OXYGEN AVAILABILITY FALLS when one ascends to high altitude or when atmospheric oxygen percentage is artificially reduced. Human adaptation to chronic low oxygen exposure involves responses that might act to mitigate reductions in convective oxygen delivery (5). Next to prominent adaptations such as erythropoiesis and elevated pulmonary ventilation, the body additionally responds to hypoxia by initiating skeletal muscle catabolism, leading in some circumstances to muscle wasting. This loss of muscle mass at high altitude is hypothesized not to be a de facto pathophysiological dysregulation but rather a protective mechanism to decrease oxygen diffusion distance to mitigate reductions in oxygen delivery to the fibers (11, 19). In addition, a decrease in overall muscle mass can lead to a drop in oxygen dependent basal metabolic rate (22).

Indeed, a series of independent high-altitude studies have reported reductions up to 15–20% in skeletal muscle cross sectional area (CSA) (2, 11, 17, 18). Interestingly, this finding is contrasted by others who did not report any decline in skeletal muscle fiber CSA after an hypoxic sojourn (3, 9, 12, 14, 16). Differences between studies might in part be accounted for by variation in caloric intake, physical activity, cold exposure, water metabolism, and sleep quality (reviewed in Refs. 10, 13). One study looked at the effect of hypoxic exposure on the loss of muscle mass in less active and active subjects sojourn- ing above 5,000 m (18). Muscle fiber CSA decreased by ~15% in the vastus lateralis and in the biceps, with no difference between active and less active subjects. Although it is tempting to conclude that physical activity does not help to preserve muscle mass at altitude, it should be mentioned that the active group spent around 30% more time at a higher altitude than the less active group, thereby having a higher hypoxic dose (18). As such, it is likely that the aforementioned confounding factors cannot account for all the differences seen in these high-altitude studies concerning skeletal muscle wasting.

Skeletal muscle mass is enzymatically regulated by the central molecular node mammalian target of rapamycin (mTOR), which is inhibited under conditions of low oxygen by hypoxia-inducible factor-1α (HIF-1α)-dependent genes, such as regulated in development and DNA damage responses 1 (REDD1) (4, 6) and BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) (15). This suggests a role for hypoxia per se in the regulation of skeletal muscle mass (5). Therefore, we investigated the possibility that the hypoxic dose directly relates to hypoxia-induced loss of muscle mass. We adopted the model described by Garvivan-Lewis et al. (8) in which the authors propose to use both altitude (in km) and the duration spent at this altitude in hours as an index of hypoxic dose (Table 1). Figure IA shows that the hypoxic dose for the studies having found a significant decrease (POS studies) in muscle fiber area was ~2.5-fold higher than the studies showing no effect (NEG studies). Furthermore, the negative correlation between hypoxic dose and percentage decrease in muscle fiber area was highly significant \( (r = -0.69, P < 0.02) \), further suggesting that the hypoxic dose per se could be important in the decrease of muscle mass after a hypoxic sojourn (see Fig. 1B).

Nevertheless, the question remains at which hypoxic dose HIF stabilization and other related molecular regulations occurs in human skeletal muscle. On the basis of Fig. 1, the threshold of hypoxic dose above which skeletal muscle atrophy is initiated would be situated ~5,000 km·h. Athletes undergoing altitude camps to enhance performance are generally exposed to hypoxic doses well below this 5,000 km·h. We may therefore probably expect that hypoxia-induced skeletal muscle wasting should not be a major concern for athletes training at altitude.

Noteworthy, some considerations have to be made when interpreting the relation between hypoxic dose and loss of skeletal muscle mass. It is unknown which parameter, altitude or time spent at altitude, is most decisive in the overall metric of hypoxic dose. On one hand, some arguments advocate for altitude to be the decisive parameter. The correlation between the percentage decrease in CSA and altitude \( (r = -0.74, P = 0.012) \) was stronger than with time spent at altitude \( (r = -0.59, P = 0.047) \). Furthermore, none of the NEG studies included in Fig. 1 used an altitude above 5,000 m, whereas all POS studies were performed at or above 5,000 m. On the other hand, the duration of the exposure to hypoxia is of importance as well. Patients with chronic obstructive pulmonary disease (COPD) have various levels of arterial oxygen tension \( (\text{PaO}_2) \), ranging from 45 to 90 mmHg (23). However, globally, hypoxemia is often mild, ranging between 60 and 70 mmHg (which would correspond to \( \text{PaO}_2 \) at ~1,500–3,000 m altitude for healthy subjects) (25). Still, weight loss and/or cachexia in these patients has been suggested to be, at least partially, caused by hypoxia per se due to a hypoxemia-induced rise in TNF-α and ROS (24). Furthermore, when hypoxemic COPD patients are taken off supplemental oxygen for 3 h, S6K1 phosphorylation decreased and REDD1/14-3-3
association tended to increase in skeletal muscle compared with their nonhypoxic counterparts (6). Those results suggest that skeletal muscle is indeed sensitive to fluctuations in oxygen delivery and that mTORC1 is possibly involved in hypoxia-induced muscle mass loss. Thus, although the degree of hypoxemia in COPD is not as high as seen during high-altitude expeditions, these patients still lose muscle mass over a very long period of time and hypoxemia likely plays a role in this phenomenon. Although both duration and altitude seem to be important in inducing muscle loss, it is obvious that a minimal threshold has to be reached for each of the two factors. Below this minimal threshold any compensation by the second factor is not possible and muscle loss will likely not occur.

An important question still remains unanswered, that is the role of HIF-1α stabilization in the loss of muscle mass at altitude. Data on intramuscular PO2 are sparse, but a critical threshold of 7–8 mmHg has been suggested below which intramuscular HIF-1α starts to accumulate (7). When humans are passively exposed to environmental hypoxia, the drop in intramuscular PO2 will likely not surpass this threshold (21) and HIF-1α will not stabilize, still loss of muscle mass has been observed in several studies (17, 18). Contrarily, HIF-1α can be stabilized during repeated muscle contractions in humans (1), which are known to largely decrease intramuscular PO2 (21). Hence, stabilization of HIF-1α does not necessary lead to muscle wasting, and muscle wasting can occur independently of HIF-1α. In addition, HIF-1α can be stabilized by hypoxic-independent mechanisms such as an increase in cytokines (20). It is therefore difficult to isolate the hypoxic and nonhypoxic mechanisms stabilizing HIF-1α. In summary, the contribution of HIF-1α and/or other members of the HIF family to the loss of skeletal muscle mass at altitude is still to be investigated in vivo (5).

To conclude, a review of the available literature revealed a critical threshold above which skeletal muscle wasting could be initiated at altitude. Future human time-course studies in hypoxia in combination with intramuscular PO2 measurements and control for confounding factors should provide more insight in how and when the hypoxic stimulus is severe enough to elicit skeletal muscle atrophy.

ACKNOWLEDGMENTS

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Table 1. Calculation of the hypoxic dose in each study

<table>
<thead>
<tr>
<th>Ref #</th>
<th>Study</th>
<th>Average Altitude, km</th>
<th>Average PO2, %</th>
<th>Time Spent at Altitude, h</th>
<th>Hypoxic Dose, km·h</th>
<th>Decrease Fiber Area, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.933</td>
<td>14.3</td>
<td>360</td>
<td>1,055.9</td>
<td>−5.7</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>4.100</td>
<td>NA</td>
<td>1,248</td>
<td>5,516.8</td>
<td>−6.7</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4.200</td>
<td>NA</td>
<td>480</td>
<td>2,016.0</td>
<td>+1.1</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3.454</td>
<td>NA</td>
<td>672</td>
<td>2,321.1</td>
<td>−3.4</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>4.671</td>
<td>NA</td>
<td>1,020</td>
<td>4,764.4</td>
<td>−3.4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5.600</td>
<td>NA</td>
<td>840</td>
<td>4,704.0</td>
<td>−12.2*</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>5.600</td>
<td>NA</td>
<td>1,800</td>
<td>10,080.0</td>
<td>−15.7*</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>5.526</td>
<td>NA</td>
<td>960</td>
<td>5,305.0</td>
<td>−25.6*</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>5.650</td>
<td>NA</td>
<td>1,680</td>
<td>9,492.0</td>
<td>−21.9*</td>
<td></td>
</tr>
</tbody>
</table>

Average altitude is the sum of the altitudes expressed in km for each day divided by the total days spent at altitude. All studies included are conducted at hypobaric altitude, except for (3), for which average PO2 is given. *Represents a significant decrease (P < 0.05) in fiber area as compared with prehypoxic values.

Fig. 1. Effect of altitude and exposure time on % decrease in muscle mass in humans. A: average (± SE) hypoxic dose for NEG studies (showing no effect of hypoxia on skeletal muscle CSA) (3, 9, 12, 14, 16) and POS studies (showing significant effect of hypoxia on skeletal muscle CSA) (2, 11, 17, 18). B: relation between hypoxic dose and decrease in CSA for NEG studies (solid circle) and POS studies (dashed circle). *P = 0.02 vs. NEG studies. Reference to the respective study can be found next to each data point. All studies included were carried out in humans and were written in English. Articles were identified by searches on PubMed and EMBASE with no temporal limitation. The following search equation was used: hypoxia OR altitude AND human skeletal muscle AND cross sectional area. In total, 32 articles were found and revised. Reference list of each article was checked for possible additional articles within the topic. In addition, the search terms “hypoxia”, “altitude”, “expedition”, “human muscle”, “cross sectional area”, were typed in Google Scholar to find references not indexed in PubMed and EMBASE. Articles were reviewed to identify those that used long-term (simulated) hypoxia (>2 wk, >3,000 m), had hypoxic dose sufficiently explained in the methods, and had a measurement of skeletal muscle fiber atrophy. In all studies, CSA was measured in muscle biopsies using biochemical techniques. None of the studies used methods based on body composition.

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