Impact of extreme exercise at high altitude on oxidative stress in humans

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Abstract Exercise and oxidative stress research continues to grow as a physiological subdiscipline. The influence of high altitude on exercise and oxidative stress is among the recent topics of intense study in this area. Early findings indicate that exercise at high altitude has an independent influence on free radical generation and the resultant oxidative stress. This review provides a detailed...
Introduction

Oxidative stress has been the focus of exercise-based research for more than three decades. In recent years, intense research efforts have been directed at understanding oxidative stress and exercise in climatic scenarios including high altitude. Exercise adaptations to altitude accrue in proportion to elevation, beginning around 1000–1500 m. A survey of the literature, however, reveals that responses to ‘high altitude’ are generally limited to elevations above 3000 m (Sinha et al. 2009a; Faiss et al. 2013; Miller et al. 2013; Lewis et al. 2014; McGinnis et al. 2014). Within the context of exercise, applications are often limited to endurance/ultra-endurance competitions, recreational and military-related mountain trekking, altitude considerations of living and training for elite endurance athletes, and vigorous activity as performed by high-altitude natives. What is currently known about extreme exercise and oxidative stress at high altitude is generally derived from a limited number of field studies. Additional understanding is extracted from well-controlled laboratory studies of exercise performance and blood biomarker alteration in humans exposed to normobaric hypoxia in an environmental chamber. However, current knowledge of muscle level adaptations to hypoxic exercise is largely procured from a handful of animal-based research studies. Accordingly, understanding of oxidative stress related to exercise and high altitude is still unfolding.

The aim of this review is to examine what is currently known about exercise and oxidative stress at high altitude. The paucity of published investigations specific to exercise at high altitude is such that early conclusions may need to be contextualized to exercise and oxidative stress findings from all altitudes. Moreover, modern understanding about exercise and free radicals, independent of altitude, is sometimes limited due to common misconceptions about the biomarkers used to
quantify oxidative stress. Accordingly, a brief discussion of oxidative stress biomarkers is necessary to better understand their responses during exercise and recovery at altitude.

**Examination of oxidative stress during high altitude exercise**

The oxidative biomarkers fundamental to altitude research are identical to those collected for sea-level exercise. The labile nature of oxidative stress is such that most researchers examine a composite response founded upon a biomarker panel. Since the inception of this research line in the late 1970s (Dillard et al. 1978), oxidative stress responses to exercise have been determined by (1) elevations in oxidative damage markers, (2) alterations in endogenous antioxidant systems (enzymatic and non-enzymatic antioxidants), and (3) alterations in redox-sensitive gene transcripts and their corresponding proteins.

Quantification of oxidative damage entails examination of relatively stable redox-sensitive lipid, protein and nucleotide end products (Powers et al. 2011). In addition to these 'finger print' biomarkers of oxidative damage, oxidative stress is quantified by examination of antioxidant content. Examination of antioxidant status is arguably more complex than quantification of oxidative damage markers due to the fact that enzymatic antioxidant protein content and activity can be measured. Moreover, the contribution of non-enzymatic antioxidants must also be considered (reviewed in Powers et al. 2011). In the latter instance, the contribution of low molecular mass antioxidants includes protein/non-protein, thiol/non-thiol, and lipid soluble/aqueous antioxidants. Thus, quantification of the antioxidant network is important due to the fact that a variety of antioxidants work in concert to quench a host of free radical parent molecules and their oxidized products. Within a biological fluid, oxidative stress occurs according to a biochemical pecking order such that aqueous antioxidants are depleted prior to lipid soluble antioxidants, which are then exhausted prior to the appearance of oxidative damage markers (Buettner, 1993). In reality, however, the pecking order of oxidative stress reactions is further complicated by the fact that oxidative chain reactions are not completely partitioned within or between cells and tissues. Accordingly, many researchers incorporate assays of antioxidant capacity (trolox equivalent antioxidant capacity) or radical quenching capacity (ferric reducing ability of plasma, oxygen radical absorbance capacity) as a comprehensive method of quantifying the antioxidant dynamic within a few variables (Cao & Prior, 1998). Finally, examination of redox-sensitive gene transcripts related to mitochondrial biogenesis, endogenous antioxidant up-regulation, and cellular stress responses reflects the acute exercise stimulus and holds important implications for the adaptive response to exercise at altitude (Powers et al. 2011). Collectively, comparison of these oxidative stress biomarkers across low, moderate and high altitude scenarios is fundamental to current understanding and ongoing research initiatives.

**Preliminary studies to identify oxidative stress during high altitude exercise**

Independent of exercise, exposure to a high altitude environment elicits oxidative stress as quantified by the various biometrics mentioned above. Importantly, both the hypobaric (Faiss et al. 2013) and hypoxic (Debevec et al. 2014) aspects of high altitude appear to have independent influences on the resultant oxidative stress, though the underlying mechanisms are not resolved. While research has been conducted in conjunction with a number of endurance and ultra-endurance events that included limited time at high altitude (Nieman et al. 2003; Quindry et al. 2008), the oxidative stress findings from these studies cannot be attributed to altitude alone and are excluded from the current discussion. Thus, early evidence of high altitude and oxidative stress is largely derived from field studies, expeditions, or simulated altitude lab studies where most or all of the physical effort is conducted above 3000 m (Sinha et al. 2009a; Faiss et al. 2013; Miller et al. 2013; Lewis et al. 2014; McGinnis et al. 2014).

The first human study related to high altitude and exercise-induced oxidative stress was conducted in 1988 (Simon-Schnass & Pabst, 1988). However, even after this first study, research on exercise and high altitude has been relatively infrequent. Accordingly, broader findings from exercise and oxidative stress at all altitudes were used to bridge early knowledge gaps relative to work conducted at high altitude. As a general rule, sea level participation in high intensity (Quindry et al. 2003) or extended duration (Mastaloudis et al. 2001) muscular exercise is marked by a prominent rise in circulating levels of oxidative stress biomarkers. Similar observations occur following acute bouts of physical activity performed at high altitude where short duration–high intensity exercise (Sinha et al. 2009a) and long duration–low intensity exercise (Vasankari et al. 1997; Miller et al. 2013; Krzeszowiak et al. 2014) result in a transient increase in various indices of oxidative stress. However, in regard to exercise intensity, it is important to note that due to the low $P_{O_2}$ at high altitude, the relative intensity for a given work rate increases significantly at high altitude. In fact, slow speed hiking above 8000 m can approach 100% relative intensity as $V_{O_2max}$ significantly decreases in an elevation-dependent fashion (Buskirk et al. 1967).
What are the implications of oxidative stress during high altitude exercise?

As described above, biomarker indices from multiple tissues, including blood plasma and skeletal muscle, clearly indicate that acute exercise at high altitude induces a readily identifiable oxidative stress. Oxidative stress findings, however, may be more directly related to exercise than altitude. In support, exposure to high altitude is associated with a modest increase in basal levels for multiple oxidative stress biomarkers, while acute exercise elicits an additive increase of greater magnitude (Sinha et al. 2009a).

Given the influence of exercise intensity and duration on reactive oxygen species (ROS) formation, findings of oxidative stress due to high altitude exercise may simply indicate that physical exertion at high altitude is demanding. Past notions that exercise-induced oxidative stress is deleterious to long term health are largely refuted today (reviewed in Quindry et al. 2014; Peake et al. 2015). In this regard it is important to contextualize exercise-induced oxidative stress relative to the specific biomarkers used to quantify oxidative stress in order to understand the acute and adaptive responses to exercise at high altitude. Moreover, a brief overview of oxidative stress biomarkers is helpful in overcoming common misconceptions about exercise and oxidative stress.

Because the majority of high altitude studies are conducted in human participants while at elevation in remote regions, much of the oxidative stress research reports only blood plasma markers. Categorization of oxidative damage markers from these field studies reveals that elevations in circulating levels of markers of lipid peroxidation, protein modification (usually carbonylation) and DNA damage are frequently reported. Table 1 summarizes oxidative stress findings from exercise research studies conducted either at high altitude or in laboratory settings that utilize hypoxic inspiratory gases. Biomarkers of lipid peroxidation increase as a result of exercise at high altitude, although the source of these lipids and the initiating reactions are rarely known in the context of exercise. Nonetheless, modification of F2-isoprostanes are likely to be related to arachidonic acid metabolism and signalling while an increase in lipid hydroperoxide formation is likely to result from cell membranes disrupted by oxidative reactions (Nourooz-Zadeh et al. 1994; Morrow & Roberts, 2002). While unconfirmed currently, there is reason to speculate that damaged red blood cells may be a primary source of increased circulating lipid hydroperoxides during exercise at high altitude. In relation to the current topic, red blood cell fragility and lipid peroxidation occur due to high altitude exposure, a response that is also associated with exercise participation (Sinha et al. 2009b; Vani et al. 2010). Another possible source of lipid hydroperoxides is the vascular endothelium. For example, Lewis et al. examined physiological indices of blood flow in lowland natives introduced to 5000 m altitude (Lewis et al. 2014). They reported that flow-mediated dilatation and glyceryl trinitrate-mediated vasodilatation were diminished at altitude while pulse wave velocity increased. Notably, a rise in circulating lipid hydroperoxides was inversely correlated \((r = -0.69)\) with glyceryl trinitrate-mediated vasodilatation. This finding may indicate that acute oxidative stress is associated with a corresponding decline in vasoreactivity (Lewis et al. 2014).

Similar to lipid markers of oxidative damage, protein markers of oxidative damage remain undefined in terms of source. Protein carbonyl formation is due to direct oxidation of amino acid residues, although examination of the constituent proteins is rarely performed in the context of exercise. While it is confirmed that actin and myosin are oxidatively modified due to exercise at altitude (Radak et al. 1997), there is little reason to suspect that a post-exercise spike in plasma protein carbonyls is derived from muscle in appreciable amounts. More likely, plasma albumin, which contains a cysteine residue that is readily oxidized during physiological stress, is the primary target for protein carbonylation. Just as important, albumin represents the most abundant thiol in plasma (Torres et al. 2012). As such it is tempting to speculate that oxidation of circulating albumin accounts for much of the acute spike in circulating protein carbonyls following high altitude exercise. While this notion is currently unconfirmed relative to exercise, if correct it would mean that albumin could serve as a ‘sacrificial’ protein by directly quenching free radicals. Moreover, this notion is congruent with established understanding of the antioxidant milieu in blood plasma (Cao & Prior, 1998). In this regard it is clear that more sophisticated immunoblotting and immunoprecipitation experiments are needed to better understand the nature and severity of protein oxidation products due to high altitude exercise (Goto et al. 1999).

As summarized in Table 1, an outcome of high altitude exercise is that plasma antioxidant capacity is acutely altered. To bring order to the multitude of transient responses from available laboratory and field studies, low molecular mass antioxidants and antioxidant metrics will be discussed independently of endogenous antioxidant enzymes. Of the low molecular mass antioxidants, uric acid is the most important water soluble antioxidant contributing to blood antioxidant radical trapping capacity (Cao & Prior, 1998). Several published investigations of high altitude exercise report a rise in circulating plasma uric acid levels (Sinha et al. 2009a; Peters et al. 2015). Exercise-induced elevations in plasma uric acid occur due to purine metabolism in skeletal muscle. This phenomenon includes ROS production through the generation of hydrogen peroxide at two steps of the biochemical process, and as such, does not
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AOPP, advanced oxidative protein products; CAT, catalase; FRAP, ferric reducing antioxidant potential; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; GSSG, oxidized glutathione; HNE, 4-hydroxynonenal; HMOX1, haem oxygenase 1; LOOH, lipid hydroperoxides; MDA malondialdehyde; MnSOD, manganese-dependent superoxide dismutase; NFE2L2 nuclear factor erythroid 2-like 2; NOx, nitrogen oxides (nitric oxide and nitrogen dioxide); 3NT, 3-nitrotyrosine; PC, protein carbonyl; SOD, superoxide dismutase; TAS, total antioxidant status; TBARS, thiobarbituric acid reactive substances; TEAC, trolox equivalent antioxidant capacity; UA, uric acid.
appear to be a mechanism of compensatory antioxidant fortification as some speculate. Thus, exercise-induced oxidative damage may still result concomitant to a rise in plasma uric acid and corresponding increase of plasma ferric reducing antioxidant potential (FRAP). In support, it was observed following an ultra-marathon with a peak elevation around 3000 m that the post-exercise rise in plasma uric acid was correlated with corresponding elevations in FRAP \(r = 0.621\) (Quindry et al. 2008). This outcome supports biochemical understanding of these antioxidant and radical trapping metrics that are largely influenced by acute changes in circulating uric acid (Cao & Prior, 1998). Moreover, exercise that elicits significant catecholamine release is associated with a spike in circulating levels of the water soluble antioxidant vitamin C (Quindry et al. 2003), although this response has not been measured or observed in the context of high altitude exercise and oxidative stress. Collectively, the increase in antioxidant capacity and radical quenching capacity observed following exercise at high altitude (Vasankari et al. 1997; Sinha et al. 2009a; Miller et al. 2013; Ballmann et al. 2014; Peters et al. 2015) is likely to be due to acute alterations in the low molecular mass water soluble antioxidants uric acid and vitamin C. While long term elevation in these water soluble antioxidants appears to prevent altitude-induced damage to red blood cells (Devi et al. 2007), there is no evidence to suggest that exercise-induced alterations in these antioxidants directly impact performance or recovery during exercise at altitude.

Circulating levels of endogenous antioxidant enzymes also increase acutely in response to exercise at high altitude. Specifically, circulating levels of superoxide dismutase (SOD) and catalase (CAT) are increased in altitude-habituated lowlanders (Debevec et al. 2014; Krzeszowiak et al. 2014). Notably, the isoform of SOD is not defined in the three key studies listed currently and examination of the published methods does not indicate that red blood cell isolates were collected for selective antioxidant enzyme analysis (Faiss et al. 2013; Debevec et al. 2014; Krzeszowiak et al. 2014). Nonetheless, it is reasonable to assume that these findings for endogenous antioxidant enzymes largely represent rupture of red blood cells or vascular endothelium cells. Interestingly, acute exercise at altitude does not appear to increase red blood cell concentration of these enzymes (Joanny et al. 2001), suggesting that acclimatization to altitude is a necessary co-stimulus. In support, animal studies of habituation to altitudes exceeding 5000 m and 6300 m elicit consistent increases in red blood cell content of CAT, SOD and glutathione peroxidase (GPx) (Asha Devi et al. 2005; Devi et al. 2007). Whether these findings are due to altitude-induced polycythaemia and/or cellular level adaptations is currently uncertain.

Final consideration of high altitude exercise and oxidative stress in humans raises the question of muscle level oxidative damage and adaptations. To date, no published investigations report muscle level tissue oxidative damage in humans exercising at high altitude. This fact is likely to reflect the difficulty of obtaining muscle biopsy samples, a task that may be more challenging at extreme altitude in remote locations where permanent labs do not exist and portable labs cannot be easily delivered.

To date, only two laboratory-based investigations report findings from muscle biopsies (vastus lateralis) during exercise performed in normobaric hypoxia to simulate high altitude (Ballmann et al. 2014; Peters et al. 2015). Due to the limited sample volumes from muscle biopsies, only gene transcripts for redox-sensitive markers were examined. First, the study by Ballmann et al. reported a significantly elevated transcript expression for nuclear factor erythroid 2- like 2 (NFE2L2) and SOD. In addition, a non-significant increase in haem oxygenase (HMOX1) was found (Ballmann et al. 2014). Collectively these findings from human studies are supported by a related investigation employing laboratory rats acclimatized to elevations above 4000 m where it was observed that manganese-dependent superoxide dismutase (MnSOD) protein content was up-regulated in both soleus and gastrocnemius (Radak et al. 1997). Notably, this and other animal-based research studies of multiple body tissues acclimatized to extreme high altitude (> 6000 m) suggest that long term exposure is associated with depletion of endogenous antioxidant enzyme content and a corresponding elevation in markers of oxidative damage (Radak et al. 1994; Radak et al. 1997). Notably, these extreme altitude findings may be associated with redox-sensitive muscle wasting processes that occur in normoxic environment muscle investigations (Edwards et al. 2010). The notion that extended duration exposure to extreme high altitude may be detrimental to multiple organs merits further investigation as applied to human application such as mountaineering. The reader is directed to an insightful review on the topic of muscle level responses to altitude exposure (Dosek et al. 2007), but cautioned about interpretation of findings from extreme altitudes (‘death zone’) as potentially having fundamentally different outcomes from exercise performed at lower altitudes.

**Section summary.** In summary, oxidative stress occurs in both blood and muscle due to exercise at high altitude. Acute oxidative stress responses to exercise at high altitude are transient by nature, lasting from a few hours for short duration exercise (Moller et al. 2001; Sinha et al. 2010; Gatterer et al. 2013; Ballmann et al. 2014; McGinnis et al. 2014; Peters et al. 2015), to a few days for extended trekking
Oxidative stress in highland natives and altitude acclimatized lowlanders

Based on findings from recent studies, there appears to be a subtle, but important differences in lowland dwelling versus native highland people. Differences are particularly marked for native peoples of the Himalayan region where generations have lived and worked at altitudes considered to be extreme. One notable difference is that high altitude natives appear to have higher blood concentrations of reduced glutathione (GSH)/oxidized glutathione (GSSG) and SOD as compared with altitude acclimatized or unacclimatized lowlanders (Sinha et al. 2009a,b). However, firm conclusions about these populations may not be warranted currently as the collective blood antioxidant profile, in particular for low molecular weight fat soluble and water soluble antioxidants, was not consistently elevated in highlanders as compared with their lowland counterparts (Sinha et al. 2009a,b). Whether these findings are influenced by diet in addition to genetic and other environmental factors is not currently resolved and also merits further investigation before establishing firm conclusions on the matter. Nonetheless, findings from a related study by the research group referenced above reveal that basal levels of plasma DNA oxidation products, 3-nitrotyrosine and lipid hydroperoxides were lower in native highlanders as compared with their altitude acclimated or sea level acclimated lowland counterparts (Sinha et al. 2010). Moreover, while acute maximal intensity cycle ergometer exercise at 4500 m elicited a rise in plasma oxidative stress markers in all three groups, the magnitude of the response for DNA oxidation products and lipid hydroperoxides was significantly lower in the high altitude natives (Sinha et al. 2010).

Lowland natives who are acclimated to altitude appear to have a modulated oxidative stress response in both unstressed resting and post-exercise scenarios. Several important studies reveal that basal levels of plasma oxidative damage markers and antioxidant content are elevated by 4–5 weeks of acclimation to altitude above 3500 m. In one investigation native lowland volunteers were habituated to elevation by residence at 3500 m for 1 week and then at 4500 m for 3 weeks thereafter. At the end of the habituation period plasma glutathione content was increased with GSH/GSSG being modestly but significantly higher. Related concentrations of GPx and glutathione reductase were also higher following a month at high altitude. Plasma levels of uric acid were also elevated due to acclimation, while vitamin C concentrations were lower than at sea level (Sinha et al. 2009a). Similar findings were reported by the same group of researchers, who exposed subjects to 3500 m for 1 week followed by 4 weeks at 4500 m. Increased plasma SOD, CAT, uric acid, GSH/GSSG and glutathione reductase were observed after 5 weeks at high altitude. However, lipid hydroperoxides and protein carbonyls were also elevated in these acclimatized subjects (Sinha et al. 2009b). A separate report using an identical acclimation protocol examined the acute oxidative stress response to maximal intensity cycle ergometry. Findings revealed that basal levels in plasma 3-nitrotyrosine and lipid hydroperoxides were elevated in acclimatized lowlanders, but the magnitude of exercise-induced oxidative damage was attenuated for DNA, protein and lipid biomarkers (Sinha et al. 2010). Collectively, these responses appear to support the aforementioned findings from animal studies where skeletal muscle adaptations to moderate and high altitude include antioxidant fortification to quench the increased free radical load associated with altitude (Radak et al. 1994, 1997).
there is little doubt that the acute oxidative stress responses to exercise at altitude can be attenuated by acclimatization to altitude.

**Altitude considerations for living and training**

Given the established link between high altitude exercise and oxidative stress, combinations of living elevation and training elevation must be addressed. While the primary known ergogenic advantage to living at or above 1500 m is erythropoiesis, the advantage of training at moderate to high altitudes may include cellular adaptations to the hypoxic stimulus as well. Accordingly, combinations of living and training at high versus low altitude have been examined, though not in the context of oxidative stress.

As compared with sea level dwelling athletes, there does not appear to be an overall ergogenic advantage to living high and training high (Bailey et al. 1998; Roels et al. 2006). As concluded above there is no reason to suspect that the oxidative stress and the corresponding adaptive responses to living and exercising at moderately high altitudes are ergogenic or deleterious as compared with sea level. Thus, until a testable scientific rationale for or against living high and training high is formulated, the matter does not seem pertinent to oxidative stress and exercise at high altitude.

In contrast to living and training high, living low and training high does raise interesting scientific questions related to oxidative stress. This training rationale persists despite the fact that high altitude exercise workloads are limited by altitude-dependent declines in $\dot{V}_{\text{O}_2,\text{max}}$. The most investigated cellular mechanism in regard to a hypoxic stimulus during exercise is hypoxia-inducible factor-1α (HIF-1α). Examination of skeletal muscle in humans exposed acutely to hypoxic exercise reveals that HIF-1α and vascular endothelial growth factor (VEGF) appear to be central to hypoxia-dependent adaptive responses (Hoppeler & Vogt, 2001a,b). Elevation in related blood markers for HIF-1α and VEGF also occurs following acute hypoxic exercise as compared with normoxic conditions (Mounier et al. 2009). Reductionist work in skeletal muscle from mouse models links this adaptive HIF-1α response to redox stimuli and also implicates beneficial adaptive outcomes related to metabolism and mitochondrial biogenesis (Mason & Johnson, 2007). Recent examination of mitochondrial biogenesis gene transcripts in human vastus lateralis obtained following an acute bout of hypoxic exercise reinforces the notion that adaptive responses to high altitude exercise are redox sensitive (Sivka et al. 2014). Nonetheless, human performance studies of hypoxic exercise on sea level performance are equivocal (Ventura et al. 2003; Dufour et al. 2006). Thus, as related to oxidative stress and exercise at high altitude, foundational research is needed in order to understand the role of oxidative stress and exercise adaptations as they may apply to performance and recovery outcomes.

**Live high, train low.** Living at high altitude and training at low altitude is a strategy for improving endurance exercise performance (Levine & Stray-Gundersen, 1997). While not currently examined in the context of oxidative stress research, there is scientific rationale to suspect that living at high altitude and training at sea level may be advantageous. First and foremost, the erythropoiesis observed with exercise altitude may limit oxidative damage by improved oxygen binding capacity independent of other adaptive responses (Vani et al. 2010). Moreover, high altitude living stimulates fortification of endogenous antioxidant levels in tissue and blood (Radak et al. 1997; Sinha et al. 2009a,b, 2010). Because cellular antioxidant status impacts muscular performance (reviewed in Powers et al. 2011), the live high and train low rationale may hold merit, although a need for foundational studies remains.

**A new twist: sleep high, train and recover low.** Several recent high altitude exercise and oxidative studies raise new insights on the concept of live high–train low and are presented conceptually in the Abstract figure. A series of three investigations from a collaborative group employed normobaric hypoxia in a laboratory setting to examine oxidative stress and muscle adaptive responses to cycle ergometer exercise and recovery (Ballmann et al. 2014; McGinnis et al. 2014; Peters et al. 2015). The first investigation employed a crossover study design during a 60 min exercise bout followed by 4 h of recovery (McGinnis et al. 2014). Exercise and recovery were maintained at low altitude or simulated high altitude (3000 m) and exercise workloads were matched for 60% of $\dot{V}_{\text{O}_2,\text{max}}$ at the respective elevations. Given the impact of hypoxia on exercise intensity, a control trial with the prescribed workload from 3000 m, was performed at the base elevation. Findings from blood assay of oxidative damage and antioxidant markers revealed an altitude-dependent oxidative stress (McGinnis et al. 2014) similar to outcomes described above. The authors postulated that hypoxia may have an independent effect on oxidative stress outcomes as examined during exercise versus recovery.

Accordingly, in a nearly identical follow-up study by Ballmann et al. (90 min exercise at 60% $\dot{V}_{\text{O}_2,\text{max}}$), exercise was performed at the base elevation while exercise recovery occurred at either base elevation or simulated 5000 m. Findings for several biomarkers revealed that both exercise sessions elicited an identifiable blood oxidative stress, although the magnitude of the response was attenuated when recovery occurred at 5000 m (Ballmann et al. 2014). This interesting outcome might indicate that altitude also influences the post-exercise recovery. Moreover, given that exercise adaptations are redox sensitive (Gomez-Cabrera et al. 2008), there is reason to suspect that acute adaptive responses to exercise may be attenuated in high altitude recovery. Indeed, Ballmann et al. examined vastus
lateralis muscle biopsies for redox-sensitive gene transcripts. Findings revealed that exercise-induced elevations of NFE2L2 and SOD mRNA were attenuated during recovery at a simulated 5000 m.

In order to better understand the elevation at which this response occurs, a subsequent investigation by Peters et al. employed an identical crossover study design (60 min exercise at 70% $V_{O_{2\max}}$), except that recovery was at simulated altitudes of 0, 1667, 3333, or 5000 m (Peters et al. 2015). Examination of oxidative stress blood biomarkers revealed that attenuation of the exercise-induced elevation in oxidative stress markers occurred between 1667 and 3333 m. Examination of thigh muscle biopsies produced non-significant numerical decreases in redox-sensitive transcripts at the two highest recovery altitudes (Peters et al. 2015). In support of these findings, the Operation Everest III study revealed persistent elevation in blood oxidative stress during reoxygenation at sea level (Joanny et al. 2001). Moreover, elevation in blood levels of advanced oxidation protein products persisted for at least 24 h following a 10 day exercise training regimen at high altitude (Debevec et al. 2014). These compelling findings require further examination, but might suggest that training and recovery should ideally occur at a lower altitude. Moreover, given that indices of oxidative stress can persist for more than a day, a balance in time spent at high elevation versus low elevation may need to be explored in order to elicit erythropoiesis but not attenuate redox-sensitive adaptations to exercise. One possible solution could be to exercise and recover at low altitude, while sleeping at high altitude. In support of this notion, some studies report that athletes who slept at high altitude (11 h) received the benefit of erythropoiesis (Robach et al. 2006). As with the scientific questions raised above, additional research is needed to formulate preliminary conclusions related to low altitude exercise and recovery in combination with limited high altitude living.

Section summary. Among the most important applications of high altitude exercise and oxidative stress are scenarios related to endurance athletes, recreational mountaineers, and military fighters who complete missions in mountainous terrain. The influences of oxidative stress outcomes are virtually untested in the context of high altitude exercise and recovery. As future research is conceived and executed, serious consideration should be given to incorporation of multiple biosampling times during exercise recovery. In addition, inclusion of muscle biopsy data in addition to blood biomarkers of oxidative stress is warranted. Finally, these investigations should be conducted in well-defined populations in order to minimize confounding outcomes from heterogeneous participant groups that often result from convenience sampling. These recommendations are essential for understanding highly variable tissue level responses that are sensitive to fitness level and exercise habituation (Mounier et al. 2009; Slivka et al. 2014; Peters et al. 2015).

Conclusion

Both intense and long duration exercise elicits oxidative stress, a response that is exacerbated at high altitude. Several dozen studies have directly investigated the oxidative stress response to exercise performed at high altitude, while other human and animal-based studies provide additional insight into the impact of altitude-derived hypoxia on oxidative stress and exercise adaptations. Collective understanding suggests that acute exercise performed at moderate to high altitude elicits an oxidative stress which serves as a potent adaptive stimulus for endogenous antioxidant fortification. In this regard, mechanistic links between redox and hypoxic stimuli on tissue level adaptations are likely to be redundant, although direct links to high altitude exercise have yet to be verified. Nonetheless, significant insights can be gleaned from studies of native highlanders versus lowlanders. Acclimatization to altitude is also revealing in this regard, with human- and animal-based studies providing strong evidence that exposure to high altitude is advantageous to many exercise and training scenarios. In contrast, detrimental effects attributed to high altitude exposure appear to be limited to extended duration exposures conducted at the highest (‘death zone’) elevations. Understanding of the independent and combined influence of hypoxic and oxidative stress stimulus of exercise at high altitude is still in the formative stages. This conclusion is perhaps most notable for the adaptive responses induced during exercise and the exercise recovery phase. Future research should be conducted in both human- and animal-based reductionist investigations of oxidative stress in order to understand the cellular level responses that underpin physiological outcomes to exercise at high altitude.

References


normobaric hypoxia.

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**Additional information**

**Competing interests**

None declared.

**Author contributions**

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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