Abstract: 19O

Isolated Extensor Digitorum Longus muscles from old *mdx* dystrophic mice show little force recovery 120 minutes after eccentric damage

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Duchenne muscular dystrophy is characterized by progressive wasting and cycles of regeneration in skeletal muscle. Our laboratory work suggests, branched fibres, could be responsible for the terminal phase of muscle damage in old (58–112 weeks) dystrophic mice. A recent study in 12 week old dystrophic mice reported that the majority of force loss produced by a series of eccentric contractions (EC) in extensor digitorum longus (EDL) muscles recovers (65%) within 120 minutes, concluding this is incompatible with the assumption that EC force loss is due to mechanical damage.

The aim of this project was to assess the recovery post EC damage from animals 16-88 weeks of age containing 100% regenerated dystrophic muscles. Male *mdx* mice and littermate controls were euthanized, EDL muscles dissected from the hind limbs and maintained in Krebs solution at room temperature. The muscles were maximally stimulated, and a series of 6× EC performed to assess force loss. Muscles were left to rest for up to 120 minutes whilst measuring recovery. Single muscle fibres were isolated enzymatically to assess the degree of fibre branching.

Our findings replicated force recovery in young *mdx* mice with simple fibre branches. However, minimal recovery (~24%) in muscles of 88 week old *mdx* mice at 120 minutes post EC was observed. This data supports our "tipping point" hypothesis and shows a distinct pathophysiology in aged *mdx* mice with EC force loss due to acute fibre rupture at branch nodes that occurs in "old" dystrophic EDL muscles with >70% complex branched fibres. These findings have important implications for pre-clinical drug studies that use protection from EC damage in young *mdx* mice as a marker for drug efficacy.

A better understanding of the pathology of muscle damage in *mdx* mice will improve our ability to test and interpret pre-clinical drug studies using this model.