms underlying cardiac failure in HD patients.

1784-Pos Board B554

Multi-Scale Modeling of Patient-Specific Ventricular Geometry, Fiber Structure, and Biomechanics

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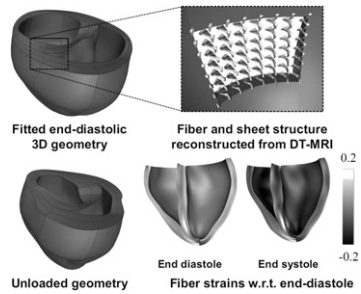
Patient-specific image data of the heart can now be obtained through advanced medical imaging. This data combined with clinical measurements can potentially be integrated into patient-specific computational models of regional cardiac function. We have developed a pipeline for patient-specific ventricular biomechanics simulations in the failing heart. Three-dimensional ventricular geometry was segmented from CT or MRI data at end-diastole from patients with congestive heart failure. Human myofiber and sheet architecture was estimated using eigenvectors computed from Diffusion Tensor MRI obtained in an isolated, fixed human organ donor heart and mapped to the patient-specific geometric model using large-deformation diffeomorphic mapping. Passive myocardial properties were optimized using semi-automated methods while simultaneously computing the unloaded reference geometry. Active cardiac-muscle contraction properties were optimized to match ventricular pressures measured by cardiac catheterization. Finally, echocardiographic data and an adaptation algorithm (CircAdapt) were used to estimate parameters of a lumped-parameter closed-loop model of the circulation. These methods were validated in three heart failure patients who gave informed consent at the San Diego VA Medical Center by comparing simulation results with echocardiographic measurements of regional wall motion and with predictions of empirical formulas derived from previous clinical studies.



1785-Pos Board B555

Cross-Bridge Cycling Kinetics in Intact Multicellular Cardiac Muscle at Physiological Temperature: Impact of Muscle Length

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The contractility of the heart is physiologically determined by load, frequency and β-adrenergic stimulation. It has been shown that these regulatory mechanisms involve post-translational modifications of myofilament proteins that can potentially influence the rate of cross-bridge cycling, an important determinant of cardiac output. We set out to develop a method for measuring cross-bridge cycling rate in intact cardiac muscle preparations where the cascades of post-translational signaling are functionally intact. With the use of a K^+ contracture protocol, we were able to induce a steady-state tension in intact trabeculae and measure the rate of tension redevelopment (k_{tr}), an index for cross-bridge cycling rate. We utilized this technique in order to investigate the effect of load on cross-bridge cycling rate. In cardiac trabeculae isolated from Brown Norway rats (n=11), the rate of tension redevelopment was measured twice at L_{opt} (optimal length) and at L_{90} (corresponding to 90% of optimal length) in each muscle. The k_{tr} for the L_{90} was 45.1 ± 7.6 s^{-1} and it was significantly decreased to 27.7 ± 3.3 s^{-1} as the muscles were stretched to their L_{opt} ($P < 0.05$). The k_{tr} for each length was measured a second time in order to show the reproducibility of the system. There was no significant difference between the duplicate measurements of each length ($P = 0.84$). In addition, we were able to apply these experiments in mammals that more closely reflect the human situation (such as the rabbit and dog) and muscle preparations isolated from explanted human hearts. This technique permits the studying of cross-bridge cycling kinetics in intact muscles in a reproducible and reliable manner, where the impact of signaling cascades leading to post-translational modifications can be studied.

1786-Pos Board B556

Differential Twitch Kinetics in Engineered Cardiac Tissue Expressing Human Cardiac Myosins

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Congestive heart failure is a debilitating disease in which the principal pathology is impaired ventricular contractility leading to diminished cardiac output, and previous work indicates that reduced contractility is based in part on the