Effect of acute hypoxia upon myostatin expression in healthy individuals

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Introduction

Skeletal muscle is the largest tissue in humans and is key in thermoregulation, locomotion, glycolysis and homeostasis. Loss of muscle (atrophy) can therefore be seen to increase mortality in a variety of disorders. Myostatin is a powerful regulator of muscle mass (figure 1)[1] and acts via multiple pathways to induce atrophy[2]. Of interest to our group is the regulation of expression of myostatin by various stimuli.

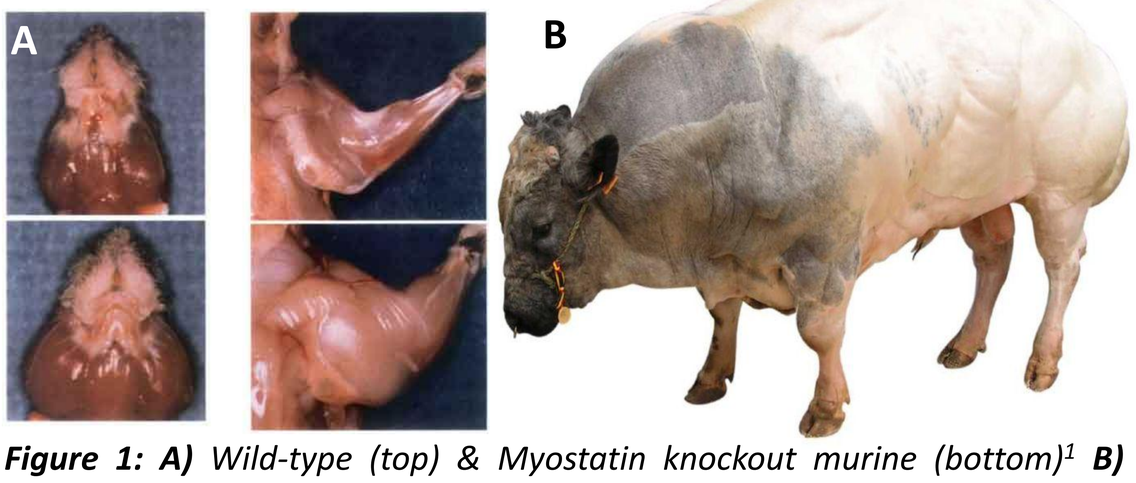

Figure 1: A) *Wild-type (top) & Myostatin knockout murine (bottom)[1]* ***B)*** *Belgium blue bovine , both showing hypertrophy due to myostatin absence.*

Hypoxia is a poorly understood inducer of muscle atrophy. Exposure to altitude is linked to increased atrophy in humans[3] and mice. In COPD, hypoxic patients show atrophy[4]. Further, mice exposed to hypoxia for two weeks show increased myostatin expression[4]. To the best of our knowledge no examination of the acute effect of hypoxia upon myostatin expression has been carried out, nor has the effect of hypoxia upon myostatin independent of disease state been examined in humans. We therefore aimed to examine the effect of hypoxia upon myostatin expression in healthy humans. We hypothesized therefore that plasma and muscle myostatin would increase in healthy individuals after hypoxic exposure.

Method

Participants (N=9, ♂) were exposed to hypoxic (12% O_2) or control (21.9% O_2) conditions in a random manner. After an overnight fast, participants were cannulated (dorsal hand vein) in a hot box for arterialised blood sampling. After a baseline biopsy and blood sample (t=-30) participants gave three further blood samples then were exposed to the experimental stimulus (12% or 21.9%) for two hours in a random order. Immediately post stimulus, participants received a second biopsy t=120, then received further biopsies at t=30 and t=320. Arterialized blood samples were taken throughout (figure 2).

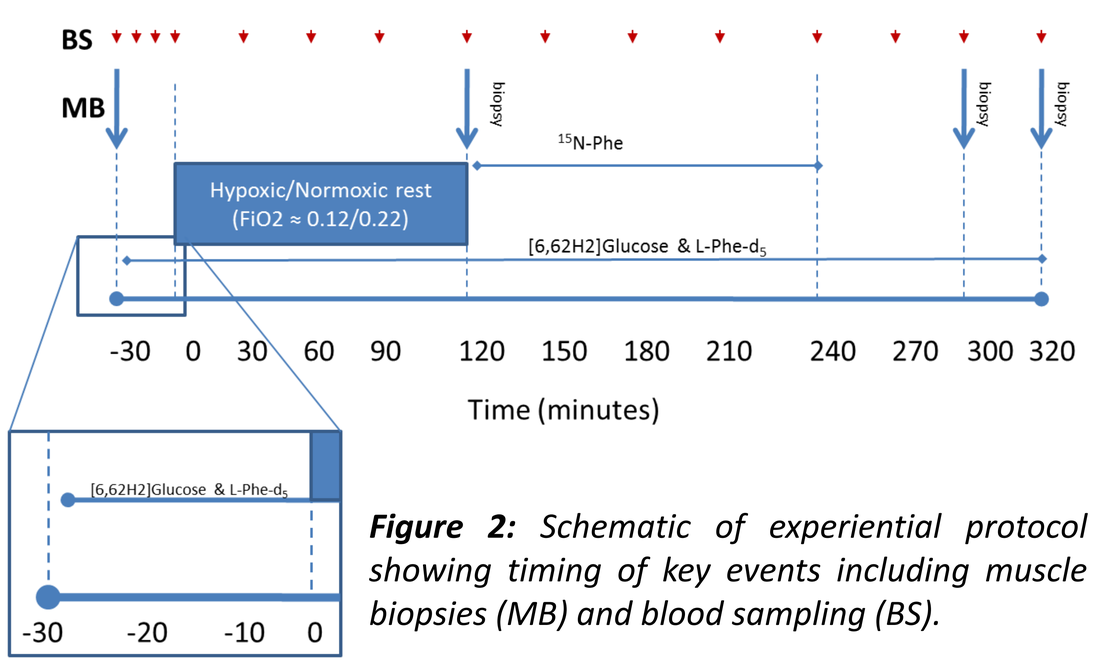

Figure 2: *Schematic of experiential protocol showing timing of key events including muscle biopsies (MB) and blood sampling (BS).*

Results

Hypoxia significantly reduced capillary O_2 (figure 3a) and increased heart rate (figure 3b) and LLAMS (not shown) during hypoxic stimulus.

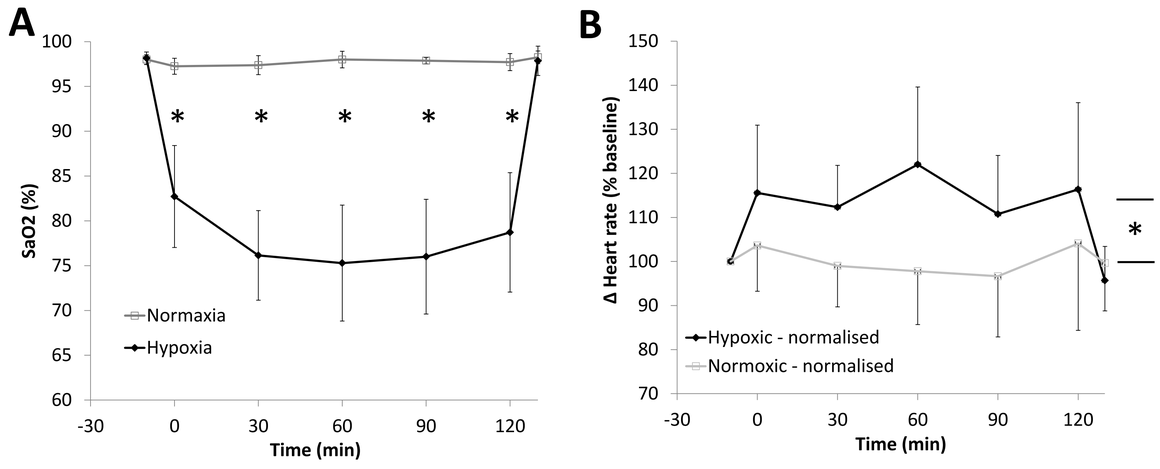

Figure 3: A) *Fingertip SaO2 and* ***B)*** *HR immediately prior to , during and post hypoxia exposure (N=8), error bars represent standard error.*

Absolute levels of muscle myostatin peptide showed no difference in expression levels at any time-point (figure 4a). Significant intra-individual variation was noted, so blot intensities were expressed as a function of baseline concentrations, which revealed a decrease in muscle myostatin expression relative to the control condition (figure 4b). Serum levels of total myostatin protein did not change any time-point or condition (Figure 4c) and were noted to be highly stable between conditions (hypoxic vs control – figure 4d).

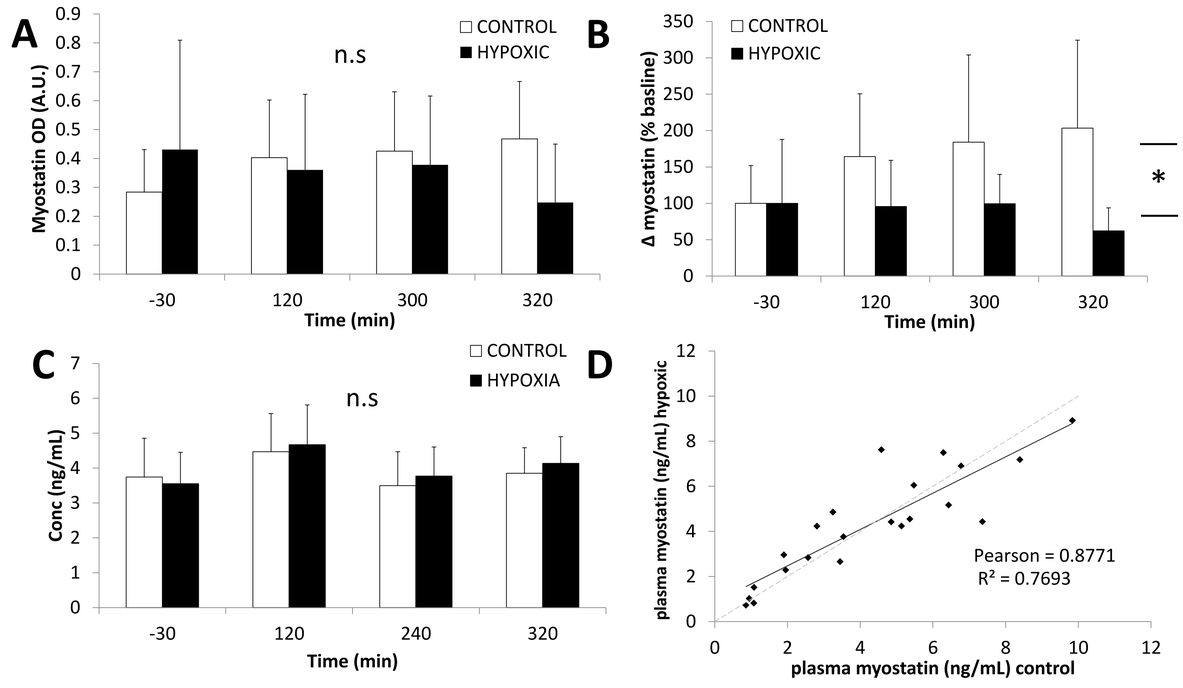

Figure 4: A) *Absolute and* ***B)*** *relative to baseline muscle myostatin peptide level.* ***C)*** *Total Plasma myostatin (ng/mL).* ***D)*** *control vs hypoxic plasma myostatin expression across all individuals and time-points. N=8.*

Discussion

Counter to our hypothesis, here we show plasma myostatin did not change in response to 2 hours hypoxia, and further, muscle myostatin is depressed in response to 2 hours hypoxia. This data results in one of two hypotheses, either muscle myostatin is depressed by acute hypoxia, or muscle myostatin concentration is elevated by acute inactivity and hypoxia depressed this response. If acute hypoxia decreases myostatin expression, it is logical to expect plasma myostatin to increase, which we did not see here. Myostatin circulates as a 26 KDa peptide, the ELISA used here measures both this peptide and the myostatin pro-peptide due to the antibody epitope crossing both regions. The relationship between total myostatin and myostatin peptide concentration in serum is unclear.

Here we show the effect of acute hypoxia upon myostatin expression. Future work will examine the effect of an increased hypoxic duration, to bridge the acute-chronic gap in the literature.

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