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International Journal of Infectious Diseases 103 (2021) 415–419

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

# Hypoxic preconditioning — A nonpharmacological approach in COVID-19 prevention

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ARTICLE INFO

*Article history:*
Received 23 October 2020
Received in revised form 17 November 2020
Accepted 21 November 2020

*Keywords:*
Hypoxic preconditioning
COVID-19
Prevention
Therapy

ABSTRACT

Hypoxia is defined by low oxygen concentration in organs, tissues, and cells. Maintaining oxygen homeostasis represents the essential cellular metabolic process for the structural integrity of tissues in different pathological conditions, including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Considering the role of hypoxia-inducible factor-1 as the regulator of cellular response to hypoxia and its involvement in angiogenesis, erythropoiesis, glucose metabolism, inflammation, we propose hypoxic preconditioning (HPC) as a novel prevention therapeutic approach on healthy contacts of patients with coronavirus disease-2019 (COVID-19). To date, several studies revealed the beneficial effects of HPC in ischemia, kidney failure, and in pulmonary function recovery of patients who underwent lung surgery. HPC increases the expression of factors that promote cell survival and angiogenesis, induces an anti-inflammatory outcome, triggers coordinated hypoxia responses that promote erythropoiesis, and mobilizes the circulating progenitor cells. Furthermore, the mesenchymal stem cells (MSC) exposed to HPC show improvement of their regenerative capacities and increases the effectiveness of stem cell therapy in different pathologies, including COVID-19. In conclusion, HPC should be considered as an approach with beneficial outcomes and without significant side effects when the organism is severely exposed to the same stressor. HPC appears as a trigger to mechanisms that improve and maintain tissue oxygenation and repair, a main goal in different pathologies, including COVID-19 or other respiratory conditions.



## Introduction

An oxygen concentration of 20% to 21% is definitory for normoxia. On the contrary, hypoxic conditions are reached at low oxygen levels in organs, tissues, and cells. The cellular response to hypoxia is mediated by the hypoxia-inducible factor-1 (HIF-1) transcription factor, which represents the key regulator of oxygen homeostasis, to promote cellular adaptation to reduced oxygen availability (Semenza, 2006; Wenger et al., 2005).

It has been shown that in response to decreased oxygen supply, HIF-1 regulates the transcription of a multitude of genes whose protein products promote different aspects of hypoxic adaptation, including angiogenesis, erythropoiesis, oxygen transport (increased oxygen delivery), glucose metabolism and metabolic adaptation, vascular tone, cell proliferation, and survival. Vascular endothelial growth factor (VEGF), erythropoietin (EPO), glucose transporters, glycolytic enzymes, NO, and adenosine are some of the key targets of HIF-1α (Semenza, 2006; Wenger et al., 2005).

Hypoxia can be caused by a variety of conditions, from intense physical effort and high altitude to lung disease, inflammation, infarction, and carcinogenesis (Kumar and Choi, 2015). Maintaining oxygen homeostasis is the key in cellular metabolic processes necessary to allow the structural integrity of tissues. Tissue hypoxia appears because of hypoxemia, oxygen delivery deficiencies, or deficiencies in the oxygen consumption at the cellular level (MacIntyre, 2014).

The improvement and maintenance of tissue oxygenation is an important goal for the future in different pathological conditions, including coronavirus disease-2019 (COVID-19). In the present paper, the very likely beneficial preventative effects of hypoxic preconditioning (HPC) on healthy contacts of patients with COVID-19 are discussed.

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https://doi.org/10.1016/j.ijid.2020.11.181

## Pathogenesis of COVID-19

The virus entry into host cells is mediated by host serine transmembrane type 2 protease (TMPRSS2), which facilitates viral entry by cleaving ACE2 and activating the S protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). ACE2 and TMPRSS2 are primarily expressed in type II alveolar epithelial cells (Wiersinga et al., 2020).

The body's inflammatory response to COVID-19 infection consists of an intense release of proinflammatory cytokines, a phenomenon described as a "cytokine storm." Scientific data analyzing the cytokine profile in patients diagnosed with COVID-19 have shown that the "cytokine storm" is directly related to lung damage and insufficiency in organs (Huang et al., 2020; Ragab et al., 2020; Ruan et al., 2020). The occurrence of the "cytokine storm" is caused by a rapid increase in proinflammatory cytokines (IL-6, IL-1, TNF-α, and interferon), leading to acute lung lesions or in more severe forms, the onset of acute respiratory failure syndrome (ARDS) (Shimizu, 2019). ARDS is associated with low levels of oxygen saturation, which is a major cause of mortality with COVID-19 (Chen et al., 2020a).

On the other hand, comparing COVID-19-associated ARDS with ARDS alone, Sihna et al. argue that IL-6 and other cytokines are elevated in COVID-19-associated ARDS, but their levels are much lower than in ARDS, suggesting that COVID-19-related "cytokine storm" may therefore not have an important role as a cause of ARDS (Sinha et al., 2020).

Gerstein et al. reported that in the case of patients with diabetes, hypoglycemia is not only the risk factor for cardiovascular and total mortality, but could also be a trigger mechanism for the "cytokine storm" during COVID-19 (Action to Control Cardiovascular Risk in Diabetes Study Group et al., 2008).

In COVID-19 pneumonia, pulmonary thrombosis is common and occurs in two forms: proximal pulmonary embolism (PE) and/or distal thrombosis. The main factor involved in thrombosis appears to be endothelial cell activation (Price et al., 2020). The presence of viral inclusion bodies has been identified in endothelial cells in several organs from the lungs to the gastrointestinal tract (Varga et al., 2020). Immune dysregulation can be initiated by pyroptosis, and is a proinflammatory form of apoptosis originally described in macrophages (Cookson and Brennan, 2001). It occurs in severe forms of COVID-19, where it is characterized by rapid viral replication and it leads to the massive release of inflammatory mediators (Li et al., 2020). In patients with COVID-19, the high rate of pulmonary thrombosis may be the result of three processes: first, endothelial inflammation, which leads to *in situ* thrombosis and microvascular thrombosis; secondly, changes in pulmonary blood flow in response to the parenchymal process, and finally, the classic and very frequent transition from deep vein thrombosis to the PE complication (Klok et al., 2020).

A study on the populations of high altitude regions (Bolivia, Ecuador, and Tibet) has shown that inhabitants living at altitudes over 2,500 m are less prone to develop severe forms of acute SARS-CoV-2 virus infection. Epidemiological data show that physiological adaptation that counterbalances the hypoxic environment in high altitudes can protect the body from severe infection with SARS-CoV-2 virus. Hypoxia mediates the decrease in ACE2 receptors in pulmonary epithelium and thus may reduce SARS-CoV-2 virus infection (Arias-Reyes et al., 2020).

## Hypoxic preconditioning

HPC first described by Lu in 1963 as "a kind of induced tolerance of tissue-cells to hypoxia" refers to the exposure of organisms, organs, tissues, or cells to noninjurious, repetitive mild or moderate hypoxic episodes, which result in increased tolerance and cell protection against subsequent severe hypoxia exposures and other stresses (Lu, 1963). This preconditioning mechanism has the role of a "warning" signal, which allows the brain and the rest of the organism to prepare for the likely occurrence of more harmful conditions (Rybnikova and Samoilov, 2015).

Several phases for HPC have been described: the initiation of hypoxic tolerance to promote the immediate adaptation to hypoxia (first phase, during the first few minutes after exposure), followed by the induction of long-term hypoxic tolerance (second phase), and the expression of hypoxic tolerance (third phase, appears after at least 24 h), when pro-adaptive genes are activated. The adaptive effects of normobaric hypoxia preconditioning lasts approximately 72 h (Rybnikova and Samoilov, 2015).

To evaluate the hypoxic status of cells *in vitro,* cobalt chloride ($CoCl_2$) solution was used as a chemical inducer of hypoxia. Additionally, modular incubator chambers can be used (Wu and Yotnda, 2011). *In vivo*, HPC was studied mostly by using 8%–13% normobaric hypoxia, which was achieved by placing animals in a hypoxic chamber. The inhalation of a hypoxic gas mixture through a mask is a noninvasive method suitable for clinical uses of HPC (Rybnikova and Samoilov, 2015). Targeting HIF-1 for organ protection could be achieved in various ways. Among these, the pharmacological activation of HIF by inhibitors of prolyl hydroxylases (PHDs) was of interest, dimethyloxaloylglycine being reported as a competitive inhibitor against 2-oxoglutarate oxygenases, including PHDs. Other approaches are the direct supplementation of HIF downstream target molecules (such as EPO or adenosine receptor agonists) or preconditioning by sevoflurane, an inhalation anesthetic (Lee et al., 2019). Yao et al. showed that preconditioning with $CoCl_2$ or desferrioxamine, agents known to increase the stability of HIF-1α, induced neuroprotective effects in inflammatory disorders of the central nervous system (Yao et al., 2008).

Adenosine signaling is associated with cellular distress conditions and is considered a safety signal in myocardial, hepatic, and renal ischemia reperfusion injury. Hypoxia promotes the hydrolysis of the proinflammatory ATP released by PMN and injured tissues to adenosine, through the HIF-1 transcriptional activation of endothelial surface proteins CD39 and CD73, that convert ATP to AMP, and respectively AMP to adenosine (Eltzschig et al., 2006; Grenz et al., 2011). Thiel et al. proved in an acute inflammatory lung injury mouse model that oxygenation inhibits the hypoxia-induced tissue protective ADORA2B signaling pathway and leads to large increase in the mice mortality rate (Thiel et al., 2005). Hypoxia-induced HIF 1α stabilization activates the extracellular adenosine signaling pathway through the transcriptional activation of ADORA2B, one of the four adenosine receptors. This pathway is part of an endogenous feedback loop that dampens hypoxia-induced inflammation and promotes ischemia tolerance and tissue repair (Poth et al., 2013).

## Protective effects of HPC in different biological processes

HPC is an effective strategy in several cardiovascular, metabolic, neurological, and ventilation respiratory diseases. Daily sessions of intermittent patient exposures to moderate hypoxia interspaced with normoxia seem to be the most promising HPC strategy to develop hypoxia tolerance (Verges et al., 2015).

To date, scientific reports demonstrated that SARS-CoV-2 infection in humans is associated with a large spectrum of clinical respiratory syndromes (Ackermann et al., 2020). Scientific studies (see below) demonstrate that HPC is related with a variety of biological processes, including angiogenesis/vascularization, inflammation, tissue repair, and regeneration, supporting the protective effects of HPC. Considering these

effects, a question occurs: could HPC be an effective strategy in COVID-19 therapy?

A variety of angiogenic mediators, including VEGF, platelet-derived growth factor B, placental growth factor, angiopoietins 1 and 2, matrix metalloproteinases 2 and 9, plasminogen-activator inhibitor-1, stromal-derived factor 1, and stem cell factor are induced by HIF-1α activation (Hadjipanayi and Schilling, 2013).

In a study from 2008, Kubo et al. showed that HPC (culture under 2% $O_2$ for 24 h) activates stress resistance mechanisms in transplanted peripheral blood mononuclear cells, which increases their survival and angiogenesis induction (Kubo et al., 2008). In another report from 2013, Li et al. demonstrated that HPC induces angiogenesis by increasing VEGF and CD31 expression in the ischemic tissue after acute cerebral infarction, thereby protecting brain tissues against ischemic injury (Li et al., 2013). Furthermore, by using a rat model of myocardial infarction, Sasaki et al. showed that HPC induces myocardial angiogenesis and increases capillary/arteriolar density and blood flow. During hypoxic adaptation, the expression of VEGF was also increased and endothelial apoptosis was decreased (Sasaki et al., 2002).

In myocardial ischemia, potential drug candidates that target the HIF-dependent HPC-signaling pathway include: HIF activators, catalysts of extracellular ATP, ADP and AMP hydrolysis to adenosine (nucleotidases and apyrase), ADORA2B agonists, and circadian rhythm protein PER2 stabilization promoters (Eltzschig et al., 2013). The PER2 promotes the myocardial adaptation to ischemia, while exposure to HPC increases the PER2 protein synthesis and reduces its proteasomal breakdown through an ADORA2B-dependent mechanism (Eckle et al., 2012).

HPC increases and mobilizes the circulating progenitor cells in a human heart injury model. HPC increases the cardiac levels of SDF-1 and VEGF in acute myocardial infarct through EPO signaling, being involved in cardioprotection (Lin et al., 2008). HIF triggers the increases of EPO production and iron uptake as well as promotes erythroid progenitor maturation and proliferation. All these hypoxia-induced responses increase erythropoiesis. A proposed therapeutic approach for the treatment of anemia induced by insufficient EPO synthesis is the pharmacological targeting of the HIF pathway (Haase, 2010). Interestingly, hydroxylase inhibitors have been identified as potential drugs to treat anemia, considering their capacity to increase hemoglobin and thus the oxygen carrying capacity of blood (Huang et al., 2018). Moreover, the hydroxylase inhibitor Vadadustat is in clinical trials for the treatment of ARDS in patients with COVID-19 (ClinicalTrials.gov Identifier: NCT04478071) (Bobrow, 2020).

The protective role of hypoxia preconditioning the brain and the heart exposed to ischemic injury is well established. A similar beneficial effect has been observed in the pulmonary function of patients who underwent lung surgery (Zhang et al., 2019). Hypoxia preconditioning promotes survival and decreases apoptosis of pulmonary endothelial cell through a TLR4-based inhibitory mechanism (Ali et al., 2013). In addition, HIF-1α downregulates ACE2 expression in pulmonary artery smooth muscle cells through angiotensin II production (Zhang et al., 2009).

Hypoxia reduces inflammation in alveolar epithelial cells through a HIF signaling pathway and HIF activators have shown promising preclinical results in lung injury models. The uptake of HIF activators through the inhaled route has been proposed as an approach to reduce their systemic effects and increase their concentration in the targeted cells (Vohwinkel et al., 2015). The extracellular adenosine reuptake through the pulmonary adenosine transporters ENT1 and ENT2 is a crosstalk pathway essential in adenosine-dependent ADORA2B signaling modulation and in lung protection during acute lung injury (ALI). During ALI, the expression of Ent1 and Ent2 is lower, which increases ADORA2B signaling, while Ent1 and Ent2 gene deletion or treatment with an inhibitor (dipyridamole) provides lung protection (Eckle et al., 2013).

Ent2 expression in mice epithelial cells is decreased during inflammatory bowel disease, which activates the ADORA2B signaling pathway described above, thus protecting the mucosal barrier. A stronger intestinal epithelium protection can be achieved by Ent2 gene deletion or treatment with ENT2 inhibitors (dipyridamole or soluflazine) (Aherne et al., 2018).

HPC dampens systemic inflammation caused by LPS in both mice and humans by activating ADORA2B signaling through increased extracellular adenosine levels, which in turn increases the release of anti-inflammatory cytokine IL-10 (Kiers et al., 2018).

Mesenchymal stem cells (MSCs) exposed to HPC show an enhanced capacity to repair the myocardium after infarction through increases in angiogenesis, vascularization, and paracrine signaling as well as reductions of apoptosis in myocardium (Hu et al., 2008). Furthermore, enhanced angiogenesis was observed after the transplantation of hypoxia preconditioned bone marrow MSCs in rats with cerebral ischemia. These findings suggest that hypoxia-preconditioned transplanted cells exhibit a regenerative capacity and possess therapeutic potential concerning ischemic stroke treatment (Wei et al., 2012). On the other hand, it has been shown that HPC of hMSCs improves their osteogenic differentiation (Volkmer et al., 2010).

Novel therapeutic approaches that use stem cells and the extracellular vesicles (EVs) secreted by them could reduce COVID-19-induced inflammation and regenerate the damaged areas of the lung. The resulting therapeutic agents may also be added to established COVID-19 therapeutic protocols (Gupta et al., 2020).

MSCs are a powerful immunomodulatory and anti-inflammatory agent, known to normalize the function of immune systems affected by COVID-19 (Chrzanowski et al., 2020). MSCs in COVID-19 increase the number of lymphocytes and regulatory dendritic cells, thus increasing their own antiviral protection, reduce the level of C-reactive protein and TNF-α, and increase the level of anti-inflammatory protein IL-10 (Leng et al., 2020, p. 19).

The immunomodulatory and regenerative potential of MSCs and their secreted EVs can be clinically useful against the COVID-19-induced "cytokine storm." There are several clinical trials on the therapeutic potential of MSCs against COVID-19. Most of them test MSC-derived exosomes that are administered either intravenously or through the inhalation route (Chrzanowski et al., 2020).

## Hypoxic preconditioning in COVID-19

There are currently more than 160 different vaccine candidates against SARS-CoV-2 in development (Joszt, 2020). The anti-COVID-19 vaccine projects of various companies are broadly based on three strategies: using DNA or RNA, weakened virus known as virus-like particles, and targeting viral proteins such as the S protein (Draft landscape of COVID-19 candidate vaccines, 2020). Each of these strategies has therapeutic or economic advantages, but with also some disadvantages (Amanat and Krammer, 2020). Given the current lack of an effective COVID-19 vaccine, moderate and intermittent HPC using an oxygen mask connected to a nitrogen cylinder is an easy way to set the organism to face the effects of various infectious lung diseases. Thus, we propose the use of daily moderate and intermittent HPC under oxygen status monitoring on the risk group represented by healthy contacts of patients with COVID-19, for the entire SARS-CoV-2 incubation period of (14 days). This is a non-invasive method that could be applied in medical clinics by the health personnel, including medical assistants.

Overall, both vaccination and HPC aim for disease prevention and not necessary for protection against infection. In the absence of a vaccine, many COVID-19 alternative treatments have been

tried, including novel and repurposed drug treatments and the use of plasma from cured patients (Chen et al., 2020b).

## Conclusions

Given the lack of any commercially available vaccine against COVID-19, HPC should be considered a hormetic approach with very likely beneficial outcomes against a future severe exposure to the same stressor like SARS-CoV-2 without significant side effects. Moreover, our proposed therapeutic approach could be used as a tool of adaptive response monitoring of each individual in a hypoxemic condition to create a specific profile of high risk developing severe ARDS after infection with SARS-CoV-2.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The publishing fee of this paper has been kindly covered by the Romanian Society of Telemicroscopy.

## Conflict of interest

The authors declare that they have no conflict of interest, financial or otherwise.

## Ethical approval and informed consent

Not applicable.

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