The Impact of Chronic Exercise on Cardiac Function in PEPCK-Cmus Mice Characterized by DENSE MRI

Yuchi Liu[1], Xunbai Mei[1], Martin W Zhu[2], Saul Flores[3], Parvin Hakimi[4], Richard Hanson[4], Michiko Watanabe[3], and Xin Yu[1]

[1]*Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OHIO, United States,* [2]*Hawken School, Gates Mills, OHIO, United States,* [3]*Department of Pediatrics, Case Western Reserve University, Cleveland, OHIO, United States,* [4]*Department of Biochemistry, Case Western Reserve University, Cleveland, OHIO, United States*

Target Audience

Researchers in myocardial remodeling, ventricular hypertrophy, and characterization of ventricular structure and function by DENSE MRI.

Introduction/Purpose

Chronic exercise leads to physiological hypertrophy of the left ventricle (LV), which is referred to as athletic heart. Unlike stress-induced pathological hypertrophy, which eventually progresses to heart failure, physiological hypertrophy is a beneficial adaptive response of the cardiovascular system. However, the mechanisms that lead to these two different types of hypertrophy are not well understood because of the lack of appropriate animal models. It is reported that mice that over-express the metabolic protein PEPCK (PEPCK-C^{mus} mice) are seven times more active in their cages than controls. [1] Therefore, it is possible that these mice may serve as models of chronic exercise. In this study, we evaluated the efficacy of using PEPCK-C^{mus} mouse as an animal model of exercise-induced hypertrophy by characterizing its cardiac structure and function using MRI. We hypothesized that the hyperactivity of PEPCK-C^{mus} mice leads to physiological hypertrophy and enhanced cardiac function.

Methods

In Vivo MRI Study The pattern and timing of LV strain and torsion in adult PEPCK-C^{mus} mice (n=6) and their age-matched controls (n=10) were evaluated in vivo. The control mice comprised of two different strains, i.e., those with the same genetic background as the PEPCK-C^{mus} mice (control, n=5) and the wildtype C57/BL6 mice (WT, n=5). Displacement-encoding with stimulated-echo (DENSE) images were acquired at apical, midventricular, and basal levels using a 9.4T Brucker Bispec horizontal scanner (Billerica, MA). LV wall thickness, volume changes, and global functional indexes were quantified using in-house developed, MATLAB-based software. Two-dimensional myocardial strain and twist, as well as the times to peak strain and torsion development, were also quantified. [2]

Results

The PEPCK-C^{mus} hearts showed a significant increase in ejection fraction (67.7±2.2%) compared to the control (62.0±5.5%) and WT (61.9±2.9%) mice (Figure 1A, $p<0.05$). PEPCK-C^{mus} hearts also showed increased end-diastolic wall thicknesses (Figure 1B, $p<0.01$), suggesting ventricular hypertrophy. In addition, heart rate during MRI scanning was also increased in PEPCK-C^{mus} mice ($p<0.05$).

Peak radial (Err) and circumferential (Ecc) strains are presented in Table 1. PEPCK-C^{mus} hearts showed a trend of increased strain; however, no statistical differences were detected. The strain rate was also similar. However, a significant reduction in time to peak strain was detected in PEPCK-C^{mus} mice. At the mid-ventricular level, the time to peak Ecc was 45.5±3.8%, 57.7±4.4%, and 52.9±4.8% percentage of cardiac cycle for PEPCK-C^{mus}, control, WT mice, respectively ($p<0.05$).

Ventricular twist at the apical, mid-ventricle, and basal levels was similar between PEPCK-C^{mus} mice and the control and WT mice. As a result, net twist and LV torsion was also similar among the three groups. These results are consistent with findings in human athletes.[3]

Table 1. Peak radial (Err) and circumferential (Ecc) strains.

		PEPCK (n=6)	Control (n=5)	WT (n=5)
Err	Base	0.174±0.036	0.162±0.034	0.149±0.049
	Mid	0.214±0.037	0.177±0.047	0.219±0.038
	Apex	0.217±0.044	0.182±0.037	0.230±0.079
Ecc	Base	-0.127±0.018	-0.136±0.042	-0.109±0.034
	Mid	-0.164±0.017	-0.131±0.047	-0.137±0.022
	Apex	-0.173±0.021	-0.137±0.039	-0.146±0.035

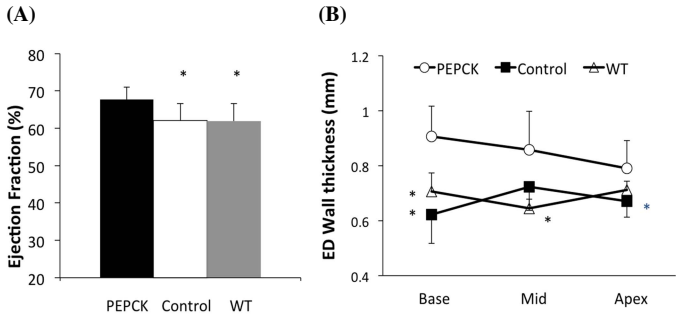

Figure 1. Ejection fraction (A) and end-diastolic wall thickness (B).

Discussion & Conclusion

Hyperactivity induced by PEPCK over-expression leads to increased left ventricular wall thickness and global ejection, which are consistent with the phenotypes of athletic heart. These observations suggest that PEPCK-C^{mus} mice can be used as an animal model of physiological hypertrophy. The establishment of such an animal model allows us to elucidate the molecular and cellular mechanisms leading to physiological hypertrophy. It also provides the opportunity to understand the differences between pathological and physiological hypertrophy, and therefore, to develop new therapeutic interventions for stress induced hypertrophy.

References

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