

Coping with hypoxemia: Could erythropoietin (EPO) be an adjuvant treatment of COVID-19?



Jorge Soliz^{a,c,*}, Edith M. Schneider-Gasser^b, Christian Arias-Reyes^a, Fernanda Aliaga-Raduan^a, Liliana Poma-Machicao^a, Gustavo Zubieta-Calleja^c, Werner I. Furuya^{d,e}, Pedro Trevizan-Baú^{d,e}, Rishi R. Dhingra^d, Mathias Dutschmann^{d,e}

^a *Institute Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ), Faculty of Medicine, Université Laval, Québec, QC, Canada*

^b *Institute of Veterinary Physiology, Vetsuisse-Faculty University of Zurich, Winterthurerstrasse 260, Switzerland*

^c *High Altitude Pulmonary and Pathology Institute IPPA, La Paz, Bolivia*

^d *Florey Institute of Neuroscience and Mental Health, Melbourne Victoria, Australia*

^e *The Florey Department of Neuroscience, University of Melbourne, Melbourne Victoria, Australia*

ARTICLE INFO

Keywords:

Silent hypoxemia
High-altitude hypoxia
Hypoxic acclimatization
Acute respiratory distress
Respiratory system

ABSTRACT

A very recent epidemiological study provides preliminary evidence that living in habitats located at 2500 m above sea level (masl) might protect from the development of severe respiratory symptoms following infection with the novel SARS-CoV-2 virus. This epidemiological finding raises the question of whether physiological mechanisms underlying the acclimatization to high altitude identifies therapeutic targets for the effective treatment of severe acute respiratory syndrome pivotal to the reduction of global mortality during the COVID-19 pandemic. This article compares the symptoms of acute mountain sickness (AMS) with those of SARS-CoV-2 infection and explores overlapping patho-physiological mechanisms of the respiratory system including impaired oxygen transport, pulmonary gas exchange and brainstem circuits controlling respiration. In this context, we also discuss the potential impact of SARS-CoV-2 infection on oxygen sensing in the carotid body. Finally, since erythropoietin (EPO) is an effective prophylactic treatment for AMS, this article reviews the potential benefits of implementing FDA-approved erythropoietin-based (EPO) drug therapies to counteract a variety of acute respiratory and non-respiratory (e.g. excessive inflammation of vascular beds) symptoms of SARS-CoV-2 infection.

1. Introduction

High-altitude environments of 2500 m above sea level (masl) are characterized by barometric hypoxia. Chronic exposure to hypobaric hypoxia in such extreme and adverse environments evokes short- and long-term physiologic adaptations to maintain tissue oxygen levels at high altitude in animals and humans. Recent work suggests that high altitude dwellers, in particular in American countries and Tibet (Arias-Reyes et al., 2020; Ortiz-Prado et al., 2020), may present with lower infection rates and/or less severe symptoms of COVID-19 compared to lowlanders (Arias-Reyes et al., 2020; Lei et al., 2020; Ortiz-Prado et al., 2020). This epidemiologic finding raises the question of whether physiological mechanisms underlying the acclimatization to high altitude or in turn the development of acute mountain sickness (AMS- that in severe cases may progress in high-altitude pulmonary and cerebral edema), may provide potential avenues for understanding the severity of symptoms and treatment of SARS-CoV-2 infection.

Here, we provide a survey of similarities of acute mountain sickness to COVID-19 and suggest that the physiologic response to high altitude, characterized by an increase in erythropoietin (EPO), may provide a framework to develop an adjuvant therapy in COVID-19. Indeed, a recently published case study from Iran supports EPO as an effective treatment of severe COVID-19 pathophysiology (Hadadi et al., 2020).

2. General similarities of acute mountain sickness and COVID-19

Initial clinical assessments of the COVID-19 pandemic provide strong evidence that many people infected with SARS-CoV-2 show no symptoms or display “classic” flu-like symptoms including low level fever, dry cough, muscle ache, and/or mild fatigue. These mild cases of SARS-CoV-2 infection recover without ever developing acute respiratory distress (Chen et al., 2020; Yang et al., 2020; Zhang et al., 2020a, b). However, a subset of cases develops severe symptoms and hypoxemia (low level of oxygen in the blood). The dichotomy of disease

* Corresponding author at: Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ) 2725, chemin Sainte-Foy, Québec, QC, G1V 4G5 Canada.
E-mail address: jorge.soliz@criucpq.ulaval.ca (J. Soliz).

severity following SARS-CoV-2 infection is partially explained by comorbidities such as hypertension, diabetes, asthma or kidney dysfunction, and is weakly linked to gender (males are more prone to develop respiratory distress (Gasmi et al., 2020)). Thus, the mechanisms underlying the dichotomy of disease severity remain unclear.

Acute mountain sickness (AMS) has a similar dichotomy in disease severity in subsets of lowlanders shortly after ascent to high altitude of > 2500 masl. These high-altitude environments have low barometric pressures and consequently low partial pressures of oxygen in inspired air (Chawla and Saxena, 2014; Frisnacho, 1975) sufficient to cause hypoxemia, which can lead to AMS. AMS usually presents with headache, nausea, dyspnea, increased heart and respiratory rates, and vomiting. In few cases, AMS evolve into high-altitude pulmonary edema (HAPE) or high-altitude cerebral edema (HACE). Interestingly, the severity of AMS depends on the altitude reached, but seems independent of fitness or general health status (Bircher et al., 1994; Smedley and Grocott, 2013). Thus, like SARS-CoV-2 infection, why some can cope with the hypoxic environment while others fail to acclimatize is not easily explained (Basnyat and Murdoch, 2003). Moreover, the same sexual dimorphism (with higher impact in males (Joseph et al., 2000; Leon-Velarde et al., 1997; Mortola and Saiki, 1996), and some genetic basis for the dichotomy in the development of severe AMS is also identified (Rupert and Koehle, 2006).

Even though AMS and COVID-19 have different pathogenic mechanisms (barometric hypoxia vs. viral infection), the disease progression and specific symptoms show remarkable overlap. Both AMS and COVID-19 trigger a perfect storm in the respiratory system, targeting the integrative layers of the respiratory system, injuring the lungs, impairing oxygen transport, compromising gas exchange and impacting neural circuits controlling breathing (see Table 1).

3. Current understanding of COVID-19 pathogenesis

Severe cases of SARS-CoV-2 infection can cause pneumonia-associated acute lung-injury and multiple-organ dysfunction where heart-

Table 1
Summary of the overlapping pathophysiology of Acute Mountain Sickness (AMS) and COVID-19.

	AMS	COVID-19
GENERAL FEATURES — UPPER AIRWAYS		
Cough	yes (in HAPE)	yes
Sore throat	—	yes
Rhinitis	—	yes
LUNG — OXYGEN UPTAKE		
Vasoconstriction	yes	yes
Shortness of breath or difficulty breathing	yes	yes
Pulmonary edema	yes	yes
BLOOD — OXYGEN TRANSPORT		
Decreased O ₂ transport by hemoglobin	yes	yes
Lymphopenia	yes	yes
Haemolysis	yes	yes
Higher leukocyte numbers	no	yes
BRAIN		
Loss of taste and smell	no	yes
Hypoxic respiratory failure	yes	yes
Impaired central respiratory network	yes	unclear
Brain edema	yes	yes
Cerebrovascular conditions (inflammation)	no	unclear
Other neurological impairment (headache, dizziness, etc)	yes	yes
SEX DIMORPHYSM		
Men most affected	yes	yes
OTHER		
Endothelial inflammation (lungs, heart, kidney)	mild	severe
Oxidative stress	mild	yes
Fever	no	yes
Diarrhea	no	yes

liver- and kidney-dysfunction are also observed (Chen et al., 2020; Yang et al., 2020). Indeed, computerized tomography (CT) images from the lungs after SARS-CoV-2 infection show ground-glass opacities localized to alveoli indicating the presence of acute lung injury (Bhatraju et al., 2020). The current working hypothesis for the pathogenesis of COVID-19 suggests that the highly-expressed angiotensin-converting enzyme 2 (ACE2) in the airway epithelia and particular the alveoli (Hamming et al., 2004) acts as primary gateway for the cellular penetration of SARS-CoV-2 causing inflammation and local cell death (Lei et al., 2020; Tansey, 2008; Zhu et al., 2020). A previous animal study supports this working hypothesis by showing that ACE2 knock-out mice develop significantly less acute lung injury after infection with SARS-CoV (Kuba et al., 2006).

Features of the disease that are more common in severe cases, while also abundant in mild cases, may reflect physiological processes involved in COVID-19 disease progression. Currently, a common consensus in both mild and severe cases of COVID-19 is an underlying increase in proinflammatory cytokine levels, but also an acute loss of lymphocytes (Chen et al., 2020; Zhang et al., 2020a, b), and also a loss of red blood cells (Chen et al., 2020). These features suggest a strong and generalized immune response (cytokine storm) involving many cytokine mediators in severe cases of COVID-19. Organ damage, especially acute lung injury, is thought to be a common consequence of the cytokine storm that injures tissues and triggers a compensatory fibrotic healing mechanism that can result in persistent organ dysfunction (Tisoncik et al., 2012). Several reports of vascular damage in patients with severe respiratory symptoms support the hypothesis that endothelial cells are at high risk for damage by a cytokine storm (Qin et al., 2020; Xu et al., 2005; Yao et al., 2020; Zhang et al., 2020b; Zhu et al., 2020). Thus, damage to the heart, lung, kidneys and brain may be mediated by excessive inflammation following SARS-CoV-2 infection. Similarly, the respiratory distress evoked by SARS-CoV-2 infection could also be exacerbated by vascular damage in the lungs. Indeed, autopsies report oedematous, congested and widened lung blood vessels and focal haemorrhage in lung tissue (Yao et al., 2020; Zhang et al., 2020b). Although a cytokine storm appears to be a central pathologic mechanism following SARS-CoV-2 infection, anti-inflammatory therapies were reported to be ineffective or not recommended due to their potential to increase disease progression by delaying the development of adaptive immunity (Zhang et al., 2020a). Recent clinical reports show that respiratory distress in COVID-19, may have a more complex pathogenesis (Gattinoni et al., 2020). These authors report that while hyperventilation indicated severe hypoxemia, paradoxically lung compliance (elasticity) appears to be still normal (silent hypoxemia). In other words, hyperventilation and therefore increased minute ventilation fails to compensate for hypoxemia, while primary lung function appears to be only modestly impaired by lung edema. The silent hypoxemia seen COVID-19 could relate reports of decreased erythrocyte counts (Chen et al., 2020; Liu and Li, 2020; Yang et al., 2020) and low hematocrit (Du et al., 2020; Liu et al., 2020). These observations further suggest that SARS-CoV-2 may target several components of the respiratory system including impaired oxygen uptake, oxygen transport and potentially also effects on the central regulation of breathing (further details see below).

Overall, the current understanding is that the pathogenesis of COVID-19 appears to be heterogeneous and may require individual approaches to treat respiratory distress caused by pathophysiologicals across several functional parts of the respiratory and other organ systems.

4. Physiological acclimatization to life in high altitude – clues for treating COVID-19

High-altitude environments above 2500 masl have a low partial pressure of oxygen (Chawla and Saxena, 2014; Frisnacho, 1975). Despite living in such a challenging environment, people acclimatize and

adapt to life at high-altitude (Hochachka and Monge, 2000). Acclimatization to hypobaric hypoxia depends on both immediate and gradual physiological adjustments of the respiratory system (Chawla and Saxena, 2014). Hyperventilation is the immediate acute response that compensates emerging hypoxia (Hochachka and Monge, 2000; Martin and Windsor, 2008) via a sensor-mediated increase in minute ventilation. The hyperventilation is mediated by augmented synaptic input from the carotid bodies, the peripheral arterial oxygen sensors, that evoke a centrally-mediated increase of respiratory rate and tidal volume (Kumar and Phil, 2007; Lopez-Barneo et al., 1988; Wyatt et al., 1995). The compensatory hyperventilation in high altitude emerges immediately and raises alveolar ventilation by 25–30 % depending on the altitude reached. Consequently, the increased partial pressure of oxygen in the alveolar space helps to restore physiological oxygen diffusion gradients between the alveoli and blood.

In addition to the initial carotid body-mediated compensatory hyperventilation, gradually increasing numbers of circulating erythrocytes are observed after exposure to hypobaric hypoxia (Martin and Windsor, 2008; Storz and Moriyama, 2008; Zubieta-Calleja et al., 2007). Erythropoietin (EPO), an essential hormone for the stimulation of the production of red blood cells increases during sustained hypoxemia (Martin and Windsor, 2008; Storz and Moriyama, 2008). At high altitude, the increase in EPO secretion from the kidneys and liver triggers a gradual increase of red blood cells over a period of two weeks (or longer, depending on the reached altitude) and is the major effector of the acclimatization to a high altitude environment (Tansey, 2008).

Other hormonal and molecular mechanisms also play important regulatory functions during gradual acclimatization to high altitude hypoxia. As such, hypoxia (itself) is the main stimulus causing hypoxic diuresis and natriuresis by inhibition of renal tubular sodium reabsorption (Honig, 1989; Karim and al-Obaidi, 1993; Schmidt et al., 1985). This process leads to the loss of body water (hypovolemia) and reduction of the plasma volume generating haemoconcentration, a phenomenon that efficiently increases the oxygen carrying capacity of the blood (Chawla and Saxena, 2014). However, since prolonged and pronounced hypoxic diuretic response may lead to dehydration, diuresis is regulated by action of the renin–angiotensin–system (RAS). As such, activation of the RAS system during the first hours of exposure to hypoxia regulates diuresis, but in parallel helps to counterbalance pulmonary vasoconstriction by leading a transient increase of ACE2 receptors in lung during the early stages of hypoxia (Veit and Weissmann, 2013; Zhang et al., 2009). However, later on, the expression of ACE2 in lung (and other tissues) finally decreases after the accumulation of the hypoxia-inducible factor-1 (HIF-1) (Dang et al., 2020; Zhang et al., 2009). These physiological mechanisms of acclimatization to high altitude hypoxia might be an important link for the reported decrease in severity of COVID-19 in high-altitude dwellers since cell penetration of SARS-CoV-2 via ACE2 might be diminished after high-altitude acclimatization (Arias-Reyes et al., 2020; Ortiz-Prado et al., 2020).

5. Neurological pathogenesis of COVID-19 and acute mountain sickness

Both COVID-19 and AMS are associated with neurologic symptoms. High-altitude induces hypoxemia, which when uncompensated (or only partially compensated) can lead to dizziness, nausea, headaches, and shortness of breath. Further development of AMS associates with the onset of high-altitude cerebral edema (HACE) and then, the neurological symptoms progress to loss of consciousness possibly leading to fatal ataxia (including the failure of motor control of breathing) (Dehnert and Bartsch, 2017; Kedzierewicz and Cabane, 2013; Mazzuero et al., 2008).

Similarly, SARS-CoV-2 infection in the central nervous system may trigger diffuse neurological symptoms such as headache, nausea and dizziness and have been observed in substantial numbers of severe

COVID-19 cases (Li et al., 2020). These neurological symptoms are largely attributed to inflammation in the cerebral vasculature but also in the central nervous system (CNS) causing brain edemas. An early COVID-19 report indicated that SARS-CoV-2 could be found in the cerebrospinal fluid and was associated with encephalitis caused by excessive inflammatory response on cerebral blood endothelium (Moriguchi et al., 2020). However, SARS-CoV-2 may affect the brain directly, as SARS-CoV infects central neural tissue in humans (Gu et al., 2005; Xu et al., 2005). Similarly, animal studies also demonstrate that intranasal inoculation with human strains of the virus MERS-CoV and SARS-CoV infect the central nervous system (Li et al., 2016; McCray et al., 2007; Netland et al., 2008). Infected areas in the brain specifically included cardiorespiratory control areas in the brainstem (Netland et al., 2008). The route of infection of the brainstem could be either linked to a leaky blood-brain barrier after viral infection (Spindler and Hsu, 2012) or could be also taken up by sensory nerves, particularly by those innervating the airways (e.g. nasal trigeminal and pulmonary vagal nerves). Further, ACE2 is expressed in the brainstem (Doobay et al., 2007) suggesting that brainstem cardio-respiratory circuits may be most susceptible for viral infection. Together, these observations raise the hypothesis that impaired neuronal activities within the brainstem cardio-respiratory network may contribute to pathophysiological manifestations of SARS-CoV-2 infection.

The growing evidence of silent hypoxemia in COVID-19 (low blood oxygen levels associated without respiratory distress; (Gattinoni et al., 2020; Xie et al., 2020) implies an inadequate response of centrally-mediated increased minute ventilation which fails to compensate for the developing hypoxemia. Such an inadequate physiological response to hypoxia is discussed for AMS (Gamboa et al., 2003; Richalet et al., 2012). Thus, we speculate that arterial oxygen sensors of the carotid body (CB) that mediate hyperventilation to compensate for the low arterial oxygen levels (Lopez-Barneo et al., 2016; Powell et al., 1998; Prabhakar and Semenza, 2016) are impaired in some severe cases of COVID-19. Consistent with this hypothesis, ACE2 is expressed in the CB (Li and Schultz, 2006). Thus, it is possible that SARS-CoV-2 specifically infects and impairs the oxygen-sensing glomus cells of the CB (Fig. 1). However, COVID-19 patients with silent hypoxemia do hyperventilate and appear to increase their minute ventilation (Gattinoni et al., 2020; Marini and Gattinoni, 2020). Thus, at first sight the COVID-19 hyperventilation contradicts the hypothesis of an impaired function of the CB. However, we cannot find any detailed information regarding tidal volumes of hypoxemic COVID-19 patients. Therefore, it is presently unclear whether hyperventilation is caused by the CB mediated physiological response that includes both increase in respiratory frequency and tidal volume (Brunner et al., 1982), or if the observed hyperventilation rather reflects the pattern of rapid shallow breathing that can be linked to a variety of other COVID-19 symptoms (fever, inflammation, etc.).

Since silent hypoxemia has not (yet) been attributed to significantly impaired lung function (Gattinoni et al., 2020; Marini and Gattinoni, 2020) in these subsets of patients (Gattinoni et al., 2020; Marini and Gattinoni, 2020), reduced pulmonary oxygen uptake also cannot be the primary cause of hypoxemia. Instead, the loss of red blood cells (Chen et al., 2020; Liu and Li, 2020; Yang et al., 2020) and low hematocrit (Du et al., 2020; Liu et al., 2020) may be linked to the low oxygen concentration in the blood (Fig. 1). Therefore, we suggest that the otherwise uncommon silent hypoxemia in COVID-19 might be caused by a combination of impaired oxygen-sensing mechanisms in the CB and a reduced capacity for oxygen transport in the blood (Fig. 1; for more details see 5.1.).

6. EPO is a strong candidate for the treatment of respiratory and non-respiratory symptoms of COVID-19

Because of the potential protective role of high-altitude acclimatization outlined above, we suggest that EPO could be an adjuvant

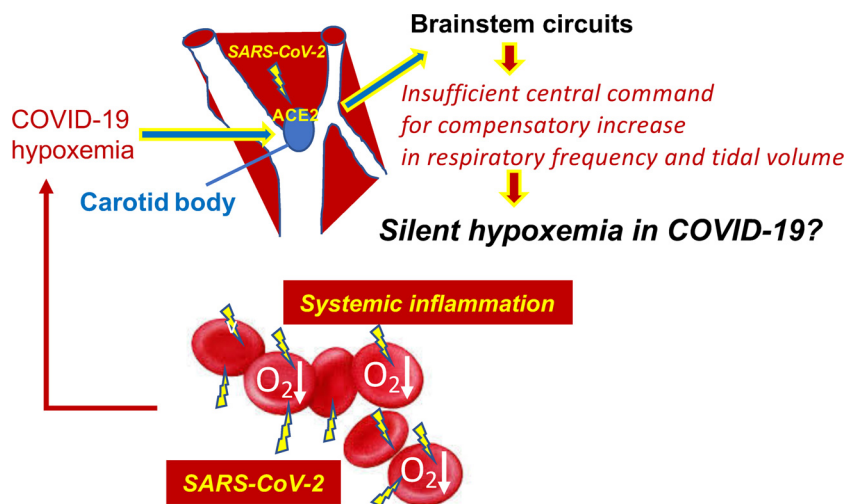


Fig. 1. SARS-CoV-2 infections are associated with silent hypoxemia. The figure illustrates the working hypothesis that silent hypoxemia is linked to both SARS-CoV-2 infection of oxygen-sensing glomus cells of the carotid body via the ACE2 gate and SARS-CoV-2 infection or systemic inflammation may reduce the oxygen carrying capacity of erythrocytes. We postulate that these convergent mechanisms could cause hypoxemia while impairing carotid body function. Therefore, the failure to trigger the centrally mediated increase in respiratory rate and tidal volume that normally would compensate for low blood oxygen level may cause silent hypoxemia seen in COVID-19 patients.

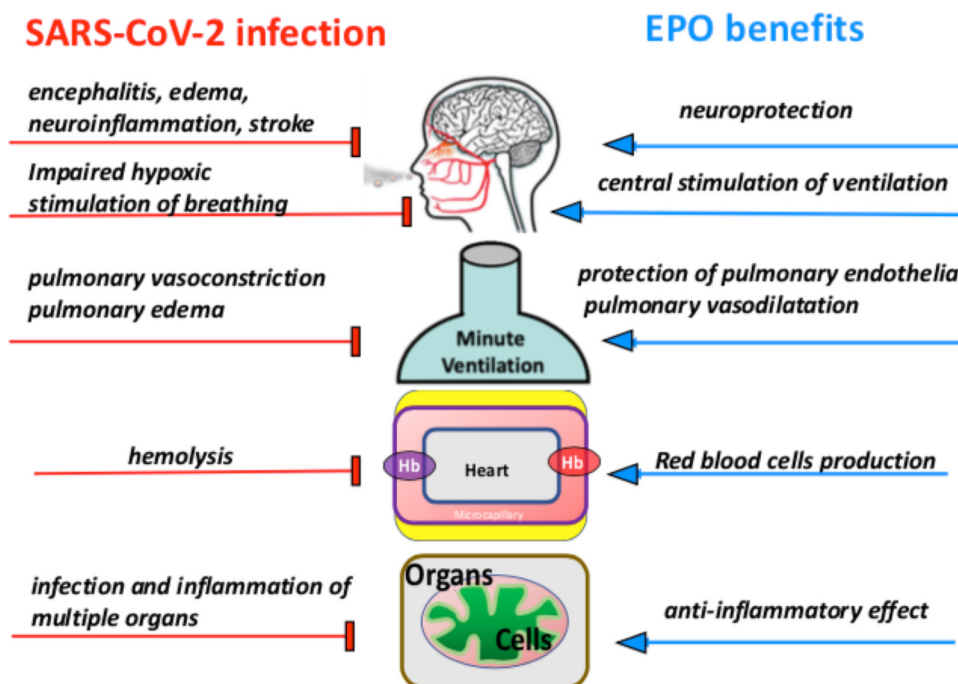


Fig. 2. Graphical illustration of the impact of SARS-CoV-2 on the integrated level of the respiratory system (left column of the figure). On the right column of the figure we summarize the potential benefits of erythropoietin (EPO) treatment on impaired respiratory functions in COVID-19.

therapy to treat or mitigate hypoxemia and lethality in COVID-19. Importantly, permanent citizens of major towns at high altitude, particularly in South America, have 2–4-fold increases in serum levels of EPO compared to lowlanders (Beall et al., 1998). Thus, while the proposed protective effect of living at high altitude on COVID-19 severity (Arias-Reyes et al., 2020; Ortiz-Prado et al., 2020) certainly requires further validation, below, we propose a mechanism as to why EPO could be a potential adjuvant treatment alleviating various symptoms of COVID-19 (Fig. 2).

6.1. EPO stimulates oxygen uptake and transport

EPO stimulates erythropoiesis and heme synthesis and thereby can compensate COVID-19 associated loss of red blood cells and reduction in oxygen binding. The kidneys are the primary sources of EPO that targets erythroid progenitor cells in the bone marrow to stimulate red blood cell production (Jelkmann, 2007). As such, EPO treatment after SARS-CoV-2 infection may help to restore hemoglobin levels and

improve oxygen delivery to the tissues. Importantly, in the context of COVID-19, EPO also contributes to the regulation of heme production (Chung et al., 2017). Indeed, a highly controversial (see commentary by (Read, 2020)) biological modelling study suggested a likelihood that SARS-CoV-2 may attack the beta-chain of hemoglobin (Liu and Li, 2020). Beside direct effects of SARS-CoV-2 on erythrocytes, it is even more likely that inflammatory mediators cause insufficient erythropoiesis by promoting structural and functional alterations of erythrocytes (Scharte and Fink, 2003) in COVID-19. Thus, independent of the underlying pathophysiological mechanism, EPO treatment will allow for both an increase of red blood cells, as well as heme metabolism, and could improve oxygen transport to the tissues in COVID-19 patients as demonstrated clinically by Hadadi and colleagues (Hadadi et al., 2020).

Since a previous clinical trial showed that EPO injections once a week for four consecutive weeks is an effective prophylactic treatment for AMS (Heo et al., 2014), we speculate that EPO could be effective for treating at least the subsets of COVID-19 patients that have developed

hypoxemia in association with low red blood cell counts or low hematocrit (Du et al., 2020; Liu et al., 2020). Indeed, a most recent case study reports that EPO treatment has helped to stabilize a severe COVID-19 patient admitted to intensive care (Hadadi et al., 2020). Recombinant human EPO was used as a final treatment option for an 80-year-old COVID-19 patient who recovered from the severe stage of the disease (Hadadi et al., 2020). In this case, one week before the therapy, the patient already had hemoglobin deficiency, which further declined as the disease progressed. With EPO treatment, his hemoglobin levels eventually improved to physiologic levels and the patient was discharged from intensive care.

6.2. EPO protects pulmonary vascular beds and counteract hypoxic pulmonary vasoconstriction

COVID-19 patients show ground-glass opacities localized to alveoli indicating the presence of acute lung injury (Bhatraju et al., 2020; Solaimanzadeh, 2020). Thus, given the prevalence of vascular bed damage in the lungs and other organ systems of COVID-19 patients, a key mechanism of EPO is the protection of pulmonary endothelium and the prevention of pulmonary edema (Moeini et al., 2013). Experiments performed in mice demonstrated that EPO protects against renal ischemia-reperfusion-induced acute lung injury, playing a key role in suppressing pulmonary edema as well as attenuating alveolar epithelial cell swelling (Zhu et al., 2019). Moreover, protective anti-inflammatory effects of EPO against lung injury was also observed in several animal disease models such as sepsis, lung injury and inflammation (Korkmaz et al., 2014; Nairz et al., 2012; Rocha et al., 2015; Turhan et al., 2016; Zhang and Dong, 2019).

A key mechanism for developing high-altitude pulmonary edema (HAPE) is the hypoxia-mediated vasoconstriction of pulmonary arteries and capillary beds (Swenson and Bartsch, 2012; Sylvester et al., 2012) as well as the redistribution of blood flow from basal to apical levels of the lungs (Dunham-Snary et al., 2017; Swenson and Bartsch, 2012; Sylvester et al., 2012). Here, EPO counteracts the pulmonary vasoconstriction by increasing the endothelial capacity to produce the vasodilator nitric oxide (NO) (Beleslin-Cokic et al., 2011; Beleslin-Cokic et al., 2004). Studies performed in transgenic mice (Tg6) that over-express human EPO constitutively showed that, despite extremely high hematocrit values (80 % hematocrit), blood pressure, heart rate, and cardiac output were normal (Ruschitzka et al., 2000). In fact, the adaptive mechanisms to excessive erythrocytosis in these animals also involved an increased activity of endothelial NO synthase (eNOS). Thus, the eNOS-mediated enhanced NO synthesis in Tg6 mice results in generalized peripheral vasodilatation (Ruschitzka et al., 2000). In human, elevation of NO metabolism in the lung is reported for Tibetans and Andeans as an adaptive mechanism that counteracts high-altitude hypoxia (Beall, 2007). Therefore, as actions of the non-erythropoietic effects of EPO have immediate action, it is reasonable to propose that EPO may be an effective therapeutic strategy that could alleviate SARS-CoV-2-mediated acute lung injury and lung edema by protecting the pulmonary microvascular endothelium integrity and by preventing vasoconstriction in pulmonary arteries.

6.3. EPO protects the nervous system

In addition to its erythropoietic function, EPO can be also secreted by neurons and astrocytes (Alnaeeli et al., 2012; Bernaudin et al., 1999; Juul et al., 1998) and thus directly affects local brain circuits and cerebral microenvironments. Following systemic administration, EPO crosses the blood-brain barrier attaining peak concentrations in the brain after 4–6 h (Banks et al., 2004; Juul et al., 2009; Statler et al., 2007; Xenocostas et al., 2005). Accordingly, EPO exerts a neuroprotective function in ischemic stroke and traumatic brain injury models in rodents, monkeys and humans (Brines et al., 2004; Gassmann et al., 2003; Ghezzi and Brines, 2004; Gorio et al., 2002) and can prevent

cardio-respiratory dysfunction following exposure to chronic intermittent hypoxia (Elliot-Portal et al., 2018). Stroke and brain injury models are associated with local inflammation cerebrovascular system and brain edema. Thus, EPO could alleviate general neurological symptoms in severe COVID-19 cases by acting both centrally and peripherally.

As discussed above, SARS-CoV-2 infection may specifically affect the function of the brainstem. Via its neuroprotective effects, EPO can counteract SARS-CoV-2 infection by acting specifically on these primary central control circuits. First, experiments performed in cohorts of rats that were housed permanently at high-altitude (La Paz, Bolivia, 3600 masl), showed that EPO expression was drastically increased in the brainstem (but not in the forebrain) regions (Seaborn et al., 2011). Second, centrally acting EPO stimulates hypoxic ventilation independent of stimulation of the oxygen sensors of the carotid body (Soliz et al., 2005). This centrally mediated hypoxic hyperventilation was abolished after application with an EPO antagonist (Ballot et al., 2015; Soliz et al., 2007). This action of EPO could be of particular interest in COVID-19 patients since the central action of EPO could restore a compensatory hypoxic hyperventilatory response in cases associated with impaired function of peripheral oxygen sensors. Since EPO can act on the brain within 4–6 hours (Banks et al., 2004; Statler et al., 2007; Xenocostas et al., 2005), EPO could be utilized as a short acting emergency treatment, in particular in patients with silent hypoxemia of unknown origins.

6.4. Anti-inflammatory therapeutical effects of EPO

Increasing numbers of clinical reports raise concerns that SARS-CoV-2 infections can also cause kidney and heart failure due to excessive inflammation (cytokine storm) targeting the vascular beds. EPO can exert potent effects to heal and protect vascular beds in animal models of hemorrhage (Buemi et al., 1993; Chong et al., 2002; Squadrito et al., 1999). In this context, EPO can prevent and/or protect against tissue damage and inflammation in several tissues and vascular beds (Nairz et al., 2012). Anti-inflammatory effects of EPO were evident in animal models of chronic inflammation and infectious diseases (Cuzzocrea et al., 2005; Nairz et al., 2011; Yuan et al., 2008). Importantly, a positive effect of EPO on the clinical outcome was shown in critically ill patients suffering from sepsis (Corwin et al., 2007; Napolitano et al., 2008). Thus, in addition to the beneficial effects of EPO on several aspects of the respiratory system, EPO might also counteract COVID-19 effects on the vascular beds of other vital organs such as the heart and kidneys.

6.5. Limitations of EPO as adjuvant therapy in COVID-19

Growing evidence suggests that SARS-CoV-2 infection may also predispose patients to thrombosis (Bikdeli et al., 2020). Therefore, it needs to be stressed that thrombotic complications (especially venous thromboembolism) have also been reported in patients undergoing chronic therapy with EPO stimulating agents (Lippi et al., 2010). However, EPO derivatives such as carbamylated EPO (CEPO) (Chen et al., 2015) and asialo EPO (Sonoda et al., 2014) have significantly reduced hematopoietic function, but remain fully organ-protective (Chen et al., 2015). Finally, co-treatment of EPO with anti-coagulant or anti-thrombotic factors, such as heparin should be able to circumvent such complications in hospitalized COVID-19 patients.

7. Conclusion

Symptomatic similarities between SARS-CoV-2 virus infection and AMS suggest that the physiologic mechanisms underlying acclimatization to high-altitude hypoxia may identify therapeutic targets for the prophylaxis and treatment of COVID-19. Infection with SARS-CoV-2 results in a series of multi-organ complications that vary according to

the severity of the disease: inflammatory endothelial damage, shortness of breath, pulmonary vasoconstriction, pulmonary edema, neuroinflammation, cardiac thrombosis, cerebral stroke, hemolysis, and potentially impaired carotid body mediated oxygen-sensing resulting in an inadequate central hypoxic response. Increasing EPO levels, one of the most important adaptations to hypobaric hypoxia, may have a major therapeutic impact on most of the aforementioned pathological features and may be especially effective in counteracting the silent hypoxemia and loss of erythrocytes in severe COVID-19 cases.

Acknowledgements

Jorge Soliz is supported by the “Fonds de recherche du Quebec-Santé” (FRQ-S; FQ121919) and the IUCPQ Foundation. Mathias Dutschmann is currently supported by a NHMRC project grant (APP1165529).

The authors have no financial/nonfinancial arrangements or connections that are pertinent to the submitted manuscript.

References

- Alnaeeli, M., Wang, L., Piknova, B., Rogers, H., Li, X., Noguchi, C.T., 2012. Erythropoietin in brain development and beyond. *Anat. Res. Int.* 12, 953264.
- Arias-Reyes, C., Zubieta-DeUrioste, N., Poma-Machicao, L., Aliaga-Raduan, F., Carvajal-Rodriguez, F., Dutschmann, M., Schneider-Gasser, E.M., Zubieta-Calleja, G., Soliz, J., 2020. Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? *Resp Physiol and Neurobiol* in press.
- Ballot, O., Joseph, V., Soliz, J., 2015. Endogenous brain erythropoietin is a potent sex-specific respiratory stimulant in adult and newborn mice. *J. Appl. Physiol.* 00143 (1985), 02015 jap.
- Banks, W.A., Jumbe, N.L., Farrell, C.L., Niehoff, M.L., Heatherington, A.C., 2004. Passage of erythropoietic agents across the blood-brain barrier: a comparison of human and murine erythropoietin and the analog darbepoetin alfa. *Eur. J. Pharmacol.* 505, 93–101.
- Basnyat, B., Murdoch, D.R., 2003. High-altitude illness. *Lancet* 361, 1967–1974.
- Beall, C.M., 2007. Two routes to functional adaptation: tibetan and Andean high-altitude natives. *Proc Natl Acad Sci U S A* 104 (Suppl 1), 8655–8660.
- Beall, C.M., Brittenham, G.M., Strohl, K.P., Blangero, J., Williams-Blangero, S., Goldstein, M.C., Decker, M.J., Vargas, E., Villena, M., Soria, R., Alarcon, A.M., Gonzales, C., 1998. Hemoglobin concentration of high-altitude tibetans and bolivian Aymara. *Am. J. Phys. Anthropol.* 106, 385–400.
- Beleslin-Cokic, B.B., Cokic, V.P., Yu, X., Weksler, B.B., Schechter, A.N., Noguchi, C.T., 2004. Erythropoietin and hypoxia stimulate erythropoietin receptor and nitric oxide production by endothelial cells. *Blood* 104, 2073–2080.
- Beleslin-Cokic, B.B., Cokic, V.P., Wang, L., Piknova, B., Teng, R., Schechter, A.N., Noguchi, C.T., 2011. Erythropoietin and hypoxia increase erythropoietin receptor and nitric oxide levels in lung microvascular endothelial cells. *Cytokine* 54, 129–135.
- Bernaudin, M., Marti, H.H., Rousset, S., Divoux, D., Nouvelot, A., MacKenzie, E.T., Petit, E., 1999. A potential role for erythropoietin in focal permanent cerebral ischemia in mice. *J. Cereb. Blood Flow Metab.* 19, 643–651.
- Bhatraju, P.K., Ghassemieh, B.J., Nichols, M., Kim, R., Jerome, K.R., Nalla, A.K., Greninger, A.L., Pipavath, S., Wurfl, M.M., Evans, L., Kritek, P.A., West, T.E., Luks, A., Gerbino, A., Dale, C.R., Goldman, J.D., O'Mahony, S., Mikacenic, C., 2020. Covid-19 in critically ill patients in the Seattle region - case series. *N. Engl. J. Med.*
- Bikdeli, B., Madhavan, M.V., Jimenez, D., Chuich, T., Dreyfus, I., Driggin, E., Nigoghossian, C., Ageno, W., Madjid, M., Guo, Y., Tang, L.V., Hu, Y., Giri, J., Cushman, M., Quere, I., Dimakakos, E.P., Gibson, C.M., Lippi, G., Favaloro, E.J., Fareed, J., Caprini, J.A., Tafur, A.J., Burton, J.R., Francese, D.P., Wang, E.Y., Falanga, A., McLintock, C., Hunt, B.J., Spyropoulos, A.C., Barnes, G.D., Eikelboom, J.W., Weinberg, I., Schulman, S., Carrier, M., Piazza, G., Beckman, J.A., Steg, P.G., Stone, G.W., Rosenkranz, S., Goldhaber, S.Z., Parikh, S.A., Monreal, M., Krumholz, H.M., Konstantinides, S.V., Weitz, J.I., Lip, G.Y.H., 2020. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J. Am. Coll. Cardiol.*
- Bircher, H., Eichenberger, U., Maggiorini, M., Oelz, O., Bartsch, P., 1994. Relationship of mountain-sickness to physical fitness: J and exercise intensity during ascent. *J. Wilderness Med.* 5, 302–311.
- Brines, M., Grasso, G., Fiordaliso, F., Sferacteria, A., Ghezzi, P., Fratelli, M., Latini, R., Xie, Q.W., Smart, J., Su-Rick, C.J., Pobre, E., Diaz, D., Gomez, D., Hand, C., Coleman, T., Cerami, A., 2004. Erythropoietin mediates tissue protection through an erythropoietin and common beta-subunit heteroreceptor. *Proc Natl Acad Sci U S A* 101, 14907–14912.
- Brunner, M.J., Sussman, M.S., Greene, A.S., Kallman, C.H., Shoukas, A.A., 1982. Carotid sinus baroreceptor reflex control of respiration. *Circ. Res.* 51, 624–636.
- Buemi, M., Allegra, A., Aloisi, C., Privitera, M., Morabito, N., Frisina, N., 1993. Influence of the treatment with recombinant human erythropoietin on plasma concentration of interleukin-1-alpha and tumour necrosis factor-alpha in hemodialyzed subjects. *Nephron* 64, 333–334.
- Chawla, S., Saxena, S., 2014. Physiology of high-altitude acclimatization. *Reson* 19, 538–548.
- Chen, J., Yang, Z., Zhang, X., 2015. Carbamylated erythropoietin: a prospective drug candidate for neuroprotection. *Biochem. Insights* 8, 25–29.
- Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., Zhang, L., 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395, 507–513.
- Chong, Z.Z., Kang, J.Q., Maiese, K., 2002. Hematopoietic factor erythropoietin fosters neuroprotection through novel signal transduction cascades. *J. Cereb. Blood Flow Metab.* 22, 503–514.
- Chung, J., Wittig, J.G., Ghamari, A., Maeda, M., Dailey, T.A., Bergonia, H., Kafina, M.D., Coughlin, E.E., Minogue, C.E., Hebert, A.S., Li, L., Kaplan, J., Lodish, H.F., Bauer, D.E., Orkin, S.H., Cantor, A.B., Maeda, T., Phillips, J.D., Coon, J.J., Pagliarini, D.J., Dailey, H.A., Paw, B.H., 2017. Erythropoietin signaling regulates heme biosynthesis. *Elife* 6.
- Corwin, H.L., Gettinger, A., Fabian, T.C., May, A., Pearl, R.G., Heard, S., An, R., Bowers, P.J., Burton, P., Klausner, M.A., Corwin, M.J., 2007. Efficacy and safety of epoetin alfa in critically ill patients. *N. Engl. J. Med.* 357, 965–976.
- Cuzzocrea, S., Mazzon, E., di Paola, R., Genovese, T., Patel, N.S., Britti, D., de Majo, M., Caputi, A.P., Thiemermann, C., 2005. Erythropoietin reduces the degree of arthritis caused by type II collagen in the mouse. *Arthritis Rheum.* 52, 940–950.
- Dang, Z., Su, S., Jin, G., Nan, X., Ma, L., Li, Z., Lu, D., Ge, R., 2020. Tsantan Sumtang attenuated chronic hypoxia-induced right ventricular structure remodeling and fibrosis by equilibrating local ACE-AngII-AT1R/ACE2-Ang1-7-Mas axis in rat. *J. Ethnopharmacol.* 250, 112470.
- Dehnert, C., Bartsch, P., 2017. Acute Mountain Sickness and High-Altitude Cerebral Edema. *Ther. Umsch.* 74, 535–541.
- Doobay, M.F., Talman, L.S., Obr, T.D., Tian, X., Davison, R.L., Lazartigues, E., 2007. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292, R373–381.
- Du, Y., Tu, L., Zhu, P., Mu, M., Wang, R., Yang, P., Wang, X., Hu, C., Ping, R., Hu, P., Li, T., Cao, F., Chang, C., Hu, Q., Jin, Y., Xu, G., 2020. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. *Am. J. Respir. Crit. Care Med.*
- Dunham-Snary, K.J., Wu, D., Sykes, E.A., Thakrar, A., Parlow, L.R.G., Mewburn, J.D., Parlow, J.L., Archer, S.L., 2017. Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. *Chest* 151, 181–192.
- Elliot-Portal, E., Laouafa, S., Arias, C., Janes, T.A., Joseph, V., Soliz, J., 2018. Cerebral erythropoietin prevents cardio-respiratory dysfunction induced by chronic intermittent hypoxia. *Sleep* 41, 1–13.
- Frisancho, A.R., 1975. Functional adaptation to high altitude hypoxia. *Science* 187, 313–319.
- Gamboa, J., Macarlapu, J.L., Rivera-Chira, M., Monge, C.C., Leon-Velarde, F., 2003. Effect of domperidone on ventilation and polycythemia after 5 weeks of chronic hypoxia in rats. *Respir. Physiol. Neurobiol.* 135, 1–8.
- Gasmi, A., Noor, S., Tippairote, T., Dadar, M., Menzel, A., Bjorklund, G., 2020. Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. *Clin. Immunol.*, 108409.
- Gassmann, M., Heinicke, K., Soliz, J., Ogunshola, O.O., 2003. Non-erythroid functions of erythropoietin. *Adv. Exp. Med. Biol.* 543, 323–330.
- Gattinoni, L., Chiumello, D., Caironi, P., Busana, M., Romitti, F., Brazzi, L., Camporota, L., 2020. COVID-19 pneumonia: different respiratory treatment for different phenotypes? *Intensive Care Med.* <https://doi.org/10.1007/s00134-020-06033-2>.
- Ghezzi, P., Brines, M., 2004. Erythropoietin as an antiapoptotic, tissue-protective cytokine. *Cell Death Differ.* 11 (Suppl 1), S37–44.
- Gorio, A., Gokmen, N., Erbayraktar, S., Yilmaz, O., Madaschi, L., Cichetti, C., Di Giulio, A.M., Vardar, E., Cerami, A., Brines, M., 2002. Recombinant human erythropoietin counteracts secondary injury and markedly enhances neurological recovery from experimental spinal cord trauma. *Proc. Natl. Acad. Sci. U.S.A.* 99, 9450–9455.
- Gu, J., Gong, E., Zhang, B., Zheng, J., Gao, Z., Zhong, Y., Zou, W., Zhan, J., Wang, S., Xie, Z., Zhuang, H., Wu, B., Zhong, H., Shao, H., Fang, W., Gao, D., Pei, F., Li, X., He, Z., Xu, D., Shi, X., Anderson, V.M., Leong, A.S., 2005. Multiple organ infection and the pathogenesis of SARS. *J. Exp. Med.* 202, 415–424.
- Hadadi, A., Mortezaazadeh, M., Kolehrouzan, K., Alavian, G., 2020. Does recombinant human Erythropoietin administration in critically ill COVID-19 patients have miraculous therapeutic effects? *J. Med. Virol.*
- Hamming, I., Timens, W., Bultuis, M.L., Lely, A.T., Navis, G., van Goor, H., 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* 203, 631–637.
- Heo, K., Kang, J.K., Choi, C.M., Lee, M.S., Noh, K.W., Kim, S.B., 2014. Prophylactic effect of erythropoietin injection to prevent acute mountain sickness: an open-label randomized controlled trial. *J. Korean Med. Sci.* 29, 416–422.
- Hochachka, P.W., Monge, C., 2000. Evolution of human hypoxia tolerance physiology. *Adv. Exp. Med. Biol.* 475, 25–43.
- Honig, A., 1989. Peripheral arterial chemoreceptors and reflex control of sodium and water homeostasis. *Am. J. Physiol.* 257, R1282–1302.
- Jelkmann, W., 2007. Erythropoietin after a century of research: younger than ever. *Eur. J. Haematol.* 78, 183–205.
- Joseph, V., Soliz, J., Pequignot, J., Sempore, B., Cottet-Emard, J.M., Dalmaz, Y., Favier, R., Spielvogel, H., Pequignot, J.M., 2000. Gender differentiation of the chemoreflex during growth at high altitude: functional and neurochemical studies. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 278, R806–816.
- Juul, S.E., Anderson, D.K., Li, Y., Christensen, R.D., 1998. Erythropoietin and erythropoietin receptor in the developing human central nervous system. *Pediatr. Res.* 43, 40–49.

- Juul, S.E., Beyer, R.P., Bammler, T.K., McPherson, R.J., Wilkerson, J., Farin, F.M., 2009. Microarray analysis of high-dose recombinant erythropoietin treatment of unilateral brain injury in neonatal mouse hippocampus. *Pediatr. Res.* 65, 485–492.
- Karim, F., al-Obaidi, M., 1993. Modification of carotid chemoreceptor-induced changes in renal haemodynamics and function by carotid baroreflex in dogs. *J. Physiol.* 466, 599–610.
- Kedzierewicz, R., Cabane, D., 2013. Acute mountain sickness and high altitude cerebral and pulmonary edema. *Rev. Prat.* 63, 18–26.
- Korkmaz, T., Kahramansoy, N., Kilicgun, A., Firat, T., 2014. The effect of erythropoietin to pulmonary injury and mast cells secondary to acute pancreatitis. *BMC Res. Notes* 7, 267.
- Kuba, K., Imai, Y., Rao, S., Jiang, C., Penninger, J.M., 2006. Lessons from SARS: control of acute lung failure by the SARS receptor ACE2. *J. Mol. Med.* 84, 814–820.
- Kumar, P., Phil, D., 2007. Translating blood-borne stimuli: chemotransduction in the carotid body. *Sheng Li Xue Bao* 59, 128–132.
- Lei, Y., Huang, X., Lang, B., Lan, Y., Lu, J., Zeng, F., 2020. Clinical features of imported cases of coronavirus disease 2019 in Tibetan patients in the Plateau area. *MedRxiv*. <https://doi.org/10.1101/2020.03.09.20033126>.
- Leon-Velarde, F., Ramos, M.A., Hernandez, J.A., De Idiaquez, D., Munoz, L.S., Gaffo, A., Cordova, S., Durand, D., Monge, C., 1997. The role of menopause in the development of chronic mountain sickness. *Am. J. Physiol.* 272, R90–94.
- Li, Y.L., Schultz, H.D., 2006. Enhanced sensitivity of Kv channels to hypoxia in the rabbit carotid body in heart failure: role of angiotensin II. *J. Physiol.* 575, 215–227.
- Li, K., Wohlford-Lenane, C., Perlman, S., Zhao, J., Jewell, A.K., Reznikov, L.R., Gibson-Corley, K.N., Meyerholz, D.K., McCray Jr, P.B., 2016. Middle east respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *J. Infect. Dis.* 213, 712–722.
- Li, Y.C., Bai, W.Z., Hashikawa, T., 2020. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J. Med. Virol.*
- Lippi, G., Franchini, M., Favaloro, E.J., 2010. Thrombotic complications of erythropoiesis-stimulating agents. *Semin. Thromb. Hemost.* 36, 537–549.
- Liu, W., Li, H., 2020. COVID-19: attacks the 1-Beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. *ChemRxiv*. https://chemrxiv.org/articles/COVID-19_Disease_ORF8_and_Surface_Glycoprotein_Inhibit_Heme_Metabolism_by_Binding_to_Porphyrin/11938173.
- Liu, K., Chen, Y., Lin, R., Han, K., 2020. Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. *J. Infect.* 80, e14–e18.
- Lopez-Barneo, J., Lopez-Lopez, J.R., Urena, J., Gonzalez, C., 1988. Chemotransduction in the carotid body: K⁺ current modulated by PO₂ in type I chemoreceptor cells. *Science* 241, 580–582.
- Lopez-Barneo, J., Gonzalez-Rodriguez, P., Gao, L., Fernandez-Aguera, M.C., Pardal, R., Ortega-Saenz, P., 2016. Oxygen sensing by the carotid body: mechanisms and role in adaptation to hypoxia. *Am. J. Physiol., Cell Physiol.* 310, C629–642.
- Marini, J.J., Gattinoni, L., 2020. Management of COVID-19 respiratory distress. *Jama*.
- Martin, D., Windsor, J., 2008. From mountain to bedside: understanding the clinical relevance of human acclimatization to high-altitude hypoxia. *Postgrad. Med. J.* 84, 622–627 quiz 626.
- Mazzuero, G., Mazzuero, A., Pascariello, A., 2008. Severe acute mountain sickness and suspect high altitude cerebral edema related to nitroglycerin use. *High Alt. Med. Biol.* 9, 241–243.
- McCray Jr, P.B., Pewe, L., Wohlford-Lenane, C., Hickey, M., Manzel, L., Shi, L., Netland, J., Jia, H.P., Halabi, C., Sigmund, C.D., Meyerholz, D.K., Kirby, P., Look, D.C., Perlman, S., 2007. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. *J. Virol.* 81, 813–821.
- Moeini, M., Nematbakhsh, M., Fazilati, M., Talebi, A., Pilehvarian, A.A., Azarkish, F., Eshraghi-Jazi, F., Pezeshki, Z., 2013. Protective role of recombinant human erythropoietin in kidney and lung injury following renal bilateral ischemia-reperfusion in rat model. *Int. J. Prev. Med.* 4, 648–655.
- Moriguchi, T., Harii, N., Goto, J., Harada, D., Sugawara, H., Takamino, J., Ueno, M., Sakata, H., Kondo, K., Myose, N., Nakao, A., Takeda, M., Haro, H., Inoue, O., Suzuki-Inoue, K., Kubokawa, K., Ogihara, S., Sasaki, T., Kinouchi, H., Kojin, H., Ito, M., Onishi, H., Shimizu, T., Sasaki, Y., Enomoto, N., Ishihara, H., Furuya, S., Yamamoto, T., Shimada, S., 2020. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int. J. Infect. Dis.* 94, 55–58.
- Mortola, J.P., Saiki, C., 1996. Ventilatory response to hypoxia in rats: gender differences. *Respir. Physiol.* 106, 21–34.
- Nairz, M., Schroll, A., Moschen, A.R., Sonnweber, T., Theurl, M., Theurl, I., Taub, N., Jammig, C., Neurauder, D., Huber, L.A., Tilg, H., Moser, P.L., Weiss, G., 2011. Erythropoietin contrastingly affects bacterial infection and experimental colitis by inhibiting nuclear factor-kappaB-inducible immune pathways. *Immunity* 34, 61–74.
- Nairz, M., Sonnweber, T., Schroll, A., Theurl, I., Weiss, G., 2012. The pleiotropic effects of erythropoietin in infection and inflammation. *Microbes Infect.* 14, 238–246.
- Napolitano, L.M., Fabian, T.C., Kelly, K.M., Bailey, J.A., Block, E.F., Langhoff, W., Enny, C., Corwin, H.L., 2008. Improved survival of critically ill trauma patients treated with recombinant human erythropoietin. *J. Trauma* 65, 285–297 discussion 297–289.
- Netland, J., Meyerholz, D.K., Moore, S., Cassell, M., Perlman, S., 2008. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J. Virol.* 82, 7264–7275.
- Ortiz-Prado, E., Simbaña-Rivera, K., Gomez-Barreno, L., Rubio-Neira, M., Guaman, L.P., Kyriakidis, N., Muslin, C., Gomez-Jaramillo, A.M., Barba, C., Cevallos, D., Sanchez-San Miguel, H., Unigarro, L., Zalakeviciute, R., Gadian, N., López-Cortés, A., 2020. Clinical, Molecular and Epidemiological Characterization of the SARS-CoV2 Virus and the Coronavirus Disease 2019 (COVID-19): A Comprehensive Literature Review. Preprints. <https://doi.org/10.20944/preprints202004.0283.v1>. 2020050085 2020040283.
- Powell, F.L., Milsom, W.K., Mitchell, G.S., 1998. Time domains of the hypoxic ventilatory response. *Respir. Physiol.* 112, 123–134.
- Prabhakar, N.R., Semenza, G.L., 2016. Regulation of carotid body oxygen sensing by hypoxia-inducible factors. *Pflugers Arch.* 468, 71–75.
- Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., Xie, C., Ma, K., Shang, K., Wang, W., Tian, D.S., 2020. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin. Infect. Dis.*
- Read, R., 2020. Flawed methods in “COVID-19: attacks the 1-Beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. *ChemRxiv*. <https://doi.org/10.26434/chemrxiv.12120912.v2>. Preprint.
- Richalet, J.P., Larmignat, P., Poitrine, E., Letournel, M., Canoui-Poitrine, F., 2012. Physiological risk factors for severe high-altitude illness: a prospective cohort study. *Am. J. Respir. Crit. Care Med.* 185, 192–198.
- Rocha, J., Eduardo-Figueira, M., Barateiro, A., Fernandes, A., Brites, D., Pinto, R., Freitas, M., Fernandes, E., Mota-Filipe, H., Sepodes, B., 2015. Erythropoietin reduces acute lung injury and multiple organ failure/dysfunction associated to a scald-burn inflammatory injury in the rat. *Inflammation* 38, 312–326.
- Rupert, J.L., Koehle, M.S., 2006. Evidence for a genetic basis for altitude-related illness. *High Alt. Med. Biol.* 7, 150–167.
- Ruschitzka, F.T., Wenger, R.H., Stallmach, T., Quaschnig, T., de Wit, C., Wagner, K., Labugger, R., Kelm, M., Noll, G., Rulicke, T., Shaw, S., Lindberg, R.L., Rodenwaldt, B., Lutz, H., Bauer, C., Luscher, T.F., Gassmann, M., 2000. Nitric oxide prevents cardiovascular disease and determines survival in polyglobulic mice overexpressing erythropoietin. *Proc. Natl. Acad. Sci. U.S.A.* 97, 11609–11613.
- Scharte, M., Fink, M.P., 2003. Red blood cell physiology in critical illness. *Crit. Care Med.* 31, S651–657.
- Schmidt, M., Ledderhos, C., Honig, A., 1985. Kidney function during arterial chemoreceptor stimulation. I. Influence of unilateral renal nerve section, bilateral cervical vagotomy, constant artificial ventilation, and carotid body chemoreceptor inactivation. *Biomed. Biochim. Acta* 44, 695–709.
- Seaborn, T., Isidoro, M.G., Villalpando, G., Grenacher, B., Soria, R., Soliz, J., 2011. Enhanced erythropoietin expression in the brainstem of newborn rats at high altitude. *Neurosci. Lett.* 502, 33–36.
- Smedley, T., Grocott, M.P., 2013. Acute high-altitude illness: a clinically orientated review. *Br. J. Pain* 7, 85–94.
- Solaimanzadeh, I., 2020. Acetazolamide, nifedipine and phosphodiesterase inhibitors: rationale for their utilization as adjunctive countermeasures in the treatment of coronavirus disease 2019 (COVID-19). *Cureus* 12, e7343.
- Soliz, J., Joseph, V., Soulage, C., Becskei, C., Vogel, J., Pequignot, J.M., Ogunshola, O., Gassmann, M., 2005. Erythropoietin regulates hypoxic ventilation in mice by interacting with brainstem and carotid bodies. *J. Physiol.* 568, 559–571.
- Soliz, J., Gassmann, M., Joseph, V., 2007. Downregulation of soluble erythropoietin receptor in the mouse brain is required for the ventilatory acclimatization to hypoxia. *J. Physiol.* 583 (1), 329–336.
- Sonoda, A., Nitta, N., Tsuchiya, K., Otani, H., Watanabe, S., Mukaisho, K., Tomozawa, Y., Nagatani, Y., Ohta, S., Takahashi, M., Murata, K., 2014. Asialoerythropoietin ameliorates bleomycin-induced acute lung injury in rabbits by reducing inflammation. *Exp. Ther. Med.* 8, 1443–1446.
- Spindler, K.R., Hsu, T.H., 2012. Viral disruption of the blood-brain barrier. *Trends Microbiol.* 20, 282–290.
- Squadrito, F., Altavilla, D., Squadrito, G., Campo, G.M., Arlotta, M., Quartarone, C., Saitta, A., Caputi, A.P., 1999. Recombinant human erythropoietin inhibits iNOS activity and reverses vascular dysfunction in splanchnic artery occlusion shock. *Br. J. Pharmacol.* 127, 482–488.
- Statler, P.A., McPherson, R.J., Bauer, L.A., Kellert, B.A., Juul, S.E., 2007. Pharmacokinetics of high-dose recombinant erythropoietin in plasma and brain of neonatal rats. *Pediatr. Res.* 61, 671–675.
- Storz, J.F., Moriyama, H., 2008. Mechanisms of hemoglobin adaptation to high altitude hypoxia. *High Alt. Med. Biol.* 9, 148–157.
- Swenson, E.R., Bartsch, P., 2012. High-altitude pulmonary edema. *Compr. Physiol.* 2, 2753–2773.
- Sylvester, J.T., Shimoda, L.A., Aaronson, P.I., Ward, J.P., 2012. Hypoxic pulmonary vasoconstriction. *Physiol. Rev.* 92, 367–520.
- Tansey, E.A., 2008. Teaching the physiology of adaptation to hypoxic stress with the aid of a classic paper on high altitude by Houston and Riley. *Adv. Physiol. Educ.* 32, 11–17.
- Tisoncik, J.R., Korth, M.J., Simmons, C.P., Farrar, J., Martin, T.R., Katze, M.G., 2012. Into the eye of the cytokine storm. *Microbiol. Mol. Biol. Rev.* 76, 16–32.
- Turhan, A.H., Atici, A., Muslu, N., Polat, A., Sungur, H.A., 2016. Erythropoietin may attenuate lung inflammation in a rat model of meconium aspiration syndrome. *Exp. Lung Res.* 42, 199–204.
- Veit, F., Weissmann, N., 2013. Angiotensin-converting enzyme 2 activation for treatment of pulmonary hypertension. *Am. J. Respir. Crit. Care Med.* 187, 569–571.
- Wyatt, C.N., Wright, C., Bee, D., Peers, C., 1995. O₂-sensitive K⁺ currents in carotid body chemoreceptor cells from normoxic and chronically hypoxic rats and their roles in hypoxic chemotransduction. *Proc. Natl. Acad. Sci. U.S.A.* 92, 295–299.
- Xenocostas, A., Cheung, W.K., Farrell, F., Zakszewski, C., Kelley, M., Lutynski, A., Crump, M., Lipton, J.H., Kiss, T.L., Lau, C.Y., Messner, A., 2005. The pharmacokinetics of erythropoietin in the cerebrospinal fluid after intravenous administration of recombinant human erythropoietin. *Eur. J. Clin. Pharmacol.* 61, 189–195.
- Xie, J., Covassin, N., Fan, Z., Singh, P., Gao, W., Li, G., Kara, T., Somers, V.K., 2020. Association between hypoxemia and mortality in patients with COVID-19. *Mayo Clin. Proc.*
- Xu, J., Zhong, S., Liu, J., Li, L., Li, Y., Wu, X., Li, Z., Deng, P., Zhang, J., Zhong, N., Ding, Y., Jiang, Y., 2020. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin. Infect. Dis.* 41, 1089–1096.

- Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S., Shang, Y., 2020. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir. Med.*
- Yao, X.H., Li, T.Y., He, Z.C., Ping, Y.F., Liu, H.W., Yu, S.C., Mou, H.M., Wang, L.H., Zhang, H.R., Fu, W.J., Luo, T., Liu, F., Chen, C., Xiao, H.L., Guo, H.T., Lin, S., Xiang, D.F., Shi, Y., Li, Q.R., Huang, X., Cui, Y., Li, X.Z., Tang, W., Pan, P.F., Huang, X.Q., Ding, Y.Q., Bian, X.W., 2020. A Pathological Report of Three COVID-19 Cases by Minimally Invasive Autopsies. *Zhonghua Bing Li Xue Za Zhi* 49, E009. .
- Yuan, R., Maeda, Y., Li, W., Lu, W., Cook, S., Dowling, P., 2008. Erythropoietin: a potent inducer of peripheral immuno/inflammatory modulation in autoimmune EAE. *PLoS One* 3, e1924.
- Zhang, X., Dong, S., 2019. Protective effects of erythropoietin towards acute lung injuries in rats with Sepsis and its related mechanisms. *Ann. Clin. Lab. Sci.* 49, 257–264.
- Zhang, R., Wu, Y., Zhao, M., Liu, C., Zhou, L., Shen, S., Liao, S., Yang, K., Li, Q., Wan, H., 2009. Role of HIF-1 α in the regulation ACE and ACE2 expression in hypoxic human pulmonary artery smooth muscle cells. *Am. J. Physiol. Lung Cell Mol. Physiol.* 297, L631–640.
- Zhang, J.J., Dong, X., Cao, Y.Y., Yuan, Y.D., Yang, Y.B., Yan, Y.Q., Akdis, C.A., Gao, Y.D., 2020a. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*.
- Zhang, W., Zhao, Y., Zhang, F., Wang, Q., Li, T., Liu, Z., Wang, J., Qin, Y., Zhang, X., Yan, X., Zeng, X., Zhang, S., 2020b. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the Perspectives of clinical immunologists from China. *Clin. Immunol.* 214, 108393.
- Zhu, M., Wang, L., Yang, J., Xie, K., Zhu, M., Liu, S., Xu, C., Wang, J., Gu, L., Ni, Z., Xu, G., Che, M., 2019. Erythropoietin ameliorates lung injury by accelerating pulmonary endothelium cell proliferation via Janus Kinase-Signal transducer and activator of transcription 3 pathway after kidney ischemia and reperfusion injury. *Transplant. Proc.* 51, 972–978.
- Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G.F., Tan, W., China Novel Coronavirus, I., Research, T., 2020. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* 382, 727–733.
- Zubieta-Calleja, G.R., Paulev, P.E., Zubieta-Calleja, L., Zubieta-Castillo, G., 2007. Altitude adaptation through hematocrit changes. *J. Physiol. Pharmacol.* 58 (Suppl 5), 811–818.