Results
Passive tension over the entire range of sarcomere lengths did not differ between sarcomere-mutation positive and mutation-negative male HCM patients. Passive tension in myocytes from sarcomere mutation-positive women was significantly higher compared to female mutation-negative HCM patients. Female MYH7 cardiomyocytes showed a higher sarcomere stiffness compared to male MYH7.
Conclusion
Our measurements suggest that high sarcomere passive stiffness may contribute to diastolic dysfunction in female HCM patients harboring a mutation in genes encoding thick filament proteins.

1751-Pos Board B481
Sex-Related Differences in Myosin Heavy Chain Isoforms of Human Failing and Non-Failing Atria
Peter J. Reiser[1], Christine S. Moravec[2].
[1]Oral Biology, Ohio State University, Columbus, OH, USA, [2]Kaufman Center for Heart Failure, Cleveland Clinic, Cleveland, OH, USA.
Mammalian hearts express two myosin heavy chain (MHC) isoforms, which drive contractions with different kinetics and power-generating ability. The expression of the isoform that is associated with more rapid contraction kinetics and greater power output, MHC-α, is down-regulated, with a concurrent increase in the relative amount of the slower isoform, MHC-β, during the progression to experimentally-induced or disease-related heart failure. This change in protein expression has been well studied in right and left ventricles in heart failure models and in humans with failure. Relatively little quantitative data exists regarding MHC isoform expression shifts in human failing atria. We previously reported significant increases in the relative amount of MHC-β in the human failing left atrium. The results of that study suggested that there might be a sex-related difference in the level of MHC-β in the left atrium, but the number of female subjects was insufficient for statistical analysis. The objective of this study was to test whether there is, in fact, a sex-related difference in the level of MHC-β in the right and left atria of humans with cardiomyopathy. The results indicate that significant differences exist in atrial MHC isoform expression between men and women who are in failure. The results unexpectedly also revealed a two-fold greater amount of MHC-β in the non-failing left atrium of women, compared to men. The observed sex-related differences in MHC isoform expression could impact ventricular diastolic filling during normal daily activities, as well as during physiologically stressful events.

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Myocardial Infarction-Induced N-Terminal Fragment of Cmybp-C Impairs Myofilament Function in Human Left Ventricular Myofibrils
Namthip Witayavanitkul[1], Jason Sarkey[1], Younss Aitmou[1], Diederik W.D. Kuster[1], Ramzi J. Khairallah[1], Suresh Govindan[1], Xin Chen[2], Ying Ge[2], Sudarsan Rajan[3], David F. Wieczorek[3], Thomas Irving[4], Pieter P. de Tombe[1], Sakthivel Sadayappan[1].
[1]Department of Cell and Molecular Physiology, Health Sciences Division, Loyola University Chicago, Maywood, IL, USA, [2]Human Proteomics Program, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA, [3]Department of Molecular Genetics, Biochemistry, and Microbiology, University of Cincinnati College of Medicine, Cincinnati, OH, USA, [4]Biology, Chemistry & Physical Sciences, Argonne National Laboratory, Lemont, IL, USA.
Rationale: Myocardial infarction (MI) is associated with depressed cardiac contractile function and progression to heart failure. Cardiac myosin binding protein-C (cMyBP-C), a cardiac-specific myofilament protein, is proteolyzed post-MI in humans and results in an N-terminal fragment, C0C1f. The presence of C0C1f in cultured adult cardiomyocytes results in decreased Ca^{2+} transients and cell shortening, in addition to the induction of heart failure in a mouse model. However, the underlying mechanisms remain unclear.
Objective: To determine how C0C1f causes altered contractility in human cardiac myofilaments in vitro.
Methods and Results: We generated recombinant human C0C1f (hC0C1f) and incorporated it into skinned human left ventricular myocytes. Mechanical properties were then studied at sarcomere lengths of 2.0 and 2.3 μm. Our data demonstrate that the presence of hC0C1f in the sarcomere decreased maximal force myofilament Ca^{2+} sensitivity, increased cooperative activation at short lengths and enhanced length-dependent activation. Furthermore, hC0C1f led to increased cross-bridge cycling kinetics and tension cost at both short and long sarcomere lengths. We further established that the detrimental effects of hC0C1f occur through direct interaction with the thin filament proteins actin and α-tropomyosin (α-TM).
Conclusions: Our data demonstrate that the presence of hC0C1f in the sarcomere is sufficient to induce depressed myofilament function and Ca^{2+} sensitivity in otherwise healthy human donor myofilament preparations. Decreased cardiac function post-MI may result, in part, from the ability of hC0C1f to bind actin and α-TM, suggesting that cleaved C0C1f could act as a poison peptide and disrupt the interaction of native cMyBP-C with the thin filament.
Keywords: Cross-bridge cycling kinetics; length-dependent activation; cMyBP-C; C0C1f protein.

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Beta-Adrenergic Response in Human HCM Myocardium: Effects of Ranolazine
Cecilia Ferrantini[1], Raffaele Coppini[1], Benedetta Tosi[1], Josè Manuel Pioner[1], Laura Sartiani[1], Iacopo Olivotto[1], Chiara Tesi[1], Luiz Belardinelli[2], Elisabetta Cerbai[1], Alessandro Mugelli[1], Corrado Poggesi[1].
[1]Centro Interuniversitario di Medicina Molecolare e Biofisica Applicata (C.I.M.M.B.A.), Florence, Italy, [2]Gilead Inc., Palo Alto, CA, USA.
Background: Rest or exercise obstruction is present in two thirds of patients with hypertrophic cardiomyopathy (HCM) and is a major determinant of symptoms and disability. Hypercontractile upper septum is the main pathophysiological determinant of obstruction, thus negative inotropic interventions such as dysopiramide or beta-blockers are the only available options to pharmacologically treat obstruction, commonly with partial efficacy. We have previously demonstrated that ranolazine ameliorates diastolic function in trabeculae from septal samples of obstructive HCM patients undergoing myectomy (Coppini et al, Circulation 2013).
Methods: Patch clamp studies and intracellular Ca^{2+} recordings were performed in isolated myocytes from myectomy samples of obstructive HCM patients; intact trabeculae were used for mechanical measurements. Myocardial specimens from non-failing non-hypertrophic patients or patients with secondary hypertrophy were used as controls.
Results: Dysopiramide (Dys) reduced twitch tension in a dose dependent manner and 5μM Dys accelerated contraction kinetics in HCM trabeculae. Isoproterenol 10^{-7} mol/L (Iso) determined a significant potentiation of twitch amplitude and an accelleration of contraction kinetics (both time to peak and relaxation). Changes induced by Iso in control trabeculae were similar. Interestingly, Iso caused APD prolongation in HCM cardiomyocytes instead of the shortening observed in control cells. This was likely related to the unbalance between depolarizing and repolarizing currents, including increased Late-Na^+ current (I_{NaL}). The I_{NaL} blocker Ranolazine 10 μM (Ran) applied on top of Iso (Iso+Ran) markedly reduced isometric twitch tension of HCM trabeculae, while Ran alone showed no negative inotropic effect. Contraction kinetics in Iso+Ran were still significantly faster compared to baseline.
Conclusions: Beta adrenergic stimulation may enhance septal contractility and determine obstruction in HCM. Ranolazine, by reducing septal tension at peak exercise but not at rest, may represent a safe therapeutic option for obstruction.

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Depressed Contractility at Low-Load Spontaneous Oscillatory Contractions in Human Hypertrophic Cardiomyopathy with MYBPC3 Mutations
Amy Li[1], J. Martijn Bos[2], Michael J. Ackerman[2], Filip Braet[1], Murat Kekic[1], Shin'ichi Ishiwata[3], Cristobal G. dos Remedios[1].
[1]University of Sydney, Sydney, Australia, [2]Mayo Clinic, Rochestser, MN, USA, [3]Waseda University, Tokyo, Japan.
We examined the role of missense and nonsense myosin-binding protein mutations in human tissue of patients with hypertrophic cardiomyopathy in an essentially unloaded isotonic system by partial Ca^{2+}-activation, i.e. Ca-spontaneous oscillary contractions (SPOC). Despite considerable literature suggesting that hypercontractility is a feature of HCM-causing mutations, we observe: (1) prolonged durations of both the lengthening ($p<0.0001$) and shortening ($p<0.001$) phases of the SPOC cycle in MYBPC3 mutants; (2) depressed contractility where the rates of both lengthening ($P<0.01$) and shortening ($p<0.05$) were reduced; however (3) the amplitude of the SPOC cycles did not vary between mutated MYBPC3 and healthy donor samples under essentially unloaded isotonic conditions. We found no difference between MYBPC3 samples containing missense or nonsense mutations. Unexpectedly, principal component analysis demonstrated that the contractile properties of human derived cardiomyocytes under low-load conditions were distinctively different for mutations in MYBPC3 and troponin genes. We conclude that, at least under the isotonic