Cigarette smoke exposure does not accelerate locomotor myofiber injury but delays regeneration after lengthening contractions.

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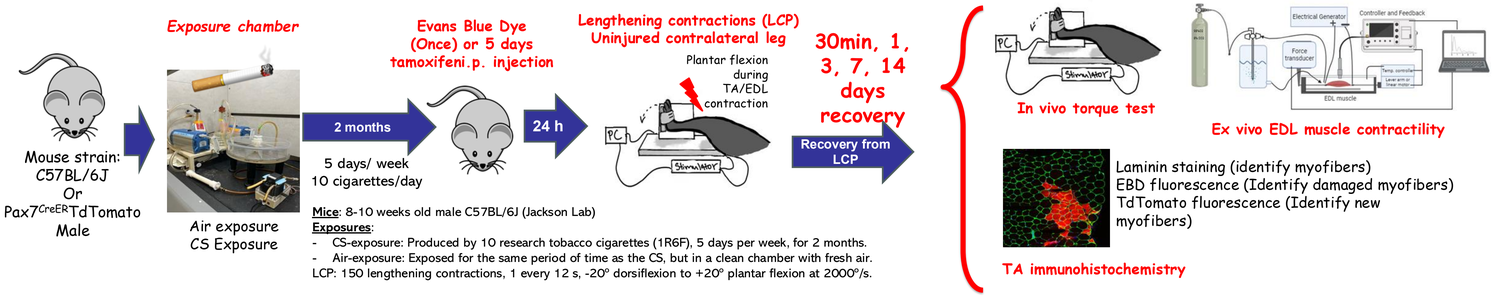
Introduction and Aims

The use of tobacco products has been associated with a greater incidence of muscle injuries and slow recovery after strenuous exercise. Our group has shown that muscles from mice exposed to cigarette smoke (CS) before COPD development (2 months) contain fewer satellite cells (cells that participate in the regeneration process, and slower myofiber growth recovery after eccentric contractions. Eccentric exercise-induced muscle injury develops several hours post-exercise, and it has been proposed that excess free radicals and intracellular calcium overload play important roles in injury development. It is also well established that CS exposure induces systemic inflammation and oxidative stress. However, it is unknown whether CS exposure alters the risk of muscles to injury after eccentric exercise.

Aim: Our aim was to determine whether two months of CS exposure impact changes in *in vivo* torque of dorsiflexor muscles, *ex vivo* isolated EDL muscle force, and myofiber damage and recovery between Air and CS-exposed mice after a session of lengthening contractions.

Experimental Strategy



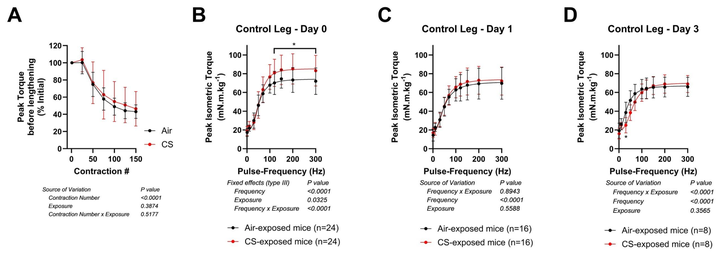
Mice: 8-10 weeks old male C57BL/6J (Jackson Lab)

Exposures:
- CS-exposure: Produced by 10 research tobacco cigarettes (1R6F), 5 days per week, for 2 months.
- Air-exposure: Exposed for the same period of time as the CS, but in a clean chamber with fresh air.

LCP: 150 lengthening contractions, 1 every 12 s, -20° dorsiflexion to +20° plantar flexion at 2000°/s.

Results

In vivo dorsiflexion torque



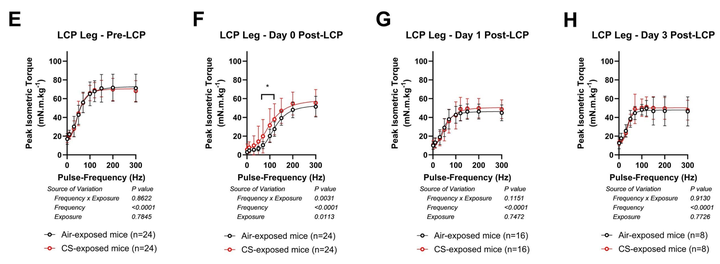


Figure 1: CS exposure does not affect LCP-induced decay in nerve-stimulated dorsiflexion torque compared to air-exposed mice. A) Peak isometric torque before the lengthening phase during LCP; B-H) Peak isometric torque evoked by different pulse frequencies before (B and E), immediately (F), 24 hours (C and G), and 74 hours (D and H) post-LCP; B-D) Control leg; E-H) LCP-subjected leg. Two-way ANOVA, Bonferroni post-test. Data are shown as mean ± s.d.

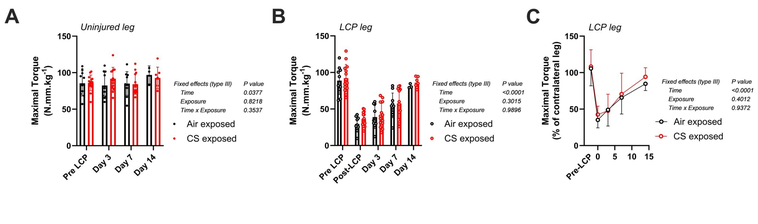


Figure 2. In vivo isometric dorsiflexion torque measurements during electrical stimulation of the peroneal nerve before and after LCP in male Pax7CreER+/-TdTomato+/- mice. A-B) Comparison of maximal torque obtained in Air and CS groups in uninjured legs (A) and in LCP-subjected legs (B); C) Maximal torque obtained in LCP-subjected leg normalized by the torque obtained in uninjured legs at the same days. Right next to each figure are the results from a two-way ANOVA. Data are presented as mean ± SD.

Ex vivo EDL isometric force

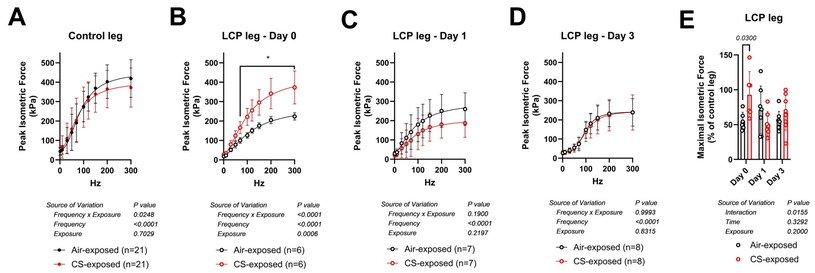


Figure 3: The initial decay of force post-LCP in isolated EDL muscle is significantly inhibited by CS exposure, but force rapidly decays 24 and 72 hours after LCP. A) Peak force evoked by direct electrical stimulation in dissected EDL muscle from the control leg; B-D) Peak EDL force immediately (B), 24 hours (C), and 74 hours (D) post-LCP; E) Maximal force normalized by the peak force produced by the control leg. Two-way ANOVA, Bonferroni post-test. Data are shown as mean ± s.d.

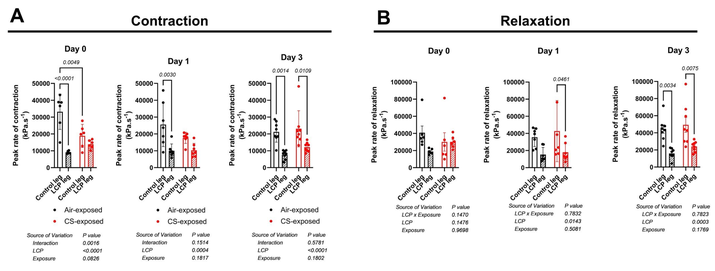


Figure 4: Rates of contraction (A) and relaxation (B) from the maximal tetanic force developed by each EDL muscle between exposure groups (Air vs CS) and between legs (Control vs LCP). Two-way ANOVA, Bonferroni post-test. Data are shown as mean ± s.d.

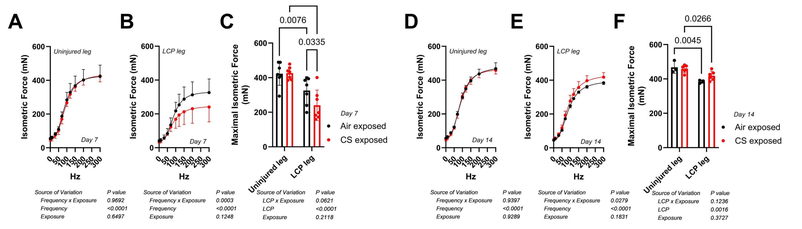


Figure 5. EDL muscle ex vivo isometric force in male Pax7CreER+/-TdTomato+/+ mice exposed to Air (black symbols) or CS (red symbols). Force was measured after 7 days (A-C) or 14 days (D-F) of recovery from lengthening contractions. Below each figure are the results from a two-way ANOVA, and above the bars are the post-hoc Bonferroni tests that achieved statistical significance. Data are presented as mean ± SD..

Immunohistochemistry of tibialis anterior muscle

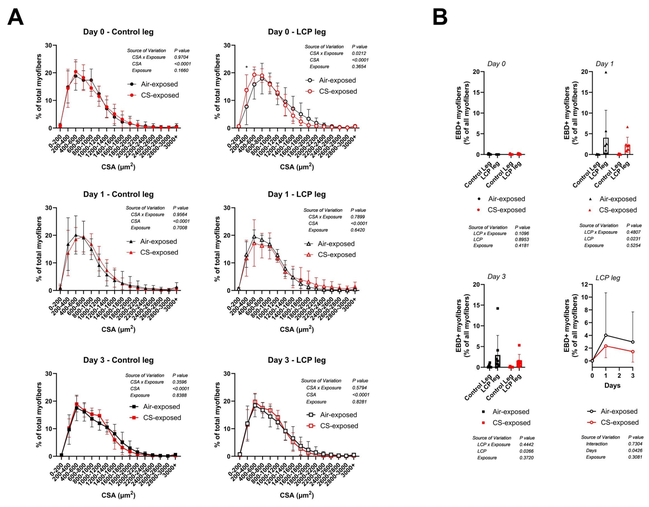


Figure 6: Two months of CS exposure transiently decreases the cross-sectional area (CSA) of a population of myofibers in the LCP-subjected TA muscles but does not change the number of membrane-damaged myofibers. A) Distribution of myofibers across different CSAs in muscles dissected immediately, 24 hours, or 72 hours after LCP; B) Percentage of myofibers containing Evans Blue Dye (EBD), indicating muscle fiber membrane damage. Two-way ANOVA, Bonferroni post-test. Data are shown as mean ± s.d.

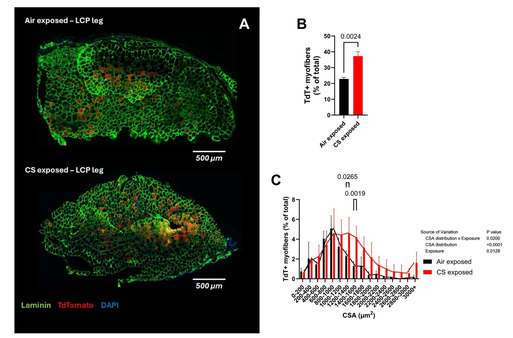


Figure 7. Formation of new myofibers and myofibers with satellite cells incorporated in TA muscles after 14 days of recovery from lengthening contractions in Air and CS exposed male mice. A) Representative immunohistochemistry image of TA muscles from LCP-subjected legs; B) Percentage of TdTomato expressing muscle fibers (TdT+ myofibers). P<0.05, Student's two-tailed T-test. C) Distribution of TdT+ myofibers at various cross-sectional areas between the exposure groups. Data are presented as mean ± SD..

Conclusions & Future Directions

Conclusions:

- Data from wild-type mice indicates that CS exposure may transiently protect against non-damaging mechanisms of force decay induced by eccentric exercise. However, CS exposure did not protect against or enhance the prolonged decay in muscle force or the appearance of damaged myofibers induced by lengthening contractions. The data suggest that two months of cigarette smoke exposure does not accelerate post-exercise injury.
- Data from Pax7CreER+/-TdTomato+/- mice indicates that CS exposure only delays the initial recovery of muscle force (7 days) but not late recovery (14 days).

Future directions: It is unclear whether longer periods of CS exposure, which are known to cause permanent lung damage, would interfere with muscle injury during eccentric exercise. In addition, since LCP produced a low grade of damage, it is not known whether the isolated myofibers damaged by LCP would have their contractile function differentially affected by CS exposure.

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