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Utility of hypoxic modalities for musculoskeletal injury rehabilitation in athletes: A narrative review of mechanisms and contemporary perspectives

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ABSTRACT

Recent evidence suggests that different hypoxic modalities might accelerate the rehabilitation process in injured athletes. In this review, the application of hypoxia during rehabilitation from musculoskeletal injury is explored in relation to two principles: (1) facilitating the healing of damaged tissue, and (2) mitigating detraining and inducing training adaptations with a reduced training load. Key literature that explores the underlying mechanisms for these themes is presented, and considerations for practice and future research directions are outlined. For principle (1), passive intermittent hypoxic exposures might accelerate tissue healing through angiogenic and osteogenic mechanisms. Experimental evidence is largely derived from rodent research, so further work is warranted to establish whether clinically meaningful effects can be observed in humans, before optimal protocols are determined (duration, frequency, and hypoxic severity). Regarding principle (2), a hypoxia-related increase in the cardiometabolic stimulus imposed by low-load exercise is appealing for load-compromised athletes. As rehabilitation progresses, a variety of hypoxic modalities can be implemented to enhance adaptation to energy-systems and resistance-based training, and more efficiently return the athlete to competition readiness. While hypoxic modalities seem promising for accelerating musculoskeletal injury rehabilitation in humans, and are already being widely used in practice, a significant gap remains regarding their evidence-based application.

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Introduction

Hypoxic training modalities are typically used by athletes for acclimatisation purposes in preparation for events scheduled at moderate-high altitude (Chapman et al., 2016). Additionally, these modalities are recognised for inducing adaptations that can enhance sea-level exercise performance (Girard et al., 2020). Recently, hypoxia has garnered attention for its potential role in expediting the injury rehabilitation process in athletes, supported by two primary principles. Firstly, hypoxia may facilitate the healing of injured tissue (Santocildes et al., 2023; Zhang et al., 2021). Secondly, the detraining effects of an injury-induced reduction in training load could be mitigated – and retraining with reduced load subsequently enhanced – by performing exercise under hypoxic conditions (Girard, Matic Girard, et al., 2021). Together, these putative effects of hypoxic modalities suggest they have the potential to accelerate the return-to-play. However, the mechanisms underpinning the beneficial effects that hypoxia may have in injured athletes are not fully elucidated.

Therefore, the purpose of this narrative review is to explore potential mechanisms through which hypoxia could facilitate musculoskeletal injury rehabilitation, particularly concerning tissue healing with passive hypoxic exposure, and adaptation *via* reduced-load training under hypoxic conditions. Subsequent sections will address critical considerations around the already prevalent use of these techniques in practice, and suggest avenues for future research to help to connect the theoretical and the applied settings.

Hypoxia

Environmental hypoxia arises from either exposure to terrestrial altitude or the simulation of high-altitude conditions. Reductions in the partial pressure of inspired oxygen (PiO_2) are brought about by lower barometric pressure, or manipulations in the fraction of inspired air comprising oxygen (FiO_2), respectively. Alternatively, localised hypoxia can be induced by occluding blood flow to target tissue, inducing a specific peripheral stimulus rather than having a systemic effect. In turn, hypoxic techniques can vary based on application level (i.e., local vs. systemic), as well as mode (i.e., active or passive) and exposure duration (i.e., acute, intermittent or chronic) (Girard, Brocherie, et al., 2020).

Reducing oxygen levels in arterial blood, by environmental manipulation of PiO_2, stabilises hypoxia-inducible factor 1-alpha (HIF1-α), a transcription factor regulating the coordinated cellular response to hypoxia (Semenza, 2000). This upregulates the transcription of genes implicated in oxygen delivery, including central haematological adaptations induced by chronic hypoxic exposure (Hauser et al., 2017), and further downstream effects of HIF1-α expression which may aid in tissue repair (Kallio, 1998). These putative molecular effects of

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hypoxic exposure may therefore be of interest with regards to healing mechanisms after an injury has occurred.

Regarding functional responses, a hypoxia-induced decrease in arterial oxygen content prompts acute relative increases in ventilation and heart rate during fixed submaximal absolute exercise intensities (Sheel et al., 2010; Siebenmann et al., 2015). Metabolic adjustments at the muscular level also lead to greater reliance on carbohydrates as a fuel source (Brooks et al., 1991; Goda & Kanai, 2012), reflecting a shift towards anaerobic metabolism due to low oxygen levels. These hypoxic effects collectively accentuate exercise-induced physiological strain, a principle which also extends to resistance training responses (Feriche et al., 2017). Hence, hypoxia has the potential to elicit a higher physiological stimulus with reduced mechanical load, offering valuable modalities for load-compromised individuals, such as athletes during injury rehabilitation (Girard, Matic Girard, et al., 2020).

Injury

Injury incidence and implications

Elite athletes often undertake heavy training loads and saturated competition schedules, which can lead to injury. Serious injuries, reinjuries and the fear of reinjury can all impede an athlete's return to their previous performance levels and may prematurely end their sporting careers (Kvist et al., 2005). Typical injury incidence rates in individual sports range from ~1.8 (Lundberg Zachrisson et al., 2020) to ~5.2 (Richardson et al., 2017) per 1000 h of training, while team-sport athletes sustain more frequent injuries; between 6.3 and 17.1 per 1000 h (Richardson et al., 2017). A 52-week prospective cohort study involving 284 elite adolescent athletes revealed that 91.6% of participants self-reported an injury across the one-year period, with over one fifth of injuries resulting in a minimum two-month absence from full training (von Rosen et al., 2018). Prolonged rehabilitation durations can exacerbate the social and psychological impacts of injuries (Toale et al., 2021), while elevated stress levels can independently impact the healing process (Gouin & Kiecolt-Glaser, 2011). The rate and extent of deconditioning as a result of injury depends on training status and begins after a few days of inactivity (Mujika & Padilla, 2000a). Intuitively, the more prolonged the de-loading period, the more difficult it becomes for an athlete to return to their competitive performance levels. Furthermore, time-loss injuries are consistently negatively associated with performance across various team sports (Eliakim et al., 2020; Hägglund et al., 2013; Williams et al., 2016), with estimates suggesting that such decrements cost English Premier League teams approximately £45 m per season (Eliakim et al., 2020). Taken together, these statistics highlight the value of effective interventions in enhancing the injury rehabilitation process, facilitating recovery and minimising time away from training and competition.

Healing processes

To contextualise the potential effects of hypoxia against healing mechanisms, we offer concise summaries of the processes occurring at the sites of injury. These summaries are derived from comprehensive reviews of general healing mechanisms (DeFrates et al., 2021), as well as tissue-specific healing processes in bone (Marsell & Einhorn, 2011), ligament (Kelc et al., 2013), tendon (Darrieutort-Laffite et al., 2024) and muscle (Laumonier & Menetrey, 2016) tissue. The interested reader is directed to these articles for more complete discussions of these processes. Importantly, these summaries concern typical mechanisms occurring in response to traumatic injuries, and the extent and nuance of the processes are likely dependent on the injury aetiology and severity. Nonetheless, these summaries provide a general overview within which the relevance of hypoxic modalities may be appreciated.

The healing process in mammals generally consists of three overlapping phases; inflammation, new tissue formation, and remodelling. Each phase may be influenced by oxygen status, which supports such processes as infection prevention, cell proliferation, collagen synthesis, and tissue reorganization (DeFrates et al., 2021). Immediately after an injury, blood flow disruption from vessel damage creates a local hypoxic environment (Knighton et al., 1981), stabilising HIF-1α and activating proinflammatory cytokines (R. Li et al., 2023). The phase of new tissue formation is underpinned primarily by fibroblast activity, which promotes the formation of an extracellular collagen-rich matrix, and increases vascular endothelial growth factor (VEGF) activity, a protein acting downstream of HIF-1α to promote angiogenesis (Cialdai et al., 2022). The remodelling phase, which may span for many years, constitutes the replacement of tissue within the extracellular matrix. This phase is also largely orchestrated by fibroblast activity which, if poorly regulated, may lead to a state of fibrosis in which the recovery of the biomechanical properties of the tissue is impaired (Lieber & Ward, 2013).

Regarding bone specifically, a fracture induces blood-vessel injury which causes a local haematoma persisting for up to six days. White blood cells release cytokines to regulate early healing stages and promote differentiation of mesenchymal stem cells (MSCs) towards osteogenesis. Fibroblasts form granulation tissue around the fracture, while bony tissue degenerates and is resorbed by osteoclasts. The subsequent phase of new tissue formation is characterised by the formation of a fibrocartilaginous callus, initially soft due to a lack of calcium but stiffening through mineralisation. Within the fracture site, where blood flow is relatively limited, MSCs differentiate into chondroblasts to form cartilage. Meanwhile, distal MSCs differentiate into osteoblasts and begin to form woven bone. The callus and woven bone are then replaced by lamellar bone, and the subsequent remodelling phase consists of bone-cell turnover until the tissue regenerates to reflect pre-injury shape and strength.

Similar to bone healing, local blood-vessel injury in ligament injury forms a clot, initiating cytokine release for debris clearance, collagen production and fibroblast recruitment. Fibroblast proliferation and extracellular matrix production follow, alongside *de novo* angiogenesis. Together, these processes work to expand the extracellular matrix, provide the site with extrinsic cells, nutrients and growth factors, and begin to clear scar tissue. During the remodelling phase, type III collagen is gradually replaced with stronger type I collagen. Vascularity (and therefore cellularity) is reduced,

and the collagen fibres begin to align in the direction of mechanical loading. While the vascularity and collagen composition of the healed tissue closely resembles the pre-injury state, the collagen diameter and cross-linking frequently remain inferior.

The inflammatory phase of damaged tendon tissue involves the formation of a fibrin clot, together with neutrophil and macrophage migration in response to the local inflammatory signal. Tenocytes then synthesise collagen to produce the extracellular matrix, a process underpinned by transcription factors notably including scleraxis (He et al., 2022). The remodelling phase in tendon is largely orchestrated by growth factors which, similarly to ligament healing, is characterised by the gradual increase in type I collagen content and density in place of type III collagen tissue (Molloy et al., 2003).

Upon injury, muscle fibres undergo necrosis triggered by disruption of local homoeostasis and an influx of calcium. This initiates the degeneration/inflammation phase, characterised by the infiltration of neutrophils, which secrete pro-inflammatory molecules to create a conducive environment for subsequent repair processes. Macrophages then remove cellular debris and promote myoblast proliferation. The subsequent tissue formation phase begins when satellite cells become activated and proliferate, generating myoblasts which differentiate into new muscle fibres. In the remodelling phase, the maturation of these muscle fibres occurs alongside the formation of scar tissue to stabilise the injury site. Angiogenesis, driven by growth factors, promotes the restoration of blood supply to the injured muscle. The innervation of regenerated muscle fibres completes the healing process, ensuring functional recovery.

Hypoxic modalities for injury healing

Bone and ligament tissue

Hypoxia *per se* may facilitate the processes underpinning bone and ligament healing. For example, pharmacological and genetic activation of the HIF1-α pathway were found to promote *in vivo* blood vessel formation and greater woven bone density 38 days after surgically induced bone fracture in rodents (Wan et al., 2008). Inhibition of VEGF abolished the blood vessel growth and osteogenesis induced by HIF1-α (Wan et al., 2008). These findings highlight the critical roles of HIF1-α and VEGF in bone fracture angiogenesis, and show that sufficient artificial activation of these pathways to facilitate bone repair is possible in rodents. Regarding connective tissue injuries, HIF1-α upregulation in human cruciate-ligament fibroblast cultures induced significant increases in VEGF messenger ribonucleic acid (mRNA) expression and concentration (Wang et al., 2012), indicating enhanced VEGF protein activity. Concurrently, a hypoxic environment is considered essential to the healing of connective tissue due to the chondrogenic and angiogenic pathways regulated by HIF1-α (Zhao et al., 2011). This is in-part due to connective tissue inherently being a site of limited blood supply which is exacerbated by injury. Nonetheless, hypoxia *per se* is purported to promote reconstruction (Zhao et al., 2011), providing a clear link to the inflammation and new tissue formation stages presented above.

Bone morphogenetic proteins (BMPs), crucial cytokines in skeletal development, are also pertinent to fracture healing (Lissenberg-Thunnissen et al., 2011). Specifically, the isoform BMP-2 is essential for chondrocyte differentiation and proliferation, and is fundamentally necessary for the initiation of healing mechanisms (Tsuji et al., 2006). The independent and combined stimulation of microvascular endothelial cells with hypoxia and VEGF *in vitro* induces up to a four-fold increase in BMP-2 mRNA expression for up to 24 h (Bouletreau et al., 2002). Cell culture work has also demonstrated the *in vitro* role of hypoxia in the proliferation and preferential differentiation of MSCs towards osteogenesis (J. Huang et al., 2011; Wagegg et al., 2012). These findings are however not consistent across studies, caveated for example by data from M. Camacho-Cardenosa et al. (2020), who revealed that cyclic hypoxic exposure of MSCs *in vitro* delayed their differentiation into adipocytes and osteoblasts, reducing lipid-droplet formation and cell mineralisation, respectively. The longer the duration of the hypoxic stimulus within the cyclic exposure protocol, the greater the delay on MSC differentiation into both cell types, suggesting that responses are highly sensitive to exposure duration, frequency, and dose.

Interestingly, multiple *in vivo* studies from varying perspectives support the notion that hypoxic exposure can enhance bone metabolic processes. For example, rats subjected to chronic hypobaric hypoxia for three weeks showed almost 15-fold increases in MSC mobilisation relative to a control group (Rochefort et al., 2006). Similarly, the *in vitro* study by M. Camacho-Cardenosa et al. (2020) was accompanied by an *in vivo* investigation in humans, through which a moderate cyclic hypoxic exposure protocol administered in older adults (>75 y) increased bone mineral density significantly relative to the control participants. While these changes in bone mineral density were not observed by Timon and colleagues (2022), fundamental markers of bone metabolism were modulated towards bone formation after a similar moderate cyclic hypoxic protocol administered across 24 weeks in older adults (68 to 75 y). It therefore appears possible that the remodelling phase of bone tissue repair may be facilitated by cyclic exposures to moderate hypoxia.

While some mechanistic research appears to support the notion that hypoxia could facilitate healing mechanisms, it is important to consider that vascular disruption induced by injury itself causes a local hypoxic environment (Lu et al., 2008). The degree to which environmental hypoxia can further decrease oxygen levels at the injury site, and the subsequent effects on healing, is as yet untested in humans. It could be speculated that the extent of vascular disruption, particularly relative to pre-injury vascular supply, could mediate this effect. Moreover, it is important to consider whether the revascularisation that occurs naturally as part of the healing process impacts the potential effectiveness of environmentally induced hypoxia. Indeed, chronic environmental hypoxia has been found to inhibit fracture healing in dogs (Heppenstall et al., 1976), while supplemental oxygen treatment appears to enhance osteoblast proliferation,

angiogenesis, and fracture healing in rodents (Kawada et al., 2013; Rocha et al., 2015). In addition, a study conducted in injured athletes indirectly demonstrated the potential use of hyperbaric hyperoxia for healing purposes, by indicating an exposure of this type to decrease levels of creatine kinase and myoglobin in blood serum (C.-Y. Chen et al., 2019). However, further human studies are necessary to substantiate the use of this technique (Moghadam et al., 2020). In any case, it appears that bone healing mechanisms are sensitive to changes in environmental PiO_2, but the extent to which these variations can elicit beneficial or detrimental effects has not been thoroughly investigated. On balance, it appears that chronic environmental hypoxia impairs the initial healing process, whereas intermittent resting hypoxic exposures, potentially interspersed with hyperoxia (Behrendt et al., 2022), could facilitate repair. In line with this hypothesis, an intermittent hypoxic protocol consisting of daily 6 h exposures to hypobaric hypoxia at 5000 m, was recently found to enhance fracture healing and associated biomarkers across an 8-week intervention in rats (Zhang et al., 2021). Specifically, the chronic intermittent hypobaric hypoxia group demonstrated increased levels of HIF1-α and VEGF expression, and enhanced bone mass and strength throughout the intervention, relative to a normoxic control group. Considering that this duration and severity of hypoxic exposure could induce acute mountain sickness in humans (Cobb et al., 2021), it would be of interest to assess the effect of shorter milder intermittent passive hypoxia, or indeed very short periods of severe hypoxia, potentially interspersed with hyperoxic periods, on angiogenic, osteogenic and body composition markers in humans.

Tendon tissue

Research indicated that both *in vivo* and *in vitro* hypoxic conditions enhance MSC differentiation into tenocytes, suggesting a potential role of hypoxia also in tendon repair (T.-F. Huang et al., 2013). Hypoxia notably promotes tenogenic differentiation of adipose-derived MSCs and bone marrow stem cells (G. Chen et al., 2020) as well as significantly increasing scleraxis gene expression (Yu et al., 2016). Potential interactions between *in vitro* hypoxic conditions and fundamental tendon-related growth factors have also been established and discussed (Zulkifli et al., 2023). Together, these processes likely facilitate the development of the extracellular matrix during the new tissue formation and subsequent remodelling stages. Whether sufficient modulation of tissue hypoxia *in vivo* is possible with safe doses of inspired hypoxic gas has not yet been investigated, with only pharmacological manipulation of local HIF-1α activity so far proposed as a therapeutic method of mimicking hypoxic conditions to facilitate tendon repair (Zulkifli et al., 2023).

Muscle tissue

Evidence suggests that hypoxia could influence the healing of muscle tissue through the modulation of satellite cell activity. *In vitro* evidence on the effects of chronic hypoxia on the proliferation and differentiation of satellite cells suggest fine margins in the potential for benefits or detriments. In particular, cell culture at O_2 levels ranging from 3–6% O_2 may enhance myogenic differentiation, relative to conditions near 20% O_2, whereas severe reductions in O_2 levels to <1% tend to inhibit beneficial responses (Chaillou & Lanner, 2016). Critically, this 3–6% O_2 may in fact reflect normoxic conditions for *in vivo* muscle tissue (Gnaiger, 1991), and it may therefore be more appropriate to consider this claim as evidence against the implementation of hyperoxic treatment, rather than for the implementation of hypoxic treatment, at least based on current evidence and specifically in relation to satellite cell mobilisation. A further line of evidence demonstrated that chronic hypoxic exposure post-injury in rodents disrupted the formation and growth of new muscle fibres across 7 days; effects that were underpinned by reduced mTOR signalling and increased markers muscle atrophy (Chaillou et al., 2014). Interestingly, however, by day 28, differences between groups had been abolished. This implies a hypoxia-induced delay in healing, rather than prevention, and the potential existence of compensatory acceleration beyond the inflammatory phase and into the phases of new tissue formation and remodelling. In any case, it certainly appears that chronic hypoxia impairs the skeletal muscle healing process, at least acutely after the injury. Prolonged hypoxic exposures are therefore not advisable based on current experimental evidence.

While chronic hypoxia may prove detrimental, intermittent hypoxic protocols may in fact be promising in the context of injury healing. Santocildes et al. (2023) recently performed a study in which they surgically induced gastrocnemius injuries in rodents, designed to mimic the anatomical and degeneration/regeneration characteristics of grade I-II skeletal muscle injuries in humans. Rats were subsequently randomised to various conditions, to investigate whether intermittent hypobaric hypoxic exposure, equivalent to 4500 m of simulated altitude for 4 h per day, could facilitate muscle regeneration at 9- and 21-days post-injury. After 21 days, the control group still maintained lower peak force and tetanic force in the injured leg relative to the non-injured leg. Conversely, in the intermittent hypobaric hypoxia group, these functional parameters had already recovered after only 9 days. Histological analyses revealed that the presence of fibres with developmental myosin heavy chain, and collagen deposition at the injury site, were both reduced after 9 days in the hypoxia group to similar values observed after 21 days in the control group. Reduced collagen deposition is indicative of a lesser degree of fibrosis, which is known to have a considerable impact on the biomechanical properties of muscle (Lieber & Ward, 2013). Taken together, these observations indicate that newly formed myofibers were developing more rapidly, and collagen deposition was better regulated, in the group of rats subjected to daily hypoxic exposure compared to the control group. Assessments of molecular pathways revealed an overexpression of AMPKα in the intermittent hypoxia-treated animals after the injury, which may have initiated the molecular cascade required to enhance these

healing responses. Indeed, as a result of these data, the use of hypoxic modalities for muscle injury rehabilitation was discussed (Kambič & Burtscher, 2024). Intermittent hypoxic exposures during the new tissue formation and remodelling phases of muscle tissue healing may be worthy of consideration within a rehabilitation protocol.

Hypoxic modalities for reduced-load training adaptations

Endurance exercise adaptation

Sufficient hypoxia-induced HIF1-α activation, and the associated benefits to oxygen uptake capacity, are believed to require a minimum exercise stimulus (Millet et al., 2016). Concurrently, several beneficial muscle morphological and vascular adaptations were observed in highly trained rats exposed to intermittent hypobaric hypoxia (equivalent to ~4000 m) followed by short bouts of low-load aerobic exercise across two weeks, relative to equally-highly-trained rats exposed to equivalent doses of intermittent hypoxia with no physical activity, and another equally trained group exposed to neither hypoxia nor accompanying exercise (Rizo-Roca et al., 2018). Given the relatively low-intensity exercise stimulus applied during the intervention (<50% maximal oxygen uptake), it is unlikely that a normoxic exercise condition could have elicited comparable effects to those observed in the hypoxic exercise group. It is thus reasonable to hypothesise that 4 h exposures to hypobaric hypoxia followed by very-low-load exercise could enhance oxidative capacity compared to an equivalent absolute exercise intensity in normoxia. In another study, ten healthy but inactive male adults completed a four-week training intervention, with one leg exercising in normoxia and the other exercising in hypobaric hypoxia equivalent to 2300 m (Terrados et al., 1990). Participants exercised each leg 3–4 times per week for 30 min at 65% of the respective single-leg maximal aerobic power in normoxia, and the exercise intensity was progressively increased in proportion to performance improvements. The authors observed no differences in muscle fibre type or capillarisation, but found significant increases in mitochondrial enzyme activity and myoglobin concentrations in the leg training under hypoxic conditions only. Moreover, baseline time to fatigue was 28 ± 10 min, whereas post-intervention this had increased to 97 ± 27 min and 117 ± 40 min for the control and the hypoxically trained legs respectively. The considerable increases also observed in the control leg demonstrate either central adaptations to the intervention, remote conditioning induced by cross-education (Lee & Carroll, 2007), or a combination of the two. Given, however, that both legs were trained at the same intensity for the same period of time across the intervention, the apparent differences in oxidative capacity and exercise capacity suggest a beneficial effect of (hypobaric) hypoxic exercise training in this context.

Hypoxia can also be combined with other rehabilitation training strategies aimed to reduce mechanical load in an attempt to maintain a similar physiological stimulus, such as antigravity treadmill training (Vincent et al., 2022). Under a similar principle, enhanced metabolic solicitation is possible when low-intensity exercise is performed in hypoxia, and this appears to also apply at increased workloads. Indeed, when performing hypoxic (0.12 FiO_2) incremental exercise tests, heart rate and cardiac output were significantly higher across all workloads compared to normoxia in nine healthy male lowlanders (Siebenmann et al., 2015). In a study by Vogt et al. (2001), participants trained at either high (4–6 mmol·L^{-1} blood lactate concentration) or low (2–3 mmol·L^{-1} blood lactate concentration) intensity, and in either normobaric hypoxia (0.129 FiO_2) or normoxia, five times per week for six weeks. To achieve the desired training intensity, the hypoxic groups exercised at 54% and 43% of maximal power output (W_{max}), whereas those in normoxia exercised at 67% and 58% W_{max}. Similar increases in maximal oxygen uptake and W_{max} were observed in all groups. However, elevated levels of HIF1-α mRNA were seen after hypoxic training only, along with downstream targets including VEGF and myoglobin. This indicated a greater capacity to transport and utilise oxygen, despite the lower absolute exercise intensity in hypoxia, suggesting that compensatory adaptations were induced to offset the reduced mechanical stimulus induced by the lower absolute load. Thus, when mechanical load is restricted, it is possible to increase metabolic solicitation and advance markers of aerobic fitness through the addition of a hypoxic stimulus. By extension, hypoxia can therefore be used to induce an internal workload, which would otherwise require a higher external workload under normoxic conditions. Quantitative evidence for this notion was recently provided by S. N. Li et al. (2023), who demonstrated responses to heart-rate clamped cycling exercise between 2500 m and 3500 m of simulated altitude to remain consistent, despite stepwise reductions in power output in line with concomitant FiO_2 reductions. Enhanced exercise-induced adaptations, to the cardiovascular system in particular, may therefore be possible with reduced-load training under hypoxic conditions.

An assessment of the effects of exercise training in hypoxia compared to normoxia requires careful consideration of exercise prescription, from both a scientific perspective and when generalising results to specific contexts. Indeed, a large proportion of studies investigating the effects of hypoxic (relative to normoxic) exercise demonstrate no benefits of hypoxia for exercise performance, or in any physiological capacity (Debevec et al., 2010; Roels et al., 2005, 2007; Truijens et al., 2003; Ventura et al., 2003). However, these findings can largely be attributed to the fact that exercise is typically prescribed relative to condition-specific exercise capacity, so the absolute exercise intensity is lower in hypoxia. As a result, the *cardiometabolic* load imposed by each condition is comparable, while the *mechanical* load is lower with hypoxia. Given that each of these studies showed that the reduced *mechanical* load in hypoxia did not impair any training adaptations, it is reasonable to speculate that an equivalent *mechanical* load in hypoxia (and thus an increased *cardiometabolic* load) would enhance training adaptation. Some evidence for this was provided in the aforementioned study by Vogt et al. (2001), in which their "hypoxic high-intensity" group demonstrated greater HIF1-α-related molecular training adaptations compared to their "normoxic low-intensity" group, despite approximately equivalent *mechanical* load. Additional evidence also exists at higher exercise intensities, through the observation that repeated sprint training appears to elicit greater improvements in repeated-

sprint performance when conducted in hypoxia compared to normoxia (maximal absolute exercise in both cases) (Brocherie et al., 2017). Ultimately, as athletes are limited in their ability to *mechanically* load the musculoskeletal system during injury rehabilitation, it is a direct comparison of equivalent *mechanical* load that is of interest in this context. Therefore, further research is required to compare the training effects of low-load hypoxic and normoxic exercise interventions in injured athletes whilst matching for absolute exercise intensity, thus reflecting *mechanical* load limitations.

Another strategy to accelerate cardiovascular reconditioning during late-stage injury rehabilitation is the potential for chronic passive hypoxic exposures to induce haematological adaptations. Injury-induced detraining is associated with a haemoglobin mass decrease of around 2–3% depending on the timeframe, the individual, the nature of their sport and their injury characteristics (Gough et al., 2013); 15–20% decreases have been observed in more extreme cases (Gough et al., 2013; Schumacher et al., 2008). Chronic passive hypoxic exposures, where athletes live under hypoxic conditions, upregulate red blood cell production by stimulating erythropoietin release from the kidneys (Levine & Stray-Gundersen, 1997). In addition, "live-high" paradigms are also believed to enhance oxidative enzyme activity, mitochondrial biogenesis, angiogenesis and fatty acid oxidation (Bailey & Davies, 1997), all pertinent to endurance performance at sea-level, and to inactivity-induced endurance-related detraining (Mujika & Padilla, 2000b). Altitude camps are thus frequently completed by athletes and, assuming considerations regarding dose, iron status and illness are addressed (Constantini et al., 2017), interventions are likely to induce haematological benefits. However, given the potential detrimental effects of chronic hypoxic exposure on initial healing mechanisms, injured athletes should be assessed on a case-by-case basis before partaking in such "live-high" protocols. More specifically, the athletes should be screened to determine their healing progression, and be exposed to chronic hypoxia only if the injured tissue shows adequate signs of recovery, and the potential for haematological benefits is deemed to outweigh the risk of mitigated healing processes.

Repeated sprint-related exercise ability

As injury rehabilitation progresses, mechanical loading of the musculoskeletal system can be gradually increased, providing more scope for hypoxic modalities to be applied. This is particularly relevant to athletes from team, racquet and other intermittent sports, as it is often necessary for them to return to intermittent maximal exercise conditioning as soon as possible. As these sports are typically characterised by short, all-out sprints, interspersed with incomplete recoveries, repeated-sprint training could be appropriate to improve sport-specific conditioning for these athletes (Bishop et al., 2011; Girard et al., 2011). Two studies conducted in elite rugby union players observed that just four sessions of repeated-sprint training in hypoxia across two weeks significantly improved repeated-sprint ability relative to baseline, and relative to a normoxic control group (Beard, Ashby, Chambers, et al., 2019; Beard, Ashby, Kilgallon, et al., 2019). Similar evidence was provided by Mckee et al. (2024), who found repeated-sprint training with blood-flow restriction (local hypoxia) to induced similar improvements in repeated-sprint ability to a control group who worked at a higher external load during the intervention. Hypoxia-related improvements have been attributed to an upregulation of HIF1-α and its downstream targets, the compensatory vasodilation following hypoxic exposure (Faiss et al., 2013), and a higher proportional delivery of oxygen to fast-twitch muscle fibres (Brocherie et al., 2017). The enhanced blood flow to, and oxygen extraction by, exercised muscles induced by these effects, is hypothesised to accentuate training adaptations. Separate to the physiological adaptations that may be induced by such training methods, repeated-sprint training in hypoxia has also been shown to enhance subjective effort perception relative to similar repeated-sprint workloads in normoxia (Álvarez-Herms et al., 2016). Enhanced effort perception of this type may help athletes to recover their ability to tolerate exercise-associated discomfort in late-stage rehabilitation. Thus, repeated-sprint training in hypoxia, or with blood-flow restriction, could prove beneficial for team sport athletes who are aiming to return to competition fitness.

Resistance exercise adaptation

Local hypoxia within the muscle augments the strength and cross-sectional area increases induced by resistance training (Feriche et al., 2017). Exacerbating local hypoxia *via* blood-flow restriction proximal to the exercising muscle(s) is therefore a popular modality to enhance the effect of low-load resistance training (Girard, Brocherie, et al., 2020). Indeed, this approach is generally accepted amongst practitioners and researchers to induce substantial muscular adaptations despite the reduced mechanical load under which the joints and muscle are working (Scott et al., 2023). Systemic hypoxaemia through resistance training in hypoxia has received less widespread attention, despite promising results in the literature (Scott et al., 2014). For example, very-low-load resistance training (20% 1RM) to task failure in hypoxia three times per week for five weeks elicited greater improvements in peak power, muscular endurance and lower-limb muscle cross-sectional area than load-matched normoxic training in well-trained female netball players (Manimmanakorn et al., 2013). Importantly, and pertinent to the context of injury healing, hypoxic resistance training does not appear to impair bone mineral density or affect markers of bone metabolism in healthy individuals (Honda et al., 2020). In fact, resistance training in hypoxia might actually preferentially modulate bone metabolism (A. Camacho-Cardenosa et al., 2022). Whether this is the case in individuals recovering from an injury has not been directly investigated. However, appropriately implemented resistance training in hypoxia might mitigate age-induced sarcopenia (Jung et al., 2021), an effect which may translate to alleviate the sarcopenia induced by a reduced training load in injured athletes.

The favourable metabolic milieu induced by resistance training in hypoxia persists at higher training loads, and elicits greater and faster improvements in muscle strength and size, perhaps due to improved neuromuscular adaptations which do not occur at very low loads. Participants who trained at 70% 1RM in hypoxia (0.16 FiO_2) achieved a similar improvement in arm flexor 1RM after three weeks, as a control group training in

normoxia achieved in six weeks (Nishimura et al., 2010), with no difference in their ratings of perceived exertion. Although the neural response to training was likely similar in both groups, hypoxic training elicited earlier hypertrophy which may have accounted for the faster improvement in muscle strength and size. In another study, Inness et al. (2016) observed significantly greater increases in resistance-trained participants who completed heavy resistance training (≥75% 1RM) in hypoxia (0.145 FiO_2) relative to those who completed the same training programme in normoxia. The precise mechanisms underpinning accelerated improvements in muscle strength and size with resistance training in hypoxia are currently unknown, but could be explained by acute hypoxia-induced satellite cell activation and proliferation (Beaudry et al., 2016; van Doorslaer de ten Ryen et al., 2021), greater exposure to blood lactate and serum growth hormone (Kon et al., 2012, 2021), or increased intramuscular angiogenesis (Kon et al., 2014, 2021). Figure 1 provides an overview of the putative mechanisms discussed in these sections through which hypoxic modalities may enhance tissue healing and reduced-load training adaption.

Practical considerations

As altitude training encompasses a range of techniques, it should be viewed not only as a single tool but as a versatile toolbox in itself. To meet certain goals the correct tool must be selected at the correct time. Therefore, the hypoxic training modality that is used may (and should) vary as injury rehabilitation progresses. In line with this view, this section provides some practical considerations in relation to the implementation of both passive and active hypoxic modalities during the rehabilitation process in injured athletes. A conceptual overview of the practical implementation of these strategies is presented in Figure 2.

Implementation of passive hypoxic modalities

Immediately after injury, if full limb immobilisation is necessary, the athlete may be restricted to passive hypoxic modalities. Based on current understanding of healing mechanisms, and the potential role of hypoxia, intermittent hypoxic exposure could be beneficial in this context. However, no human study has directly investigated the extent to which hypoxic exposures are sufficient in duration or severity of tissue hypoxia to activate healing-related pathways downstream of HIF1-α. Therefore, the collection of relevant empirical data precludes the provision of substantiated recommendations. That being said, research into optimal patterns of intermittent hypoxic exposures are emerging (Serebrovskaya et al., 2013; Tobin et al., 2022). While it is commonly accepted that these types of exposures do not enhance athletic performance (Bärtsch et al., 2008), a 70-min intermittent hypoxic session, where hypoxic exposures were applied to target 75% SpO_2, was shown to induce beneficial haematological effects relative to a continuous hypoxic protocol and a normoxic control (Tobin et al., 2022). Notably, as previously mentioned, hyperoxic exposures may also have a role in tissue repair, and in the recovery phases during cyclic intermittent hypoxic protocols (Behrendt et al., 2022). However, data from Dudnik et al. (2018) observed no beneficial haematological changes in an intermittent hypoxic protocol interspersed with hyperoxic recovery periods in cardiac patients, although improvements in cardiorespiratory fitness as a result of the intervention were noted. Moreover, from an injury prevention perspective, the implementation of a 60-minute intermittent hypoxic protocol ($FiO_2 = 0.10$) interspersed by periods

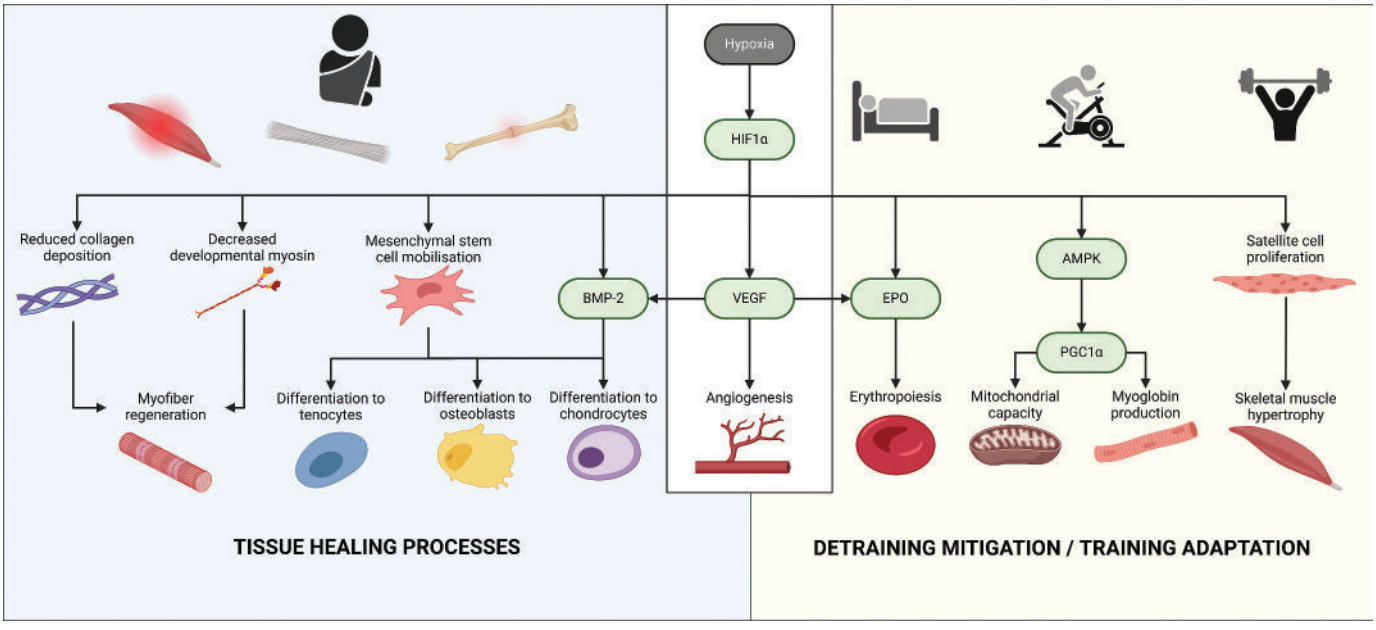

Figure 1. Schematic outline of some broad pathways through which hypoxia and/or HIF1α might facilitate healing mechanisms (blue) and enhance the adaptive response to reduced-load exercise (yellow) during the injury rehabilitation process. Created with BioRender.com. AMPK, 5′ adenosine monophosphate-activated protein kinase; BMP-2, bone morphogenetic protein-2; EPO, erythropoietin; HIF1α, hypoxia-inducible factor 1-alpha; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; VEGF, vascular endothelial growth factor.

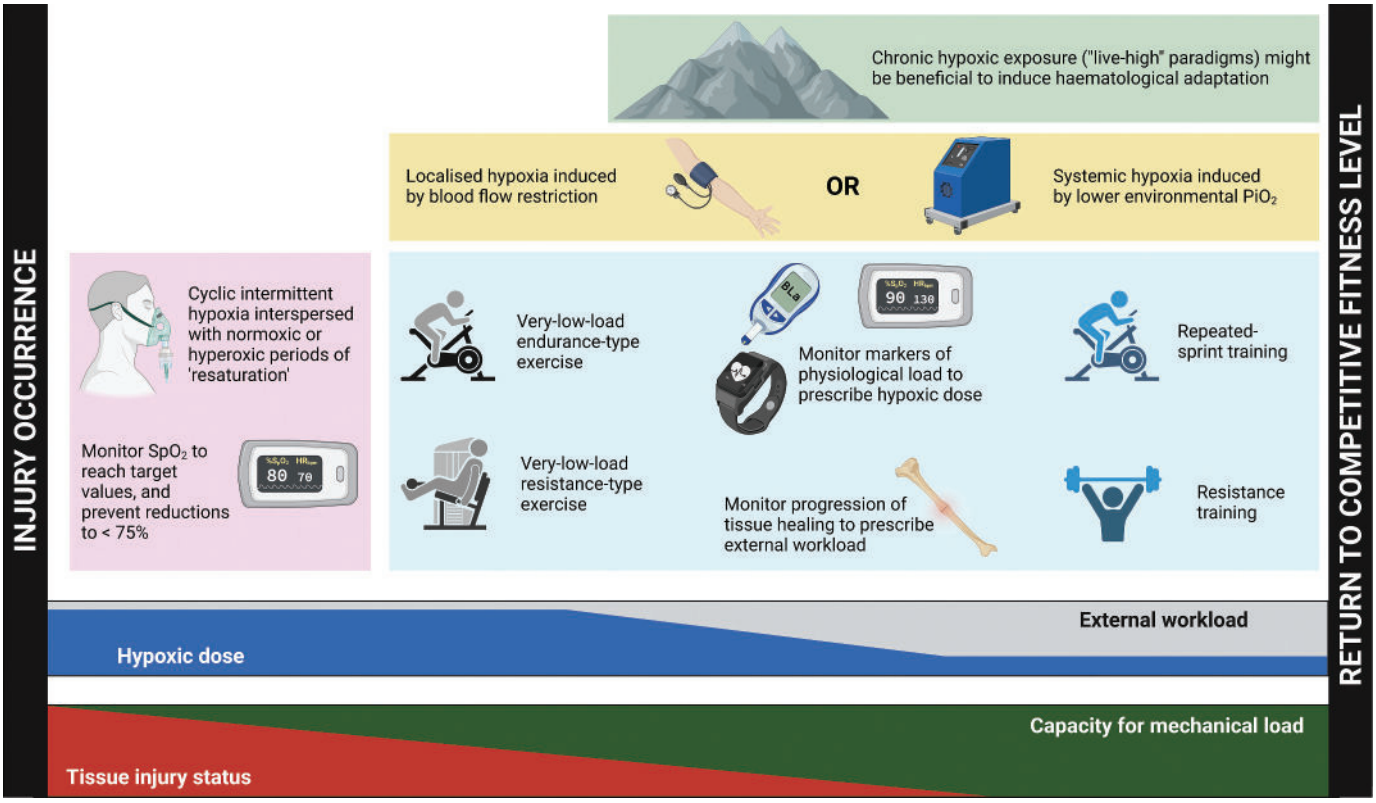

Figure 2. Schematic presentation of the potential application of hypoxic modalities throughout the injury rehabilitation process. Suggestions are conceptual only, and require further research for specific protocols to be developed. Created with BioRender.com. BLa, blood lactate concentration; HR, heart rate; PiO_2, environmental partial pressure of oxygen; SpO_2, pulse oxygen saturation.

of hyperoxia ($FiO_2 = 0.99$), mitigated the increase in muscle damage indicators (creatine kinase and myoglobin), as well as reducing perceived muscle soreness, after a subsequent resistance exercise training session (P. W. Chen et al., 2022). Crucially, none of these studies observed significant clinical symptoms as a result of the hypoxic exposures. Therefore, intermittent hypoxic exposure is unlikely to pose undue risk and appears safe if appropriately prescribed relative to SpO_2. The pursuit of an optimal "dose" in relation to intermittent hypoxia protocols is beyond the scope of this review, but has been expertly discussed elsewhere (Navarrete-Opazo & Mitchell, 2014). Lastly, chronic hypoxic exposure (e.g., Live-High Train-Low) was earlier highlighted as a method through which beneficial haematological adaptations could be passively induced. It is important, however, that the premature implementation of chronic hypoxia techniques in rehabilitating athletes could induce negative effects in relation to the damaged tissue.

Implementation of active hypoxic modalities

Complete immobilisation, followed by a sustained low training load, contributes to severe physiological deconditioning (Mujika & Padilla, 2001). The implementation of low-load exercise is of course important for rehabilitation, and this also allows for versatility in the application of hypoxic training modalities to mitigate detraining effects. When strategically introducing exercise under hypoxic conditions, it is recommended that systemic variables of metabolic strain such as heart rate and blood lactate concentration are monitored. In turn, the required training stimulus can be induced by manipulation of the hypoxic dose. Specifically, if heart rate and/or blood lactate concentration exceed the target range, the hypoxic dose may be reduced and the absolute exercise intensity can be left unchanged. When implementing higher hypoxic doses (<0.145 FiO_2), SpO_2 should be monitored to ensure that values do not decrease below 75%, a threshold below which unpleasant side effects might commonly occur (Hanning & Alexander-Williams, 1995). In this instance, the hypoxic dose should be alleviated to raise SpO_2. Notably, it may be beneficial for athletes from load-bearing sports whose injuries prevent them from performing sport-specific exercise to use alternative exercise modalities with hypoxia. It may then be possible to reflect the systemic physiological load of their primary sport by adjusting the hypoxic dose accordingly. Moreover, it may also be beneficial to consider the application of alternative environmental stressors such as cold (Santocildes et al., 2023) or heat stress (Ihsan et al., 2019), in isolation or together with hypoxia, to elicit specific physiological responses from which injured athletes may benefit during rehabilitation.

To mitigate muscle atrophy, resistance training can also be conducted with systemic or localised hypoxia. The variety of strength exercises and multi-joint movements that can be performed without the need to continuously (re-)apply an occlusion cuff suggests that resistance training in hypoxia may be more versatile. Conversely, the occlusive stimulus of blood flow restriction training could independently augment hypertrophy through mechanisms

related to cell swelling (Loenneke et al., 2012), so much lower training loads may be required. As such, muscular atrophy may initially be mitigated to a greater (and safer) extent with very-low-load blood flow restriction training. As the athlete becomes increasingly capable of tolerating higher mechanical loads, resistance training in hypoxia may become a more useful technique.

In general, incremental increases in mechanical load and concomitant reductions in hypoxic dose, alongside perceptual (pain) and anatomical (scan) assessment of injured tissue, may prove to be a useful indication of rehabilitation progression. Practitioners could prescribe hypoxic doses accordingly, to maintain a specified metabolic training stimulus which, over time, is increasingly induced by the absolute exercise intensity and less so by manipulation of PiO_2. Subsequent implementation of repeated-sprint training in hypoxia may then prove to be a useful tool for athletes whose sport demands align with such protocols.

Limitations

This narrative review has several limitations that should be acknowledged. Firstly, unlike a systematic review, this narrative review did not employ a rigorous, predefined search strategy. As a result, the selection of literature may be subject to selection bias and may not comprehensively cover all relevant studies on this topic. That being said, the current literature base on the use of hypoxia specifically for injured athletes is notably sparse, so the topic was approached from several perspectives, outlining multiple factors that may be relevant in the assessment of whether hypoxic modalities could be appropriate in this context. Consequently, much of the evidence presented in this review is indirect, often extrapolated from studies conducted in healthy humans, in rodents or in cells. This means that the application of these findings to injured athletes is currently not evidence based, and should therefore be interpreted and implemented with caution. In line with these limitations, we present some considerations and directions for future research in this area below.

Research considerations

Causal inference

This research field is a particularly challenging area of causal investigation. Firstly, to design an appropriate ecologically valid study, the sampling frame must be injured athletes with identical injury characteristics, and their participation would be required immediately post-injury if the aim is to investigate early rehabilitation phases. Secondly, many factors would likely contribute to the effectiveness of a rehabilitative intervention (Drole & Paravlic, 2022). These might include sociodemographic and injury characteristics, availability of further rehabilitation methods/facilities, psychological predisposition, and the social environment (Forsdyke et al., 2016). Given that an independent groups design would be necessary (a repeated measures crossover would require "identical re-injuries"), it may be challenging to balance confounding factors between the intervention and control groups. The type-II error rate associated with an inability to control for confounding variables is typically accounted for by an increased sample size to enhance statistical power (Batterham & Atkinson, 2005). However, the difficulty in recruiting injured athletes means an adequate sample size may be unattainable. Ultimately, it is clear why a lot of the current evidence for these techniques exists from cell and/or animal research, or is anecdotal and/or practitioner-lead. There are indeed currently few solutions to the challenge of identifying causal relationships pertinent to this field.

Research translation

Many research questions that cannot ethically or feasibly be conducted in humans, may instead be investigated in animal models. Often these studies are intended to reveal mechanisms that underpin observed effects, or predict whether an effect that is immeasurable in humans – at least with current technology – might nevertheless exist. Particularly pertinent to animal studies, beyond whether an effect observed in animals exists in humans, is the more complex question of how a specific hypoxic protocol might translate between species. For example, even if some arbitrary beneficial effect of hypoxia that is demonstrated in rats *could* be translated to humans, should the administered hypoxic dose be adapted in some way, to induce quantitatively similar outcomes? A comparative analysis of various mammals' responses to a fixed level of hypoxia indeed demonstrates inconsistencies in the magnitudes, and even the directions, of various physiological effects, such as the pattern of acute ventilatory and metabolic responses (Mortola et al., 1989). This is an equally important challenge when translating the results from single-cell studies to the whole-body, as the translation of the hypoxic stimulus to an integrated physiological model may not be equivalent (e.g., environmental vs. systemic vs. tissue hypoxia (Donnelly et al., 2022)). This could however itself form an interesting area of research, to facilitate our understanding of comparative research translation in the more general field of environmental hypoxia and mammalian physiology.

Research directions

Mechanistic research

Many of the preliminary findings from in cell and animal models need to be corroborated and, crucially, specific hypoxic dosing strategies must be investigated. Therefore, angiogenic and osteogenic pathways should be assessed at the molecular level in response to various doses of hypoxia (duration, frequency, severity), to more clearly establish the balance between beneficial and detrimental responses. In terms of detraining mitigation, animal models could also be used to simulate limb immobilisation in combination with considerable reductions in training load, to investigate some basic cellular and molecular outcomes with regards to detraining effects

such as muscle atrophy and markers of oxidative capacity alongside exercise capability. The greater our understanding of the basic physiology that underlies the responses to the proposed hypoxic techniques, the more valid our judgement on whether these techniques may benefit injured athletes. Ultimately, however, mechanistic observations at the molecular level must be tested at the systems level to appropriately formulate applied recommendations.

Human research

Despite the clear utility of animal and cell research to enhance our understanding, it is clear that human research specifically pertaining to the use of hypoxia during injury rehabilitation is warranted. Here, two approaches are proposed: (1) extrapolate from human participants who do not perfectly represent the target population of injured athletes, (2) accumulate ecologically valid case studies.

Regarding (1), it is certainly feasible for some mechanistic outcomes to be investigated in healthy, recreationally active individuals, as there are cases in which these may indeed be extrapolated to injured athletes. Therefore, certain tightly controlled efficacy studies could be conducted in a more readily available sample, assuming the associated considerations around translation are acknowledged. For example, a direct investigation of various passive intermittent hypoxic protocols on HIF1-α and VEGF protein expression, alongside bone-related factors such as osteogenic markers and bone mineral density, is necessary to establish the potential for passive hypoxia to be effective during the acute inflammatory phase. Healthy recreationally-active individuals could also be recruited to assess the training effect of very-low-load exercise in hypoxia and normoxia, to further assess the potential for cardiometabolic solicitation with a limited absolute exercise intensity. On the other hand, this type of research would not provide direct evidence of whether these protocols accelerate healing and/or mitigate detraining in a clinically meaningful way. As such, effectiveness research should be confined to injured athletes, as the real-world benefits of these strategies can only be determined in the environment in which they are to be used. Thus, suggestion (2) is to accumulate case study data from practitioners who are already applying these techniques where athletes and their support staff team feel they are justified. Indeed, this topic seems to be an example of a practitioner-lead area, where the field is implementing strategies which are yet to meticulously tested in a scientific context. While case studies are far from appropriately statistically powered randomised controlled trials, and should therefore be interpreted with caution, they may be the highest level of ecologically valid evidence available. As such, an accumulation of these types of cases might reveal certain considerations around their potential effectiveness, helping to guide future research and practice beyond the theory on which it is currently, to a large extent, founded.

Conclusions

Several well-controlled mechanistic studies elude to a possible beneficial effect of hypoxia on tissue healing mechanisms through downstream effects of HIF1-α stabilisation. Moreover, the theoretical premise of inducing a greater cardiovascular strain with reduced mechanical load implies that certain hypoxic techniques could facilitate adaptations to reduced-load training during rehabilitation. However, current evidence regarding the utility of hypoxia during injury rehabilitation in athletes is largely indirect or inconclusive. Thus, the practical considerations presented in this narrative review are intended as an initial reference point for practitioners. Moreover, the research-related considerations may act as a premise from which future investigations can be conducted to consolidate and develop practical strategies. Ultimately, an injury rehabilitation programme containing appropriately tailored hypoxic modalities could represent an innovative method of accelerating athlete rehabilitation.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Disclosure statement

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Author contributions

Author contributions to this review article are as follows: conception, BJN and JFPB; literature search, BJN, KD and JFBP; drafting and revising, BJN, KD, JFPB, PSRG and TD. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

References

Álvarez-Herms, J., Julià-Sánchez, S., Gatterer, H., Blank, C., Corbi, F., Pagès, T., Burtscher, M., & Viscor, G. (2016). Anaerobic training in hypoxia: A new approach to stimulate the rating of effort perception. *Physiology & Behavior*, *163*, 37–42. https://doi.org/10.1016/j.physbeh.2016.04.035

Bailey, D. M., & Davies, B. (1997). Physiological implications of altitude training for endurance performance at sea level: A review. *British Journal of Sports Medicine*, *31*(3), 183–190. https://doi.org/10.1136/bjsm.31.3.183

Bärtsch, P., Dehnert, C., Friedmann-Bette, B., & Tadibi, V. (2008). Intermittent hypoxia at rest for improvement of athletic performance. *Scandinavian*

Journal of Medicine & Science in Sports, *Suppl 18*(s1), 50–56. https://doi.org/10.1111/j.1600-0838.2008.00832.x

Batterham, A. M., & Atkinson, G. (2005). How big does my sample need to be? A primer on the murky world of sample size estimation. *Physical Therapy in Sport*, *6*(3), 153–163. https://doi.org/10.1016/j.ptsp.2005.05.004

Beard, A., Ashby, J., Chambers, R., Brocherie, F., & Millet, G. P. (2019). Repeated-sprint training in hypoxia in international rugby union players. *International Journal of Sports Physiology & Performance*, *14*(6), 850–854. https://doi.org/10.1123/ijspp.2018-0170

Beard, A., Ashby, J., Kilgallon, M., Brocherie, F., & Millet, G. P. (2019). Upper-body repeated-sprint training in hypoxia in international rugby union players. *European Journal of Sport Science*, *19*(9), 1175–1183. https://doi.org/10.1080/17461391.2019.1587521

Beaudry, M., Hidalgo, M., Launay, T., Bello, V., & Darribère, T. (2016). Regulation of myogenesis by environmental hypoxia. *Journal of Cell Science*, *129*(15), 2887–2896. https://doi.org/10.1242/jcs.188904

Behrendt, T., Bielitzki, R., Behrens, M., Herold, F., & Schega, L. (2022). Effects of intermittent hypoxia–hyperoxia on performance- and health-related outcomes in humans: A systematic review. *Sports Medicine - Open*, *8*(1), 70. https://doi.org/10.1186/s40798-022-00450-x

Bishop, D., Girard, O., & Mendez-Villanueva, A. (2011). Repeated-sprint ability — part II: Recommendations for training. *Sports Medicine*, *41*(9), 741–756. https://doi.org/10.2165/11590560-000000000-00000

Bouletreau, P. J., Warren, S. M., Spector, J. A., Peled, Z. M., Gerrets, R. P., Greenwald, J. A., & Longaker, M. T. (2002). Hypoxia and VEGF up-regulate BMP-2 mRNA and protein expression in microvascular endothelial cells: Implications for fracture healing. *Plastic and Reconstructive Surgery*, *109*(7), 2384–2397. https://doi.org/10.1097/00006534-200206000-00033

Brocherie, F., Girard, O., Faiss, R., & Millet, G. P. (2017). Effects of repeated-sprint training in hypoxia on sea-level performance: A meta-analysis. *Sports Medicine*, *47*(8), 1651–1660. https://doi.org/10.1007/s40279-017-0685-3

Brooks, G. A., Butterfield, G. E., Wolfe, R. R., Groves, B. M., Mazzeo, R. S., Sutton, J. R., Wolfel, E. E., & Reeves, J. T. (1991). Increased dependence on blood glucose after acclimatization to 4,300 m. *Journal of Applied Physiology (1985)*, *70*(2), 919–927. https://doi.org/10.1152/jappl.1991.70.2.919

Camacho-Cardenosa, A., Camacho-Cardenosa, M., Martínez-Guardado, I., Leal, A., Andrada, J. M. V., & Timón, R. (2022). Resistance circuit training combined with hypoxia stimulates bone system of older adults: A randomized trial. *Experimental Gerontology*, *169*, 111983. https://doi.org/10.1016/j.exger.2022.111983

Camacho-Cardenosa, M., Quesada-Gómez, J. M., Camacho-Cardenosa, A., Leal, A., Dorado, G., Torrecillas-Baena, B., & Casado-Díaz, A. (2020). Effects of normobaric cyclic hypoxia exposure on mesenchymal stem-cell differentiation–pilot study on bone parameters in elderly. *World Journal of Stem Cells*, *12*(12), 1667–1690. https://doi.org/10.4252/wjsc.v12.i12.1667

Chaillou, T., Koulmann, N., Meunier, A., Pugnière, P., McCarthy, J. J., Beaudry, M., & Bigard, X. (2014). Ambient hypoxia enhances the loss of muscle mass after extensive injury. *Pflügers Archiv - European Journal of Physiology*, *466*(3), 587–598. https://doi.org/10.1007/s00424-013-1336-7

Chaillou, T., & Lanner, J. T. (2016). Regulation of myogenesis and skeletal muscle regeneration: Effects of oxygen levels on satellite cell activity. *FASEB Journal*, *30*(12), 3929–3941. https://doi.org/10.1096/fj.201600757R

Chapman, R. F., Karlsen, T., Ge, R. L., Stray-Gundersen, J., & Levine, B. D. (2016). Living altitude influences endurance exercise performance change over time at altitude. *Journal of Applied Physiology*, *120*(10), 1151–1158. https://doi.org/10.1152/japplphysiol.00909.2015

Chen, C.-Y., Chou, W.-Y., Ko, J.-Y., Lee, M. S., & Wu, R.-W. (2019). Early recovery of exercise-related muscular injury by HBOT. *BioMed Research International*, *2019*, 1–10. https://doi.org/10.1155/2019/6289380

Chen, G., Zhang, W., Zhang, K., Wang, S., Gao, Y., Gu, J., He, L., Li, W., Zhang, C., Zhang, W., Li, M., Hao, Q., Zhang, Y., & Sorrenti, V. (2020). Hypoxia-induced mesenchymal stem cells exhibit stronger tenogenic differentiation capacities and promote patellar tendon repair in rabbits. *Stem Cells International*, *2020*, 1–16. https://doi.org/10.1155/2020/8822609

Chen, P. W., Hsu, C. C., Lai, L. F., Chi, C. P., & Yu, S. H. (2022). Effects of hypoxia–hyperoxia preconditioning on indicators of muscle damage after acute resistance exercise in male athletes. *Frontiers in Physiology*, *13*, 824210. https://doi.org/10.3389/fphys.2022.824210

Cialdai, F., Risaliti, C., & Monici, M. (2022). Role of fibroblasts in wound healing and tissue remodeling on Earth and in space. *Frontiers in Bioengineering and Biotechnology*, *10*, 958381. https://doi.org/10.3389/fbioe.2022.958381

Cobb, A. B., Levett, D. Z. H., Mitchell, K., Aveling, W., Hurlbut, D., Gilbert-Kawai, E., Hennis, P. J., Mythen, M. G., Grocott, M. P. W., Martin, D. S., Ahuja, X. E., Aref-Adib, G., Burnham, R., Chisholm, A., Clarke, K., Coates, D., Coates, M., Cook, D.,and Mythen, M. and, Xtreme Everest 2 investigators. (2021). Physiological responses during ascent to high altitude and the incidence of acute mountain sickness. *Physiological Reports*, *9*(7), e14809. https://doi.org/10.14814/phy2.14809

Constantini, K., & Wilhite, D. P. & Chapman, R. F. (2017). A clinician guide to altitude training for optimal endurance exercise performance at sea level. *High Altitude Medicine & Biology*, *18*(2), 93–101. https://doi.org/10.1089/ham.2017.0020

Darrieutort-Laffite, C., Blanchard, F., Soslowsky, L. J., & Le Goff, B. (2024). Biology and physiology of tendon healing. *Joint, bone, spine : revue du rhumatisme*, *91*(5), 105696. https://doi.org/10.1016/j.jbspin.2024.105696

Debevec, T., Amon, M., Keramidas, M. E., Kounalakis, S. N., Pišot, R., & Mekjavic, I. B. (2010). Normoxic and hypoxic performance Following 4 weeks of normobaric hypoxic training. *Aviation, Space, and Environmental Medicine*, *81*(4), 387–393. https://doi.org/10.3357/ASEM.2660.2010

DeFrates, K. G., Franco, D., Heber-Katz, E., & Messersmith, P. B. (2021). Unlocking mammalian regeneration through hypoxia inducible factor one alpha signaling. *Biomaterials*, *269*, 120646. https://doi.org/10.1016/j.biomaterials.2020.120646

Donnelly, C., Schmitt, S., Cecatto, C., Cardoso, L., Komlódi, T., Place, N., Kayser, B., & Gnaiger, E. (2022). The ABC of hypoxia - what is the norm. *MitoFit Preprints*, *25*(2). https://doi.org/10.26124/mitofit:2022-0025.v2

Drole, K., & Paravlic, A. H. (2022). Interventions for increasing return to sport rates after an anterior cruciate ligament reconstruction surgery: A systematic review [Journal Article]. *Frontiers in Psychology*, *13*. https://doi.org/10.3389/fpsyg.2022.939209

Dudnik, E., Zagaynaya, E., Glazachev, O. S., & Susta, D. (2018). Intermittent hypoxia–hyperoxia conditioning improves cardiorespiratory fitness in older comorbid cardiac outpatients without hematological changes: A randomized controlled trial. *High Altitude Medicine & Biology*, *19*(4), 339–343. https://doi.org/10.1089/ham.2018.0014

Eliakim, E., Morgulev, E., Lidor, R., & Meckel, Y. (2020). Estimation of injury costs: Financial damage of English Premier League teams' underachievement due to injuries. *BMJ Open Sport and Exercise Medicine*, *6*(1), e000675. https://doi.org/10.1136/bmjsem-2019-000675

Faiss, R., Léger, B., Vesin, J.-M., Fournier, P.-E., Eggel, Y., Dériaz, O., Millet, G. P., & Vinciguerra, M. (2013). Significant molecular and systemic adaptations after repeated sprint training in hypoxia. *PLOS ONE*, *8*(2), e56522. https://doi.org/10.1371/journal.pone.0056522

Feriche, B., García-Ramos, A., Morales-Artacho, A. J., & Padial, P. (2017). Resistance training using different hypoxic training strategies: A basis for hypertrophy and muscle power development. *Sports Medicine - Open*, *3*(1), 12–12. https://doi.org/10.1186/s40798-017-0078-z

Forsdyke, D., Smith, A., Jones, M., & Gledhill, A. (2016). Psychosocial factors associated with outcomes of sports injury rehabilitation in competitive athletes: A mixed studies systematic review. *British Journal of Sports Medicine*, *50*(9), 537–544. https://doi.org/10.1136/bjsports-2015-094850

Girard, O., Brocherie, F., Goods, P. S., & Millet, G. P. (2020). An updated panorama of "living low-training high" Altitude/Hypoxic methods. *Frontiers in Sports and Active Living*, *2*. https://doi.org/10.3389/fspor.2020.00026

Girard, O., Brocherie, F., Goods, P. S. R., & Millet, G. P. (2020). An updated panorama of "Living Low-Training High" Altitude/Hypoxic Methods [Perspective]. *Frontiers in Sports and Active Living*, *2*, (26). https://doi.org/10.3389/fspor.2020.00026

Girard, O., Matic Girard, I., & Peeling, P. (2020). Hypoxic conditioning: A novel therapeutic solution for load-compromised individuals to achieve similar exercise benefits by doing less mechanical work! *British Journal of Sports Medicine*, *55*(17), 944–945. https://doi.org/10.1136/bjsports-2020-103186

Girard, O., Matic Girard, I., & Peeling, P. (2021). Hypoxic conditioning: a novel therapeutic solution for load-compromised individuals to achieve similar exercise benefits by doing less mechanical work!. *British Journal of Sports Medicine*, *55*(17), 944–945. https://doi.org/10.1136/bjsports-2020-103186

Girard, O., Mendez-Villanueva, A., & Bishop, D. (2011). Repeated-sprint ability — part I: Factors contributing to fatigue. *Sports Medicine*, *41*(8), 673–694. https://doi.org/10.2165/11590550-000000000-00000

Gnaiger, E. (1991). Animal energetics at very low oxygen: Information from calorimetry and respirometry. In R. Woakes, M. Grieshaber, & C. R. Bridges (Eds.), *Physiological strategies for gas exchange and metabolism* (illustrated ed. Vol. 41, pp. 149–171). Cambridge University Press.

Goda, N., & Kanai, M. (2012). Hypoxia-inducible factors and their roles in energy metabolism. *International Journal of Hematology*, *95*(5), 457–463. https://doi.org/10.1007/s12185-012-1069-y

Gough, C. E., Sharpe, K., Garvican, L. A., Anson, J. M., Saunders, P. U., & Gore, C. J. (2013). The effects of injury and illness on haemoglobin mass. *International Journal of Sports Medicine*, *34*(9), 763–769. https://doi.org/10.1055/s-0033-1333692

Gouin, J.-P., & Kiecolt-Glaser, J. K. (2011). The impact of psychological stress on wound healing: Methods and mechanisms. *Immunology and Allergy Clinics of North America*, *31*(1), 81–93. https://doi.org/10.1016/j.iac.2010.09.010

Hägglund, M., Waldén, M., Magnusson, H., Kristenson, K., Bengtsson, H., & Ekstrand, J. (2013). Injuries affect team performance negatively in professional football: An 11-year follow-up of the UEFA Champions League injury study. *British Journal of Sports Medicine*, *47*(12), 738–742. https://doi.org/10.1136/bjsports-2013-092215

Hanning, C. D., & Alexander-Williams, J. M. (1995). Fortnightly Review: Pulse oximetry: A practical review. *BMJ*, *311*(7001), 367–370. https://doi.org/10.1136/bmj.311.7001.367

Hauser, A., Troesch, S., Saugy, J. J., Schmitt, L., Cejuela-Anta, R., Faiss, R., Steiner, T., Robinson, N., Millet, G. P., & Wehrlin, J. P. (2017). Individual hemoglobin mass response to normobaric and hypobaric "live high–train low": A one-year crossover study. *Journal of Applied Physiology*, *123*(2), 387–393. https://doi.org/10.1152/japplphysiol.00932.2016

He, P., Ruan, D., Huang, Z., Wang, C., Xu, Y., Cai, H., Liu, H., Fei, Y., Heng, B. C., Chen, W., & Shen, W. (2022). Comparison of tendon development versus tendon healing and regeneration [review]. *Frontiers in Cell and Developmental Biology*, *10*. https://doi.org/10.3389/fcell.2022.821667

Heppenstall, R. B., Goodwin, C. W., & Brighton, C. T. (1976). Fracture healing in the presence of chronic hypoxia. *Journal of Bone and Joint Surgery*, *58*(8), 1153–1156. https://doi.org/10.2106/00004623-197658080-00022

Honda, A., Kon, M., Matsubayashi, T., & Suzuki, Y. (2020). Short-term intermittent hypoxic resistance training does not impair osteogenic response in sea level residents. *High Altitude Medicine & Biology*, *21*(2), 160–166. https://doi.org/10.1089/ham.2019.0089

Huang, J., Deng, F., Wang, L., Xiang, X.-R., Zhou, W.-W., Hu, N., & Xu, L. (2011). Hypoxia induces osteogenesis-related activities and expression of core binding factor α1 in mesenchymal stem cells. *The Tohoku Journal of Experimental Medicine*, *224*(1), 7–12. https://doi.org/10.1620/tjem.224.7

Huang, T.-F., Yew, T.-L., Chiang, E.-R., Ma, H.-L., Hsu, C.-Y., Hsu, S.-H., Hsu, Y.-T., & Hung, S.-C. (2013). Mesenchymal stem cells from a hypoxic culture improve and engraft achilles tendon repair. *The American Journal of Sports Medicine*, *41*(5), 1117–1125. https://doi.org/10.1177/0363546513480786

Ihsan, M., Périard, J. D., & Racinais, S. (2019). Integrating heat training in the rehabilitation toolbox for the injured Athlete [Opinion]. *Frontiers in Physiology*, *10*. https://doi.org/10.3389/fphys.2019.01488

Inness, M. W. H., Billaut, F., Walker, E. J., Petersen, A. C., Sweeting, A. J., & Aughey, R. J. (2016). Heavy resistance training in hypoxia enhances 1RM squat performance [Original research]. *Frontiers in Physiology*, *7*, 502. https://doi.org/10.3389/fphys.2016.00502

Jung, W.-S., Kim, S.-W., Kim, J.-W., & Park, H.-Y. (2021). Resistance training in hypoxia as a new therapeutic modality for Sarcopenia—A narrative review. *Life*, *11*(2), 106. https://doi.org/10.3390/life11020106

Kallio, P. J. (1998). Signal transduction in hypoxic cells: Inducible nuclear translocation and recruitment of the CBP/p300 coactivator by the hypoxia-inducible factor-1alpha. *The EMBO Journal*, *17*(22), 6573–6586. https://doi.org/10.1093/emboj/17.22.6573

Kambič, T., & Burtscher, J. (2024). Making PEACE and LOVE in hypoxia: An emerging therapy for accelerated muscle injury regeneration? *Journal of Physiology, Paris*, https://doi.org/10.1113/JP286241

Kawada, S., Wada, E., Matsuda, R., Ishii, N., & Zadpoor, A. A. (2013). Hyperbaric hyperoxia accelerates fracture healing in mice. *PLOS ONE*, *8*(8), e72603–e72603. https://doi.org/10.1371/journal.pone.0072603

Kelc, R., Naranda, J., Kuhta, M., & Vogrin, M. (2013). The physiology of sports injuries and repair processes. In M. J. Hamlin & N. Draper (Eds.), *Current issues in sports and exercise medicine*. IntechOpen. https://doi.org/10.5772/56649

Knighton, D. R., Silver, I. A., & Hunt, T. K. (1981). Regulation of wound-healing angiogenesis-effect of oxygen gradients and inspired oxygen concentration. *Surgery*, *90*(2), 262–270.

Kon, M., Ikeda, T., Homma, T., & Suzuki, Y. (2012). Effects of low-intensity resistance exercise under acute systemic hypoxia on hormonal responses. *The Journal of Strength & Conditioning Research*, *26*(3), 611–617. https://doi.org/10.1519/JSC.0b013e3182281c69

Kon, M., Ikeda, T., Homma, T., & Suzuki, Y. (2021). Responses of angiogenic regulators to resistance exercise under systemic hypoxia. *The Journal of Strength & Conditioning Research*, *35*(2), 436–441. https://doi.org/10.1519/jsc.0000000000002695

Kon, M., Ohiwa, N., Honda, A., Matsubayashi, T., Ikeda, T., Akimoto, T., Suzuki, Y., Hirano, Y., & Russell, A. P. (2014). Effects of systemic hypoxia on human muscular adaptations to resistance exercise training. *Physiological Reports*, *2*(6), e12033. https://doi.org/10.14814/phy2.12033

Kvist, J., Ek, A., Sporrstedt, K., & Good, L. (2005). Fear of re-injury: A hindrance for returning to sports after anterior cruciate ligament reconstruction. *Knee Surgery, Sports Traumatology, Arthroscopy*, *13*(5), 393–397. https://doi.org/10.1007/s00167-004-0591-8

Laumonier, T., & Menetrey, J. (2016). Muscle injuries and strategies for improving their repair. *Journal of Experimental Orthopaedics*, *3*(1), 15. https://doi.org/10.1186/s40634-016-0051-7

Lee, M., & Carroll, T. J. (2007). Cross education: Possible mechanisms for the contralateral effects of unilateral resistance training. *Sports Medicine*, *37*(1), 1–14. https://doi.org/10.2165/00007256-200737010-00001

Levine, B. D., & Stray-Gundersen, J. (1997). "Living high-training low": Effect of moderate-altitude acclimatization with low-altitude training on performance. *Journal of Applied Physiology*, *83*(1), 102–112. https://doi.org/10.1152/jappl.1997.83.1.102

Li, R., Ye, J. J., Gan, L., Zhang, M., Sun, D., Li, Y., Wang, T., & Chang, P. (2023). Traumatic inflammatory response: Pathophysiological role and clinical value of cytokines. *European Journal of Trauma and Emergency Surgery*, *50*(4), 1313–1330. https://doi.org/10.1007/s00068-023-02388-5

Li, S. N., Peeling, P., Scott, B. R., Peiffer, J. J., Shaykevich, A., & Girard, O. (2023). Maintenance of internal load despite a stepwise reduction in external load during moderate intensity heart rate clamped cycling with acute graded normobaric hypoxia in males. *Journal of Science & Medicine in Sport*, *26*(11), 628–635. https://doi.org/10.1016/j.jsams.2023.09.006

Li, S. N., Peeling, P., Scott, B. R., Peiffer, J. J., Shaykevich, A., & Girard, O. (2023). Maintenance of internal load despite a stepwise reduction in external load during moderate intensity heart rate clamped cycling with acute graded normobaric hypoxia in males. *Journal of Science & Medicine in Sport*, *26*(11), 628–635. https://doi.org/10.1016/j.jsams.2023.09.006

Lieber, R. L., & Ward, S. R. (2013). Cellular Mechanisms of Tissue Fibrosis. 4. Structural and functional consequences of skeletal muscle fibrosis. *American Journal of Physiology-Cell Physiology*, *305*(3), C241–C252. https://doi.org/10.1152/ajpcell.00173.2013

Lissenberg-Thunnissen, S. N., de Gorter, D. J. J., Sier, C. F. M., & Schipper, I. B. (2011). Use and efficacy of bone morphogenetic proteins in fracture healing. *International Orthopaedics*, *35*(9), 1271–1280. https://doi.org/10.1007/s00264-011-1301-z

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Abe, T., & Bemben, M. G. (2012). The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. *Medical Hypotheses*, *78*(1), 151–154. https://doi.org/10.1016/j.mehy.2011.10.014

Lu, C., Rollins, M., Hou, H., Swartz, H. M., Hopf, H., Miclau, T., & Marcucio, R. S. (2008). Tibial fracture decreases oxygen levels at the site of injury. *The Iowa Orthopaedic Journal*, *28*, 14–21. https://pubmed.ncbi.nlm.nih.gov/19223943https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2603344/

Lundberg Zachrisson, A., Ivarsson, A., Desai, P., Karlsson, J., & Grau, S. (2020). Athlete availability and incidence of overuse injuries over an athletics season in a cohort of elite Swedish athletics athletes - a prospective study. *Injury Epidemiology*, *7*(1), 16. https://doi.org/10.1186/s40621-020-00239-0

Manimmanakorn, A., Hamlin, M. J., Ross, J. J., Taylor, R., & Manimmanakorn, N. (2013). Effects of low-load resistance training combined with blood flow restriction or hypoxia on muscle function and performance in netball athletes. *Journal of Science & Medicine in Sport*, *16* (4), 337–342. https://doi.org/10.1016/j.jsams.2012.08.009

Marsell, R., & Einhorn, T. A. (2011). The biology of fracture healing. *Injury*, *42* (6), 551–555. https://doi.org/10.1016/j.injury.2011.03.031

Mckee, J. R., Girard, O., Peiffer, J. J., Hiscock, D. J., De Marco, K., & Scott, B. R. (2024). Repeated-sprint training with Blood-flow restriction improves repeated-sprint ability similarly to unrestricted training at reduced external loads. *International Journal of Sports Physiology & Performance*, *19*(3), 257–264. https://doi.org/10.1123/ijspp.2023-0321

Millet, G. P., Debevec, T., Brocherie, F., Malatesta, D., & Girard, O. (2016). Therapeutic use of exercising in Hypoxia: Promises and limitations. *Frontiers in Physiology*, *7*, 224–224. https://doi.org/10.3389/fphys.2016.00224

Moghadam, N., Hieda, M., Ramey, L., Levine, B. D., & Guilliod, R. (2020). Hyperbaric oxygen therapy in sports musculoskeletal injuries. *Medicine & Science in Sports and Exercise*, *52*(6), 1420–1426. https://doi.org/10.1249/mss.0000000000002257

Molloy, T., Wang, Y., & Murrell, G. A. C. (2003). The roles of growth factors in tendon and ligament healing. *Sports Medicine*, *33*(5), 381–394. https://doi.org/10.2165/00007256-200333050-00004

Mortola, J. P., Rezzonico, R., & Lanthier, C. (1989). Ventilation and oxygen consumption during acute hypoxia in newborn mammals: A comparative analysis. *Respiration Physiology*, *78*(1), 31–43. https://doi.org/10.1016/0034-5687(89)90140-0

Mujika, I., & Padilla, S. (2000a). Detraining: Loss of training-induced physiological and performance adaptations. Part I. *Sports Medicine*, *30*(2), 79–87. https://doi.org/10.2165/00007256-200030020-00002

Mujika, I., & Padilla, S. (2000b). Detraining: Loss of training-induced physiological and performance adaptations. Part II. *Sports Medicine*, *30*(3), 145–154. https://doi.org/10.2165/00007256-200030030-00001

Mujika, I., & Padilla, S. (2001). Cardiorespiratory and metabolic characteristics of detraining in humans. *Medicine & Science in Sports and Exercise*, *33* (3), 413–421. https://doi.org/10.1097/00005768-200103000-00013

Navarrete-Opazo, A., & Mitchell, G. S. (2014). Therapeutic potential of intermittent hypoxia: A matter of dose. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *307*(10), R1181–R1197. https://doi.org/10.1152/ajpregu.00208.2014

Nishimura, A., Sugita, M., Kato, K., Fukuda, A., Sudo, A., & Uchida, A. (2010). Hypoxia increases muscle hypertrophy induced by resistance training. *International Journal of Sports Physiology & Performance*, *5*(4), 497–508. https://doi.org/10.1123/ijspp.5.4.497

Richardson, A., Clarsen, B., Verhagen, E. A. L. M., & Stubbe, J. H. (2017). High prevalence of self-reported injuries and illnesses in talented female athletes. *BMJ Open Sport and Exercise Medicine*, *3*(1), e000199. https://doi.org/10.1136/bmjsem-2016-000199

Rizo-Roca, D., Bonet, J. B., Ínal, B., Ríos-Kristjánsson, J. G., Pagès, T., Viscor, G., & Torrella, J. R. (2018). Contractile activity is necessary to trigger intermittent hypobaric hypoxia-induced fiber size and vascular adaptations in skeletal muscle [original research]. *Frontiers in Physiology*, *9*(481). https://doi.org/10.3389/fphys.2018.00481

Rocha, F. S., Gomes Moura, C. C., Rocha Rodrigues, D. B., Zanetta-Barbosa, D., Nakamura Hiraki, K. R., & Dechichi, P. (2015). Influence of hyperbaric oxygen on the initial stages of bone healing. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *120*(5), 581–587. https://doi.org/10.1016/j.oooo.2015.06.039

Rochefort, G. Y., Delorme, B., Lopez, A., Hérault, O., Bonnet, P., Charbord, P., Eder, V., & Domenech, J. (2006). Multipotential mesenchymal stem cells are mobilized into peripheral blood by hypoxia. *Stem Cells*, *24*(10), 2202–2208. https://doi.org/10.1634/stemcells.2006-0164

Roels, B., Millet, G. P., Marcoux, C. J. L., Coste, O., Bentley, D. J., & Candau, R. B. (2005). Effects of hypoxic interval training on cycling performance. *Medicine & Science in Sports and Exercise*, *37*(1), 138–146. https://doi.org/10.1249/01.Mss.0000150077.30672.88

Roels, B., Thomas, C., Bentley, D. J., Mercier, J., Hayot, M., & Millet, G. (2007). Effects of intermittent hypoxic training on amino and fatty acid oxidative combustion in human permeabilized muscle fibers. *Journal of Applied Physiology*, *102*(1), 79–86. https://doi.org/10.1152/japplphysiol.01319.2005

Santocildes, G., Viscor, G., Pagès, T., & Torrella, J. R. (2023). Simulated altitude is medicine: Intermittent exposure to hypobaric hypoxia and cold accelerates injured skeletal muscle recovery. *Journal of Physiology, Paris*. https://doi.org/10.1113/JP285398

Schumacher, Y. O., Ahlgrim, C., Ruthardt, S., & Pottgiesser, T. (2008). Hemoglobin Mass in an elite endurance Athlete before, during, and after injury-related immobility. *Clinical Journal of Sport Medicine*, *18*(2), 172–173. https://doi.org/10.1097/JSM.0b013e31815e981e

Scott, B. R., Girard, O., Rolnick, N., McKee, J. R., & Goods, P. S. R. (2023). An updated panorama of blood-flow-restriction methods. *International Journal of Sports Physiology & Performance*, *18*(12), 1461–1465. https://doi.org/10.1123/ijspp.2023-0135

Scott, B. R., Slattery, K. M., & Dascombe, B. J. (2014). Intermittent hypoxic resistance training: Does it provide added benefit? *Frontiers in Physiology*, *5*, 397. https://doi.org/10.3389/fphys.2014.00397

Semenza, G. L. (2000). HIF-1: Mediator of physiological and pathophysiological responses to hypoxia. *Journal of Applied Physiology*, *88*(4), 1474–1480. https://doi.org/10.1152/jappl.2000.88.4.1474

Serebrovskaya, T. V., Nosar, V. I., Bratus, L. V., Gavenauskas, B. L., & Mankowska, I. M. (2013). Tissue oxygenation and mitochondrial respiration under different modes of intermittent hypoxia. *High Altitude Medicine & Biology*, *14*(3), 280–288. https://doi.org/10.1089/ham.2013.1012

Sheel, A. W., MacNutt, M. J., & Querido, J. S. (2010). The pulmonary system during exercise in hypoxia and the cold. *Experimental Physiology*, *95*(3), 422–430. https://doi.org/10.1113/expphysiol.2009.047571

Siebenmann, C., Rasmussen, P., Sørensen, H., Bonne, T. C., Zaar, M., Aachmann-Andersen, N. J., Nordsborg, N. B., Secher, N. H., & Lundby, C. (2015). Hypoxia increases exercise heart rate despite combined inhibition of β-adrenergic and muscarinic receptors. *American Journal of Physiology-Heart and Circulatory Physiology*, *308*(12), H1540–H1546. https://doi.org/10.1152/ajpheart.00861.2014

Terrados, N., Jansson, E., Sylven, C., & Kaijser, L. (1990). Is hypoxia a stimulus for synthesis of oxidative enzymes and myoglobin? *Journal of Applied Physiology*, *68*(6), 2369–2372. https://doi.org/10.1152/jappl.1990.68.6.2369

Timon, R., González-Custodio, A., Vasquez-Bonilla, A., Olcina, G., & Leal, A. (2022). Intermittent hypoxia as a therapeutic tool to improve health parameters in older adults. *International Journal of Environmental Research and Public Health*, *19*(9), 5339. https://doi.org/10.3390/ijerph19095339

Toale, J. P., Hurley, E. T., Hughes, A. J., Withers, D., King, E., Jackson, M., & Moran, R. (2021). The majority of athletes fail to return to play following anterior cruciate ligament reconstruction due to reasons other than the operated knee. *Knee Surgery, Sports Traumatology, Arthroscopy*, *29*(11), 3877–3882. https://doi.org/10.1007/s00167-020-06407-5

Tobin, B., Costalat, G., & Renshaw, G. M. C. (2022). Pre-acclimation to altitude in young adults: Choosing a hypoxic pattern at sea level which provokes significant haematological adaptations. *European Journal of Applied Physiology*, *122*(2), 395–407. https://doi.org/10.1007/s00421-021-04837-8

Truijens, M. J., Toussaint, H. M., Dow, J., & Levine, B. D. (2003). Effect of high-intensity hypoxic training on sea-level swimming performances. *Journal of Applied Physiology*, *94*(2), 733–743. https://doi.org/10.1152/japplphysiol.00079.2002

Tsuji, K., Bandyopadhyay, A., Harfe, B. D., Cox, K., Kakar, S., Gerstenfeld, L., Einhorn, T., Tabin, C. J., & Rosen, V. (2006). BMP2 activity, although dispensable for bone formation, is required for the initiation of fracture healing. *Nature Genetics*, *38*(12), 1424–1429. https://doi.org/10.1038/ng1916

van Doorslaer de ten Ryen, S., Francaux, M., & Deldicque, L. (2021). Regulation of satellite cells by exercise in hypoxic conditions: A narrative review. *European Journal of Applied Physiology*, *121*(6), 1531–1542. https://doi.org/10.1007/s00421-021-04641-4

Ventura, N., Hoppeler, H., Seiler, R., Binggeli, A., Mullis, P., & Vogt, M. (2003). The response of trained athletes to six weeks of endurance training in hypoxia or normoxia. *International Journal of Sports Medicine*, *24*(3), 166–172. https://doi.org/10.1055/s-2003-39086

Vincent, H. K., Madsen, A., & Vincent, K. R. (2022). Role of antigravity training in rehabilitation and return to sport after running injuries. *Arthroscopy, Sports Medicine, and Rehabilitation*, *4*(1), e141–e149. https://doi.org/10.1016/j.asmr.2021.09.031

Vogt, M., Puntschart, A., Geiser, J., Zuleger, C., Billeter, R., & Hoppeler, H. (2001). Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. *Journal of Applied Physiology*(*1985*)*91*(1), 173–182. https://doi.org/10.1152/jappl.2001.91.1.173

von Rosen, P., Heijne, A., Frohm, A., Fridén, C., & Kottorp, A. (2018). High injury burden in elite adolescent athletes: A 52-week prospective study. *Journal of Athletic Training*, *53*(3), 262–270. https://doi.org/10.4085/1062-6050-251-16

Wagegg, M., Gaber, T., Lohanatha, F. L., Hahne, M., Strehl, C., Fangradt, M., Tran, C. L., Schönbeck, K., Hoff, P., Ode, A., Perka, C., Duda, G. N., Buttgereit, F., & Covas, D. T. (2012). Hypoxia promotes osteogenesis but suppresses adipogenesis of human mesenchymal stromal cells in a hypoxia-inducible factor-1 dependent manner. *PLOS ONE*, *7*(9), e46483. https://doi.org/10.1371/journal.pone.0046483

Wan, C., Gilbert, S. R., Wang, Y., Cao, X., Shen, X., Ramaswamy, G., Jacobsen, K. A., Alaql, Z. S., Eberhardt, A. W., Gerstenfeld, L. C., Einhorn, T. A., Deng, L., & Clemens, T. L. (2008). Activation of the hypoxia-inducible factor-1α pathway accelerates bone regeneration. *Proceedings of the National Academy of Sciences*, *105*(2), 686–691. https://doi.org/10.1073/pnas.0708474105

Wang, Y., Tang, Z., Xue, R., Singh, G. K., Liu, W., Lv, Y., & Yang, L. (2012). Differential response to CoCl2-stimulated hypoxia on HIF-1α, VEGF, and MMP-2 expression in ligament cells. *Molecular and Cellular Biochemistry*, *360*(1–2), 235–242. https://doi.org/10.1007/s11010-011-1061-5

Williams, S., Trewartha, G., Kemp, S. P., Brooks, J. H., Fuller, C. W., Taylor, A. E., Cross, M. J., & Stokes, K. A. (2016). Time loss injuries compromise team success in Elite Rugby Union: A 7-year prospective study. *British Journal of Sports Medicine*, *50*(11), 651–656. https://doi.org/10.1136/bjsports-2015-094798

Yu, Y., Zhou, Y., Cheng, T., Lu, X., Yu, K., Zhou, Y., Hong, J., & Chen, Y. (2016). Hypoxia enhances tenocyte differentiation of adipose-derived mesenchymal stem cells by inducing hypoxia-inducible factor-1α in a co-culture system. *Cell Proliferation*, *49*(2), 173–184. https://doi.org/10.1111/cpr.12250

Zhang, L., Jin, L., Guo, J., Bao, K., Hu, J., Zhang, Y., Hou, Z., & Zhang, L. (2021). Chronic intermittent hypobaric hypoxia enhances bone fracture healing [Original research]. *Frontiers in Endocrinology*, *11*. https://doi.org/10.3389/fendo.2020.582670

Zhao, J., Zhang, P., Qin, L., & Pan, X. H. (2011). Hypoxia is essential for bone-tendon junction healing: The molecular biological evidence. *International Orthopaedics*, *35*(6), 925–928. https://doi.org/10.1007/s00264-010-1157-7

Zulkifli, A., Ahmad, R. E., Krishnan, S., Kong, P., Nam, H. Y., & Kamarul, T. (2023). The potential mechanism of hypoxia-induced tenogenic differentiation of mesenchymal stem cell for tendon regeneration. *Tissue & Cell*, *82*, 102075. https://doi.org/10.1016/j.tice.2023.102075