The Impact of Myosin Heavy Chain Isoforms on Contractile Behavior of the Heart

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In mammalian hearts, two distinct isoforms of myosin heavy chain (MHC), α-MHC and β-MHC, have been identified in cardiac myocytes. Previous studies have shown that the composition of the two myocardial MHC isoforms may change under pathophysiological conditions. Despite 93% similarity in amino acids, the two isoforms exhibit different biochemical and mechanical properties. In vitro studies have shown that increased expression of β-MHC can significantly slow the rate of cross-bridge recruitment and detachment in skinned myocardium [2]. However, the impact of this change on in vivo ventricular function has yet to be determined. In the present study, we evaluated changes in contractile behavior of rats with shifted MHC expression induced by thyroid-deficiency. Our results show that increased expression of β-MHC not only reduced the magnitude of peak systolic strain and torsion, but also altered the timing when the myocardium reached peak systole, leading to deteriorated cardiac function in hypothyroid rat hearts.

Methods Cardiac MR studies were performed on rats underwent thyroidectomy (2-3 months, n=12) and their age-matched controls (n=7) with a 9.4T Bruker Biospec (Billerica, MA) horizontal bore scanner. Three weeks after the surgery, displacement encoding with stimulated-echo (DENSE) images were acquired both at baseline state and under cardiac stress induced by intravenous administration of dobutamine (10 μg/kg/min). Two-dimensional myocardial strain and torsion were computed at base and apex for each rat [3]. Time to peak strain and torsion development was also quantified.

Results Hypothyroidism induced a shift of MHC isoforms from α-MHC to β-MHC in rat myocardium. As a result, thyroid-deficient rats showed significantly reduced EF as compared to control rats expressing mainly α-MHC (55.8 ± 4.9% vs. 38.9 ± 5.0%, P<0.001). Under dobutamine stimulation, EF increased significantly in both groups but was lower in hypothyroid rats (76.4 ± 3.3% vs. 56.3 ± 8.9%, P<0.001). From the analysis of DENSE images, hypothyroid rats exhibited a significant decrease in the magnitude of principal strains (E_1 and E_2, Figs. 1&2) and peak ventricular torsion (Fig. 3) at both baseline and during dobutamine stimulation. In addition to decreased magnitude, hypothyroid rats also showed delayed strain and torsion development (Figs. 2&3). Further analysis showed that the time to reach maximal ventricular torsion was statistically different between the control and hypothyroid rats (46.7 ± 3.9% vs. 55.6 ± 5.8% of cardiac cycle; P<0.01).

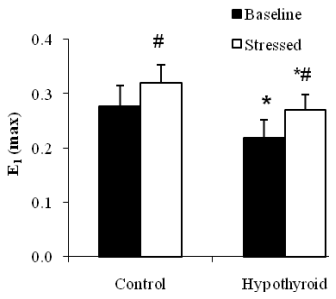

Fig. 1: Maximal principal strain (E_1) at apex. *P<0.05 control vs. hypothyroid; #P<0.05 baseline vs. stressed.

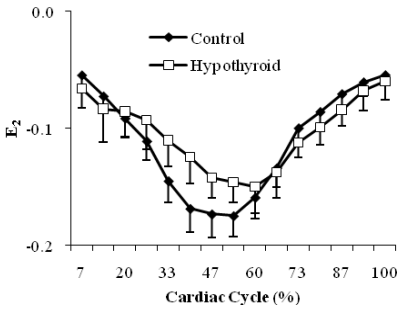

Fig. 2: Time course of principal strain (E_2) at base in one cardiac cycle. The results were obtained at the baseline state.

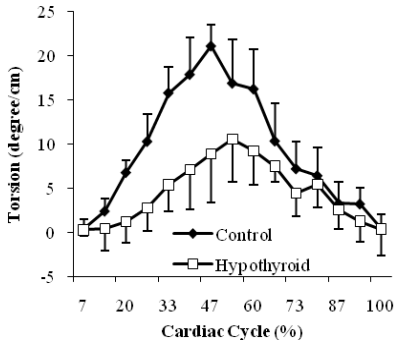

Fig. 3: Time course of ventricular torsion in one cardiac cycle at the baseline state.

Discussion In this study, we investigated the impact of MHC isoform on global and regional cardiac function. Compared to the control rats that express mainly α-MHC, hypothyroid rats with a majority of β-MHC showed significantly reduced EF, myocardial strain and ventricular torsion. In addition, the time to peak systole was also delayed. This delay in systolic function is likely due to the slower actin-activated ATPase activity, shortening velocity and cross-bridge cycling kinetics of β-MHC, which further deteriorates the cardiac function in the hypothyroid rat hearts. On the other hand, dobutamine stress induced significant increase in peak-systolic strains and torsion, suggesting that the cardiac response to dobutamine stimulation was not compromised by the shift in MHC isoform expression.

References

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