# The effect of repetitive acute intermittent hypoxia on ankle force steadiness and serum serotonin concentration

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## Summary

Promoting walking recovery in individuals with incomplete spinal cord injury (iSCI) is critical for enhancing quality of life and functional independence. Acute intermittent hypoxia (AIH) is a promising adjuvant to rehabilitation to promote neuroplasticity and improve walking performance [1,2] after iSCI likely via serotonin (5-HT) dependent processes [3]. AIH induced changes in 5-HT availability may elicit adaptive neuromodulatory effects on lower limb motoneuronal output, contributing to gains in walking performance. We demonstrate that repetitive AIH improves ankle force steadiness and reduces serum 5-HT concentration.

## Introduction

Brief, mild exposures to low-oxygen air (AIH) improves walking performance and ankle torque production in individuals with iSCI [2]. Rodent models suggest that motor gains depend on increased serotonergic drive to motor neurons [3], though this is not yet confirmed in humans. Increased 5-HT concentration enhances force production by modulating the gain of motor neuron activity [5]. This may influence force steadiness–the ability to maintain a constant force output during submaximal contractions [4]. In humans, the relationship between increased 5-HT concentration and force steadiness remains unclear [5,6]. However, impaired ankle force steadiness is associated with poorer walking performance in individuals with multiple sclerosis [7]. Thus, AIH-induced gains in walking performance may be partially driven by 5-HT mediated modulation of ankle force steadiness. We examined the relationship between changes in serum 5-HT concentration and force steadiness after AIH exposure. We hypothesized that repetitive AIH exposure would: (1) improve ankle force steadiness and (2) increase serum 5-HT concentration.

## Methods

Able-bodied individuals received four consecutive days of AIH to assess changes in ankle force steadiness and serum 5-HT concentration. We measured the coefficient of variation (CV) of force (SD of force/mean force) as a measure of ankle force steadiness during submaximal contractions at 20% and 40% of maximum voluntary contraction (MVC). Venous blood was analysed using 5-HT specific enzyme-linked immunosorbent assays (ELISA). Blood and CV of force were assessed prior to AIH and following the final AIH exposure.

## Results and Discussion

AIH improved ankle force steadiness (Fig. 1) evidenced by a significant reduction in CV of force during dorsiflexion (DF) at 40% MVC and a similar trend during plantarflexion (PF) at 40% MVC. There was no effect of AIH on ankle force steadiness at 20% MVC. These data suggest AIH-mediated improvements in the lower limb force control may be activation level dependent. Serum 5-HT concentrations were reduced following repetitive AIH but were not associated with improvements in plantarflexion force steadiness.

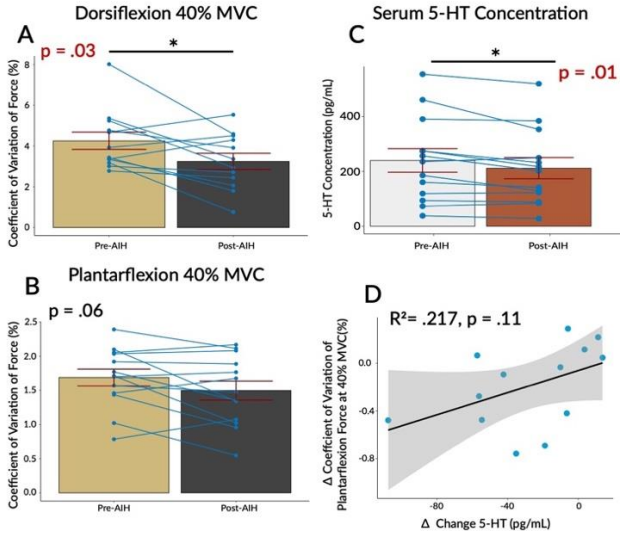


**Figure 1**: A&B) AIH-induced changes in ankle force steadiness and C) serum 5-HT concentration. D) The relationship between change in 5-HT concentration and change in CV of PF force at 40% MVC.

## Conclusions

The improvement in CV of force at only 40% MVC suggests that AIH may induce greater performance gains in tasks that require greater volitional drive. Our findings do not align with pharmacological lines of research that indicate enhanced 5HT availability improves force steadiness. One limitation is that we assessed peripheral neurochemical effects of AIH at course sampling times. Further examining the latency of AIH-induced changes in serum 5-HT and the corresponding biomechanical effects may clarify mechanisms that drive improvements in walking performance after iSCI.

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