The Affect of Genetic Variability on Gastrocnemius Muscle Due to Disuse

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DISCLOSURES: none

INTRODUCTION: Extended period of mechanical disuse, such as during spaceflight or bedrest, can cause significant changes to the musculoskeletal system, particularly impacting the volume and strength of the affected bone and muscle by up to 20% in the first month[1]. Genetics are known to play a large role in the proportion of lean mass and risk for sarcopenia with age, though the role of genetic variability in muscle adaptation to mechanical unloading is unknown[2]. Diversity outbred (DO) mice are a genetically heterogeneous population of mice that can be used as a model to understand how genetic variability influences the response of the musculoskeletal system subjected to mechanical unloading. We hypothesize that genetic variation would impact the extent of muscle volume and strength loss due to mechanical unloading via single limb immobilization (SLI).

METHODS: Thirty-eight male and female 16-week-old DO mice were used to simulate disuse via SLI in the right leg. After three weeks of immobilization, mice were sacrificed. Low resolution (60µm) µCT scans of the lower limbs were taken at baseline (day 0) and after 21 days to analyze gastrocnemius muscle volume and cross-sectional area. Gastrocnemius muscle strength (twitch force and tetanus force) was measured using a muscle force tester at baseline (day 0) and immediately prior to sacrifice. At sacrifice, gastrocnemius muscle mass was recorded.

RESULTS: Immobilization of the right limb caused a significant sex dependent increase in gastrocnemius muscle volume and mean cross-sectional area (CSA). (Fig. 1) This outcome is consistent with observations seen during the study, including significant swelling and inflammation in the casted leg. The sex-dependent aspect of these results is consistent with the fact that the males are statistically large at baseline compared to the females. Gastrocnemius mass was significantly lower in the immobilized limb (Fig. 2). In addition, maximum tetanus force was significantly decreased in the immobilized limb compared to baseline.

DISCUSSION: This is one of the first studies performed to understand the influence of genetic variability on the response of the lower limb muscles to disuse. We found that immobilization highly influences the response of muscle to disuse, by increasing the muscle volume and mean CSA. When examining the mice during the experiment, it is apparent that the muscle becomes weaker under immobilization and there is significant inflammation in the area due to the cast itself. In conjunction with the data showing a decrease in muscle mass and strength, the increase in volume and CSA is consistent with the infiltration of immune cells and fluid. The sex-dependent nature of the results suggest that males are more susceptible to inflammation due to casting, since males and female receive the same size cast. All mice lost gastrocnemius muscle, which suggests there could be common genetic influences that causes mice to lose muscle when immobilized. This is the first study where the muscle strength was obtained at baseline to be able to compare the strength lost due to immobilization. These results suggest that genetic variability plays a large role in the response of gastrocnemius muscle to disuse.

SIGNIFICANCE: These results suggest that genetic variation, sex and their interaction play a role in the response of muscle to unloading.

REFERENCES: 1. Juhl et al. NPJ Microgravity, 2021. 2. Parry and Puthucheary et al. Extreme Physiology & Medicine, 2015.

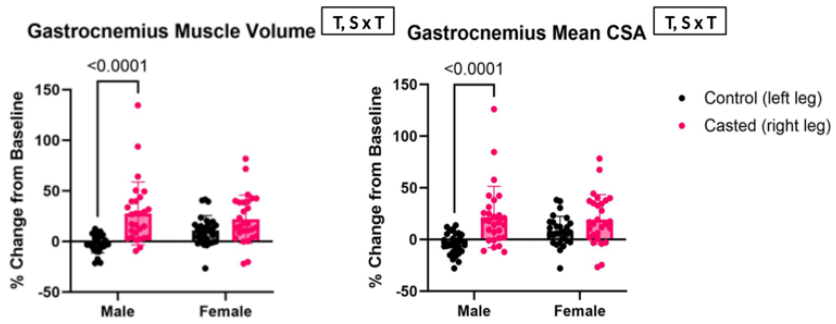

Figure 1. Gastrocnemius muscle volume and mean cross-sectional area (mean ± SD) after three weeks of single limb immobilization in the right leg of 16-week-old DO mice. Immobilization causes a sex dependent increase in muscle volume and mean cross-sectional area in the males. T – treatment main effect, S x T – sex x treatment interaction (2-way repeated measures ANOVA)

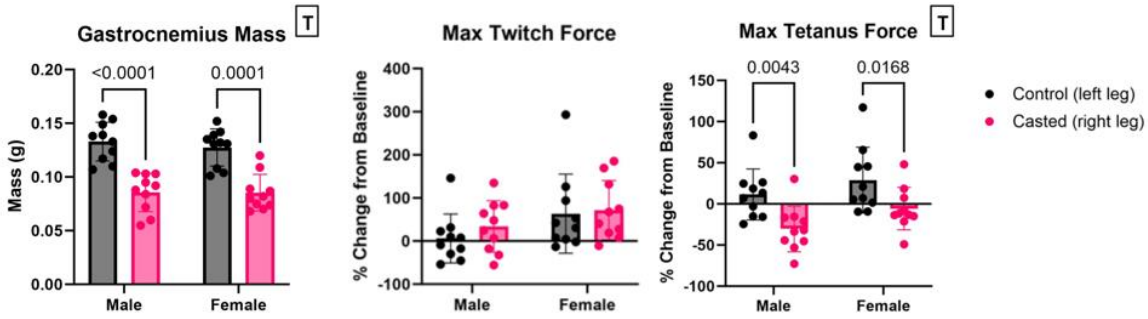

Figure 2. Gastrocnemius mass, maximum twitch and tetanus force (mean ± SD) after three weeks of single limb immobilization in the right leg og 16-week-old DO mice. Immobilization causes decrease in muscle mass and a decrease in maximum tetanus force. T – treatment main effect (2-way repeated measures ANOVA)