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TOPICAL REVIEW

Mechanisms of haemoglobin mass expansion following heat stress

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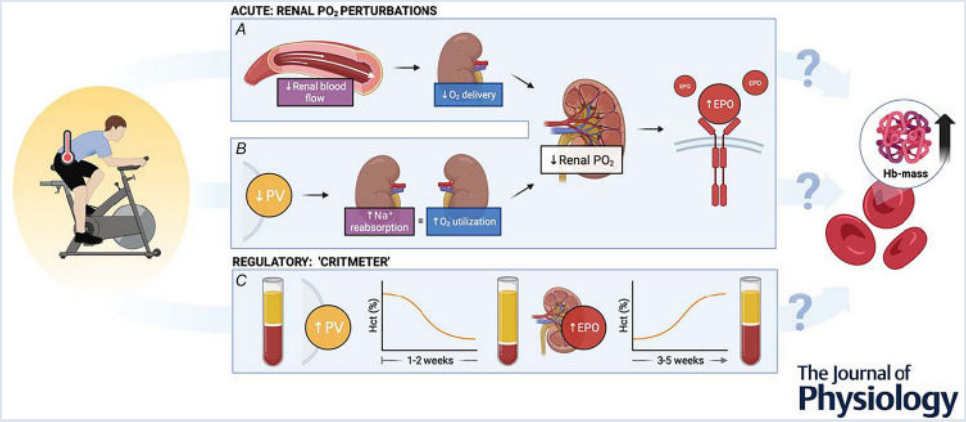

Abstract figure legend Theorised mechanisms of heat stress-induced erythropoiesis which may facilitate the expansion of haemoglobin mass. *A*, acute: heat stress-induced renal ischaemia. Redistribution of blood flow away from the kidneys to facilitate thermoregulation during heat stress could reduce renal oxygen delivery, subsequently lowering renal P_{O_2} and triggering erythropoietin (EPO) production. *B*, acute: increased renal sodium (Na^+) reabsorption. Plasma volume (PV) contraction caused by heat exposure increases sodium reabsorption in the kidneys, elevating renal oxygen utilisation, thereby potentially decreasing parenchymal renal P_{O_2} and stimulating EPO synthesis. *C*, regulatory: critmeter theory. Sustained plasma volume expansion during heat acclimation decreases haematocrit (Hct). After ∼3–4 weeks, the kidney – having detected the resulting reduction in renal tissue O_2 tension due to lowered Hct – may initiate EPO production to restore optimal Hct and oxygen delivery.

Abstract Haemoglobin mass is a critical determinant of oxygen delivery to working muscle, with even modest increases enhancing maximal oxygen uptake ($\dot{V}_{O_2max}$) and endurance performance. While altitude training has long been utilised to increase haemoglobin mass, its efficacy is

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increasingly debated, due to concerns over maladaptation, inter-individual variability, cost and environmental impact. More recently, heat training – traditionally employed for acclimatisation ahead of competition in warm climates – has emerged as a feasible long-term stimulus capable of eliciting comparable haemoglobin mass expansion. Long-term heat acclimation (≥5 weeks) shows promise as an environmental intervention to improve oxygen-carrying capacity via haematological adaptation, with each study published to date reporting meaningful (∼2–4%) haemoglobin mass expansion and concurrent improvements in $\dot{V}_{O_2max}$. Erythropoiesis underpins the haematological adaptations to long-term heat acclimation, though it appears to diverge from established hypoxia-driven mechanisms. This review will discuss how heat exposure may stimulate erythropoietin via distinct cellular stress signalling, altered renal oxygen tension or plasma volume perturbations. These responses may act through distinct pathways, complementing or deviating from those traditionally associated with hypoxia. While published long-term heat acclimation studies have primarily utilised exercise under heat stress conditions, we discuss the potential for passive heating methods to yield similar adaptations. Based on our review of the literature, we highlight the need for research that elucidates precise mechanisms, compares differing modes of heat stress, and explores broader applications of long-term heat acclimation. However, current evidence supports long-term heat acclimation as an effective alternative or adjunct to altitude training for enhancing oxygen-carrying capacity.

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Introduction

Haemoglobin (Hb) mass is an important determinant of the capacity to deliver oxygen (O_2) to exercising muscle, with a 1 g increase corresponding to an ∼4 ml min^{-1} enhancement in maximal oxygen uptake ($\dot{V}_{O_2max}$), based on cross-sectional modelling (Schmidt & Prommer, 2010). While elite athletes already possess an elevated Hb mass when compared to inactive controls (Montero & Lundby, 2018), they often seek environmental interventions to further optimise haematological adaptations for endurance performance. Even modest Hb mass increases – as little as 2–4% (∼15—30 g depending on baseline levels) – can lead to meaningful performance gains, particularly in well-trained athletes operating near their physiological ceiling (Lundby & Robach, 2015). Year after year, athletes sojourn to higher altitudes, with models such as 'live-high, train-low' now frequently practised for their potential to increase Hb mass, $\dot{V}_{O_2max}$ and subsequent sea-level performance (Girard et al., 2023; Levine & Stray-Gundersen, 1997). The haematological response to hypoxic acclimatisation has been studied thoroughly, with the body increasing haemoglobin concentration to restore arterial O_2 content in the face of lowered arterial O_2 pressure (Siebenmann et al., 2017). Initially, this haemoconcentration results from plasma volume contraction (Schlittler et al., 2021). However, after several weeks, a gradual rise in Hb mass, primarily stimulated by elevated erythropoietin (EPO) levels, further enhances the blood's O_2-carrying capacity (Siebenmann et al., 2017). Despite these well-known adaptations to altitude training, its efficacy remains debated (Millet & Brocherie, 2020; Siebenmann & Dempsey, 2020). While the potential for adaptation with moderate-duration (3–4 weeks) hypoxic exposures is acknowledged, costs may exceed any potential gains. Adverse effects may include disrupted recovery, characterised by poor sleep quality and nocturnal periodic breathing, as well as potential maladaptation such as pulmonary vascular remodelling, vascular dysfunction and sympathoexcitation (Dempsey & Morgan, 2015). Significant inter-individual variability of the erythropoietic response to hypoxia should also be considered. For instance, Friedmann et al. (2005) showed that after 4 h of normobaric hypoxia (F_{IO_2} = 0.15), circulating EPO levels increased by 10–185% across individuals. These acute EPO surges did not predict subsequent Hb mass gains, highlighting the limited utility of early EPO responses in forecasting adaptation. Similarly, Hb mass responses to altitude training are highly variable: Nummela et al. (2021) found that Hb mass increased in only 65% of camps conducted above 2000 m, and among athletes who completed multiple camps, 60% exhibited both positive and negative responses across exposures. Performance outcomes show similar variability, with individuals classified as 'responders' or 'non-responders' (based on time-trial performance after one exposure) often failing to retain that classification in subsequent exposures (Robertson et al., 2010). This inconsistency

Table 1. Summary of long-term heat acclimation protocols to date (minimum 5-week duration) and their effects on haemoglobin mass and performance outcomes

Citation	Participants	Heating protocol	△Hb mass	Performance outcomes
Oberholzer et al. (2019), Mikkelsen et al. (2019)	21 sub-elite male cyclists. HEAT = 12 CON = 9	1-h moderate intensity cycling in 35–40°C, 5 days/week for 5.5 weeks	34 g ↑ in HEAT 2 g ↑ in CON	$\dot{V}_{O_2max}$ and PPO unchanged. Similar improvements in TT performance and mean power
Rønnestad et al. (2021)	23 elite male cyclists. HEAT = 11 CON = 12	50-min mod intensity cycling in 38°C, 5 days/week for 5 weeks	42 g ↑ in HEAT 6 g ↑ in CON	4% ↑ $\dot{V}_{O_2max}$ (ns compared to CON). Small to no difference in other performance parameters
Rønnestad et al. (2022a)	25 elite male XC-skiers. HEAT = 13 CON = 12	50-min low intensity cycling wearing heat suit, 5 days/week for 5 weeks	19 g ↑ in HEAT 10 g ↓ in CON	2% ↑ $\dot{V}_{O_2max}$ (ns compared to CON). No group differences observed for other performance parameters
Rønnestad, Urianstad et al. (2022)	34 elite male cyclists. HEAT = 23 (12 heat chamber, 11 suit) CON = 11	50-min low intensity cycling in 35°C or heat suit, 5 days/week for 5 weeks, 3 days/week for 3 weeks thereafter	2.4% and 2.6% ↑ in HEAT (chamber, suit) 0.7% ↓ in CON. 3.3% ↑ in HEAT with 3 additional weeks	Pooled 5% improvement in performance index (power output at 4 mmol l^{-1} $[La^-]_b$, W_{max}, and 15-min mean power) in HEAT. 2% ↑ $\dot{V}_{O_2max}$ versus CON (ns)
Lundby et al. (2023)	47 elite male & female cyclists (27 M; 20 F). HEAT = 25 (15M, 10F) CON = 22 (12M, 10F)	50-min mod intensity cycling wearing heat suit, 5 days/week for 5 weeks	33 and 25 g ↑ in HEAT (M, F) 22 and 11 g ↑ in CON (M, F)	↑ $\dot{V}_{O_2max}$ (4% M and 6% F), lactate threshold, 15 min mean power output ($P < 0.05$) following HEAT in both M and F compared to CON
Cubel et al. (2024)	20 elite male cyclists HEAT = 10 CON = 10	60-min mod intensity cycling wearing heat suit, 6 days/week for 5 weeks	30 g ↑ (3 weeks) and 40 g ↑ (5 weeks) in HEAT 23 g ↓ in CON	$\dot{V}_{O_2max}$ unchanged. PPO increased by 12 ± 10 W (17 ± 12%, $P = 0.001$) from pre- to post-heat acclimation. No effect in CON

Note: Data are means as they were presented in respective studies. Abbreviations: CON, control group; HEAT, heat intervention group; $[La^-]_b$, blood lactate concentration; ns, not significant; PPO, peak power output; TT, time trial; $\dot{V}_{O_2max}$, maximal aerobic capacity; W_{max}, maximum power.

of response poses a significant challenge for athletes and coaches who may see their time, efforts and resources invested into a practice that yields negligible benefits. In addition to plausible physiological drawbacks, altitude training also presents practical challenges, including high costs (in terms of time and money), limited accessibility and environmental impact.

As a result of the discourse surrounding altitude training, alternative environmental training stimuli have grown in popularity. While heat training is typically practised for its adaptive benefits ahead of competition in warmer climates (Périard et al., 2015), only recently have acclimation protocols moved beyond traditional 1- to 2-week durations and looked at the effects of heat when utilised as a longer-term stimulus. Protocols consisting of five weekly heat training sessions across 5-week periods have consistently shown that long-term heat acclimation increases Hb mass (Table 1) (Lundby et al., 2023; Oberholzer et al., 2019; Rønnestad et al., 2021; Rønnestad, Lid et al., 2022; Rønnestad, Urianstad et al., 2022). Despite consistent efficacy, the mechanistic basis for Hb mass expansion following long-term heat acclimation remains poorly understood. While heat training is increasingly being utilised in practice, a stronger evidence base is needed to optimise its application in elite sport. Without a clearer mechanistic understanding, altitude remains the advocated environmental training stimulus for endurance athletes preparing for temperate, sea-level competition (Baranauskas et al., 2021).

In light of the emerging use of heat acclimation to increase Hb mass, the aims of this review are threefold: (1) to discuss the predominant theories surrounding the

mechanisms of Hb mass expansion following heat stress, with a particular focus on the relationship between heat stress and EPO synthesis; (2) to explore how long-term heat acclimation has been applied thus far (i.e. modes of heat stress, populations studied); and (3) to establish future research directions and discuss the capacity for heat to become more commonly practised as a method of environmental training (i.e. as a feasible alternative to altitude).

Proposed mechanisms

The haematological adaptations observed with long-term heat acclimation are understood to be mediated by erythropoiesis. While various factors – including iron availability, hormonal regulators and cellular stress signals – can influence red blood cell production, EPO remains the principal hormonal stimulus for sustained erythropoiesis (Adamson, 1996; Semenza, 2012; Shahani et al., 2009). To date, only limited and equivocal evidence exists regarding the magnitude and time course of the EPO response to long-term heat acclimation. Increases in circulating EPO have been reported acutely following hot-water immersion (DiMarco et al., 2024) and after 10 days of exercise in the heat (Rendell et al., 2017). However, no change was observed following a 4-week post-exercise sauna protocol (3 exposures/week) (Sitkowski et al., 2022), underscoring the limited and inconsistent nature of current data. As such, despite the absence of definitive evidence characterising the EPO response to long-term heat acclimation, our focus on EPO in this review is based on its well-established physiological role and its necessity for meaningful Hb mass expansion. It is possible that additional mechanisms, such as hypoxia-inducible factor (HIF)-mediated effects on progenitor cell survival or iron metabolism, contribute to this response (Haase, 2017). However, in the absence of empirical data, EPO remains the most plausible primary driver of heat-induced haematological adaptation.

Erythropoietin: sources and roles. EPO is a glycoprotein hormone central to red blood cell production, binding to erythroid progenitor cells in the bone marrow to promote their differentiation into erythrocytes – cells predominantly composed of haemoglobin (Caulier & Sankaran, 2022; Kaza et al., 2021). Although the literature broadly considers the kidney as the dominant source of EPO production, this view underestimates the complexity of EPO regulation and may not extend to heat stress. Non-renal sources of EPO, such as the brain, heart, liver, skeletal muscle, adipose tissue and spleen, also respond to hypoxia, ischaemia, exercise or a combination of these stimuli (Allwood et al., 2024; Baker & Parise, 2016; De Franciscis et al., 1965; Deji et al., 2015; Northrup et al., 2024). However, the extent to which these tissues contribute to circulating EPO in humans remains unclear (Rasmussen et al., 2012), particularly in response to heat stress where regulatory pathways may differ from those of hypoxia. Beyond erythropoiesis, EPO supports a range of adaptive processes that may improve performance, including neovascularisation, muscle contractility, mitochondrial function, cytoprotection and cell proliferation (Suresh et al., 2019). These adaptations occur when EPO binds to receptors on non-erythroid cells, including adipose, cardiac, endothelial, neural and skeletal muscle cells (Anagnostou et al., 1994; Marti et al., 1996; Rundqvist et al., 2009; Teng et al., 2011; Tramontano et al., 2003). The regulation and role of EPO can also differ depending on the stimulus (Bonnas et al., 2017). This is perhaps to be expected, given that the body's broader physiological responses to stressors such as anaemia, exercise, hypoxia or ischaemia also differ by both stimulus nature and intensity. Thus, it is clear that the regulation and function of EPO are complex. Non-renal sites of EPO production could influence the haematological response to heat stress; however, no research to date has investigated the source of EPO in response to this stimulus.

Regulation of EPO synthesis: roles of hypoxia-inducible factors and heat-induced signalling. EPO is synthesised *de novo* – not stored intracellularly (Beru et al., 1986; Schooley & Mahlmann, 1972); thus, EPO production is primarily regulated at the transcriptional level. Most research on the transcriptional regulation of EPO has focused on HIFs, a family of transcription factors that sense and respond to disruptions in cellular O_2 partial pressure (P_{O_2}) by increasing EPO expression when O_2 availability is low (reviewed by Haase, 2013). HIFs are heterodimers composed of α and β subunits (Wang & Semenza, 1995). While HIF-β remains stable under normoxia, HIF-α is continuously degraded in the presence of oxygen, limiting its transcriptional activity. This occurs through hydroxylation by prolyl hydroxylase domain (PHD) enzymes, which targets it for degradation, and inactivation by factor-inhibiting HIF (FIH), which prevents co-activator interaction (Zhang et al., 2010). During hypoxia, however, the reduced O_2 availability inhibits PHD activity, stabilising HIF-α, which then translocates to the nucleus and heterodimerises with HIF-β. This dimer binds to hypoxia-response elements in the promoter region of target genes, initiating the transcription of EPO and promoting erythropoiesis to restore O_2-carrying capacity.

Importantly, the regulation of HIF activity is not solely governed by cellular O_2 tension. Reactive oxygen species (ROS) and other cellular stress signals can modulate PHD and FIH activity, stabilising HIF-1α and enhancing its transcriptional output even in normoxia

(Callapina et al., 2005). In addition, phosphorylation represents another regulatory layer, with kinases such as glycogen synthase kinase 3 (GSK3) and protein kinase A (PKA) shown to stabilise HIF-1α independently of hypoxia, particularly in response to exercise or cellular stress (Bullen et al., 2016; Kietzmann et al., 2016). Emerging evidence suggests that heat stress may engage similar pathways. Specifically, heat stress can activate the p38 mitogen-activated protein kinase (MAPK) pathway, promoting ROS accumulation in glial cells (Li et al., 2018), which may, in turn, influence HIF-1α stability via post-translational modification. While direct evidence of heat stress-induced phosphorylation of HIF-1α is lacking, the activation of cellular stress pathways, such as ROS and MAPK signalling, supports the possibility that heat may modulate HIF activity and EPO synthesis via hypoxia-independent mechanisms.

The HIF-α subunit has two significant isoforms that regulate EPO expression: HIF-1α and HIF-2α, which are differentially expressed across tissues (Stroka et al., 2001; Wiesener et al., 2003). While these isoforms share functions related to restoring O_2 supply (e.g. angiogenesis; Jaśkiewicz et al., 2022), they also regulate distinct downstream target genes (Loboda et al., 2010). For example, in endothelial cells, many genes specific to HIF-1α promote glycolysis and lactate production, while HIF-2α controls genes related to fatty acid mobilisation and transport (Downes et al., 2018) – though this may differ in other cell types. To our knowledge, only one study has investigated the effect of heat stress on HIF-1 activation. Specifically, Maloyan et al. (2005) found that heat stress increased HIF-1α levels and EPO expression in rat hearts but did not examine HIF-2α. While HIF-2α is primarily implicated in the erythropoietic response in adult tissues (Gruber et al., 2007; Rankin et al., 2007), whether this isoform is the primary responder to heat stress, and in which tissue(s) this occurs, remains to be determined.

The concept of cross-adaptation between heat stress and hypoxia, whereby exposure to one stressor can enhance tolerance to the other (Horowitz, 2007; Willmott et al., 2024), offers a useful framework for exploring shared molecular pathways that may mediate heat-induced modulation of the HIF pathway. A key mediator of this phenomenon is the family of heat shock proteins (HSPs), particularly HSP90, which is robustly upregulated in response to elevated core temperatures (Kuhlenhoelter et al., 2016; Richter et al., 2010). Once expressed, HSP90 interacts directly with components of the HIF pathway, stabilising HIF-1α under both hypoxic and normoxic conditions (Isaacs et al., 2002; Liu & Semenza, 2007). This interaction suggests that heat-induced HSP90 expression may facilitate the non-hypoxic stabilisation of HIF-1α, potentially contributing to EPO synthesis via mechanisms analogous to hypoxic signalling. Such a mechanism could underpin the haematological adaptations observed following long-term heat acclimation, including increased red blood cell volume and Hb mass. However, the role of HSP-mediated HIF stabilisation in driving EPO production following heat exposure has yet to be demonstrated. For a detailed overview of the physiological and cellular cross-tolerance mechanisms between heat acclimation and hypoxia, readers are encouraged to consult Ely et al. (2014).

Altitude- and heat-induced hypoxia: distinct stimuli for erythropoiesis. While the production of EPO is regulated by hypoxia, this stressor can manifest via distinct physiological conditions typically classified into four types: hypoxaemic, anaemic, ischaemic and histotoxic hypoxia. Each of these mechanisms uniquely affects EPO production, reflecting their role in O_2 transport and delivery (Auer & Sutherland, 2002; Jepson, 1968; Shadduck et al., 1968). Among these, hypoxaemic hypoxia (commonly induced by high-altitude environments) has been extensively studied in the context of altitude training (Płoszczyca et al., 2018). The reduced atmospheric pressure at altitude decreases arterial O_2 partial pressure (P_{aO_2}), which in turn reduces arterial oxygen content (C_{aO_2}), a critical variable regulating EPO production (Montero & Lundby, 2019). Sustained reductions in C_{aO_2} trigger compensatory mechanisms, including the upregulation of EPO synthesis, stimulating red blood cell production and enhancing the blood's O_2-carrying capacity to restore tissue oxygenation (Haase, 2010; Peacock, 1998).

In contrast to the hypoxic stimulus provided by altitude, heat stress has been proposed to elicit ischaemic hypoxia (Amorim & Schlader, 2025). Heat stress initiates blood redistribution away from the kidneys, redirecting it to the periphery to facilitate thermoregulation and skin cooling (Chapman et al., 2021). This reduction in renal blood flow could decrease renal tissue O_2 tension, subsequently activating EPO synthesis. Although direct evidence for reductions in renal tissue O_2 tension during heat stress is currently lacking, recent findings from DiMarco et al. (2024) demonstrate a reduction in renal blood velocity and subsequent increases in circulating EPO levels following hot water immersion, supporting a possible link between heat-induced changes in renal perfusion and erythropoietic responses. Under normal physiological conditions, intrarenal oxygenation is maintained by reducing O_2 consumption in response to decreased blood flow, preserving a stable O_2 extraction fraction (Evans et al., 2008; Levy, 1960). However, prolonged or severe heat stress may challenge this compensation by subsequently increasing renal O_2 demand due to elevated sodium reabsorption (Kiil et al., 1961; Ravanelli et al., 2021). Despite the kidneys' high baseline blood flow and low O_2 extraction per unit of blood (Edwards & Kurtcuoglu, 2022), significant heat-induced reductions in

renal perfusion could impair their homeostatic capacity, potentially leading to localised tissue hypoxia. Whether this heat-induced ischaemic hypoxia is sufficient to drive the sustained increases in red blood cell volume and Hb mass observed following long-term heat acclimation remains to be established. Further research is required to clarify the role of renal oxygenation dynamics in these haematological adaptations.

Renal oxygenation and EPO production. Ge et al. (2002) were among the first to propose renal parenchymal O_2 tension, governed by the balance between renal O_2 delivery and utilisation, as a critical regulator of EPO production. In their investigation of EPO release during short-term hypobaric hypoxia, they observed a strong correlation between erythropoiesis and urinary P_{O_2}, where a reduction in urinary P_{O_2} (indicating decreased renal O_2 delivery and/or increased renal O_2 utilisation) was associated with elevated EPO levels. While this relationship is largely correlational, it suggests that a reduction in parenchymal P_{O_2}, regardless of the specific driver, may serve as a key trigger for EPO synthesis.

In hypoxia, diminished O_2 availability increases renal O_2 extraction to maintain tissue oxygenation (Kainuma et al., 1990). In contrast, heat stress may increase renal O_2 utilisation indirectly through compensatory responses to plasma volume contraction, such as activation of sodium-retaining mechanisms. Enhanced sodium reabsorption in the renal interstitium, a major site of O_2 consumption, has been shown to elevate renal O_2 demand (Kiil et al., 1961). Theoretically, this increased O_2 consumption, driven by repeated sodium reabsorption, could contribute to EPO production following heat stress. However, as Jelkmann (1992) notes, heat-induced reductions in renal blood flow may simultaneously reduce renal O_2 demand, acting as a protective mechanism against a self-perpetuating cycle of polycythaemia. This feedback could prevent excessive renal hypoxia and mitigate overstimulation of EPO synthesis.

Ultimately, both hypoxia and heat stress may lower renal P_{O_2} via distinct upstream mechanisms but converge on a common O_2-sensing pathway that promotes erythropoiesis. While it is evident that the kidneys' sensitivity to intrarenal O_2 homeostasis plays a central role in regulating red blood cell production, further research is warranted to clarify the precise mechanisms linking renal O_2 dynamics to EPO synthesis, particularly in the context of heat stress.

'Critmeter' theory. The leading mechanism proposed by Rønnestad et al. (2021) following their heat training–Hb mass study was the 'critmeter' theory. This theory suggests that the plasma volume expansion associated with 1–2 weeks of heat acclimation results in a lowered (or diluted) haematocrit (Hct), which is recognised by the kidneys' 'critmeter', stimulating the synthesis of EPO. Specifically, the critmeter hypothesis posits that the kidneys regulate Hct around a homeostatic set-point at which arterial O_2 content and blood viscosity are finely balanced to optimise O_2 delivery to peripheral tissues (Dunn & Donnelly, 2007). Although this optimal value has been reported to be ∼45% (Fan et al., 1980), it should be acknowledged that human homeostatic set-points are inherently plastic, exhibiting considerable variability within and between individuals (Thirup, 2003). To maintain this balance, the kidneys are thought to obtain sensory feedback from renal tissue O_2 pressure and the fluid in the extracellular space, regulating red cell mass through EPO synthesis and plasma volume via excretion of salt and water (Donnelly, 2001). Notably, the renin–angiotensin–aldosterone system (RAAS), known for its role in volume regulation, may also influence renal EPO synthesis independently via angiotensin II (Vlahakos et al., 2010). However, the direct interaction between RAAS signalling and the 'critmeter' mechanism remains poorly defined. After a single bout of heat stress, an initial period of plasma volume contraction (driven by fluid loss during the stressor) precedes a super-compensatory expansion within hours of cessation (Fellmann, 1992). The degree of dehydration experienced can modulate both the extent of contraction and the magnitude of the subsequent plasma volume rebound (Akerman et al., 2017). However, its specific role in driving haematological adaptations, such as Hb mass expansion, remains unclear. This plasma volume expansion is facilitated by an increase in intravascular albumin content, which raises oncotic pressure and draws water into the vascular compartment from the interstitial space (Nelson et al., 2023; Patterson et al., 2004). The transient nature of this hypervolaemia requires repeated bouts to provide continued adaptation, with expansion peaking after ∼6 days (Périard et al., 2015; Sawka et al., 2011). After 1–2 weeks of heat acclimation, plasma volume expansion can range from 5% to 20% (Rønnestad et al., 2021; Sawka et al., 2000), decreasing resting Hct by as much as 4% after 11 days (Harrison et al., 1981). After ∼3–4 weeks (e.g. the same time it takes to see measurable increases in Hb mass at high altitude (Levine & Stray-Gundersen, 2007), it is thought that the critmeter – having detected the resulting difference in renal O_2 tension and begun synthesising EPO – increases red blood cell mass to push Hct back toward a more optimal set-point. Although physiologically plausible, the critmeter hypothesis remains untested, as no long-term heat acclimation study has collected time-resolved blood volume and compartment data, or directly assessed renal EPO production. Such data would be critical for evaluating the temporal relationship between volume shifts, Hct changes and EPO responses, and for providing

insight into the validity and kinetics of this proposed mechanism.

Beyond dilution: fluid balance and EPO regulation. In contrast to the critmeter theory, findings from Ehmke et al. (1995) indicate that dextran infusion alone does not affect circulating EPO levels, as a 12% blood volume expansion in conscious dogs left EPO concentrations unchanged. However, a 20% reduction in blood volume (in the absence of any change in Hct) led to a 1.5-fold increase in EPO within 5 h of the induced hypovolaemia. Although these increases may be attributed to the resultant decline in Hb mass due to haemorrhage, these data indicate that acute blood volume contraction may serve as a stimulus for EPO synthesis. While an expanded dilution space following plasma volume expansion may obscure modest increases in circulating EPO, the absence of detectable elevations across volume-loading studies suggests that any such increases are minimal or absent. Supporting these findings, Roberts et al. (2000) observed a 35 ± 6% increase in serum EPO within 24 h of plasmapheresis – an ∼7% plasma volume contraction following the removal of 500 ml of plasma, comparable to that seen during heat stress (Harrison, 1985) – despite a concurrent 2% increase in Hct. However, methodological limitations of this study, including the repeated withdrawal and reinfusion of red blood cells during the plasmapheresis process, make it difficult to fully disentangle whether the observed EPO increase was driven purely by hypovolaemia or influenced by a transient anaemic response. Collectively, these findings challenge the critmeter theory, suggesting that blood volume contraction, rather than plasma expansion, may be a more potent driver of EPO synthesis. The confounded methodologies used in these models underscore the need for research that can isolate hypovolaemia from reductions in red blood cell mass when investigating EPO regulation.

As with the hypovolaemic conditions described above, heat stress leads to plasma volume contraction. This effect, combined with the concurrent redistribution of blood to the skin to support thermoregulation, contributes to a reduction in central venous pressure (CVP) (Morimoto, 1990). Indeed, reductions in CVP alone can independently stimulate EPO production. Montero et al. (2016) show that orthostatic stress-induced reductions in CVP increase circulating EPO levels, an effect closely associated with elevated vasopressin, as indicated by copeptin concentrations. This suggests that baroreflex-mediated activation of fluid-regulatory mechanisms, including vasopressin and RAAS, may contribute to the EPO response. Supporting this, recent findings indicate that angiotensin II may stimulate renal EPO synthesis by upregulating HIF-2α expression in tubular cells, independent of hypoxia (Yasuoka et al., 2021). Thus, repeated plasma volume contractions and associated RAAS activation during heat acclimation may act as chronic stimuli for EPO production. Over time, as speculated by Lundby et al. (2023), these perturbations could accumulate to promote increases in red blood cell volume and Hb mass through sustained erythropoiesis.

Long-term heat acclimation: usage to date

Modes of heat. While most long-term heat acclimation studies have come from one laboratory, protocol design has varied. A complete summary of study methodologies and key findings is provided in Table 1. To date, all research on this topic has utilised cycling exercise under conditions of heat stress, imposed via changes to environmental temperature or clothing (i.e. heat suits). As exercise already serves as a form of metabolic heat stress, these heating modalities accentuate this stress by adding to the heat balance equilibrium (Brotherhood, 2008), increasing convective heat gain and/or limiting evaporative capacity. It stands to reason that passive modes of heating could be implemented with a similar effect, as short-term interventions – such as that of Kissling et al. (2022) – have observed no differences in the magnitude or kinetics of traditional heat adaptation outcomes (i.e. plasma volume expansion, resting core temperature decrease) between exercise in heat, hot water immersion, or sauna across a week of acclimation. Long-term heat acclimation protocols incorporating passive heat modes may be advantageous for athletes seeking to limit additional physiological strain, as exercise in the heat elevates cardiovascular and metabolic stress (Periard et al., 2021), which, if not managed appropriately, can compromise training intensity, overall workload and recovery. Among passive heat modalities, hot water immersion presents distinct physiological challenges. Not only is water's thermal conductivity substantially greater than air's (enabling an accelerated rise in core temperature), but it also introduces hydrostatic pressure (Kissling et al., 2022) – a factor that, independent of thermal stress, has been shown to acutely increase plasma EPO concentrations (Chudek et al., 1997). Future research should explore alternative passive heating strategies and their potential efficacy in eliciting haematological adaptations similar to those observed with active heat exposure.

Populations studied

Sex. Sex hormones appear to play a role in regulating EPO expression, though this relationship is tissue-specific and context-dependent. Oestrogen can suppress hypoxia-induced renal EPO production (Mukundan et al., 2002), while conversely stimulating EPO synthesis in

reproductive tissues such as the uterus and oviduct under oestrogen- and oxygen-dependent conditions (Masuda et al., 2000; Yasuda et al., 1998). Given these hormonal influences, sex differences may contribute to variability in erythropoietic responses to heat acclimation, with transient increases in EPO observed in females but not males following hot water immersion (DiMarco et al., 2024). Whether these transient sex-based differences in EPO response translate into differences in Hb mass expansion across a multi-week heat acclimation protocol remains unclear, particularly given that acute EPO elevations have not consistently predicted long-term changes in Hb mass following altitude exposure (Friedmann et al., 2005).

Only one study has investigated haematological outcomes following 5 weeks of heat training in females, observing similar adaptations to those seen in male participants (Lundby et al., 2023). It has been suggested that for traditional heat acclimation outcomes (i.e. attenuated thermal strain, cardiovascular adjustments and improved exercise performance in the heat), women may require longer acclimation periods to achieve the same levels of adaptation, with differences in metabolic heat generation and body composition resulting in lower thermal loads when compared to men (Wickham et al., 2021). As Lundby et al. (2023) prescribed participant workloads via perceived exertion, exercise-induced heat generation may have differed between individuals, making it difficult to discern whether differences arose as a result of differing stress or from sex. While concerns surrounding the varying effects of the menstrual cycle persist (as naturally menstruating females will go through every phase of their cycle across a 5-week protocol), overall adaptation may be unaffected, with trained women exhibiting no significant differences in thermoregulatory responses between phases of the menstrual cycle following a singular bout of heat stress (Kuwahara et al., 2005). For lesser trained women, however, the load of heat stress may need to be tailored depending on their menstrual cycle phase, with heat loss responses being further inhibited in the luteal phase when compared to the mid-follicular phase, demonstrating reduced sweat rates, lower cutaneous blood flow and a higher core temperature threshold for the onset of heat loss responses (Kuwahara et al., 2005; Lei et al., 2017).

Geographic location/ethnicity. To date, published research on long-term heat acclimation has exclusively come from laboratories based in Scandinavia: Lillehammer, Norway and Copenhagen, Denmark – municipalities with a maritime climate and cool summers (average highs of ∼21°C). Consequently, it is unknown whether populations residing in more tropical or arid climates would experience the same magnitude of adaptation. Notably, only two of the studies listed in Table 1 report the time of year in which protocols were conducted (respectively, August–September and October–November), leaving open the possibility that seasonality or baseline thermal exposure may influence responsiveness.

Ethnic differences in heat adaptation have been attributed to both morphological factors, such as higher surface area-to-mass ratios facilitating heat dissipation, and physiological responses, including differences in sweating patterns and thermoeffector sensitivity (Taylor, 2006). These factors may influence how different populations respond to long-term heat acclimation, with potential variations in the magnitude or kinetics of adaptation. For a detailed review on these ethnic variations and their potential evolutionary or phenotypic bases, readers are directed to Taylor (2006).

Fitness level. The majority of current literature focuses on elite athletes, with just Oberholzer et al. (2019) and Mikkelsen et al. (2019) investigating effects on a sub-elite cohort. Where typically studies seeking to improve elite athlete performance will observe marginal gains or what has been termed a 'ceiling effect', it appears that long-term heat acclimation may be just as potent a stimulus irrespective of baseline fitness levels, with elite athlete cohorts undergoing similar absolute Hb mass expansions as a sub-elite cohort (see Table 1). It is reasonable to expect that lesser-trained individuals would also exhibit haematological and performance adaptations; however, further research is needed to clarify the extent of these responses.

Although not undertaken for Hb mass or performance improvements, long-term heat acclimation has been implemented in less active/clinical cohorts, with 8- to 12-week interventions shown to improve skin vascular function, endothelial function, arterial stiffness and blood pressure (Akerman et al., 2019; Brunt et al., 2016; Roxburgh et al., 2025), suggesting potential benefits beyond those related to performance for elite athletes.

Perspectives: why use heat over altitude

As the exploration into long-term heat acclimation for athletic performance continues, its capacity to become a more commonly practised mode of environmental training (i.e. as an alternative to altitude) is evident (Fig. 1). As it stands within current published literature, long-term heat acclimation boasts comparable Hb mass adaptation to that observed following altitude training camps (Table 1; Nummela et al., 2021). In addition, heat offers benefits unattainable through altitude training alone. Unlike the latter, passive/active heat acclimation triggers physiological adaptations with ergogenic potential that extend beyond haematological parameters, conferring positive cardiovascular adaptation alongside the well-known thermoregulatory benefits

(e.g. lower resting core temperatures, increased sweating sensitivity/power and greater thermal tolerance) (Périard et al., 2015; Rodrigues et al., 2024).

While financial support does not guarantee international sporting success, those countries and organisations that receive less funding for athletic pursuits face tough decisions about where to allocate their limited resources (De Bosscher et al., 2015). The cost-effectiveness of heat training makes it an attractive option for individuals and teams with budgetary considerations. For a single United Kingdom-based endurance athlete departing from London, return flights to Flagstaff, Arizona (a popular location for altitude training) can cost £700–1200, while 4 weeks of accommodation may cost an additional £1500 (prices variable). In contrast, the electrical or gas cost of running a hot bath is less than £10 across a 5-week protocol, while putting on thermal layers of clothing to exercise in is free. The environmental implications of these choices should also be considered. Heat training may largely circumvent the ecological footprint associated with travel to high altitude alone, with the economy flights listed above emitting 2.6 tonnes of CO_2 per person (Tipton & Montgomery, 2022). In contrast, hot water immersion generates ∼25 kg across 5 weeks (assuming 5× baths/week, dependent on gas versus electricity; https://www.carbonindependent.org), ∼1% of the CO_2 emissions. Heat stress induced by additional clothing layers during exercise requires no direct energy input, producing only minimal emissions associated with increased metabolic needs. Given that altitude training is often periodised into multiple camps throughout an athlete's season (Mujika et al., 2019), these economic and environmental costs can accumulate considerably over the course of an elite athletic career.

Heat training offers a versatile solution for athletes worldwide, circumventing geographical constraints. Even in the absence of environmental chambers, athletes can utilise thermal clothing or hot water immersion protocols via baths or hot tubs to simulate heat stress (Lundby et al., 2021). It is important to note, however, that home-based

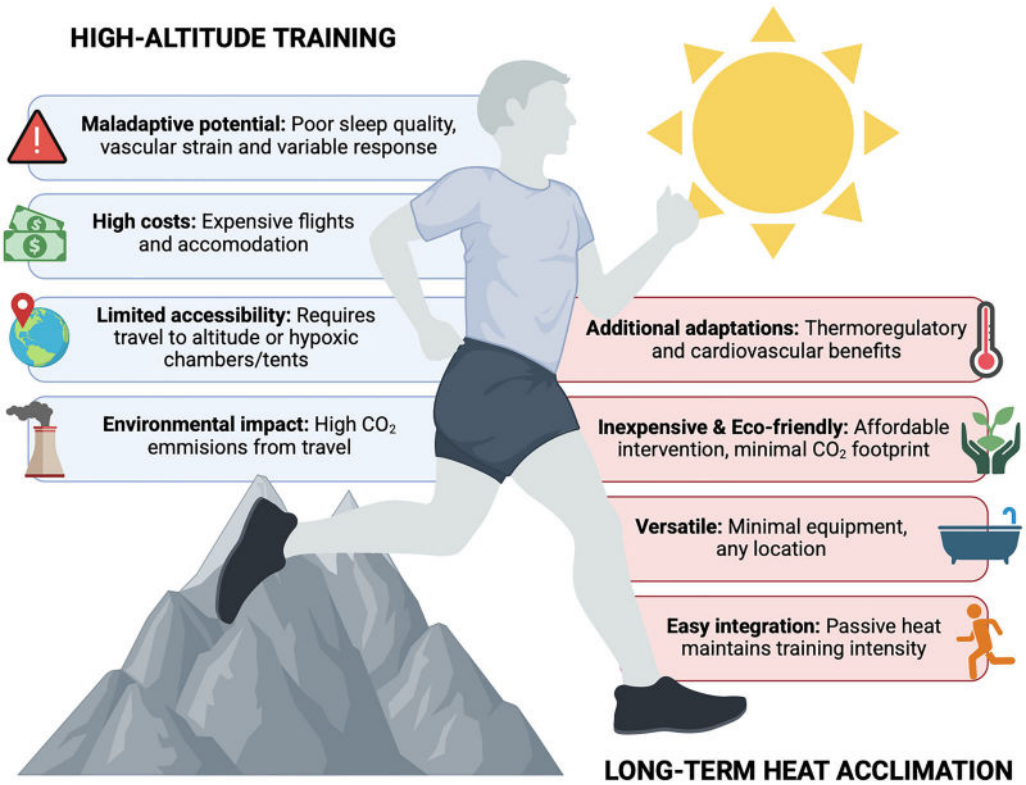

Figure 1. Comparison of high-altitude training and long-term heat acclimation as environmental interventions to enhance hemoglobin mass
High-altitude training is associated with potential maladaptive effects (poor sleep quality, vascular strain, variable responsiveness), high financial costs, limited accessibility, and substantial environmental impact due to travel. In contrast, long-term heat acclimation offers additional thermoregulatory and cardiovascular adaptations, is inexpensive and eco-friendly, highly versatile with minimal equipment needs, and can be easily integrated into training without compromising intensity.

heat alternatives may not fully replicate the training camp effect observed during altitude or warm-weather training camps (Levine & Stray-Gundersen, 1997), whereby athletes can undergo positive adaptation as a result of focused, supervised training in a new location and not necessarily environmental stimuli *per se*. Therefore, sporting organisations, coaches and athletes should aim to gain a thorough understanding of the advantages and drawbacks of both altitude and heat training interventions to make informed decisions about resource allocation. For a measured perspective on these environmental stimuli, as they relate to prolonged stage races in cycling, readers are encouraged to seek out the work of Nybo et al. (2024).

Additionally, the application of heat acclimation remains viable even within strict regulatory environments. Notably, since the Olympic Winter Games in Sochi in 2014, the International Olympic Committee (IOC) has banned the use of hypoxic chambers within the Olympic Village, restricting the ability to simulate altitude conditions for training during the Games. In contrast, heating solutions, such as hot water immersion or the use of thermal clothing, remain permissible, offering athletes a practical and compliant alternative to maintain physiological adaptations.

Lastly, it is important to note that these long-term heat acclimation interventions are not without safety and practical considerations. While severe altitude illness is relatively rare during supervised altitude training camps, particularly at the moderate altitudes most commonly used (i.e. 2000–2500 m) (Schommer et al., 2012), the risk of heat-related illnesses such as heat stroke may be heightened if heat training is undertaken without appropriate monitoring, hydration strategies and gradual progression (Coris et al., 2004). Athletes and practitioners should ensure that protocols are implemented with caution, especially when using passive or home-based heating methods that lack direct supervision (Menzies et al., 2025). In addition to these safety considerations, practical factors should also be acknowledged. While altitude training can elicit measurable Hb mass increases within 2–3 weeks (Levine & Stray-Gundersen, 2007), heat stress studies have typically utilised 5-week protocols, with only Cubel et al. (2024) reporting meaningful gains after 3 weeks (though further increases were seen by week 5). This suggests that longer durations may be needed to maximise adaptations, forming an important consideration for coaches and athletes when planning training macrocycles and periodisation strategies. Finally, while existing literature supports heat exposure as a potent stimulus for erythropoiesis, all studies to date have examined it in combination with exercise, leaving its independent effect unclear. Further research is needed to disentangle the specific contributions of heat stress from those of the underlying training stimulus.

Future directions

Despite growing interest in long-term heat acclimation, our understanding of its physiological mechanisms and applications remains incomplete. Characterising the EPO response to long-term heat acclimation – including its time course, magnitude and daily variability – represents a critical gap in the current literature, as does identifying the specific physiological driver(s) of EPO synthesis in response to heat stress. While reductions in renal blood flow have been observed alongside increases in EPO following heat exposure, the relative contribution of this response compared to the critmeter's role in Hb mass expansion is unclear. Moreover, it is not yet known whether the kidney is the primary source of EPO following heat stress, or whether non-renal tissues contribute to this response. Future research should determine whether renal blood flow reductions alone are sufficient to trigger a sustained erythropoietic response or whether they primarily act as an acute stimulus, with the critmeter providing a longer-term regulatory mechanism. Studies employing targeted renal blood flow manipulations, tissue-specific EPO measurements, and longitudinal tracking of EPO kinetics and Hb mass are warranted to help clarify the relative contributions of these proposed mechanisms. From an applied perspective, and as mentioned above, it is important to determine whether passive modes of heat acclimation (hot water immersion or sauna bathing) can provide a similar effect on haematological outcomes as those already published using active exercise-based protocols. Post-exercise hot water immersion, in particular, may offer a more effective and convenient strategy for long-term heat acclimation, having been shown to enhance thermal adaptation over a conventional 12-day protocol (McIntyre et al., 2022). Given that nearly all existing data come from active heating studies in well-trained or elite athletes, investigations involving passive heating in sub-elite or recreational populations are notably lacking and merit further exploration. Additionally, given the overlap in mechanisms supporting the favourable health outcomes of passive heating and aerobic exercise (Cullen et al., 2020), it is reasonable to anticipate that these heating modes could induce similar adaptations to those seen in active heat-acclimation interventions. Exploring the capacity for heat acclimation to be used in conjunction with altitude is of additional interest, particularly upon altitude deacclimation, where EPO synthesis is fully withdrawn within days (Klein et al., 2021). If incorporating multiple days of heating in the week(s) following descent were to sustain EPO levels and prolong haematological adaptations gained at altitude, the continued practice of high-altitude training camps may become slightly more efficacious (Rønnestad et al., 2024).

Conclusions

This review underscores the promising potential of long-term heat acclimation as an environmental intervention to improve O_2 carrying capacity via haematological adaptation. Although the exact mechanisms driving Hb mass expansion in response to heat stress remain uncertain, EPO appears to play a pivotal role. It may be that mechanisms overlap such that, acutely, the heat stress-induced plasma volume depletion/repletion cycle and reduced renal O_2 tension elevate circulating EPO, while effects of the 'critmeter' are protracted.

While long-term heat acclimation studies have exclusively utilised cycling exercise under heat stress conditions, there is significant potential for passive heating methods to yield similar adaptations. Research studies elucidating precise mechanisms, differing modes of heat stress and various applications of long-term heat acclimation are warranted, as is the endorsement of long-term heat acclimation (as a feasible alternative to altitude) amongst the endurance athlete community.

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Additional information

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Author contributions

All authors contributed to the design and writing of the manuscript. All authors approved the final version of the

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