Remote ischemic preconditioning for prevention of high-altitude diseases: fact or fiction?

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Preconditioning refers to exposure to brief episodes of potentially adverse stimuli and protects against injury during subsequent exposures. This was first described in the heart, where episodes of ischemia/reperfusion render the myocardium resistant to subsequent ischemic injury, which is likely caused by reactive oxygen species (ROS) and proinflammatory processes. Protection of the heart was also found when preconditioning was performed in an organ different from the target, which is called remote ischemic preconditioning (RIPC). The mechanisms causing protection seem to include stimulation of nitric oxide (NO) synthase, increase in antioxidant enzymes, and downregulation of proinflammatory cytokines. These pathways are also thought to play a role in high-altitude diseases: high-altitude pulmonary edema (HAPE) is associated with decreased bioavailability of NO and increased generation of ROS, whereas mechanisms causing acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) seem to involve cytotoxic effects by ROS and inflammation. Based on these apparent similarities between ischemic damage and AMS, HACE, and HAPE, it is reasonable to assume that RIPC might be protective and improve altitude tolerance. In studies addressing high-altitude/hypoxia tolerance, RIPC has been shown to decrease pulmonary arterial systolic pressure in normobaric hypoxia (13% O2) and at high altitude (4,342 m). Our own results indicate that RIPC transiently decreases the severity of AMS at 12% O2. Thus preliminary studies show some benefit, but clearly, further experiments to establish the efficacy and potential mechanism of RIPC are needed.

acute mountain sickness; high-altitude cerebral edema; high-altitude pulmonary edema; hypoxia; nitric oxide

LIFE-THREATENING DISEASES related to exposure to high altitude and hypoxia, such as acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE), and ischemic tissue damage might share common pathophysiologic mechanisms. Because ischemic cell and organ damage can be attenuated or even prevented by remote ischemic preconditioning (RIPC), it is conceivable that RIPC might also prevent AMS, HACE, and HAPE. In this overview, we will address the questions if and how the mechanisms underlying preconditioning could affect high-altitude-/hypoxia-related diseases and summarize the results of the present clinical trials.

MEANS TO IMPROVE HIGH-ALTITUDE TOLERANCE

Increasing numbers of tourists travel to altitudes above 3,000 m for mountaineering, trekking, and skiing. Furthermore, workers—such as miners or astronomers in the Andes or people working in a normobaric hypoxic environment in industrial settings that serve the purpose of avoiding fire or oxidation—may be exposed to altitude. Medical problems occurring at high altitude are primarily related to the altitude-induced decrease in oxygen partial pressure. Guidelines for ascents to altitudes above 3,000 m recommend ascent rates not exceeding 300-500 m/day and a rest day every 3–4 days (9, 60). The underlying rationale is to provide enough time for acclimatization processes at organ and molecular levels.
Spending several days at altitudes of 3,000 m before ascending to a higher altitude is also an effective means of preconditioning or acclimatization (87). However, due to time constraints, many individuals may not be able to follow these recommendations. A variety of pharmacological alternatives is instead frequently used to prevent high-altitude-related diseases. Although these effectively prevent and treat AMS (e.g., dexamethasone, acetazolamide) and HAPE (nifedipine, tadalafil, dexamethasone), they bear the risk of side effects and should be considered only in selected populations and high-risk settings (60, 85). Therefore, the development of time-saving, easily applicable, and well-tolerated alternatives for preventing high-altitude diseases has been the target of numerous studies. If preventive measures fail, then high-altitude diseases may occur: whereas AMS and HACE represent the cerebral form of high-altitude diseases, HAPE constitutes the pulmonary form.

REMOTE ISCHEMIC PRECONDITIONING

In a landmark study in 1986, Murry and colleagues (68) demonstrated that brief, nonlethal episodes of myocardial ischemia and reperfusion protected the myocardium from a subsequent, sustained ischemic insult, a phenomenon now known as myocardial ischemic preconditioning. This concept was later modified by Birnbaum et al. (12), who showed that transient ischemia of the limbs induces protection of the heart from ischemia-reperfusion injury, such as the brain, lung, kidney, intestine, liver, stomach, and the skeletal muscle (22, 46, 50, 55, 64, 73, 77).

Protocols for RIPC

There are two phases of protection following an RIPC stimulus: an early phase develops within minutes from the initial ischemic stimulus and lasts for a few hours, and a second late phase becomes apparent 12–24 h later and lasts 3–4 days (Fig. 1). Both phases are separated by a window of no protection (13). To elicit a protective effect, the RIPC stimulus needs to exceed the threshold for the activation of the respective signaling cascade. This activation may depend on the type and the duration of the RIPC stimulus and on the individual threshold that needs to be overcome and may vary from organ to organ and among different species (33). A variety of protocols has been used to establish biomarkers indicating the effectiveness of RIPC. Most protocols represent three to four times of 5-min ischemia of the arm or leg, followed by 5 min of reperfusion; sometimes, these protocols were repeated several times/day and sometimes, once/day for extended periods (54). The number of repeats and the duration of ischemia and reperfusion seem to influence the magnitude of the preconditioning effect (50). Previous studies suggest that ischemic periods shorter than 5 min or longer than 15 min are not effective (16, 72, 97) and that multiple stimuli are likely more effective than a single stimulus (12). However, the optimal sequence of the preconditioning stimulus has not been identified, and it has been postulated that an excessive number of preconditioning episodes may be deleterious (43). Whether long-term RIPC can eliminate the window of no protection between the early and the second protective phase remains speculative. In either case, RIPC is induced by inflating a standard blood-pressure cuff on a limb to values higher than the systolic blood pressure to render the limb ischemic. As shown recently, ischemia can be induced in the upper limb at lower cuff-inflation pressures compared with the standard 200-mmHg pressure generally used for RIPC, provided the cuff-inflation pressure is ~30 mmHg higher than the systolic blood pressure. In the lower limb, a higher inflation pressure, ~55 mmHg above systolic blood pressure, is required to induce ischemia (90).

Mechanisms Underlying RIPC

The molecular mechanisms involved in RIPC-induced protection are complex and are still a matter of debate (54). To date, numerous triggers, mediators, and effectors are considered responsible for the signal generation and its propagation to the target organ. The humoral hypothesis of RIPC suggests that the ischemic stimulus in the remote organ leads to the production of substances that enter the circulation and reach the target organ, where they exert a protective effect. However, the actual identity of the humoral mediator remains unknown (31).

Different mechanisms account for the early and late phase of RIPC. The early phase is attributed to the effects of mediators, such as nitric oxide (NO) and adenosine, which modulate ion channel activity, whereas in the late phase, protection is due to altered gene expression affecting endothelial function, immune response, and cellular energy metabolism (54, 77, 81). Signal-
ing molecules that cause protection are released into the blood, as has been shown by transferring protection by blood transfusion from preconditioned into naïve animals (26, 53). Blood-borne mediators under discussion are erythropoietin, adenosine, prostaglandins, and others (58). More details on the molecular mechanisms can be found, e.g., in Gill et al. (31) and Randhawa et al. (77). This article focuses on potential mechanisms that may relate to HAPE and AMS.

**NO and NO species.** NO is a potent vasodilator that has originally been described as an endothelium-derived relaxation factor (69). NO is mainly generated by NO synthases (NOS; neuronal, inducible, and endothelial), which convert l-arginine to NO and l-citrulline in a reaction that requires oxygen (21). The neuronal isoform is constitutively expressed in nerve cells, skeletal muscle, and the heart (21). The inducible isoform is expressed in many cell types as a response of the immune system, e.g., in macrophage cells on exposure to LPS or to cytokines (35, 92). NO generation through the endothelial isoform, which is constitutively expressed in cells lining blood vessels, primarily depends on blood flow-induced shear stress and causes vasodilation by increased formation of cGMP and smooth muscle hyperpolarization (51). Therefore, the function of the vascular endothelium and NO-dependent vasodilation can be assessed by intravascular injection of acetylcholine, because acetylcholine responses in the human vasculature are almost exclusively mediated through stimulation of endothelial NOS (10). Other sources of NO relevant to the cardiovascular system include platelets and red blood cells, as well as generation of NO through NOS-independent reduction of nitrate and nitrite (32).

Several studies have shown that RIPC increases the generation of NO and nitrate, respectively (14, 78), but the underlying mechanisms are unclear. However, shear-stress-related stimulation of endothelial NOS secondary to reactive hyperemia at the remote site of RIPC may play a role (43, 78). That NO plays an important role in mediating the preconditioning effect (70, 104) is indicated by studies showing that the protective effect of an RIPC stimulus on the myocardium can be blocked by administration of a NOS inhibitor (14) and by genetic ablation of endothelial NOS (75). Guo et al. (36) observed that preconditioning of mice, in which inducible NOS has been knocked out, developed larger infarcts upon ischemia compared with preconditioned wild-type mice. Furthermore, pharmacological and genetic inhibition of endothelial NOS, both at the remote site of the preconditioning stimulus and in the target tissue, i.e., the myocardium, increased infarct size, indicating that NO is both a trigger signal and is also formed in the target organ (78). In pigs, Heinzl et al. (41) found increased expression of inducible NOS 3 h after the last preconditioning stimulus. In Fig. 2, the potential molecular mechanisms underlying the RIPC-induced, NO-mediated protection are illustrated. It summarizes some of the NO-dependent pathways that induce the protective preconditioning effect, although the last piece of the puzzle, i.e., the final target interacting with NO, is missing. After RIPC, NO induces likely adverse effects by K+-channel modulation, increased reactive oxygen species (ROS) formation, and mitochondrial depolarization, as well as via prostaglandin and carbon monoxide. It can be assumed that weak, i.e., only mildly damaging induction of these pathways stimulates the defense mechanisms that cause protection from more severe insults for several days (54).

**Reactive oxygen species.** The pivotal role of endogenous free radicals in RIPC-mediated protection has been demonstrated in numerous studies, e.g., by blocking protection by use of the ROS scavenger mercapropionyl-glycine (19, 98). How exactly they contribute to RIPC-induced protection remains, however, unclear, because elevated ROS typically have detrimental effects, such as lipid peroxidation of the plasma membrane, oxidation of DNA, and opening of the mitochondrial transition pore, all of which cause cell damage (49). In stroke, they have been linked to increased neurocognitive deficits and increased infarct size (76). By interaction with NO and free iron, they increase the generation of peroxynitrite and hydroxyl radicals, which are cytotoxic (66). ROS also increase inflammatory processes by formation of oxidant-dependent proinflammatory mediators and up-regulation of cytokines (49).

ROS are among the chemical substances released upon an RIPC stimulus in both the remote as well as in the target organ (42, 96). They seem to trigger the second phase of protection of an RIPC stimulus (27), e.g., in the heart and brain (49). Dong et al. (27) found that RIPC-induced tolerance to spinal-cord ischemia was attenuated when a free-radical scavenger was administrated before the RIPC stimulus was applied. ROS

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**Fig. 2.** Simplified schematic presentation of the nitric oxide (NO) signaling pathway in remote ischemic preconditioning. For details see text. eNOS, endothelial NO synthase; iNOS, inducible NOS; COX-2, cyclooxygenase-2; HO-1, heme oxygenase 1; SGC, soluble guanylyl cyclase; PGI2, prostacyclin; PGE2, prostaglandin E2; PKG, protein kinase G; GSK3β, glycogen synthase kinase 3β; KATP, ATP-sensitive potassium channels; ROS, reactive oxygen species; mPTP, transient mitochondrial permeability transition pore.
contribute to the activation of a complex signaling cascade involving protein kinase G and increased expression of a variety of protective proteins (81). It has also been proposed that the opening of ATP-sensitive potassium channels in response to the RIPC stimulus causes a transient increase in ROS, which in turn, decreases ROS production during the subsequent hypoxic or ischemic insult (65).

It is hard to imagine how a cell can distinguish between the dual role of ROS acting as a signaling mediator of protection upon preconditioning and as a critical determinant of cell death during a sustained hypoxic or ischemic/reperfusion event. Kalogeris et al. (49) proposed that the divergent effects may be explained by the type of ROS produced, by the amount of ROS that is generated (small amounts may have a signaling function; excessive amounts may be detrimental), and by the time point of their production.

**Inflammatory pathways.** There are only few clinical studies correlating RIPC and inflammatory processes, and findings appear contradictory. RIPC has been found to induce anti-inflammatory changes in circulating leukocytes and to suppress proinflammatory genes that are involved in chemotaxis, adhesion, and migration (57). These changes occur within minutes after RIPC and are even more pronounced after 24 h (56). However, also, increased cytokines have been reported in response to RIPC in cardio-surgical patients in the first phase of RIPC-induced protection (1). A number of proinflammatory cytokines have previously been reported to trigger the delayed protective phase. Those include TNF-α, IL-1β, and IL-6 (40). Yamashita and coworkers (105) demonstrated that administration of neutralizing antibodies to TNF-α and IL-β before preconditioning abolished the infarct-limiting effect 24 h later, suggesting that these cytokines are required to elicit delayed protection. These findings indicate that effects of RIPC on inflammatory pathways are complex and may involve multiple signaling cascades.

**HIGH-ALTITUDE AND HYPOXIA-RELATED DISEASES**

**AMS and HACE**

AMS is a syndrome of nonspecific neurologic symptoms, experienced by nonacclimatized persons within 6–12 h at altitudes above 2,500 m (9). The cardinal symptom is headache that is usually accompanied by anorexia, nausea, dizziness, malaise, sleep disturbance, or a combination of these symptoms (9, 91). Progression of AMS may result in HACE, indicating that both entities share the same pathophysiology, with HACE representing the end stage of the disease process (7, 79, 99). Typical signs of HACE are truncal ataxia, decreased consciousness, and mild fever, which develop after at least 48 h spent at altitudes above 4,000 m (101). Details on incidence, prophylaxis, and treatment have been reviewed recently (9, 37, 59, 60).

The precise mechanisms causing AMS and HACE are incompletely understood. Hypoxia-induced cerebral vasodilation is considered to play a pivotal role in high-altitude-induced headache, probably by activation of the trigeminovascular system (37), which can also account for other symptoms of AMS, such as nausea and malaise. It has recently been suggested that a small impairment of cerebral outflow in relation to increased cerebral inflow contributes to the activation of the trigeminovascular system and thus to the typical signs of AMS (102). Whether ROS are involved in the pathophysiology of AMS is questionable, and studies using antioxidants for prevention of AMS yield controversial results (2, 4, 6).

Numerous proinflammatory markers have been involved in AMS. At the South Pole, elevated levels of TNF-α were found in subjects with AMS (39), whereas another investigation at 4,559 m did not (52). The authors suggested that hypoxia causes tissue inflammation, which again, aggravates hypoxia and thus favors the development of AMS (39). This finding is in line with a recent study by Julian et al. (47), suggesting that resistance to AMS is related to sufficient anti-inflammatory and anti-permeability responses during hypoxic exposure. Results on anti-inflammatory drugs, e.g., dexamethasone, which effectively prevent AMS, support this notion (59).

Susceptibility-weighted MRI in survivors of HACE (48, 89) demonstrates deposition of hemosiderin predominantly in the corpus callosum, indicating microhemorrhages due to vasogenic edema that are most likely caused by a combination of hemodynamic stress and increased permeability of the blood brain barrier. Whereas cerebral vasodilation and possibly impaired venous outflow could account for the hemodynamic stress, increased expression of VEGF (103) and increased levels of ROS might favor the development of a capillary leak and thus of cerebral edema formation by causing direct structural damage to the microvascular endothelium of the blood brain barrier (5, 17). ROS may also downregulate Na+/K+-ATPase, thus causing cell swelling and cytotoxic edema (80).

**High-Altitude Pulmonary Edema**

HAPE is a form of noncardiogenic pulmonary edema occurring in otherwise healthy individuals within the first days after rapid ascent to altitudes above 3,000–4,000 m (23). Detailed reviews that include incidence, prophylaxis, and treatment have been published recently (9, 23, 93). Briefly, HAPE has long been related to an exaggerated and uneven hypoxic pulmonary vasoconstriction (HPV) and pulmonary capillary pressure (25, 44, 62). This high pressure induces mechanical injury to the pulmonary capillaries and starts a cascade of events that ultimately results in the development of HAPE. This injury, termed “stress failure,” was first described by John West (100) and refers to mechanically induced breaks in the blood gas barrier. Major evidence for the key role of the exaggerated HPV in the pathophysiology of HAPE comes from studies on HAPE prophylaxis, where nifedipine (8) and tadalafil (61) decrease PASP and prevent HAPE. However, recent data indicate that factors other than the abnormally high PASP have to be involved, because high-altitude, naïve individuals, who show exaggerated HPV in normobaric hypoxia, have no increased risk to develop HAPE when exposed to high altitude compared with a nonselected population (83). A recent study by Dehnert et al. (24) supports this notion by demonstrating that an abnormally high PASP in hypoxia cannot be taken as a surrogate marker for susceptibility to HAPE. Inflammation has been ruled out as the additional factor, because in early HAPE, no elevated cytokines have been found in plasma and bronchoalveolar lavage (95). However, at a later stage, HAPE is associated with elevated cytokines (88). Only elevated IL-6 levels in blood have been reported repeatedly in early HAPE (18, 38, 45, 67, 71, 94).
Another mechanism contributing to HAPE is a decreased capacity of alveolar reabsorption (63, 82), but measurements of transepithelial ion transport as a driving force for reabsorption allow no clear distinction between individuals with and without HAPE susceptibility. Hypoxia may decrease further the clearance of fluid filtered into the alveolar space, because hypoxia has been shown to inhibit alveolar reabsorption (34, 74). Inhibited reabsorption has been associated with elevated ROS formation by hypoxic cells (20).

Pathomechanisms causing HAPE on a molecular level are not clear. NO seems to play a role, because HAPE susceptibles have been found to have decreased exhaled NO (15, 28) and decreased nitrate and nitrite in the systemic circulation (10) and in bronchoalveolar lavage fluid (95) and because the vasodilator NO improves alveolar gas exchange (86). Furthermore, HAPE susceptibles show decreased NO-dependent peripheral vasodilatation (10). Elevated endothelin-1 plasma levels in HAPE susceptibles in hypoxia (10) and at high altitude (84) may indicate shear stress and related ROS release, as discussed previously (3), but this has not been explored in detail.

In summary, current understanding of the pathophysiology of HAPE suggests that at a molecular level, an increase in endothelin-1 and ROS and a decrease in the availability of NO species play a pivotal role. Figure 3 summarizes the pathophysiological principles leading to HAPE.

EFFECTS OF RIPC ON HIGH-ALTITUDE DISEASES

As outlined above, there seem to be some similarities between signaling in hypoxia/ischemia/reperfusion and high-altitude-associated diseases, such as increased plasma levels of ROS and proinflammatory mediators, as well as NO-dependent signaling. RIPC attenuates the signaling cascade of these conditions and rather than causing severe tissue damage, stimulates intrinsic defense mechanisms, which lead to a kind of short-term adaptation and a state of hypoxic/ischemic tolerance. Therefore, it appears possible that RIPC reduces the detrimental effects of ROS, NO deficiency, and proinflammatory genes in hypoxia and at high altitude and thus protects against AMS, HACE, and HAPE. There are, however, only a few clinical studies that have investigated the effects of RIPC in healthy humans acutely exposed to hypoxia, which are discussed below, and provide some support for this hypothesis.

EFFECTS OF RIPC ON AMS AND HACE

There is no study on the effect of RIPC on HACE, and only one study so far addressed the effect of RIPC on AMS. In this latter study (11), we investigated whether RIPC decreases the severity of AMS compared with a control group not undergoing RIPC in normobaric hypoxia. Individuals were exposed to 18 h of normoxia or normobaric hypoxia (12% O2) in a blinded, randomized order. The RIPC protocol consisted of four cycles of bilateral lower-limb ischemia (5 min), interspersed by 5 min of reperfusion, and RIPC was performed immediately before entering the hypoxia laboratory. An independent control group was exposed to hypoxia (12% O2) but without RIPC. We found that RIPC significantly reduced AMS severity after 5 h of hypoxia, as indicated by a decreased Lake Louise Score (1.9 vs. 3.2) and AMS-Cerebral Score (0.4 vs. 0.8). However, after 18 h in hypoxia, AMS scores were not different between both study groups. It is possible that the lack of an effect of RIPC on AMS severity after 18 h was due to the biphasic response of RIPC-induced protection (Fig. 1), and it can be hypothesized that after longer-lasting exposure, individuals might again obtain protection.
In this study, we measured ROS to address possible pathophysiologic mechanisms (11). After 5 h in hypoxia, plasma levels of ROS were significantly lower in the RIPC group than in the non-RIPC control group. Plasma levels of ROS remained decreased even after 18 h in hypoxia, although AMS scores had increased. The dissociation between low plasma levels of ROS and increased severity of AMS suggests that increased oxidative stress is not involved in the pathophysiology of AMS. However, it remains unclear how well systemic plasma levels of ROS reflect ROS metabolism of the brain, and it is conceivable that local transitory ROS generation initiates a local, cerebral, inflammatory/vasoactive cascade that is not reflected in the systemic circulation. In addition, the study showed that the decrease in ROS after RIPC was paralleled by a decrease in L-ascorbate, indicating that an increased antioxidant plasma capacity was not responsible for the RIPC-induced reduction in ROS. Whether circulating NO species derived from shear stress-dependent stimulation of endothelial NOS contributed to reduced ROS formation upon RIPC, as recently suggested by Rassaf et al. (78), requires further exploration.

**EFFECT OF RIPC ON HPV**

There are no studies that addressed effects of RIPC on the development of HAPE. However, two studies assessed the effect of RIPC on HPV in normobaric hypoxia (30) and at high altitude (29).

In the first study (30), the effects of RIPC on PASP and on exercise performance were studied in eight individuals in normoxia and normobaric hypoxia (13% O₂). RIPC was induced by four cycles of occlusion of blood flow on one thigh by inflating a blood-pressure cuff for 5 min, followed by deflation for 5 min. At rest, PASP increased from 25.6 mmHg in normoxia to 41.8 mmHg after 90 min in hypoxia. However, the increase in PASP in hypoxia was blunted by RIPC reaching only 32.4 mmHg. Exercise performance in hypoxia was not affected by RIPC. Similar experiments were then performed in a study at high altitude (4,342 m) (29). RIPC (as before) and placebo preconditioning (by inflation of the cuff to only 40 mmHg) were administered daily for 5 days before high-altitude exposure. Measurements at high altitude were performed after a passive ascend to 3,800 m, followed by a 12.8-km run to the summit. The PASP at the summit was slightly but significantly lower in the RIPC group than in the placebo condition (36 vs. 38 mmHg, respectively).

These studies suggest that RIPC attenuates the normal hypoxic increase in PASP at high altitude. In none of the studies have molecular mechanisms been addressed. Therefore, it remains speculative whether RIPC attenuated HPV by enhancing NO availability and by decreasing ROS and inflammatory responses, as outlined above.

**CONCLUSION**

It is well documented that RIPC protects against ischemia/reperfusion injury. The fact that RIPC decreases PASP in hypoxia and that RIPC, at least transiently, decreases the severity of symptoms of AMS indicates a potential role for RIPC to protect against high-altitude diseases. The mechanisms by which RIPC activates the intrinsic defense systems improving high-altitude tolerance remain uncertain and may include effects on vasoactive and endothelial substances (e.g., NO and ROS) and on the inflammatory system (induction of anti-inflammatory processes and suppression of proinflammatory genes). However, due to the sparse experimental evidence, RIPC cannot be recommended at present as an easy means of improving high-altitude tolerance.

Future trials may identify a suitable biomarker of preconditioning, which would help to define the optimal preconditioning stimulus and would be useful for the dose selection of RIPC protocols. In the case of interindividual variability of protection induced by preconditioning, biomarkers would also allow differentiating between good and poor responders by quantifying the biological response of preconditioning.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

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