The Impact of Cystic Fibrosis on Cardiac Function and Stress Response

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Introduction

The cystic fibrosis transmembrane conductance regulator (CFTR) functions as a cAMP-activated Cl^- channel. Disruption of CFTR leads to cystic fibrosis (CF), the most common lethal genetic disease in Caucasians. Clinical manifestations of CF include chronic airway obstruction, exocrine pancreatic insufficiency, intestinal malabsorption, and infertility; however, pulmonary disease is the main cause of morbidity and mortality. CFTR has been most notably studied in epithelial cells but has also been identified in cardiac myocytes. Recent studies suggest that CFTR disruption may also impact ventricular contractility. However, whether functional alteration occurs at cellular level or organ level is not completely understood.

Materials and Methods

Animal Models Mice with CFTR disruption do not develop pulmonary disease. It provides an ideal model to study the impact of CFTR disruption on cardiac function. Two CF mouse models were used: global CFTR knockout (S489X) and muscle-specific knockout (MSKO). 2~3 month male CF mice and their age-matched control littermates were characterized.

In Vivo Cardiac Function by CINE and DENSE MRI Both CF models (n=5 for S489X and $CNTR_{S489X}$ mice, 10 for MSKO and $CNTR_{MSKO}$ mice) were used in this study. In vivo cardiac function was characterized at baseline and under stress. Cardiac stress was induced by continuous intravenous infusion of dobutamine at a dose of 40 μg/kg/min. CINE MRI was used to assess global cardiac function such as ejection fraction, wall thickness, and endocardial volume. Displacement-encoding with stimulated echoes (DENSE) MRI was applied to quantify regional cardiac function such as myocardial strain, ventricular twist, and torsion.

All MRI studies were performed on a horizontal 9.4T animal scanner (Bruker Biospin, Billerica, MA) with a 35 mm inner diameter volume coil. All mice were anesthetized with 1% isoflurane and their body temperature was maintained at ~36°C. CINE and DENSE images of three short-axis slices located at basal, mid-ventricular, and apical levels of the heart were acquired using the following parameters: number of FLASH images per cardiac cycle, 13; flip angle, 30°; slice thickness, 1.0 mm; FOV, 3x3 cm^2. A displacement encoding frequency at 1.11 cycles/mm was used in DENSE MRI.

Myocyte Contractility and Ca^{2+} Transients Myocyte contractility and Ca^{2+} transients were measured at baseline (n=7 for MSKO and 8 for $CNTR_{MSKO}$) and under stress (n=5 for MSKO and $CNTR_{MSKO}$) induced by 100 nM isoproterenol., Electric stimulation at 1 Hz was applied to induce cell contraction. Cardiomyocyte contractility was measured by tracking changes in cell length during contraction. Characterized parameters included fractional shortening and time to peak shortening. Fluorescence microscopy was used to quantify amplitude of Ca^{2+} transients and decay constant (Tau) in cells incubated with 2.5 μM fura-2-acetoxymethyl ester, a Ca^{2+} indicator.

Results

Cardiac Function at Baseline Representative peak-systolic displacement maps for basal and apical slices in MSKO and $CNTR_{MSKO}$ mice are shown in Fig. 1a-d. A trend of increase in twist angles was found in both basal and apical slices. As a result, peak torsion in MSKO mice was significantly increased (Fig. 1f). An increase in peak torsion was also observed in S489X mice (Fig. 1e). Systolic torsion rates were also increased in both CF models. Radial and circumferential strains were similar between the two CF models and their respective controls. In addition, MSKO mice showed mild increase in ejection fraction and basal wall thickness and a decrease in endocardial volume.

Cardiac Function under Stress Peak torsions in S489X and MSKO mice and their respective controls under stress are also shown in Fig. 1e-f. CF mice showed similar ventricular torsion as their wildtype controls under dobutamine stimulation. Given that there was increased torsion at baseline, CF mice showed a smaller percent increase in peak torsion compared to their respective controls (Fig. 1g).

Myocyte Contractility and Ca^{2+} Transients In vitro studies showed similar myocyte contractility and Ca^{2+} transients between MSKO and $CNTR_{MSKO}$ mice, both at baseline and under stress.

Conclusion

Disruption of CFTR leads to an increase in ventricular torsion at baseline. However, CF mice showed a smaller percent increase in torsion under stress, leading to similar torsion between CF and control mice. With unaltered myocyte contractility both at baseline and under stress, the observed increase in ventricular torsion at baseline may be associated with changes in ventricular structure in CF mice. However, future studies are needed to confirm such changes.

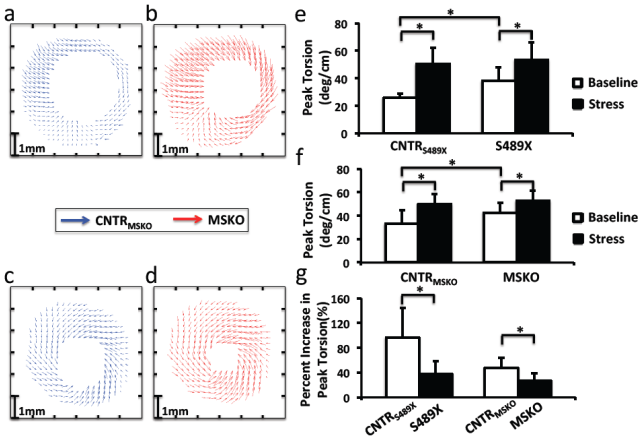

Figure 1. Displacement maps and torsion by DENSE MRI. **a-d.** Representative peak-systolic displacement maps of basal (**a, b**) and apical (**c, d**) slices in MSKO and $CNTR_{MSKO}$ mice at peak systole. **e-f.** Peak torsions in S489X (**e**) and MSKO (**f**) mice and their respective controls at baseline and under stress. **g**. Percent increase in peak torsion (stress vs. baseline) in S489X and MSKO mice and their respective controls. *P<0.05.

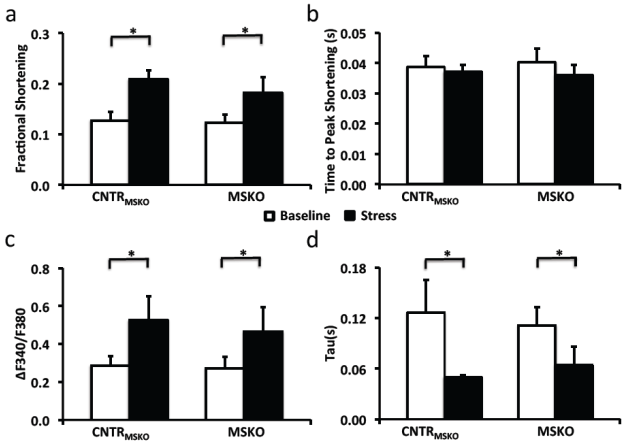

Figure 2. Cardiomyocyte contractility and Ca^{2+} transients in MSKO and $CNTR_{MSKO}$ mice at baseline and under stress. **a-b.** Fractional shortening (**a**) and time to peak shortening (**b**). **c-d.** Ca^{2+} transients (c) and decay constant (d). *P<0.05.