

Evaluation of Strain and Torsion in Physiologic and Pathologic Left Ventricular Hypertrophy

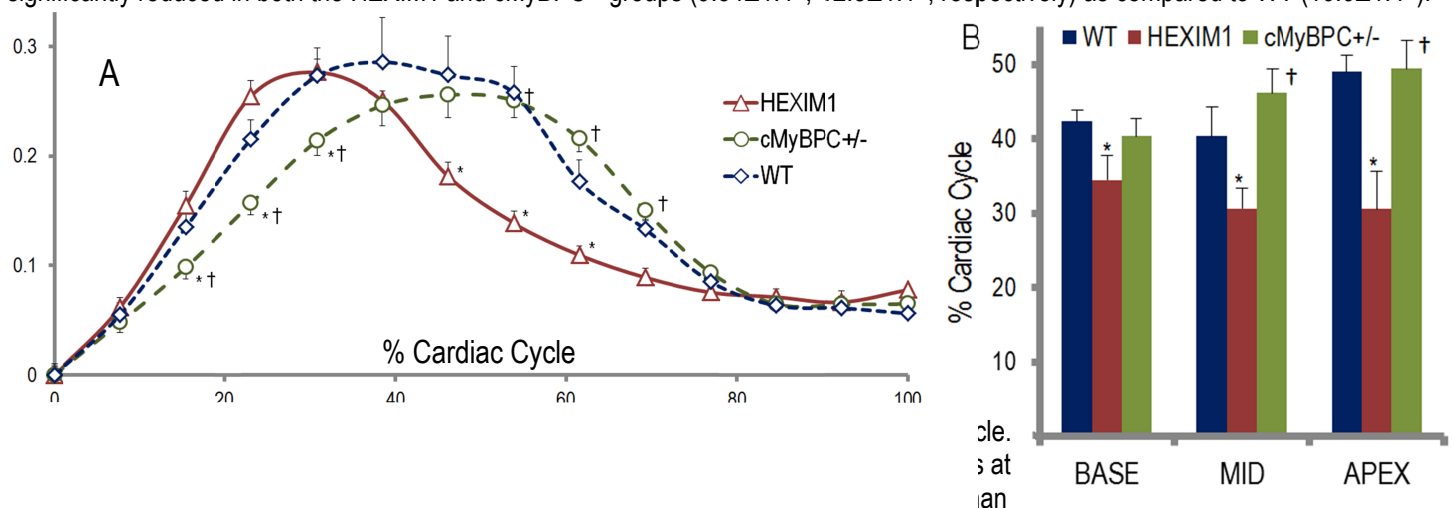
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Cardiac responses to increased workload and environmental stresses may result in physiologic or pathologic remodeling of cardiomyocyte size and vascularization. Physiologic, or adaptive responses, as in the case of the trained athletic heart, are characterized by balanced changes in both the cardiomyocytes and in the vasculature to enhance cardiac performance. Pathologic hypertrophy occurs in the setting of cardiovascular disease, and will ultimately lead to dilatation of the left ventricle (LV), fibrosis, and cardiomyocyte death (Weeks KL and McMullen JR, 2011). Distinguishing pathologic from physiologic hypertrophy at an early stage could be critical for clinical management of patients. The transcription factor Hexamethylene-bis-acetamide-inducible protein 1 (HEXIM1) is critical for coronary vessel development and myocardial growth during development. HEXIM1 reexpression induced in adult cardiomyocytes results in physiologic left ventricular hypertrophy (LVH). Cardiac myosin binding protein-C (cMyBPC) is a thick filament-associated sarcomeric protein important for modulating muscle contraction. Deficiency in cMyBPC is a common cause of inherited hypertrophic cardiomyopathy (HCM) (Harris et al., 2011).

Methods: The pattern and timing of LV strain and torsion in 2–3 month mice with induced HEXIM1 expression (n=6) or heterozygous expression of cMyBPC (n=8) 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 twist 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 (Zhong J and Yu X, ISMRM, 2009).

Results: HEXIM1 enhanced mice demonstrated significantly larger ejection fractions as compared to controls (72±6%, 64±6%, respectively) in addition to significantly slower heart rates (HEXIM1; 314±62bpm, WT; 493±57bpm), whereas cMyBPC^{+/-} showed no difference in either ejection fraction or heart rate (62.7±6%, 573±31bpm, respectively). There was no difference in maximal systolic radial and circumferential strains or twist at the base, apex, or mid-LV among the three groups, aside from a reduction in maximal circumferential strain at the mid-LV of the cMyBPC^{+/-} mice compared to WT (-0.18±0.006, -0.20±0.005, respectively). Interestingly, the time to peak radial and circumferential strains was significantly shorter in the HEXIM1 enhanced mice as compared to WT at all ventricular levels, however the time to peak strain in cMyBPC^{+/-} mice was significantly longer. The net twist (apical – basal) was significantly reduced in both the HEXIM1 and cMyBPC^{+/-} groups (9.84±1.4°, 12.5±1.1°, respectively) as compared to WT (16.6±1.4°).



Discussion: The mechanical function of the hearts from both the physiologic (HEXIM1) and pathologic (cMyBPC^{+/-}) models of LV hypertrophy was generally maintained, as indicated by the preserved ejection fractions and global strains. The presence of bradycardia without compromise of function in the induced HEXIM1 mice is suggestive of an athletic heart state, in which physiologic hypertrophy exists. The discriminating factor between the physiologic and pathologic models of LVH lies in the timing of strain development. There was a significant decrease in time to peak strain between the HEXIM1 and cMyBPC^{+/-} groups. The decreased time to maximal strain in the HEXIM1 group may be a functional consequence of the increased expression of vasculogenesis and metabolic genes, which could provide additional ATP for faster cross-bridge kinetics. When faced with LVH in the presence of preserved function in a young patient, the difference in timing of strain development may be of clinical utility to discriminate between a benign athlete's heart and HCM.