γ-Sarcoglycan deficiency reduces cardiac function and T2 in old mice

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Introduction

Cardiac dysfunction is a major cause of death in many types of muscular dystrophy. In the *mdx* mouse model, the lack of functional dystrophin localized to the cell membrane leads to enhanced muscle degeneration, myocardial fibrosis, and impaired left ventricular function in old mice (1, 4). Also, deficiencies in proteins associated with the dystrophin-glycoprotein complex, such as γ-sarcoglycan *(Sgsg$^{-/-}$)*, can lead to pronounced myocardial fibrosis and wall thickening of the myocardium (2). However, the effect of γ-sarcoglycan deficiency on *in vivo* functional cardiac measures has not been established. Thus, the purpose of this study was to compare left ventricular function in old wild-type, *mdx*, and S*gsg*$^{-/-}$ mice. In addition, we evaluated whether magnetic resonance transverse relaxation time (T_2) of the myocardium was altered among these groups. A shorter T_2 has previously been associated with fibrosis in diabetic rat hearts (3). We hypothesized that left ventricular ejection fraction would be reduced in both *mdx* and S*gsg-/-* mice compared to controls, and that this reduction in ejection fraction would be associated with a decrease in T_2 due to fibrosis.

Methods

Cardiac functional measurements were performed on female C57Bl6 (n=6,18±0 months; mean±SEM), *mdx* (n=6, 18±2 mos), and S*gsg*$^{-/-}$ (n=6, 18±1 months) mice. All mice were imaged using a custom built transceive quadrature saddle-shaped surface coil (2 cm diameter loops) on a 4.7T Oxford Magnet using a Bruker Avance Console and Paravision software (PV4.0, Bruker BioSpin MRI, Inc). A FLASH sequence (TR/TE 6/2.2ms; FOV 20x29 mm^2; acquisition matrix, 128 x 128; slice thickness, 1.0 mm; averages, 200) with restrospective gating (IntraGate, Bruker BioSpin MRI, Inc) was utilized with 8-10 short-axis slices positioned from the apex to the base of heart. Images were reconstructed with 16-25 cardiac frames, and CAAS MRV software (Pie Medical Imaging) was used to calculate myocardial mass, end diastolic volume, end systolic volume, ejection fraction, and wall thickness. In a subset of the mice, gated T_2-weighted single spin–echo images (TR 750 ms; TE 14.7 or 30 ms; field of view, 25X25 mm^2; slice thickness, 1.0 mm; acquisition matrix size, 256 X 128; diffusion weighting, 3 mm^2/s; averages, 8) of the left ventricle in the short-axis view were acquired in C57Bl6 (n=3), *mdx* (n=5), and S*gsg*$^{-/-}$ *(*n=4) mice using a custom built quadrature volume coil (3.3 cm inner diameter). T_2 maps were generated using OsiriX software, and a slice from the mid-papillary region was selected to calculate mean T2.

Results

Myocardial mass was similar (p>0.05) among controls, *mdx* and *Sgsg*$^{-/-}$ mice (Table 1). However, left ventricular ejection fraction was lower (p<0.05) in *mdx* and S*gsg-/-* than controls (Table 1, Fig.1). The calculated mean T_2 of the myocardium was shorter (p=0.01) in *Sgsg*$^{-/-}$ (16±1 ms) than controls (30±4 ms), with a trend (p=0.18) towards T_2 being shorter in *mdx* (21±5 ms) than controls.

Table 1. Left ventricle mass and functional measures

	Controls	*mdx*	*Sgsg*$^{-/-}$
Myocardial mass (mg)	111±7	103±4	121±21
ED volume (µl)	69±6	72±4	91±21
ES volume (µl)	27±4	35±5	43±8
Ejection fraction (%)	62±2	51±3*	50±6*
Wall thickness ED (mm)	0.88±0.04	0.74±0.03*	0.80±0.05
Wall thickness ES (mm)	1.26±0.07	1.00±0.02*	1.10±0.09
Wall thickening (ED-> ES, %)	46±3	37±3	35±7

*Denotes significantly different (p<0.05) than controls

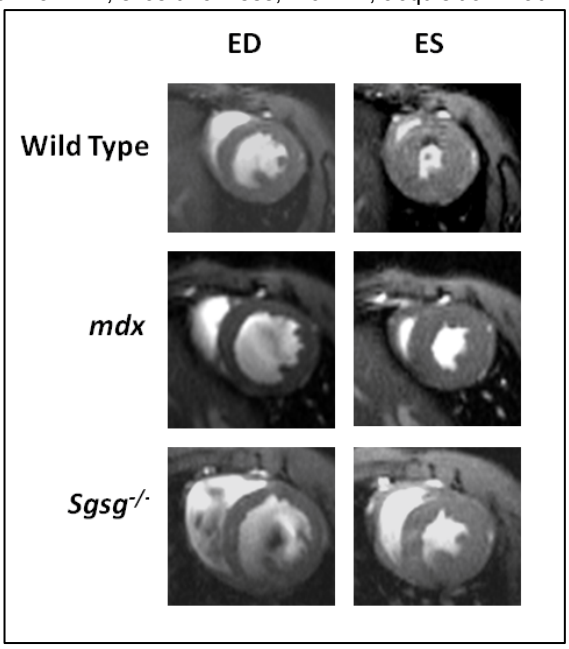

Fig. 1. Short axis view of old wild-type, *mdx* and *Sgsg*$^{-/-}$ mice hearts at end-diastole (ED) and end-systole (ES).

Conclusions

The findings of this study indicate that a deficiency in γ-sarcoglycan reduces left ventricular ejection fraction in old dystrophic mice compared to age-matched controls, with the ejection fraction being similar in *Sgsg*$^{-/-}$ and *mdx* mice. Furthermore, the shorter T_2 of the myocardium in *Sgsg*$^{-/-}$ suggests fibrosis was more prevalent compared to controls.

References

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