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

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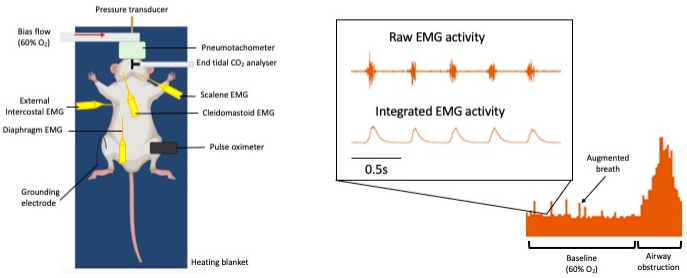
Background

- 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[1].
- We hypothesise that accessory muscle compensation limits ventilatory deficit in early dystrophic disease.

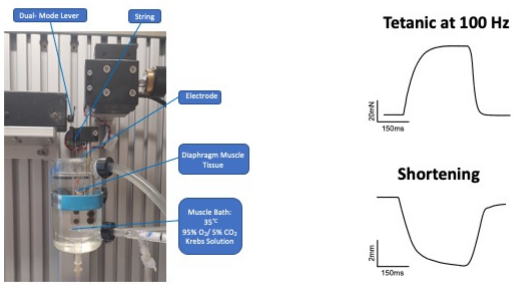
Methods

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 cleidomastoid) 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% O_2 and 5% CO_2) at 35°C.

Results

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

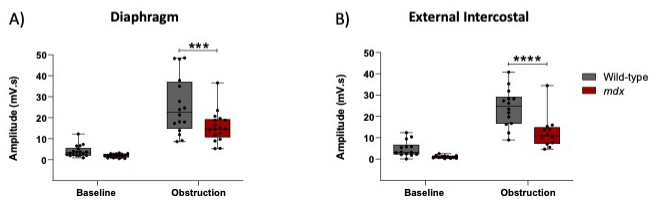


Figure 1. A-B, group data for diaphragm (A) and external intercostal (B) EMG activity during baseline conditions and during tracheal occlusion (average of 5 successive peak efforts) in 4-month-old wild type (diaphragm n=16; external intercostal n=14) and *mdx* (diaphragm n=14; external intercostal n=12) 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 cleidomastoid respiratory muscles in 4-month-old *mdx* mice.

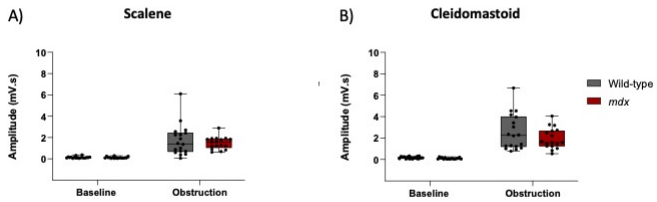


Figure 2. A-B, group data for scalene (A) and cleidomastoid (B) EMG activity during baseline conditions and during tracheal occlusion (average of 5 successive peak efforts) in 4-month-old wild type (n=18) and *mdx* (n=17) mice. Values are expressed as box and whisker plots (median, 25–75th percentile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

Scalene muscle force-generating capacity is preserved in 4-month-old *mdx* mice.

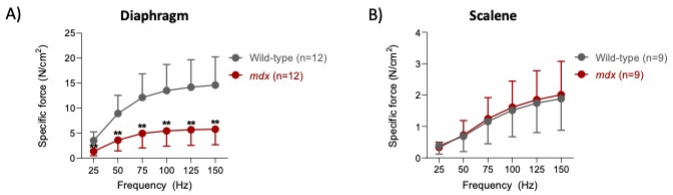


Figure 3. A-B, group data (mean ± SD) for diaphragm (A) and scalene (B) muscle force-frequency relationship *ex vivo* in 4-month-old wild type (grey) and *mdx* (red) preparations. Data were statistically compared by repeated measures two-way ANOVA (frequency x *mdx*) followed by Bonferroni *post-hoc*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

1. Burns DP, Murphy KH, Lucking EF & O'Halloran KD. Inspiratory pressure-generating capacity is preserved during ventilatory and non-ventilatory behaviours in young dystrophic *mdx* mice despite profound diaphragm muscle weakness. *J. Physiol*. 2019;597(3):831-848.

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