Preserved Accessory Muscle Function in a Mouse Model of Early Dystrophic Disease

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Background

• Duchenne muscular dystrophy (DMD) is a genetic neuromuscular disorder, characterized by progressive muscle weakness that extends to the respiratory muscles.
• Peak inspiratory pressure-generating capacity is preserved in young dystrophin-deficient mdx mice, despite diaphragm muscle weakness and reduced electromyogram (EMG) activity.
• We hypothesise that accessory muscle compensation limits ventilatory deficit in early dystrophic disease.

Methods

Electromyogram (EMG) recordings in vivo

Electromyogram (EMG) recordings were performed in urethane (1.7g/kg i.p.) anaesthetised spontaneously breathing mice in vivo to determine the electrical activation of obligatory (diaphragm & external intercostal) and accessory (scalene and cleidomastoidi) respiratory muscles in 4-month-old male wild-type and mdx mice. EMG assessments were performed during baseline and sustained tracheal occlusion producing maximal respiratory muscle activation.

Ex vivo muscle functional assessment

Diaphragm and scalene muscle force-generating capacity were examined ex vivo across a range of stimulation frequencies (25, 50, 75, 100, 125, 150Hz) in a water-jacketed tissue bath containing Krebs solution aerated with carbogen (95% O₂ and 5% CO₂) at 35°C.

Results

Decreased peak electrical activation of diaphragm and external intercostal muscles in 4-month-old mdx mice.

Figure 1. A-B, group data for diaphragm (A) and external intercostal (B) EMG activity during baseline conditions and during tracheal occlusion (average of 5 successive peak efforts) in 4-month-old wild type (diaphragm n=16; external intercostal n=14) and mdx (diaphragm n=14; external intercostal n=12) mice. Values are expressed as box and whisker plots (median, 25–75th percentile and scatter plot). Data were statistically compared by repeated measures two-way ANOVA with Bonferroni post-hoc test. ****p < 0.001, *****p < 0.0001 compared with corresponding wild-type values.

Preserved peak electrical activation of scalene and cleidomastoidi respiratory muscles in 4-month-old mdx mice.

Figure 2. A-B, group data for scalene (A) and cleidomastoidi (B) EMG activity during baseline conditions and during tracheal occlusion (average of 5 successive peak efforts) in 4-month-old wild type (n=18) and mdx (n=17) mice. Values are expressed as box and whisker plots (median, 25–75th percentile and scatter plot). Data were statistically compared by repeated measures two-way ANOVA with Bonferroni post-hoc test.

Figure 3. A-B, group data (mean ± SD) for diaphragm (A) and scalene (B) muscle force-frequency relationship ex vivo in 4-month-old wild type (grey) and mdx (red) preparations. Data were statistically compared by repeated measures two-way ANOVA (frequency x mdx) followed by Bonferroni post-hoc test. **p < 0.01 compared with corresponding wild-type value.

Conclusions

• Consistent with previous findings by our group, data from the current study indicate that there is decreased electrical activation and force-generating capacity of the diaphragm muscle in early dystrophic disease.
• The early decline in diaphragm muscle performance, suggests that compensation provided by accessory muscles is critical to the support of respiratory performance in mdx mice, which may have relevance to DMD.
• Our data suggest there is preservation of scalene electrical activation and force-generating capacity in early dystrophic disease.

References