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TRANSLATIONAL PERSPECTIVES

Is hypoxia-induced skeletal muscle dysfunction lost in space or just a matter of a time?

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A key advantage of humans over other animals in terms of maintaining homeostasis in extreme environments is the ability to create microenvironments to suit our physiology. This ability has allowed geographically extensive human habitation of our planet ranging from the equator to above the Arctic Circle and from sea level to high altitudes. In contrast, microenvironments for beyond-Earth exploration and habitation dictate conditions less favourable to human physiology due to microgravity. Microgravity affects, *inter alia*, skeletal muscle physiology wherein unloading contributes significantly to metabolic and atrophic remodelling and functional deficits. Unsurprisingly, such remodelling is of concern for the health, safety, and performance of astronauts.

If microgravity alone were not enough for astronauts, the 'Planetary Habitat Simulation' series of experiments ('PlanHab' – https://cordis.europa.eu/project/rcn/104127_en.html) throw chronic environmental hypoxia into the mix. Similar to microgravity, the hallmark of muscle adaptation to chronic hypoxia is reduced muscle mass and decreased oxidative function (Hoppeler & Vogt, 2001). The motive behind the superposed hypoxia stimulus on bedrest (simulating the unloading effects of microgravity) in PlanHab is a necessary medical–technical trade-off in potential extra-terrestrial habitats: on the one hand, hypobaria decreases the risk of decompression sickness with extra-vehicular activities; on the other hand, hypobaric normoxia increases the flammability of the environmental gas mixture due to the increased O_2 fraction. As such, the way forward for microgravity habitats is hypobaric hypoxia. Thus, the PlanHab project is specifically designed to investigate the effects of sustained bedrest and superposed environmental hypoxia on human physiology.

The study by Salvadego *et al.* (2018) published in this issue of *The Journal of Physiology* – part of the wider PlanHab project – provides new data concerning how peripheral skeletal muscles may adapt to combined environmental hypoxia and bedrest. At the Olympic Sports Centre in Slovenia (Planica-Rateče), 11 healthy recreationally active males were exposed in a randomized order to hypoxic bedrest, normoxic bedrest and hypoxic ambulatory confinement. Each experimental protocol lasting 21 days was separated by a 4-month washout period. Suffice to say, superposition of hypoxia on microgravity could be expected to spell double trouble for these individuals in terms of skeletal muscle oxidative function. Indeed, the authors hypothesized as much. However, despite changes observed in mitochondrial function (evidence that the hypoxia stimulus was strong enough to induce local muscle effects), the superposed hypoxia on bedrest did not potentiate the detrimental effects of bedrest *per se* on skeletal muscle oxidative function. This raises a critical question: would the detrimental effects of hypoxia be lost in the microgravity of space?

The authors rule out several possibilities as to why this is observed using an array of physiological and biochemical *in vivo* and *ex vivo* techniques to take measurements at both an integrated systems level and a molecular level. The exercise protocol utilized is not maximal from a cardiorespiratory perspective but is maximal from a local muscle perspective, and thus systemic limitations are avoided. Furthermore, femoral artery blood flow, O_2 extraction at the level of the muscle and cerebral O_2 extraction do not appear to play a compensatory role.

Importantly, the authors note that hypoxia-induced differential skeletal muscle remodelling may be observed with varying duration of exposure. Indeed, measurements taken after 21 days of exposure represent but one snap-shot of a time-dependent adaptive process. In 2016, Salvadego and colleagues suggested that 10 days of hypoxia superposed on bedrest can actually attenuate or prevent the impairment of muscle oxidative function by bedrest *per se* (Salvadego *et al.* 2016). That there was no apparent difference in bedrest-induced oxidative muscle function when comparing the post-10 to post-21-day exposure response (Salvadego *et al.* 2018) could imply an initial beneficial effect of hypoxia that becomes detrimental over more prolonged periods. Time may thus be a critical variable when exploring the effects of combined hypoxia and bedrest on human skeletal muscle physiology. Will a trial beyond 21 days elicit hypoxia-induced potentiation of bedrest effects on skeletal muscle? As Salvadego *et al.* (2016) conclude, '[t]he effects of longer exposures will have to be determined' (Salvadego *et al.* 2016).

Remarkably, this unique combination of stimuli tested for extra-terrestrial expeditions and habitation may shed light on physiological adaptation here on Earth. The authors conclude their results may be of interest for chronically ill patients who suffer from hypomobility/immobility and hypoxia. Indeed, these facets of disease are rarely studied together in the absence of other confounding factors of chronic diseases. Thus, research exploring physiological adaptation to microgravity and hypoxia for beyond-Earth habitation provides a unique opportunity to track and assess how these facets of disease may combine – in a time-dependent manner – to the advantage or detriment of human physiology. Such insights from healthy individuals may allow zoning in on particular components of skeletal muscle or be utilized to therapeutic advantage against skeletal muscle dysfunction in diseases characterized by immobility and hypoxia. Hypothetically, bouts of chronic hypoxia (at this stage of empirical data, no longer than 21 days) may help attenuate muscle deconditioning in those who are bedridden.

Clearly, studying how physiology copes with challenges of time spent in microenvironments created to explore space and other planets may bear significant translational relevance to clinical situations here on Earth. Overall, 'space and time' is not just a topic of interest for physics and philosophy but also for physiology!

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Additional information

Competing interests

The author reports no competing interests.

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