MRI Tagging Revealed Reduced Ventricular Torsion in Muscular Dystrophic Mice

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In this study, regional ventricular twsit and torsion in muscular dystrophic mice (*mdx* mice) were assessed with MRI tagging. Tagged MRI images of up to six short-axis slices were acquired at 0.6 mm tagging resolution. Ventricular twist in segmented LV regions was calculated using a MATLAB-base software. Despite similarities in ejection fraction and diastolic wall thickness, *mdx* mice revealed reduced ventricular torsion as compared to wildtype mice (C57/BL6), primarily due to reduction in twist at apical levels. This study suggests that ventricular twist might be a sensitive marker for detecting early and subtle defects in cardac function in patients with muscular dystrophy.

Introduction

Duchenne muscular dystrophy (DMD) results from the failure to express dystrophin, a cytoskeletal protein that links the cytoskeleton to the extracellular matrix. The *mdx* mouse, in which a nonsense mutation in the dystrophin gene eliminates expression of the dystrophin, is a model of this disorder. However, no clinically detectable defects in cardiac function are present in *mdx* mice whereas nearly all DMD patients have clinical evidence of a cardiomyopathy by age 18. What is unknown is whether other signs of myocardial dysfunction exist that preceede the manifestation of cardiomyopathy. In this study, ventricular function of *mdx* mice was characterized by MRI tagging to provide a more sensitive indicator of myocardial dysfunction.

Methods

Adult *mdx* mice (n=8) and C57/BL6 mice (wild type, n=5) were imaged on a Varian Inova 4.7T scanner with a custom-made surface coil. Mice were sedated with isoflurane by a nose cone. Tagged images of up to six short-axis slices were acquired from apex to base. The tagging sequence used a SPAMM1331 sequence applied twice immediately after ECG trigger, yielding a grid tagging pattern. The tag pulse flip angle was 140 degrees and tagging resolution was 0.6 mm. The tagging sequence was followed by gradient-echo cine sequence with the following imaging parameters: TR/TE,10.7 ms/3 ms; FOV, 4x4 cm^2; matrix size, 256x256; slice thickness, 1 mm. A total of 15 frames were acquired in one cardiac cycle. Following MRI studies, hearts were excised and fixed with 10% formalin. The tissue sections were stained with Masson trichrome.

Images were analyzed with MATLAB based software developed in our laboratory. Epicardial and endocardial boders, intersecting tag points were traced interactively. Subsequently, LV wall thickness, stroke volume, and ejection fraction were calculated. Finite element analysis method was employed to calculate ventricular twist and radial shortening. Myocardium was divided into non-overlapping triangular elements using sets of adjacent tag points as the vertices. The left ventricle was segmented into anterior, lateral, inferior, and septal regions. LV twist was calculated as the rotation angle of the centroid of triangular element around the center of LV cavity. Positive twist value indicated clockwise twist viewed from base.

Results

Histological analysis of Masson trichrome-stained sections revealed scattered fibrotic areas in five of the seven *mdx* mice studied. These lesions were primarily necrotic myocytes associated with interstitial or perivascular fibrosis. Despite the presence of lesions, LV ejection fraction was similar in *mdx* and C57/BL6 mice: (64±10)% for *mdx* mice and (74±10)% for C57/BL6 mice (p=NS). Diastolic wall thickness was also similar.

Compared to wildtype mice, *mdx* mice exhibited a significantly altered pattern of ventricular twist (Figure 1). LV twist was the same in *mdx* and wildtype mice at basal level. While both *mdx* and C57/BL6 mice demonstrated continuous shift in LV twist from conterclockwise to clockwise twist from base to apex, the magnitude was significantly reduced in mdx mice. In C57/BL6 mice, net twist shifted from -5.5±1.2° at base to 8.1±2.0° at apex. In mdx mice, twist change was from -5.7° at base to only 3.2±1.0° at apex. To account for variations in ventricular size, LV torsion was calculated as the difference in net twist between basal and apical slices, normalized by the distance between the two slices. Figure 2 indicates that there was a trend of reduced ventricular torsion in all four segments of the heart in *mdx* mice, with the changes in anterolateral regions being most significant.

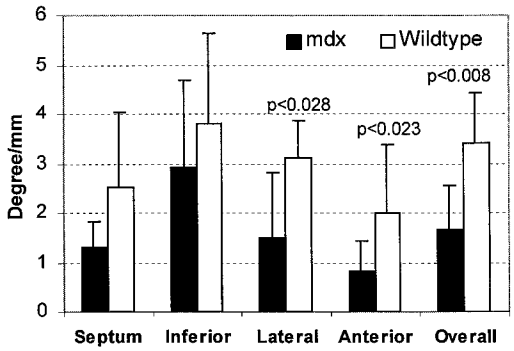

Figure 2. Altered ventricular twist in *mdx* mice.

Conclusion

Significant differences were observed in LV twist patterns in *mdx* mice despite lack of differences in traditional clinical indices of global cardiac function and anatomy. This study suggests that ventricular twist might be a sensitive marker for detecting myocardial dysfunction that could be applied clinically to define early and subtle defects in cardiac function in patients with muscular dystrophy. Such indices can only be obtained with MRI, which could render it a useful tool for phenotypic characterization of genetic diseases of the heart.

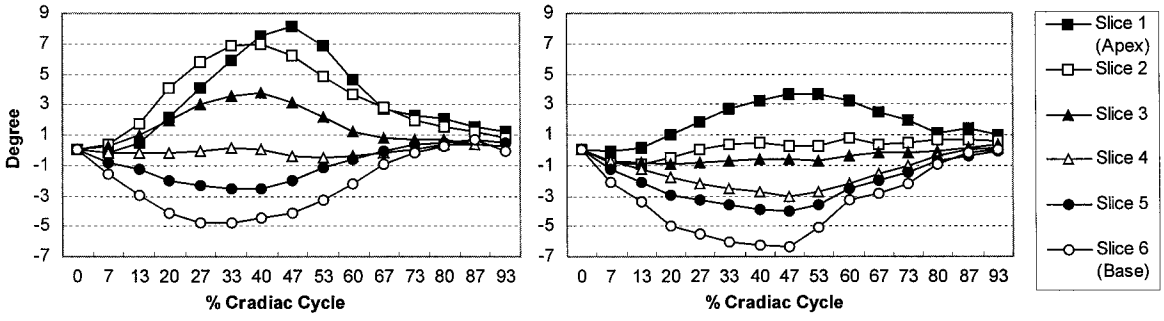

Figure 1. Time-course of left ventricular twist in C57/BL6 (left) and *mdx* (right) mice.