Quantification of *In Vivo* Left Ventricular Torsion and Principal Strains in Mouse Models of Hypertrophic and Dilated Cardiomyopathy

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The deformations and twisting of the left ventricular (LV) wall, quantified by strain and torsion, provide insight into its regional and global contractile function. In this study, we investigated the influence of proteins entailing myocyte contractility and structural stability on ventricular biomechanics using mouse models with alterations in contractile proteins. Cardiac myosin binding protein-C (cMyBP-C) is a thick filament-associated sarcomeric protein important for modulating muscle contraction. Muscle LIM protein (MLP) is a stabilizing cytoskeleton protein that is thought to be involved in the transmission of mechanical stress [1]. Complete disruption of these proteins leads to severe hypertrophic and dilated cardiomyopathy, respectively. However, the mechanical consequences of partial disruption, which presents a more clinically relevant disease model, have not been studied.

Methods:

The pattern and timing of LV strain and torsion in 2~3 month mice that lack cardiac myosin binding protein-C (cMyBP-C$^{-/-}$, n=6, cMyBP-C$^{+/-}$, n=8) and muscle LIM protein (MLP$^{-/-}$, n=6), were evaluated against age-matched wild-type mice (n=8) *in vivo* using magnetic resonance imaging. Displacement encoding with stimulated-echo (DENSE) images were acquired for each group with a 9.4T Bruker Biospec (Billerica, MA) horizontal bore scanner. Two-dimensional myocardial strain and torsion were computed at the base, apex, and mid left-ventricle for each mouse, and the times to peak strain and torsion development were also quantified [2].

Results:

Both cMyBP-C$^{-/-}$ and MLP$^{-/-}$ mice exhibited a severe depression in systolic function as indicated by decreased LV ejection fraction (32±8% and 29±9%, respectively, $p<0.05$) compared to wild-type mice (68±8%). The cMyBP-C$^{+/-}$ mice demonstrated a preserved LV ejection fraction (63±6%), however, significant LV apical wall thickening could be appreciated against wild-type (0.66±.0.07mm vs. 0.58mm± 0.07mm, $p<0.05$) at end-diastole. A significant reduction in LV torsion and principal strains E_1 and E_2, associated with radial wall thickening and circumferential shortening, respectively, were observed in cMyBP-C$^{-/-}$ and MLP$^{-/-}$ mice. Interestingly, reductions in LV torsion were also observed in heterozygous cMyBP-C null mice (cMyBP-C$^{+/-}$). The time course of peak fiber torsion and strain appeared to be accelerated in cMyBP-C$^{-/-}$ mice, while peak strain development was slowed in MLP$^{-/-}$ mice.

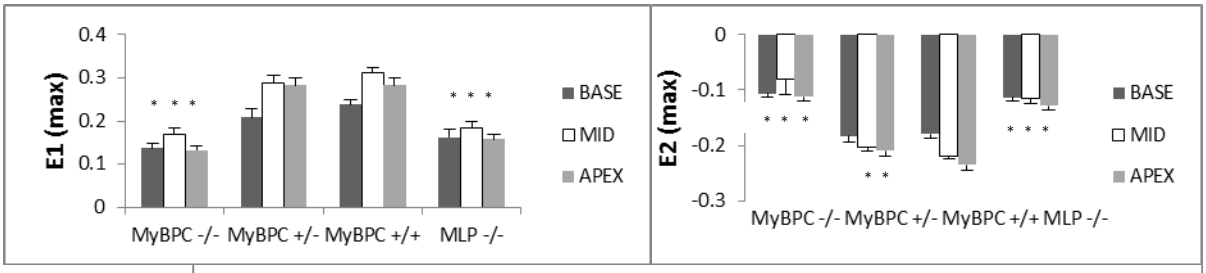
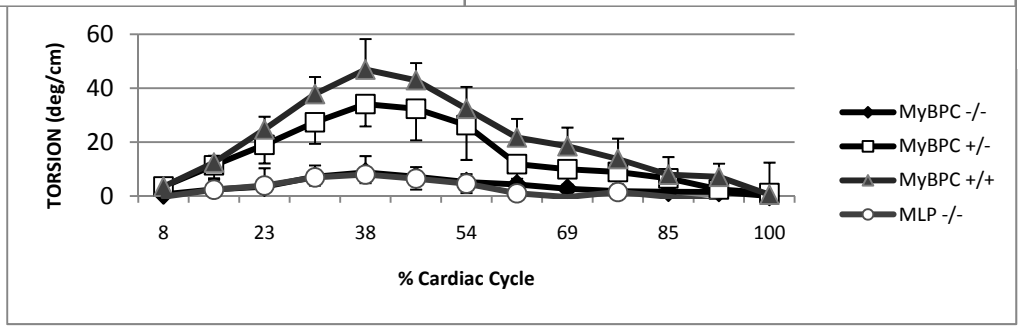


Figure 1: Maximal principal strains E1 and E2 at the base, apex, and mid-ventricle.

* $p<0.05$

Figure 2: Mean (±SD) ventricular torsion time course in one cardiac cycle.



Discussion:

In this study, we investigated the influence of proteins entailing myocyte contractility and structural stability on ventricular biomechanics using mouse models with alterations in contractile proteins. The lack of MyBP-C and MLP in the cardiac myocyte led to hypertrophic and dilated cardiomyopathy, respectively, and resulted in severe deficits in the overall contractile function of the heart. However, the pattern and time course of LV torsion and principal strain development appear to differ in these two models of heart failure, reflecting contrast in the functional roles of cMyBP-C and MLP in the myocyte. The subtle changes in thickness and torsion detected in the heterozygous cMyBP-c mice with preserved global function may provide insight into the development of a new clinical model for hypertrophic cardiomyopathy and initial disease progression.

References:

[1] Arber S, Halder G, and Caroni P, Cell, 1994, 79(2):221-31. [2] Zhong J and Yu X, ISMRM, 2009.