Remote Ischemic Preconditioning for Prevention of High Altitude Diseases: Fact or Fiction?

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Abstract

Preconditioning refers to exposure to brief episodes of potentially adverse stimuli, which protects from 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 pro-inflammatory 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 synthase, increase in anti-oxidant enzymes, and down-regulation of pro-inflammatory 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 nitric oxide 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 (4342m). 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.
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 3000 m for mountaineering, trekking, and skiing. Also workers may be exposed to altitude, such as miners or astronomers in the Andes, or people working in a normobaric hypoxic environment in industrial settings which serve the purpose of avoiding fire or oxidation. Medical problems occurring at high altitude are primarily related to the altitude-induced decrease in oxygen partial pressure. Guidelines for ascents to altitudes above 3000 m recommend ascent rates not exceeding 300-500 m per day and a rest day every 3 to 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 3000 m prior to ascending to 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. Though those 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, high altitude diseases may occur: While AMS and HACE represent the cerebral form of high altitude diseases, HAPE constitutes the pulmonary form.
Remote ischemic preconditioning (RIPC)

In a landmark study in 1986 Murry and colleagues demonstrated that brief non-lethal episodes of myocardial ischemia and reperfusion protected the myocardium from a subsequent sustained ischemic insult (68), a phenomenon now known as myocardial ischemic preconditioning. This concept was later modified by Birnbaum et al., who showed that transient ischemia of the limbs induces protection of the heart from ischemic damage upon subsequent exposure to ischemia similar to the “classic” preconditioning method (12). This finding attracted great clinical interest because it is a non-invasive intervention without the need of interrupting blood supply of vital organs, that is easily applicable to humans. Later, effects of RIPC have been demonstrated to protect also other organs 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 remote ischemic preconditioning (RIPC)

There are two phases of protection following a 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 hours later and lasts 3-4 days (Figure 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, on the individual threshold that needs to be overcome, and may vary from organ to organ and between different species (33). A variety of protocols have been used to establish biomarkers indicating the effectiveness of RIPC. Most protocols represent 3-4 times of 5 min ischemia of the arm or leg, followed by 5 min of reperfusion; sometimes these protocols were repeated several times per day, sometimes once a 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). Signaling 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-born mediators under discussion are erythropoietin, adenosine, prostaglandins, and others (58). More details on the molecular
mechanisms can be found e.g. in references (31, 77). This article focusses on potential mechanisms that may relate to HAPE and AMS.

Nitric oxide (NO) and NO species: NO is a potent vasodilator that has originally been described as endothelium-derived relaxation factor (69). NO is mainly generated by NO synthases (neuronal, inducible, and endothelial, NOS), 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 lipopolysaccharide 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 cyclic guanosine monophosphate 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 nitrite, 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 a 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. observed that preconditioning of mice in which inducible NOS has been knocked out, developed larger infarcts upon ischemia compared to preconditioned wild-type mice (36). Also, 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, Heinzel et al. found increased expression of inducible NOS three hours after the last preconditioning stimulus (41). In Figure 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 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 (ROS): 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 mercaptopropionyl-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 pro-inflammatory mediators and up-regulation of cytokines (49).

ROS are among the chemical substances released upon a 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 a RIPC stimulus (27), e.g. in the heart and brain (49). Dong et al. found that RIPC-induced tolerance to spinal cord ischemia was attenuated when a free-radical scavenger was administrated before the RIPC stimulus was applied (27). ROS 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 opening of $K_{ATP}$-channels in response to the RIPC stimulus causes a transient increase in ROS that 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. 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 (49).

**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 pro-inflammatory genes that are involved in chemotaxis, adhesion and migration (57). These changes occur within minutes after RIPC and are even more pronounced after 24 hours (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 pro-inflammatory cytokines has previously been reported to trigger the delayed protective phase. Those include tumor necrosis factor-$\alpha$, Interleukin-1$\beta$ and Interleukin-6 (40). Yamashita and co-workers demonstrated that administration of neutralizing antibodies to tumor necrosis factor-$\alpha$ and Interleukin-$\beta$ prior to preconditioning abolished the infarct-limiting effect 24 hours later, suggesting that these cytokines are required to elicit delayed protection (105). These findings indicate that effects of RIPC on inflammatory pathways are complex and may involve multiple signaling cascades.
High altitude and hypoxia related diseases

Acute mountain sickness (AMS) and high altitude cerebral edema (HACE)

AMS is a syndrome of non-specific neurologic symptoms experienced by non-acclimatized persons within 6-12 hours at altitudes above 2500 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 hours spent at altitudes above 4000 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), that can also account for other symptoms of AMS, like 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 anti-oxidants for prevention of AMS yield controversial results (2, 4, 6).

Numerous pro-inflammatory markers have been involved in AMS. At the South Pole, elevated levels of tumor necrosis factor-alpha were found in subjects with AMS (39) while another investigation at 4559 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, that effectively prevent AMS, support this notion (59).
Susceptibility weighted MRI in survivors of HACE (48, 89) demonstrate deposition of hemosiderin predominantly in the corpus callosum indicating microhemorrhages due to vasogenic edema that is most likely caused by a combination of hemodynamic stress and increased permeability of the blood brain barrier. While cerebral vasodilation and possibly impaired venous outflow could account for the hemodynamic stress, increased expression of vascular endothelial growth factor (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 down-regulate Na⁺/K⁺-ATPase, thus causing cell swelling and cytotoxic edema (80).

**High-altitude pulmonary edema (HAPE)**

HAPE is a form of non-cardiogenic pulmonary edema occurring in otherwise healthy individuals within the first days after rapid ascent to altitudes above 3000-4000 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) resulting in abnormally high pulmonary arterial systolic pressure (PASP) 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 et al. (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 other factors than the abnormally high PASP have to be involved, because high altitude naive individuals, who show exaggerated HPV in normobaric hypoxia, have no increased risk to develop HAPE when exposed to high altitude compared to a non-selected 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 broncho-alveolar 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 driving force for reabsorption allow no clear distinction between individuals with and without HAPE-susceptibility. Hypoxia may further decrease 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), decreased nitrate and nitrite in the systemic circulation (10) and in broncho-alveolar lavage fluid (95), and because the vasodilator NO improves alveolar gas exchange (86). Also, HAPE-susceptibles show decreased NO-dependent peripheral vasodilation (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 remote ischemic preconditioning 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 pro-inflammatory 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 pro-inflammatory genes in hypoxia and at high altitude and thus protects from AMS,
HACE, and HAPE. There are, however, only few clinical studies that have investigated the effects of
RIPC in healthy humans acutely exposed to hypoxia which are discussed below and which provide
some support for this hypothesis.

**Effects of remote ischemic preconditioning 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 to a control group not undergoing RIPC in normobaric hypoxia. Individuals were exposed
to 18 hours of normoxia or normobaric hypoxia (12% O2) in a blinded, randomized order. The RIPC
protocol consisted of 4 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 hours of hypoxia, as indicated by a decreased Lake Louise
score (1.9 vs. 3.2) and AMS-C score (0.4 vs. 0.8). However, after 18 hours 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 hours was due to the biphasic response of RIPC-induced protection (Figure 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 hours
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 hours 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 anti-oxidant 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 remote ischemic preconditioning on hypoxic pulmonary vasoconstriction (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 8 individuals in normoxia and normobaric hypoxia (13% O₂). RIPC was induced by 4 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 minutes 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 (4342 m) (29). RIPC (as before) and placebo preconditioning (by inflation of the cuff to only 40 mmHg) were administered daily for 5 days prior to high altitude exposure. Measurements at high altitude were performed after a passive ascend to 3800 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 molecular mechanisms have been addressed. Therefore, it remains speculative whether or not 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 from 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 from 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 pro-inflammatory 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 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 inter-individual variability of protection induced by preconditioning, biomarkers would also allow differentiating between good and poor responders by quantifying the biological response of preconditioning.


Figure legends

Figure 1. Schematic illustration of the two phases of preconditioning. An early phase (dark grey) of protection develops within minutes from the initial ischemic stimulus and lasts for a few hours. The protection of this phase is probably more powerful than the protection of the second late phase (light grey), that becomes apparent 12-24 hours later and lasts 3-4 days. Both phases are separated by a window where no protection occurs. The different time courses of protection are explained by the different mechanisms underlying both phases: While the early phase is assumed to be caused by rapid posttranslational modification of pre-existing proteins, the late phase is most likely caused by the synthesis of new protective proteins.

Figure 2. Simplified schematic presentation of the nitric oxide signalling pathway in RIPC. For details see text. eNOS = endothelial nitric oxide synthesis, iNOS = inducible nitric oxide synthesis, COX-2 = cyclooxygenase-2, HO-1 = , SGC = soluble guanylyl cyclase, PGI2 = prostacyclin, PGE2 = prostaglandin, HO-1 = heme oxygenase-1, CO = carbon monoxide, cGMP = cyclic guanosine monophosphate, PKG = protein kinase G, PKC = protein kinase C, ERK = extracellular signal-regulated kinase, GSK3β = glycogen synthase kinase 3-beta, KATP = ATP-sensitive potassium channels, K = potassium, ROS = reactive oxygen species, PKCe2 = protein kinase C epsilon-2, mPTP = transient mitochondrial permeability transition pore.

Figure 3. Schematic representation of the main pathophysiological processes leading to high-altitude pulmonary edema (HAPE). NO = nitric oxide, ROS = reactive oxygen species, ET-1 = endothelin-1. HPV = hypoxic pulmonary vasoconstriction
Figure 2

Diagram showing the relationships between eNOS, iNOS, COX-2, HO-1, nitric oxide, nitrite, SGC, cGMP, PKG, ERK, PKC, GSK3β, and K_{ATP} opening. The diagram illustrates the pathways involved in protection and the roles of various molecules and processes such as mPTP, ROS, pH, and K^+.
Figure 3

Hypoxia

endothelial dysfunction

NO availability ↓

ROS production ↑

ET-1 production ↑

impaired pulmonary vasodilation

enhanced pulmonary vasoconstriction

uneven HPV and inhomogenous lung perfusion

locally exaggerated hydrostatic pulmonary capillary pressure and stress failure

(secondary) inflammation → HAPE ← alveolar fluid clearance ↓