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Title: Integrative crosstalk between hypoxia and the cold: old data and new opportunities.

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New findings

What is the topic of this review?

- The aim is to examine the influence of hypoxia on thermoregulatory and cardiovascular control in the cold.

What advances does it highlight?

- Exposure to hypoxia seems to alter both thermoregulatory and cardiovascular control, but these conclusions are based on limited data and this review highlights the need for future research in this area.

Abstract

Cold stress and hypoxia have been the subject of research for decades; however, humans often encounter these stressors together, such as in the alpine environment. Therefore, this review summarizes previous data with respect to the influence of hypoxia on thermoregulatory and cardiovascular control in the cold and presents new ideas for the future. Altogether, little to no evidence is available on the integrative and adaptive mechanisms about how the human body regulates heat conservation, oxygen delivery, and maintenance of blood pressure.

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Introduction

When engaging in leisure activities or work in alpine environments, the risk from cold exposure, including non-freezing (frostnip) and freezing cold injury (frostbite) and hypothermia, is increased (McIntosh *et al.*, 2019). This is mainly to the exacerbation of environmental factors that cause conductive and convective heat loss including falling ambient temperatures, increased potential for wind chill (high wind speeds and lack of shelter), and precipitation (rain and snow fall) (Harirchi *et al.*, 2005). Moreover, in most alpine environments, the fall in barometric pressure reduces the partial pressure of oxygen and causes hypoxemia. As cold exposure itself causes thermoregulatory and cardiovascular adjustments to maintain homeostasis, hypoxia has the potential to affect multiple pathways relating to autonomic thermoregulation during cold exposure. Moreover, the ability to behaviourally thermoregulate may be negatively affected by a combined exposure to hypoxia and the cold.

The physiological response to hypoxia and the cold have been reviewed extensively. However, limited information has been provided on their interactive effects (Tipton, 2012), despite their mutual occurrence at high altitude. Thus, this hot topic review aims to synthesize the available literature concerning the interactive effects of hypoxia and cold on autonomic and behavioural thermoregulatory and cardiovascular responses. In each section, we briefly describe the effect of cold alone before describing how hypoxia may influence these regulatory mechanisms in thermoneutral and cold environments.

First line of defence: Cold-induced vasoconstriction. Upon cold exposure, a decrease in skin temperature stimulates reflex and local cutaneous vasoconstriction to decrease the temperature gradient between the skin and environment to maintain core temperature. Neural reflex mechanisms include increased skin sympathetic nerve activity (Sawasaki *et al.*, 2001) and subsequent discharge of noradrenaline and co-transmitters such as neuropeptide Y (Stephens *et al.*, 2004). In contrast, the direct effect of local cooling on cutaneous blood vessels produces a more protracted vasoconstriction through alterations in nitric oxide synthase activity, production of intracellular reactive oxygen species and rho-kinase signalling, ultimately leading to $alpha_{2C}$-receptor translocation and a potentiation of the response to noradrenaline (reviewed in (Johnson & Kellogg, 2018)). After the initial decline in skin temperature, cutaneous blood flow and thus temperature periodically increases due to the opening of arteriovenous anastomoses – cold-induced vasodilation (CIVD), which is considered a protective mechanism against peripheral cold injury (Aubdool *et al.*, 2014).

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Hypoxic influence. Acute hypoxia causes cutaneous vasodilation and a rise in blood flow (Simmons *et al.*, 2010) to non-acral skin, but interestingly vasoconstriction within acral skin (hands and feet) upon whole body cooling (Simmons *et al.*, 2011a; Massey *et al.*, 2018). Thus, in an alpine environment, a competition occurs between maintaining oxygen delivery within distinct vascular beds (hypoxia-induced vasodilation) and altering skin blood flow to avoid peripheral cold injury, or conserve heat/energy (cold-induced vasoconstriction).

Acral skin: Risk of peripheral cold injury. During acute hypoxia, the onset of vasoconstriction occurs earlier and the release of vasoconstriction later (Massey *et al.*, 2018), with local finger rewarming being blunted (Fahim, 1992). Some studies also show a greater rate of skin cooling and lower absolute skin temperatures when local cold exposure is combined with prolonged hypoxia (Mathew *et al*., 1977; Takeoka *et al*., 1993; Purkayastha *et al*., 1999; Daanen & van Ruiten, 2000; Kounalakis *et al*., 2017). High altitude field studies have also noted an attenuated CIVD response (Figure 1) (Mathew *et al.*, 1977; Purkayastha *et al.*, 1999; Daanen & van Ruiten, 2000). However, no differences in CIVD are observed with 30 minutes (Keramidas *et al.*, 2014) or 10 days (Keramidas *et al.*, 2015) of controlled exposure to mild hypoxia (i.e. normobaric laboratory). Surprisingly, an enhancement of CIVD has also been noted with a sleep-high train-low regime that resulted in an improved aerobic fitness and acclimatization to high altitude (Amon *et al.*, 2012). At present, it is difficult to interpret these inconsistencies as populations and experimental designs differ in studying young healthy adults, alpinist during expeditions, controlled laboratory tests, different severities of hypoxic stress and exercise training interventions (reviewed in (Cheung & Daanen, 2012)). Ultimately, it is difficult to make definitive conclusions regarding how different severities and durations of hypoxia might alter the risk of cold injury to the fingers or toes. Some evidence suggests that hypoxia increases the risk of cold injury via skin blood flow alterations. For example, hypoxia causes a profound elevation in skin sympathetic nerve activity directed towards the hand (Kollai, 1983), although it does not affect alpha-receptor sensitivity in the forearm (*see non-acral skin* (Simmons *et al.*, 2011b)). Hypoxia also increases ventilation, which may modulate cutaneous vasomotor tone during cold exposure due to respiratory-induced withdrawal of vasoconstrictor outflow (Wallin *et al.*, 1998). To the best of our knowledge, no pharmacology studies have been performed in the acral skin of hypoxic and cold humans. Yet, hypoxia does elevate circulating neuropeptide Y concentrations (Pernow *et al.*, 1989) and Y_1 receptor activity on skeletal muscle arterioles (Coney & Marshall, 2007), which might ultimately favour vasoconstrictor function if these observations translate to acral skin. Finally, conduit artery vasodilator function is typically reduced in hypoxic environments alongside an

increase in systemic reactive oxygen species production (Lewis *et al.*, 2014a). If similar observations occur in acral skin, one might expect alterations in the restoration of blood flow (CGRP, Substance P and/or nitric oxide production) and the modulation of transient receptor potential ion channel 1 function, which has recently been identified as a key regulator in the cold-induced vasoconstrictor response and restoration of blood flow after peak vasoconstriction (Aubdool *et al.*, 2014). Indeed, vitamin C supplementation improves the cold-induced vasodilatory response in hypoxia (Purkayastha *et al.*, 1999).

Non-acral skin: Risk of hypothermia. Hypoxia generally causes cutaneous vasodilation in non-acral skin (Simmons *et al.*, 2007). Although one caveat to this interpretation is that experimental models typically select short periods of severe hypoxia (SpO_2, 80%; 15–30 minutes), whereas when hypoxia is prolonged (SpO_2, 81–86%; 2–9 hours), if anything, a mild cutaneous vasoconstriction is observed (Lawley *et al.*, 2014). Nevertheless, when mild whole body air (Kottke & Phalen, 1948; Blatteis & Lutherer, 1976; Simmons *et al.*, 2010; Fukazawa *et al.*, 2013) and local water cooling (O'Brien *et al.*, 2015) are applied under hypoxic conditions, the cutaneous vasoconstrictor response seems attenuated such that skin temperature is higher, heat dissipation is increased and core temperature falls more rapidly (Cipriano & Goldman, 1975; Johnston *et al.*, 1996; Keramidas *et al.*, 2019; Gibbons *et al.*, 2020) and to a lower absolute value (Kottke & Phalen, 1948; Bullard, 1961; Cipriano & Goldman, 1975; Johnston *et al.*, 1996). However, this finding is not unanimous with some studies showing similar core cooling (Blatteis & Lutherer, 1976; Simmons *et al.*, 2011a). Further, mechanistic studies have identified that non-acral cutaneous alpha-adrenergic responsiveness remains intact with hypoxia (Simmons *et al.*, 2011b), and cutaneous vasoconstriction is actually increased with prolonged severe whole body water cooling, albeit through a non-adrenergic mechanism (Simmons *et al.*, 2011a). Thus, it seems that under rapid cooling events, such as falling in cold water, the non-acral skin vasoconstrictor response to the cold overrides the effect of hypoxia, but with milder more prolonged cooling, such as falling injured and awaiting rescue in cold air, the cutaneous circulation remains relatively dilated and the rate of core cooling maybe exaggerated. These conflicting data may reflect differing interactive mechanisms between hypoxia and thermal regulation in the neutral zone (Savage & Brengelmann, 1996) and in the rate dependency of cooling in human skin (Yamazaki *et al.*, 2006).

Second line of defence: Behavioural responses. Upon sensation of external cold temperatures below the individual's thermal comfort zone, a conscious decision is made to behaviourally thermoregulate, i.e. seeking shelter, adding clothing, or increasing physical activity. Thermal

behaviour is mediated by thermal sensations and discomfort with respect to skin, and to a smaller extent, core temperature (Mower, 1976; Schlader *et al.*, 2013).

Hypoxic influence. Thermoregulatory behaviour may be delayed in acute hypoxic conditions by a blunted cold sensation in the toes upon local cooling (Golja *et al.*, 2004), although this is not a universal observation. No changes were reported for thermal sensation and thermal comfort during local (Amon *et al.*, 2012; Keramidas *et al.*, 2014, 2015; O'Brien *et al.*, 2015) and whole body cooling (Reading *et al.*, 1996; Fukazawa *et al.*, 2013; Massey *et al.*, 2018; Keramidas *et al.*, 2019). If anything, a combination of mild hypothermia induced by whole body water immersion and acute hypoxia tended to enhance comfort in hands that were separately immersed in 8°C water (Keramidas *et al.*, 2019). Moreover, behavioural choice to preferred hand temperature upon whole body (Golja & Mekjavic, 2003) and pain sensation after local water immersion (Keramidas *et al.*, 2014, 2015) remained unchanged. Ultimately, there seems to be little effect of combined hypoxia and cold stress on thermoregulatory behaviour, but further investigations are warranted.

Third line of defence: Thermogenesis. During cold exposure, shivering is initiated at skin temperatures of ~27–28°C (Meigal, 2002) and metabolic heat production can be increased up to 5-fold of resting metabolic rate (Eyolfson *et al.*, 2001). An increase in metabolic heat production can also be achieved without overt shivering. For example, $beta_2$-adrenergic receptor activation of brown adipose tissue causes H^+ cycling and heat production (Cannon & Nedergaard, 2004). Moreover, mitochondrial “proton leak” and calcium cycling within the resting skeletal muscle is proposed to increase basal heat production (Blondin & Haman, 2018). While both mechanisms may be important for non-shivering thermogenesis in the cold, it is worth mentioning that the contribution of brown adipose tissue is suggested to be minimal (~1%) compared to muscle non-shivering thermogenesis (~24%) (Blondin *et al.*, 2017).

Hypoxic influence. Under hypoxic conditions, a hypometabolic state has been well established in animals (Gu & Jun, 2018), but conflicting evidence exists for this process in humans under thermoneutral environments (Seo *et al.*, 2017). During combined cold and hypoxia, a hypometabolic state is often observed in humans during periods of shivering (Kottke & Phalen, 1948; Blatteis & Lutherer, 1976; Johnston *et al.*, 1996; Keramidas *et al.*, 2018) (Figure 2). What remains unsettled, is the contribution of shivering versus non-shivering thermogenesis. At present, it seems that hypoxia may lower the threshold for shivering (Johnston *et al.*, 1996), but when shivering starts the intensity remains the same (Blatteis & Lutherer, 1976), albeit quantified by visual observations using an arbitrary scale. Evidence of a hypoxia-mediated inhibition of non-

shivering thermogenesis is limited to animal studies reporting diminished brown adipose tissue sympathetic nerve activity (Madden & Morrison, 2005), blood flow (Mortola *et al.*, 1999) and uncoupling protein 1 expression (Mortola & Naso, 1997). Ultimately, convincing data examining shivering and non-shivering thermogenesis in the hypoxic and cold human are lacking with very limited or no data available in relation to fuel utilization (Robinson & Haymes, 1990) or patterns of muscle recruitment during shivering.

Cardiovascular regulation. The cold evokes distinct changes within the cardiovascular system and displays regional circulatory control including a reproducible rise in blood pressure (Greaney *et al.*, 2014) that is independent of shivering, yet no change in heart rate (Wilson *et al.*, 2007). Interestingly, muscle sympathetic nerve activity is unchanged during body cooling via a water-perfused suit that does not evoke shivering, (Greaney *et al.*, 2014) (Figure 3A), yet a decrease in vascular conductance is observed in human brachial, celiac, superior mesenteric and renal arteries (Wilson *et al.*, 2007). These data suggest that vasoconstriction and the rise in blood pressure is not due to reflex sympathetic activity within the skeletal muscle, but due to either an augmentation of neurogenic sympathetic vascular transduction or circulating hormones including noradrenaline and/or the renin-angiotensin system (Hiramatsu *et al.*, 1984; Sun, 2010). However, a divergent change in sympathetic control to distinct vascular beds (muscle, renal, splanchnic) could also explain these observations. A caveat to the overview presented above is that when whole body cooling (10°C) is applied, including the head, neural sympathetic hyperactivity is observed and is directly related to the increase in blood pressure (Fagius & Kay, 1991) (Figure 3B). Indeed, covering the head attenuates the hypertensive response to the cold (Li *et al.*, 2009). Once continuous or intense shivering bursts begin and metabolic rate is elevated, cardiac output (Vogelaere *et al.*, 1992) and skeletal muscle vascular conductance are likely increased to maintain oxygen delivery, although limited data exist to support this.

Data on the influence of cold exposure on cerebral blood flow regulation in healthy humans are also sparse. Immersion in cold water causes a cold shock response, hyperventilation and a reduction in blood flow to the brain despite an elevation in cerebral perfusion pressure (Tipton *et al.*, 2000; Gibbons *et al.*, 2020). The fall in cerebral blood flow is, in large part, due to respiratory-induced hypocapnia, as normalization of $PaCO_2$ restores 58% of the reduction in brain blood flow (Gibbons *et al.*, 2020). However, in contrast to cold water immersion, mild body surface cooling caused no change in end-tidal carbon dioxide and a slight (4%) increase in middle cerebral artery blood flow velocity (Durand *et al.*, 2004).

Hypoxic influence. In contrast to cold exposure, acute hypoxia causes profound peripheral chemoreceptor-mediated sympathetic hyperactivity, an elevation in heart rate and cardiac output, yet total peripheral resistance is reduced. Moreover, hypoxia causes hyperventilation-induced hypocapnia, but cerebral blood flow is typically elevated (Lewis *et al.*, 2014b). Ultimately, the interaction of these physiological processes is to maintain oxygen delivery to both the periphery and the brain, whilst also maintaining blood pressure. To date, few studies have examined the cardiovascular effects to combined cold and hypoxia, but given the opposing physiological responses presented herein, it is likely that under some circumstances, a conflict exists between the maintenance of oxygen delivery, blood pressure and thermal balance. One recent study highlighted this complexity by combining hypoxia with cold water immersion (Gibbons *et al.*, 2020). The main findings from this study were that the pressor response to the cold remained despite the hypoxia-mediated reduction in baseline total peripheral resistance. The control of blood pressure also seemed to differ, as blood pressure was elevated as a function of tachycardia and increased cardiac output in normoxia, whereas increased peripheral vascular resistance played a major role during acute hypoxia. Moreover, core cooling (−1.0°C) caused a substantial reduction in cerebral blood flow in normoxia (−Δ252ml·min^{-1}), which was blunted when core cooling was combined with acute hypoxia (−Δ28ml·min^{-1}).

Future directions. While important observations have been made about the crosstalk between cold exposure and environmental hypoxia (Figure 4), there remain a plethora of gaps in our knowledge. For example, most studies combining hypoxia and cold stress have utilized either water immersion or a water perfused suit. While these techniques provide excellent control of skin temperature, they typically lack direct cold exposure to the head, which is common in real world conditions, and may markedly alter the physiological response (Fagius & Kay, 1991; Li *et al.*, 2009). Also, periods of whole body or local limb cooling are typically very short (minutes), whereas cold casualty rescues can last many hours, sometimes overnight, and cause prolonged periods of hypothermia. As sleeping in hypoxia causes profound cardiovascular alterations, the impact on the cold response could be substantial. Moreover, to the best of our knowledge, no studies have examined the effect of hypoxia on cardiovascular regulation or thermoregulation when a person's core temperature is in the hypothermic range for prolonged periods of time. While not a major focus of the current review, the effect of altitude acclimatization has previously been studied in relation to the cold response (e.g. (Blatteis & Lutherer, 1976)). Yet, our basic understanding regarding the effect of acclimatization and extreme altitude exposures on reflex cutaneous vasoconstriction, thermogenesis and cardiovascular responses to the cold are limited. Moreover,

prolonged periods of exercise are common before a cold casualty scenario and differences in clothing (e.g. fabrics, number of layers and covered skin surface) can impact the thermoregulatory response but are rarely studied. Like many areas of human research, most studies presented herein have been conducted with healthy males only. Indeed, we could not find a single study on the combined effect of hypoxia and the cold that included a direct sex comparison. As more and more older adults are venturing into the mountains for recreation, the risk of falls increases as does the chance of a cold casualty scenario. Aging and comorbidity are known to effect both thermoregulatory and cardiovascular physiology and their responses to the cold. How a background of hypoxemia alters these responses is practically unknown.

Conclusion. Decades of research has focused on the physiology of hypoxia and cold stress in isolation. In contrast, relatively little attention has been paid to the combination of both environmental stressors despite their frequent mutual occurrence. Future research in this area is poised to discover highly integrative and adaptive mechanisms about how the human body regulates the need to conserve heat, deliver oxygen, and maintain blood pressure.

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Conflict of interest. None.

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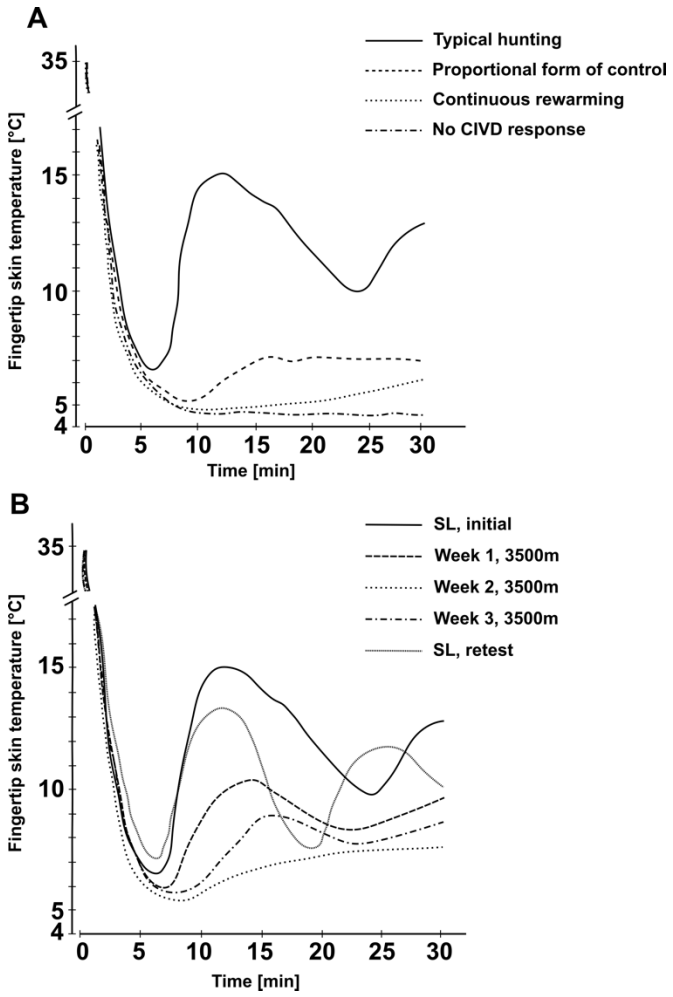

Figure 1. Interindividual variations in fingertip cold induced vasodilation and impairment at high altitude. Different patterns of cold-induced vasodilation (CIVD) that can be observed in the index fingertip when cooled in 4°C water at sea level (panel A) and reductions in the CIVD response during 3 weeks at high altitude and normalisation after return to sea level in one participant with a typical CIVD response at sea level (panel B). Redrawn from Mathew et al., 1977.

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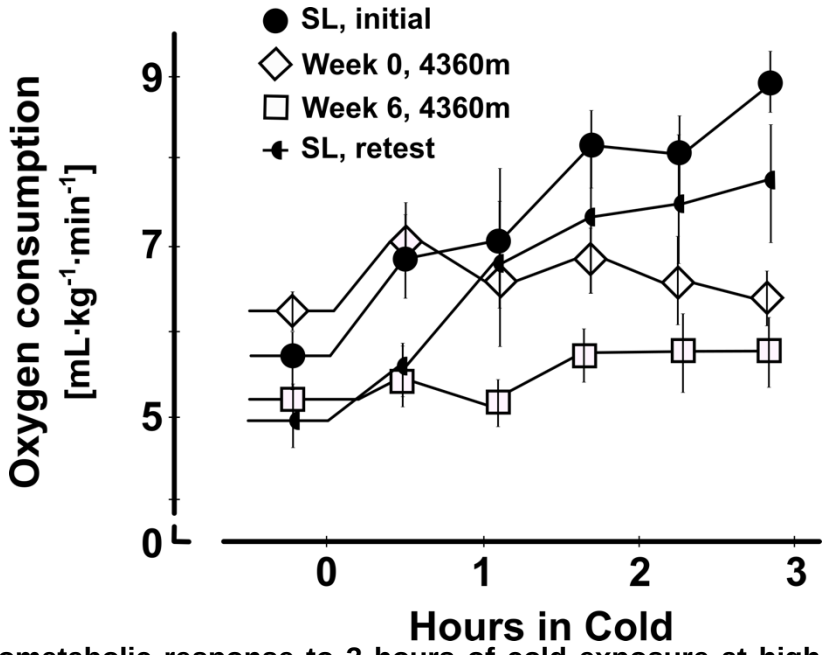

Figure 2. **Hypometabolic response to 3 hours of cold exposure at high altitude**. Oxygen consumption increases during cold exposure (10°C air) at sea level due to shivering and non-shivering thermogenesis (●, SL). However, on arrival (◇, week 0) and after 6 weeks (□) at high altitude (4,360 m), the increase in oxygen consumption to the same cold stress is attenuated, suggesting a reduction in the shivering and/or nonshivering thermogenic response to the cold. On return to SL (◖), this response is mostly normalised. Time points preceding 0 are the means of three consecutive measurements in 26°C. Redrawn from Blatteis and Lutherer, 1976.

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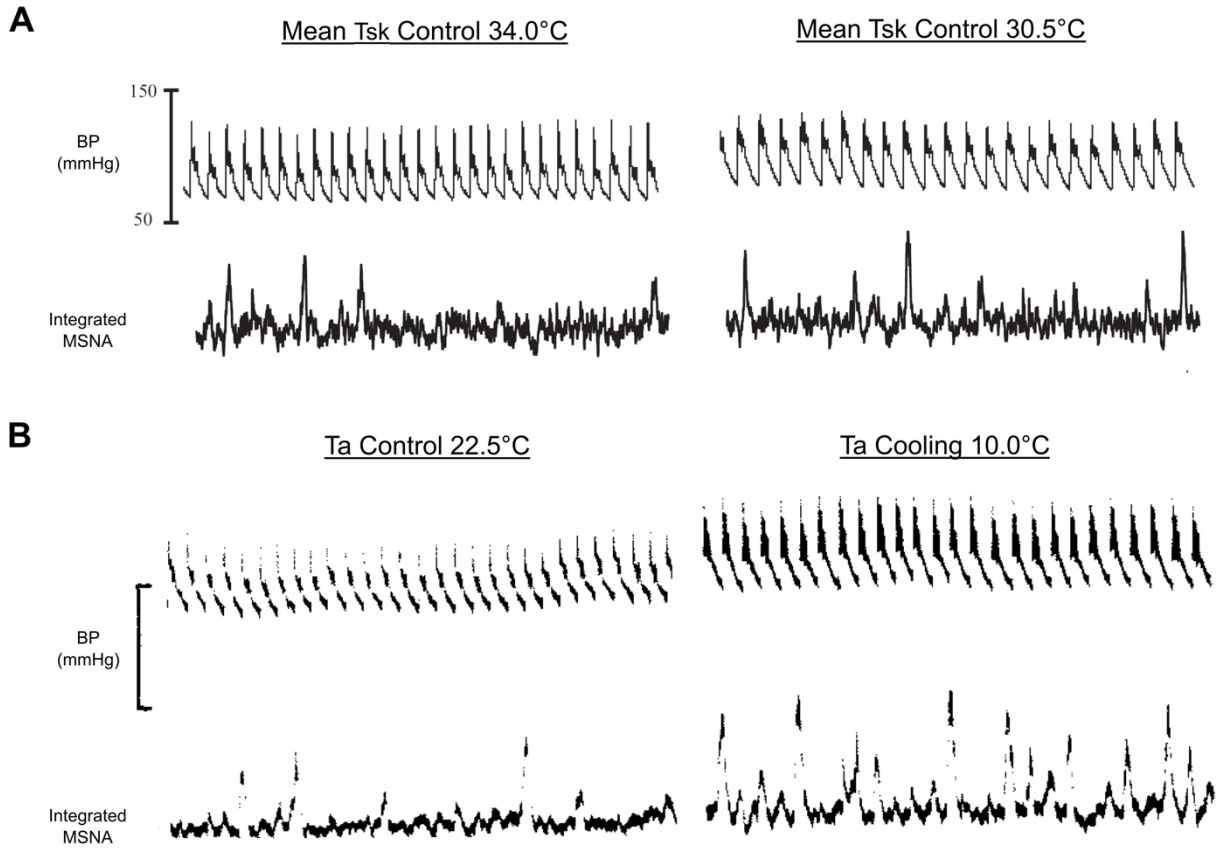

Figure 3. Divergent changes in muscle sympathetic activity in response to torso cooling only (panel A) and whole body cooling, including the face (panel B). Segments of original neural recordings showing the integrated neurogram of muscle sympathetic nerve activity (MSNA) in control conditions (T_{sk} 34.0°C) and during surface cooling (T_{sk} 30.5°C) via a water-perfused suit (panel A). Recording of mean voltage neurogram of MSNA from one subject during initial control (T_A 22.5°C) and at the lowest environmental temperature (T_A 10.0°C) when cooled in a whole body box (panel B). BP, arterial blood pressure; T_{sk}, skin temperature; T_a, ambient temperature. From Greaney et al., 2014 and Fagius and Kay, 1991.

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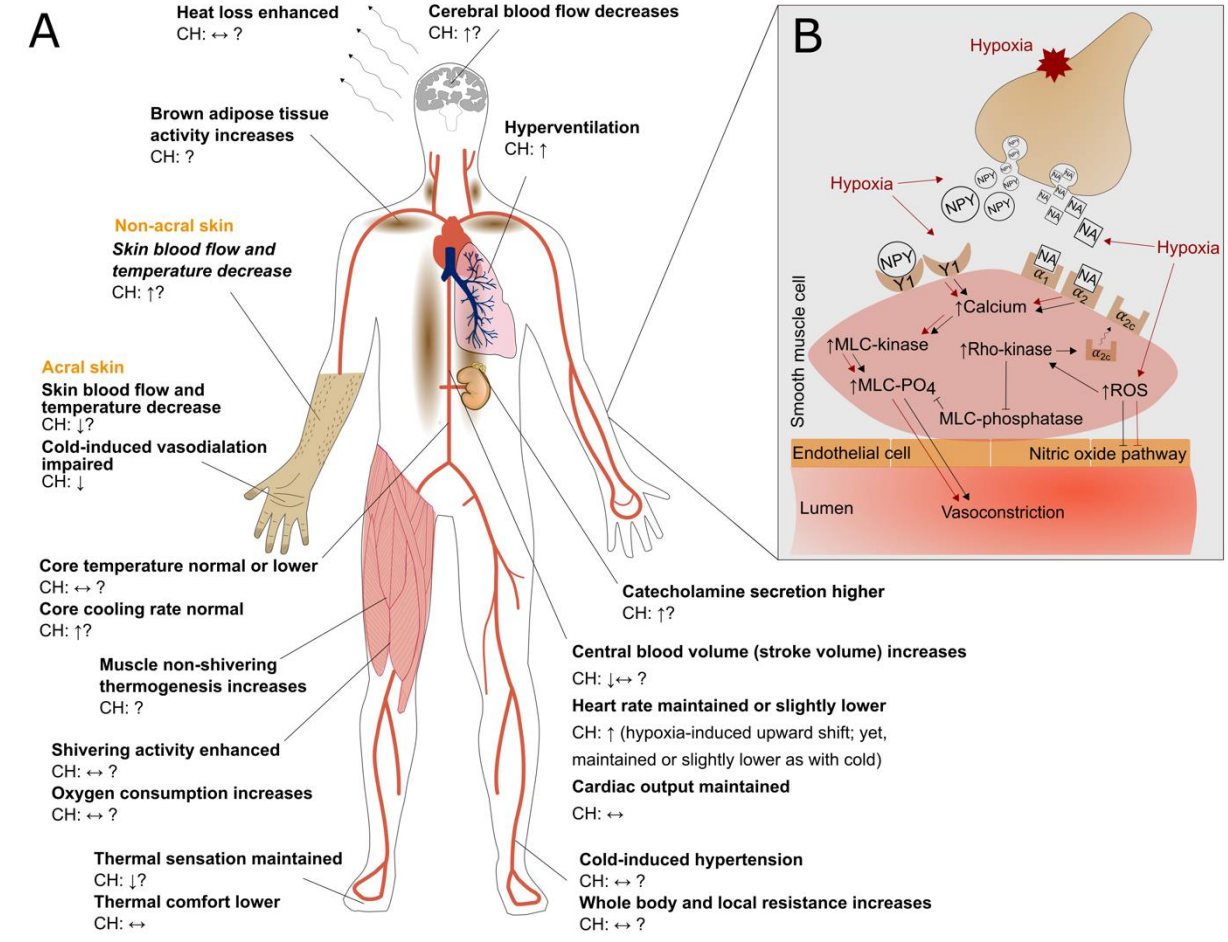

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Figure 4. The cold human and the direct effects of hypoxia – an overview. The literature is lacking and therefore, the arrows indicate a general trend of a combined cold and hypoxic exposure (regular) relative to normoxic cooling (**bold**). The direction of the arrows indicates a reduction (↓), augmentation (↑), no change (↔) or unknown effects (?) of combined cold and hypoxia compared to cold alone. CH, combined cold hypoxia (A). Mechanism of cold-induced vasoconstriction (black) of the skin with potential influence of hypoxia (red). $\alpha_{1,2}$ and $_{2c}$, alpha-adrenergic receptors 1, 2 and 2c; MLC, myosin light chain; MLC-PO4, myosin light chain phosphorylation; NA, noradrenaline; NPY, neuropeptide Y; ROS, reactive oxygen species; Y1, neuropeptide Y receptors (B).

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