Melting into Thin Air: The Role of Acute Hypoxia in Skeletal Muscle Atrophy

UNIVERSITY OF RIGOUR RESEARCH RESULTS WESTMINSTER

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Introduction

Muscle is the largest tissue in the human body and the size of muscle is significantly regulated by the protein myostatin[1,2]. Chronic hypoxemia *in vivo* induces muscle atrophy in both healthy mountaineers[3] and patients with COPD (figure 1). However, both COPD patients and mountaineers are difficult models to study due to several confounding factors. Chronic hypoxia in mice and COPD patients co-presents with elevated myostatin[4], suggestive of a causative role. We previously showed that 2 hours hypoxia (12 % O_2) induced a decrease in muscle myostatin and a trend towards increased plasma myostatin concentration in healthy individuals[5].

We therefore aimed to determine the effect of time in hypoxia, hypothesizing that an increase in hypoxic exposure time would result in a greater myostatin protein decrease in muscle and corresponding increase in plasma concentration.

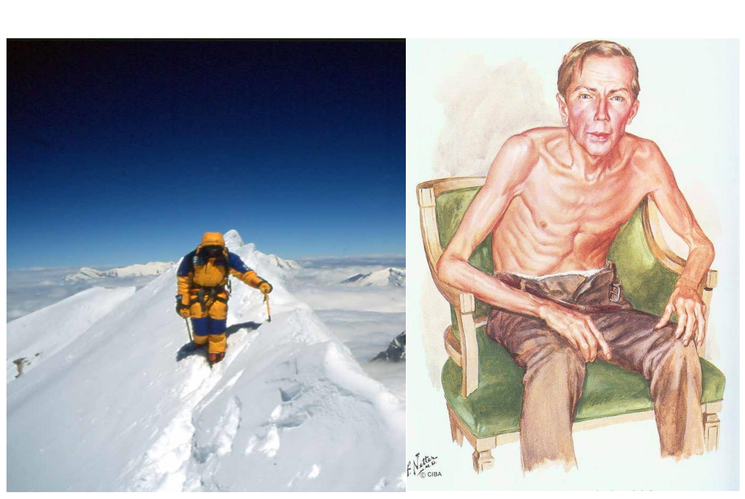

Figure 1: Both healthy individuals at altitude and hypoxemic COPD patients lose muscle mass.

Methods

Healthy males (N = 8, 30.3 years of age) visited the laboratory twice. Visit one consisted of screening and consent. In visit two, participants attended in a fasted state, immediately gave a muscle biopsy and venous plasma sample, then were placed in a normobaric hypoxic chamber (12 % O_2) for 10 hours, with a second plasma sample taken after 2 hours. Immediately post hypoxic exposure a second biopsy and third plasma sample was taken (figure 2).

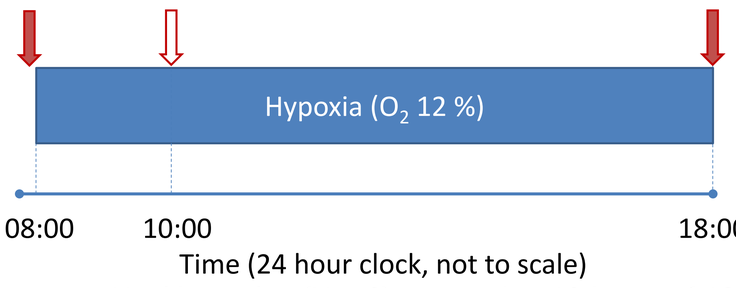

Figure 2: Healthy males (N = 8) exposed to 10 hours of 12 % O_2. Plasma collected pre, during and post exposure. Full arrows indicated plasma and biopsy, hollow arrow plasma only.

Results

Table 1: Subject characteristics (N = 8). Expressed as mean (SD).

Height (cm)	Weight (kg)	BMI ($kg.m^{-1}$)	FFM (%)	SaO_2 (%)
180	78.99	24.22	85.1	97.9
(0.70)	(9.83)	(1.79)	(7.19)	(1.1)

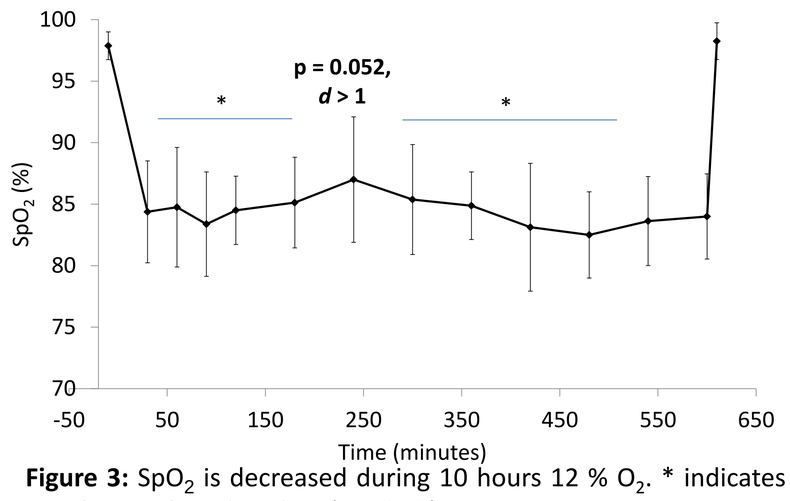

Figure 3: SpO_2 is decreased during 10 hours 12 % O_2. * indicates significance from baseline ($p < 0.05$).

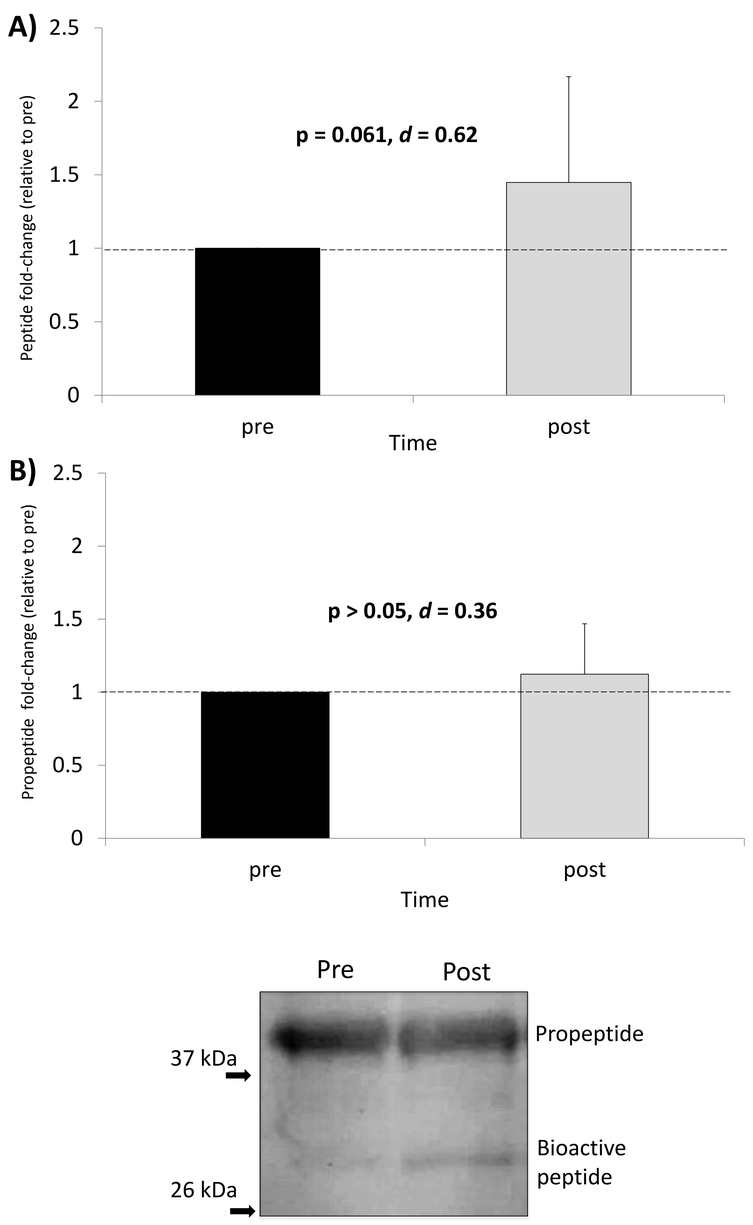

Figure 4: 10 hours of 12 % O_2 **A)** shows trends towards increased muscle myostatin **B)** but not the latency associated propeptide. Representative western blot shown.

Expression of the bioactive peptide in muscle tissue showed trends towards an increase after 10 hours hypoxia, with a 44 % increase over control values ($p = 0.06$, figure 4a). Conversely, the inhibitory propeptide did not increase (figure 4b).

Expression of pAkt (t473) / total Akt ratio did not change, nor did either individual component (Figure 5 A & B).

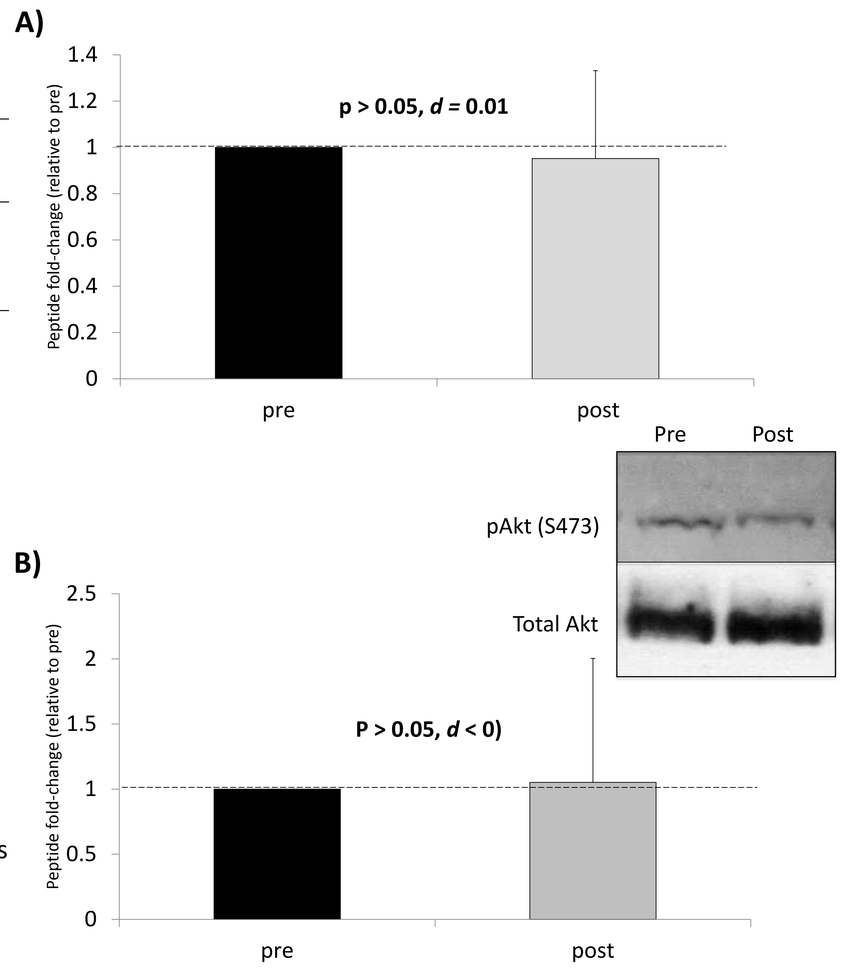

Figure 5: A) 10 hours of 12 % O_2 does not alter expression levels of phosphorylation of Akt (S473) **or B)** total Akt. Representative images shown.

Discussion

Here we show increased muscle myostatin peptide in response to 10 hours hypoxia in healthy males. Calculation of plasma myostatin responses is ongoing; we hypothesize an increase will be seen, representing muscle secreting myostatin in an endocrine manner. While here we show an increase in muscle myostatin after 10 hours hypoxia, our previous 2 hour experiment showed a decrease in muscle expression[5], suggesting a time-dependent effect. We propose a temporal response of muscle myostatin modelled below (figure 6). Lack of alteration in Akt signaling suggests hypoxic atrophy may occur via increases in degradation, not decreases in synthesis of muscle protein. This trend is similar *in vivo* in muscle from COPD patients[6]. Our next study will examine the effect of dose (12 % vs 10 % O_2) upon myostatin signalling. Increased myostatin expression in muscle may explain the witnessed atrophy seen in various hypoxic conditions such as COPD and mountaineering.

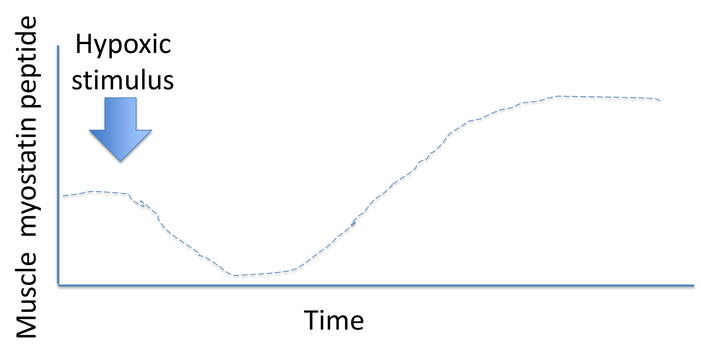

Figure 6: Proposed temporal changes in myostatin peptide in muscle in response to a hypoxic stimulus.

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Society for Endocrinology

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