Human Hypoxia Models: From Space Medicine to Human Pharmacological Studies

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Abstract

Space medicine has developed controlled terrestrial models to investigate the impacts on human health and performance, and their application should be expanded to encompass disease conditions involving hypoxia and other factors, in order to make valuable contributions to clinical drug development. Hypoxia, a condition in which the body is deprived of adequate oxygen supply, profoundly affects human physiology at multiple levels and contributes to the pathogenesis of various diseases. Experimental exposure to hypoxic conditions has gained recognition as a valuable model for studying diseases like pulmonary hypertension, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), migraine, and kidney disease. The approach may be particularly useful in mechanism-oriented early-stage clinical studies. This review will discuss the ability to mimic or induce these conditions in a controlled laboratory setting using hypoxia, making it a valuable tool for testing the efficacy and safety of new pharmaceutical interventions.

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ABSTRACT

Space medicine has developed controlled terrestrial models to investigate the impacts on human health and performance, and their application should be expanded to encompass disease conditions involving hypoxia and other factors, in order to make valuable contributions to clinical drug development. Hypoxia, a condition in which the body is deprived of adequate oxygen supply, profoundly affects human physiology at multiple levels and contributes to the pathogenesis of various diseases. Experimental exposure to hypoxic conditions has gained recognition as a valuable model for studying diseases like pulmonary hypertension, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), migraine, and kidney disease. The approach may be particularly useful in mechanism-oriented early-stage clinical studies. This review will discuss the ability to mimic or induce these conditions in a controlled laboratory setting using hypoxia, making it a valuable tool for testing the efficacy and safety of new pharmaceutical interventions.

INTRODUCTION

In space and in aeronautics, human beings are exposed to harsh environmental conditions which pose risks for health and performance. An important example is altered atmospheric pressure and composition. Aircraft cabins and spacesuits used during extravehicular activities in space face reduced atmospheric pressure [1], while carbon dioxide concentrations in spacecraft cabins can increase significantly due to the closed environment [2, 3]. However, testing influences of these conditions in space is difficult given the relatively low number of astronauts and limited availability of medical and psychological testing capabilities. Therefore, space medicine developed highly controlled terrestrial models exposing human beings to environmental conditions that are relevant to space or aeronautics. Influences of these conditions on human health and performance are then investigated using high-fidelity phenotyping. A study testing the interaction between simulated weightlessness through head-down tilt bedrest and elevated ambient carbon dioxide is prime example for this approach [4]. In this review, we will discuss how this approach could be utilized in modeling disease conditions in clinical drug development with a particular focus on hypoxia. We will focus on commonly used human preclinical hypoxia models and their relevance to human pathophysiology, with the aim of providing a comprehensive analysis of the translational gap filled by these models.

Hypoxia is a state in which the body or parts of the body are inadequately supplied with oxygen. The condition can occur for various reasons, including high altitude exposure, heart failure, intoxications, anemia, chronic vascular diseases, obstructive sleep apnea (OSA), as well as lung diseases such as cystic fibrosis, asthma and chronic obstructive pulmonary disease (COPD) [5-8]. Oxygen plays an essential role in human physiology as it is central to the tissues ability to generate energy and to maintain their cellular functions [9, 10]. Inhaled oxygen is exchanged in the lungs across the alveolar capillary membrane and transported into the blood via passive diffusion, which is driven by the difference in the partial pressures of oxygen across the membrane. Oxygen is then circulated throughout the body in the blood, primarily bound to hemoglobin, and propelled by the heart [11-13]. Once the blood reaches the capillary beds of organs, oxygen is again passively transferred by a partial pressure gradient into cells. Hence, hypoxia arises when the partial pressure gradient between alveoli and pulmonary capillaries and subsequently between capillary beds of organs is low or when blood oxygen transport capacity is reduced. Furthermore, hypoxia on a tissue level develops when capillaries are rarefied, poorly perfused, or when the distance between capillaries and cells is increased, e.g. by edema formation. As the final electron acceptor in the electron transport chain, oxygen is necessary for aerobic respiration which typically generates the majority of the cell's chemical energy [14]. Thus, hypoxia arises when oxygen levels drop and fall below energetic demands, where causing inadequate oxygenation of tissues and a poorly regulated response can contribute to chronic diseases [15].

Translational science is the process of translating findings from basic scientific research into clinical applications, and often the limiting factor in drug development. Compounds that address specific cellular processes involved in disease often show promise in animal and cellular models but fail to succeed in clinical trials [16, 17]. One of the reasons for this phenomenon is that preclinical models may not accurately reflect the complex

biology of human disease. For example, animal models do not fully capture the genetic, physiological, and environmental factors, particularly with regards to aging, that contribute to a particular disease, and cellular models cannot perfectly represent the in vivo environment [18]. Moreover, the results can be muddled by the complex nature of chronic diseases, creating a challenge in isolating the exact mechanisms that can be specifically targeted by drugs. Also, adequate phase II dosing and timing studies are often curtailed for the aim of fast clinical outcome trials [19]. This generates the need for human models that allow the study of diseases mechanisms in a controlled manner (Figure 1).

Experimentally induced hypoxia has the potential to serve as a valuable research tool. Hypoxia could be used as a human disease model mimicking or inducing the pathological responses observed in certain diseases. A potential advantage of the approach is that hypoxia exposure can elicit physiological responses in isolation from common confounding variables, in controlled and measurable amounts, with graded doses, and safely in otherwise healthy individuals. Improving the accuracy of preclinical testing is essential for improving the success rate of new drugs in clinical trials. Sophisticated models such as laboratory induced hypoxia may help bridging the gap between basic research and drug testing in patients (Figure 1).

PHYSIOLOGICAL RESPONSE TO HYPOXIA

The response to both acute, intermittent (repeat cycling in and out of hypoxia), and chronic hypoxia, is sensed by chemoreceptors. Peripheral chemoreceptors are chemical sensory cells in the aortic and carotid bodies that are activated by changes in oxygen, carbon dioxide, and pH levels in the blood which they communicate to the central nervous system. The response restores homeostasis by increasing ventilation, optimizing pulmonary ventilation-perfusion ratio, increasing cardiac function, and raising the oxygen carrying capacity of the blood [20, 21]. In addition to optimizing gas exchange, inadequate supply triggers hyperacute responses (seconds to minutes) of vascular beds which are initiated by mitochondria, acting as oxygen sensor [22]. A hypoxic vasomotor response leads to vasodilation and increased tissue blood flow in most organs, with the exception of the lungs, where hypoxia induces vasoconstriction. This hyperacute response is followed by a subacute response (minutes to hours), during which the master switch of cellular hypoxia defense, known as hypoxia-inducible factor (HIFs), is activated. These are proteins which mediate alterations in the expression of various hypoxia-sensitive genes such as erythropoietin (EPO), endothelin-1 and vascular endothelial growth factor (VEGF) [5, 20, 23]. HIF's are rapidly broken down by pyrolyl-hydroxylase enzymes under normoxic conditions, but are allowed to accumulate and alter gene transcription under hypoxia due to the oxygen dependent activity of their degrading enzymes. Increased EPO and VEGF expression promote erythropoiesis and angiogenesis respectively, which augments the oxygen delivery to cells and tissues [24]. HIF-1α can also induce glucose transporter genes to improve glucose transport and metabolism [25]. Furthermore, inflammatory stimuli trigger a metabolic shift in immune cells from oxidative phosphorylation towards glycolysis [26]. Interestingly, HIF may also be activated under normoxic conditions, thus hypoxia-independent, for instance in the situation of severe systemic bacterial infection [27, 28]. Similarly, HIF activation can occur in situations mimicking hypoxia, such as severe iron deficiency [29]. Whereas HIF-1α is the dominating HIF molecule during the first 24 hours of hypoxia exposure, HIF-2α gains dominance thereafter [30]. HIF-2α upregulation contributes to serious systemic diseases like pulmonary hypertension, pulmonary and cardiac fibrosis and polycythemia [31]. Furthermore, HIF activates the transcription of genes which are pivotal for cancer genesis, progression and metastasis [32].

LEVEL-RESPONSE RELATIONSHIP AND LIMITS OF HYPOXIA TOLERANCE

The physiological response to hypoxia involves a complex cascade of adaptive mechanisms aimed at restoring oxygen delivery to vital organs and maintaining cellular homeostasis. The time-dependent patterns of physiological responses to hypoxia observed during the acclimatization process at high altitude, are shown in Figure 2. The severity of hypoxia determines the intensity and extent of these physiological responses [33, 34].

In mild hypoxia, characterized by a modest decrease in oxygen availability, the body initiates several compensatory mechanisms to mitigate the impact of oxygen deficiency. These responses include activation of

the sympathetic nervous system, increased ventilation to enhance oxygen uptake in the lungs, peripheral vasodilation to facilitate increased blood flow and oxygen delivery to organs, increased cardiac output to ensure adequate oxygen supply, and enhanced oxygen extraction by tissues.

As hypoxia worsens to a moderate level, additional physiological responses come into play. The body increases red blood cell production to enhance oxygen-carrying capacity, and cells increasingly rely on anaerobic (glycolytic) metabolism to generate energy. This shift leads to the production of lactate and subsequent metabolic acidosis. Furthermore, the activation of HIFs occurs, regulating the expression of genes involved in oxygen transport, angiogenesis, and metabolism.

In cases of severe hypoxia, where oxygen availability reaches critical levels, the physiological responses become more pronounced. Breathing becomes more labored with increased respiratory effort. Lactate production further increases as reliance on anaerobic metabolism intensifies, resulting in severe metabolic acidosis. Cognitive function becomes impaired, resulting in confusion, impaired judgment, and potential loss of consciousness. Cardiovascular disturbances may arise, including arrhythmias, decreased cardiac output, and increased pulmonary artery pressure, which can lead to organ failure.

The limits of hypoxia tolerance refer to the thresholds beyond which the body's compensatory mechanisms are overwhelmed, resulting in critical physiological dysfunction and potentially irreversible damage. These limits can be conceptualized as a "defense zone" or a range within which compensatory mechanisms can maintain cellular homeostasis despite reduced oxygen availability. It has been postulated that this defence zone lies around 35 mmHg of arterial oxygen partial pressure [35].

It is important to recognize that individuals have different thresholds of hypoxia tolerance, influenced by factors such as genetical background, age, health status, physical fitness, and acclimatization [36]. Prolonged exposure to severe hypoxia can exceed an individual's tolerance, leading to severe complications, including organ failure and death. Furthermore, each organ exhibits a distinctive normoxic tissue oxygen partial pressure threshold, below which its physiological functions become compromised: 72 mmHg for kidneys, 58 mmHg for intestinal tissue, 41 mmHg for liver, 34 mmHg for brain, and 29 mmHg for skeletal muscle [10, 37].

Understanding the limits of hypoxia tolerance is crucial for assessing risks associated with high-altitude activities, occupational settings, and medical conditions involving hypoxia. Careful monitoring and assessment are necessary to ensure safety and mitigate potential health risks. However, the Operation Everest studies I - III, all performed in hypobaric laboratory chambers, have demonstrated safety and feasibility of exposing highly selected, healthy, young individuals, under well controlled conditions to prolonged exposure of extreme hypoxia spanning several weeks [38, 39]. In a series of current pilot trials, evidence has demonstrated the safety and feasibility of subjecting not only healthy, middle-aged individuals but also those with prior myocardial infarction to normobaric hypoxia approaching the human hypoxic limit [40-43]. Both kind of study series pave the way for pharmacological studies using human hypoxia models.

HYPOBARIC AND NORMOBARIC HYPOXIA

There are two distinct approaches to elicit ambient hypoxia: hypobaric hypoxia and normobaric hypoxia. In hypobaric hypoxia, as described by the Dalton's law of partial pressures, oxygen concentration of air remains constant at approximately 21% but hypoxia results from reduced ambient air pressure. In a large meta-analysis of high-altitude studies, a linear relationship between altitude and resulting arterial oxygen pressure could be identified for altitudes below 6000 meters. Notably, the analysis revealed a consistent decrease in arterial oxygen partial pressure by 1.6 kPa for every 1000 meters of altitude ascended [44].

In normobaric hypoxia, oxygen concentration is lowered through the addition of an inert gas, typically nitrogen, while ambient air pressure remains unchanged. Differences in the physiological response to hypobaric and normobaric hypoxia exist but have not yet been fully characterised [45, 46]. Effects of reduced pressure on the middle ear and other closed air-containing organs are evident. Important disadvantages of hypobaric hypoxia compared with normobaric hypoxia are that sophisticated and costly hypobaric chambers are

required and that study participants and staff cannot easily move in and out of the hypoxia environment. Decompression to severe hypoxia may already go along with the risk of decompression illness. Despite these challenges, hypobaric chambers offer distinct advantages over alternative methods for simulating hypoxia. These chambers can be used to precisely control the level of hypoxia, which is important for studies that require consistent and repeatable conditions. By means of air pumps, pressure regulators, and control systems, the pressure inside the chamber can be adjusted relatively rapidly as needed. Furthermore, hypobaric chambers are often used for research or training programs that require large groups to be exposed to hypoxic conditions simultaneously. On the other hand, normobaric hypoxia is easier to implement, but requires more time to adjust the oxygen concentrations. The nitrogen required for normobaric hypoxia can be supplied onsite through concentrators, which operate with molecular sieves, or from a nitrogen tank. Room-in-room solutions for normobaric hypoxia are commercially available. For short term applications, hypoxic gas mixtures can also be supplied through a face mask, which offers the notable advantage of excluding the experimenters from the condition while allowing them in close proximity to the participants.

INSIGHT FROM POPULATIONS DWELLING AT HIGH ALTITUDE

Hypoxia can also serve as a model for certain adaptations that create resilience to disease but this can only be studied by an experiment of nature. For example, studying high-lander populations has revealed a number of genes that allow for adaptation to chronic hypoxia [47]. These groups, such an Andean's, Ethiopians, and Tibetans have evolved variations in their erythrocyte homeostasis, angiogenesis, vaso-regulation, cell death, immune response, cognition, and various other processes that are often implicated in disease. The aforementioned populations had adapted a lower expression of the gene EDNRB, which has a large regulatory region of single-nucleotide polymorphisms and transcription binding sites [48]. Mice with this gene knocked out showed extreme hypoxia tolerance [49]. Congruently, patients with ischemic heart disease show significantly higher levels of EDNRB and antagonists of this gene are used to reduce induced high-altitude pulmonary artery pressure [50, 51]. All of this evidence supports this highlander adaptation as a valuable model for cardiac disease. Such studies have also identified key epigenetic shifts that require further mechanism investigation. Despite the promising translational model of highlanders, studying these groups has its limitations; they are difficult to access and have been isolated for long enough to have accrued hypoxia-unrelated and thus confounding genetic differences. This emphasizes the need to categorize variations in hypoxia related adaptations amongst the general population as well as investigate how easily inducible these epigenetic changes are for possible therapeutic intervention.

GAUGING AND MITIGATING RISKS ASSOCIATED WITH HYPOXIA EXPOSURE

Hypoxia exposure can have negative effects on human health, with the severity and duration of exposure combined with individual factors such as age, health status, and activity level influencing the risks. Cognitive impairment, cardiovascular and respiratory effects, metabolic changes, and an increased risk of accidents and injuries are among the potential consequences. Even mild hypoxia can cause temporary cognitive impairment, typically starting with impaired twilight vision at approximately 2000 meters [42, 52, 53], while severe or prolonged hypoxia can result in permanent brain damage and cognitive deficits [54]. Mitigative strategies such as gradual exposure, supplemental oxygen, hydration, and medications are recommended to reduce the risks associated with hypoxia [55]. Different levels of hypoxia exposure are considered safe for different populations, and individuals with underlying medical conditions or who are pregnant may require special precautions.

RESPONSE TO ACUTE HYPOXIA: A Challenge to Mimic Disease

Because hypoxia affects human physiology at multiple levels ranging from reflex mechanisms, such as the peripheral chemoreflex, to specific cellular pathways regulated through oxygen, experimental hypoxia could have utility in clinical research in various settings. Tonic chemoreceptor hyperactivity with subsequent sympathetic nervous system activation has been implicated in the pathogenesis of arterial hypertension [56]. Thus, peripheral chemoreceptor modulation could have therapeutic utility in this condition, particularly in patients not responding sufficiently to established therapies [57]. Recent studies demonstrated that acute

hypoxia during high-resolution functional magnetic resonance imaging (fMRI) can be used to trace peripheral chemoreceptor responses in human beings [58]. Because changes in CO_2 confound the response to hypoxic peripheral chemoreceptor stimulation, isocapnic hypoxia protocols have been proven useful in clinical research [59].

Acute hypoxia can also be used to test the tolerance in patients or those in occupational settings such as in fighter pilots. Moreover, hypoxia may produce a phenotype resembling a clinical condition, which could then be utilized to probe new therapies. However, hypoxia may also regulate a disease-relevant signaling pathway. Indeed, hypoxia plays a major role in a multitude of human diseases, either as a result of the disease, like in the case of pulmonary dysfunction, or by modifying the disease process as seen in some forms of cancer, where local hypoxia may affect differentiation of the tumor to more aggressive phenotypes [60].

PULMONARY ARTERIAL HYPERTENSION

Pathophysiological background of the disease

Pulmonary arterial hypertension is a serious, progressive vasculopathy of the lungs of different aetiologies. Patients experience dyspnea, fatigue, exercise intolerance, syncope and edema. An increased arterial pulmonary pressure is the result of an increased vascular resistance of the pulmonary vessels.

There are five main classifications of both acute and chronic mechanisms that can provoke pulmonary arterial hypertension. One group contains idiopathic and hereditary forms of primary vascular pathologies with normal lung function and basically no cardiopulmonary comorbidities. These patients show only mild to no hypoxia [61]. Other forms of pulmonary arterial hypertension are the result of failure of the left heart, chronic thromboembolic disease or of mixed or unknown origin. Because these disease forms do not originate from the pulmonary system, they are less suitable to be modelled by a human hypoxia platform. This model is better suited for the types of pulmonary arterial hypertension caused primarily by impaired lung functions or hypoxia, like COPD, interstitial lung disease, sleep-disordered breathing, and chronic exposure to high altitude.

Disease mechanisms which can be modelled with experimental hypoxia

Systemic hypoxic stress, as seen at high altitude or in a hypoxia chamber, leads to hypoxic pulmonary vasoconstriction and a large increase in pulmonary arterial pressure. Pulmonary arterial hypertension up to 66 mmHg systolic arterial pressure has been safely induced over weeks in healthy individuals by normobaric hypoxia [40]. Pulmonary arterial hypertension at altitude is not a disease per se, but it can cause a life-threatening condition if it progresses into high-altitude pulmonary edema. Studies in mountaineers have revealed that the vasoactive factors that are involved in the development of the hypoxic pulmonary vasoconstriction at altitude are also responsible for the pulmonary arterial hypertension in patients. Chronic sojourn at high altitude may eventually result in pulmonary arterial hypertension and, remodeling of the pulmonary vasculature and right heart failure.

Pulmonary arterial hypertension is caused by a disbalance between vasodilatory and vasoconstrictive factors. Relative to healthy individuals, patients with pulmonary hypertension have reduced levels of the key vasodilators nitric oxide (NO), its second messenger cGMP, and prostacyclin while vasoconstrictors endothelin-1 and thromboxane A2 are increased. Additionally, the production of reactive oxygen species is increased, which is caused by the induction of oxidase systems [62].

Open questions which can be addressed with human hypoxia models

Human hypoxia models would be particularly suitable for the testing of pharmacological interventions for pulmonary arterial hypertension that share arterial hypoxia caused by high altitude or by underlying pulmonary disease, as it captures the fundamental pathophysiological mechanism underlying the increased pulmonary vascular resistance. Considering that home oxygen therapy is often effective in reducing dyspnea and improving physical capacity in these conditions, it can be extrapolated that clinical trials under controlled ambient hypoxia can serve as a meaningful research tool. Episodes of desaturation during sleep is

another trait of pulmonary arterial hypertension, which could be easily modelled by periodic reduction of ambient oxygen.

The 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension call on to perform more studies on the responses of patients with pulmonary arterial hypertension at altitude [63]. 120 million people worldwide live above 2500 meters. Because research at geographic altitude can be a logistical challenge, these conditions could be perfectly simulated under the optimal conditions of a laboratory human hypoxia model.

Limitations of the pulmonary arterial hypertension hypoxia model

There are some limitations to the human hypoxia model for investigating pulmonary arterial hypertension that must be carefully addressed. Whilst arterial hypoxia and increased pulmonary vascular resistance can be effectively modelled, other disease characteristics are less reproducible. The duration of the experimental hypoxic exposition will not be long enough to induce relevant pulmonary remodelling in healthy participants. Trials should therefore aim to investigate acute responses in the vasculature liker oxygen metabolism, and the hypoxia-induced inflammation and fibrosis. Furthermore, pulmonary arterial hypertension related comorbidities should be carefully considered. Patients with chronic pulmonary arterial hypertension may develop right heart insufficiency, which proceeds to alter the physiology of the whole cardio-circulatory system. Healthy participants will maintain right heart function with higher cardiac outputs than pulmonary arterial hypertension patients.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Pathophysiological background of the disease

COPD encompasses inflammatory diseases that cause structural abnormalities to the airways and or pulmonary parenchyma [64], usually caused by smoking or inhaled particulates [65]. Pronounced ventilation-perfusion inequalities within poorly ventilated, yet well-perfused alveoli, result in hypoxemia and, in certain patients, hypercapnia [66]. As the disease progresses, inflammation-induced hyperplasia of respiratory glands significantly increases the production of viscoid mucus, leading to the obstruction of both smaller and larger airways. Consequently, this obstruction culminates in hypoxia and respiratory endothelial cell failure. Cough and dyspnea represent the primary symptoms of this condition. Hypoxic respiratory endothelial cells in COPD lungs exhibit an increased sodium absorption, attributed to the upregulated expression of epithelial Na+ channels (ENaC), consequently leading to mucus thickening [67]. Paradoxically, the opposite effect has been observed in healthy individuals who developed high altitude pulmonary edema. In these individuals, hypoxia reduced transepithelial sodium transport mediated by ENaC, resulting in the accumulation of fluid in the alveoli [68].

COPD is associated with systemic inflammation and numerous comorbidities, most notably cardiovascular disease [69, 70]. Hypoxia plays a vital role in this process because the increase in the HIF cascade stimulates angiogenesis within atherosclerotic plaques [69]. There is a vicious cycle between the COPD-induced inflammation and hypoxia where inflammation increases metabolic demand and hypoxia increases the levels of reactive oxidative species, an inflammatory agent. In mice, the combination of a high/fat diet and chronic intermittent hypoxia has been shown to have a significant negative impact on atherosclerosis [6]. However, the direct effect of hypoxia in connecting COPD and atherosclerosis in the absence of associated inflammation requires further investigation, which could be addressed through laboratory-induced hypoxia studies.

Disease mechanisms which can be modelled with experimental hypoxia

By isolating the effects of hypoxia in the absence of inflammation, laboratory-induced hypoxia studies can provide insights into the direct relationship between hypoxia and atherosclerosis. Additionally, human hypoxia models can be utilized to study respiratory failure in COPD [71]. Type I respiratory failure, characterized by a ventilation/perfusion mismatch with normal or low arterial partial pressure of oxygen ($PaCO_2$) levels and a reduced arterial partial pressure of oxygen (PaO_2), can be modeled using hypoxia in

combination with hypocapnia or isocapnia. Type II respiratory failure, characterized by elevated $PaCO_2$ levels and reduced PaO_2 levels, can be modeled using hypoxia and hypercapnia conditions. Human hypoxia models offer the opportunity to optimize treatment strategies during these phases of the disease.

Open questions which can be addressed with human hypoxia models

Human hypoxia models can help address several open questions in COPD research. The direct impact of hypoxia on the development of atherosclerosis in COPD, independent of associated inflammation, can be investigated. The effects of different levels and durations of hypoxic exposure on COPD progression, exacerbations, and the underlying mechanisms can also be explored [72]. Furthermore, the optimization of treatments for respiratory failure in COPD during both type I and type II phases can be studied using human hypoxia models.

Limitations of the COPD hypoxia model

It should be noted that the model may not fully replicate the complex pathophysiology of COPD: as the disease involves multiple factors beyond hypoxia, such as chronic inflammation, respiratory endothelial failure and airway remodeling. Additionally, individual variations and comorbidities associated with COPD, including cardiovascular diseases, may influence the response to hypoxia and limit generalizability. Cautious interpretation and consideration of these limitations are necessary when using the COPD hypoxia model.

CENTRAL & OBSTRUCTIVE SLEEP APNEA (CSA & OSA)

Pathophysiological background of the diseases

In central sleep apnea (CSA) a dysfunctional respiratory drive results in apnea events during sleep. These events appear periodically together with phases of hyperventilation. CSA is common in patients with heart failure. OSA is a sleep disorder characterized by recurrent episodes of cessation of airflow, with or without partial or complete upper airway obstruction during sleep, leading to disruptions in normal breathing patterns. The obstruction results in intermittent hypoxia and hypercapnia, as well as sleep fragmentation. OSA is primarily caused by anatomical and physiological factors that contribute to airway collapse, such as obesity, anatomical abnormalities, and decreased upper airway muscle tone. Newer data also suggest a pathomechanism in OSA that is dependent on respiratory drive [73]. The repetitive episodes of hypoxia and hypercapnia trigger physiological responses, including sympathetic activation, systemic inflammation, oxidative stress, and endothelial dysfunction [74]. These responses contribute to the development of neurocognitive, cardiovascular and metabolic comorbidities commonly associated with OSA, such as daytime sleepiness, hypertension, coronary artery disease, and insulin resistance [75].

Disease mechanisms which can be modelled with experimental hypoxia

Above 2000 meters, sleep in hypobaric and normobaric hypoxia produces a characteristic periodic breathing pattern, similar to central sleep apnea, which is called Cheyne-Stokes breathing (Figure 3). The apnea hypopnoea index is directly proportionally associated with increasing sleeping altitude whereas mean oxygen saturation during sleep is inversely associated [76].

Intermittent hypoxia, which mirrors the repetitive cycles of hypoxia and reoxygenation experienced by individuals with OSA during sleep can be used to model OSA. This modeling approach allows researchers to study the effects of intermittent hypoxia on various physiological processes. Oxidative stress, another important mechanism in OSA, can be replicated through hypoxia-induced imbalance between reactive oxygen species production and neutralization. Furthermore, hypoxia-induced inflammation and endothelial dysfunction, key contributors to OSA-related complications, can be investigated by simulating the inflammatory responses and impaired vascular function associated with hypoxia exposure. It is important for hypoxia models to accurately replicate the intermittent nature of hypoxia during sleep and consider the specific characteristics of OSA, including upper airway obstruction and sleep architecture. Controlling the duration and severity of hypoxia exposure is crucial to mimic the varying degrees of intermittent hypoxia observed in OSA patients. By employing hypoxia as a modeling tool, researchers can gain valuable insights into the underlying dis-

ease mechanisms of OSA and its associated complications, paving the way for the development of targeted therapeutic strategies.

Open questions which can be addressed with human hypoxia models

The animal and human models used to study OSA through intermittent hypoxia induction are inadequate as they do not fully represent all aspects of the disease [77]. Researchers are therefore seeking better models to gain a deeper understanding of the underlying mechanisms. The healthy human model of OSA is continually evolving, with some limitations that can be resolved through technological adjustments. To maximize construct validity, experiments should be conducted overnight on sleeping participants rather than during the waking hours [78]. Secondly, the intermittent hypoxia model must include hypercapnia, which is present during obstruction in OSA. Thirdly, the dose and duration of intermittent hypoxia used in healthy human models should be equivalent to moderate to severe OSA, with mild to moderate OSA and equivalent intermittent hypoxia providing beneficial physiological stimuli [79]. Fourthly, the experimental model's intermittent hypoxia should mimic the disease's characteristic slow desaturation and rapid re-saturation of oxygen during obstructive events, as opposed to the current model with a square-wave design of rapid desaturation and re-saturation. Lastly, full polysomnography is necessary to characterize sleep architecture, including frequent brain arousals. The use of dial-down CPAP during sleep can induce upper airway obstruction and negative intrathoracic pressure swings, thus creating an experimental model that closely simulates OSA [80]. However, this technique is labor-intensive, invasive, and risky. The experimental model for OSA should be tailored to the research question at hand and may or may not require the complete simulation of OSA.

Limitations of the OSA hypoxia model

There are notable construct barriers such as how the model primarily focuses on the hypoxic aspect of OSA and may not fully capture the complexities of other contributing factors, such as airway collapse and sleep fragmentation. Additionally, the duration and frequency of hypoxic exposure in experimental settings may not perfectly replicate the intermittent hypoxia experienced during sleep apnea episodes. Individual variations and comorbidities in OSA patients, as well as the influence of sleep architecture, may affect the response to hypoxia and limit generalizability. Therefore, careful interpretation and consideration of these limitations are necessary when using the OSA hypoxia model.

MIGRAINE

Pathophysiological background of the disease

Recurrent migraine is a common, debilitating, and highly elusive disorder that is notoriously difficult to treat. The condition is characterized by recurrent, enduring, unilateral, and pulsating headaches often accompanied by nausea, light and sound sensitivity, and sometimes preceded by a period of altered sensory experience (often visual hallucination) called auras. The origin of migraine is argued to be vascular and/or neurogenic but this is still under investigation [81], but the aura symptoms are known to result from a wave of neuron depolarization and subsequent depression propagating across the cortex, whereas the pain results from the activation of the trigeminovascular system and meningeal blood vessels, both through unconfirmed mechanisms [82].

Disease mechanisms which can be modelled with experimental hypoxia

Symptoms of acute mountain sickness, a disease of the brain which is developed by individuals who ascent to high altitudes to fast, are often migraine-like and include headache, nausea and vomiting [83]. An association between migraine and hypoxia has been suggested for patients with patent foramen ovale (a hole between the left and right atria of the heart). In these patients, who also suffer from migraine, PaO_2 was lower than in healthy controls and normobaric oxygen treatment attenuated the frequency and severity of their migraines [84]. Furthermore, hypoxia has been shown to act as a reliable trigger for a complete physiological migraine [85-87]. Frank et al. used normobaric hypoxia at 12.6% oxygen for 6 hours which triggered migraines in 80% of participants with over 16% presenting with aura [85]. Schoonman et al. showed that hypoxia was a more reliable migraine trigger than nitroglycerine, which is the current experimental standard [87]. Hypoxia also

offers a major safety advantage over the pharmacological models as it can be easily reversed at any point in the trial, whereas a dose of nitroglycerine cannot be withdrawn and requires the addition of a second medication like triptans to terminate its effects [88]. However, this phenomenon is under investigated as the few existing studies have relatively small population sizes. Migraine research can greatly benefit from a greater emphasis on hypoxia, both as a dependable and physiologically accurate trigger for interventional studies and as a window into the causational mechanism.

Experimental hypoxia models have been utilized to study various disease mechanisms associated with migraine. One such mechanism is cortical spreading depression (CSD), a wave of neuronal depolarization and subsequent depression that spreads across the cerebral cortex [89]. CSD has been implicated in the generation of migraine aura and is hypothesized to contribute to the initiation and propagation of migraine attacks. Hypoxia-induced CSD models have provided insights into the underlying mechanisms and potential therapeutic targets for migraine [90]. Furthermore, experimental hypoxia can be used to investigate the role of oxygen levels in modulating neurovascular function and the release of neurotransmitters, such as serotonin and CGRP, which are involved in migraine pathophysiology [91]. Hypoxia models allow researchers to examine the effects of reduced oxygen levels on cerebral blood flow, vascular reactivity, and neuroinflammatory processes, providing valuable information about the interplay between hypoxia and migraine mechanisms.

Open questions which can be addressed with human hypoxia models

Human hypoxia models offer a unique opportunity to address several open questions in migraine research. For instance, the impact of hypoxia on the trigeminovascular system and its contribution to migraine attacks can be studied in controlled settings. Understanding how hypoxia affects the release of vasoactive substances, neuronal excitability, and the propagation of CSD can provide insights into the triggers and mechanisms of migraine. Additionally, human hypoxia models can shed light on the interplay between hypoxia and other migraine triggers, such as stress, exercise, or sleep disturbances [92]. Investigating how hypoxia interacts with these triggers and influences migraine susceptibility can help uncover the complex interactions between multiple factors involved in migraine pathogenesis. Furthermore, studying the effects of hypoxia on sensory processing and perception may provide insights into the mechanisms underlying migraine-associated sensory hypersensitivity [93].

Limitations of the migraine hypoxia model

Despite having strong advantages over the leading pharmacologically induced model, the hypoxia-induced models may not fully replicate the complex and multifactorial nature of migraine attacks. Migraine is a heterogeneous disorder with various triggers and individual variations, which may not be fully captured in experimental settings. Furthermore, it is challenging to directly translate findings from hypoxia models to clinical practice. The severity, duration, and frequency of hypoxia-induced migraine-like symptoms may differ from those experienced during spontaneous migraine attacks. Moreover, hypoxia models may not fully capture the contributions of other key mechanisms involved in migraine, such as genetic factors, cortical excitability, or neuroinflammatory processes. These aspects require further investigation using complementary approaches, including genetic studies, advanced neuroimaging techniques, and animal models. Overall, experimental hypoxia models provide valuable insights into specific aspects of migraine pathophysiology, they should be interpreted in the context of the broader understanding of the disease and its multifaceted nature.

KIDNEY FUNCTION

Pathophysiological background of the disease

The oxygen sensors in the kidney control the hematocrit, produce erythropoietin in the cortex, and are able to translate tissue oxygen pressure into a measure of plasma volume [94]. However, in severe hypoxia below pO_2 40 mmHg, glomerular filtration rate declines, leading to sodium retention and water retention [95, 96]. Hence, renal function in chronic respiratory failure, like OSA or COPD, is often impaired and these patients show fluid and sodium retention [97]. This excess retention has also been described at high altitude,

especially in altitude maladapted individuals [98]. The effect of hypoxia on patients with impaired renal function can be studied in hypoxia models and this would have implications for determining their risks of long air travel or dwelling at high altitude.

Disease mechanisms which can be modelled with experimental hypoxia

Experimental hypoxia models have been used to study the mechanisms underlying kidney dysfunction. Hypoxia, or reduced oxygen availability, can occur in various renal diseases due to impaired blood flow, ischemia, or inadequate oxygenation [99]. Hypoxia can trigger cellular responses, including the activation of hypoxia-inducible factors (HIFs), which play a crucial role in adaptive mechanisms to maintain cellular homeostasis under low-oxygen conditions [100]. Experimental hypoxia models can simulate and study the impact of reduced oxygen levels on kidney cells and tissues, providing insights into the molecular and cellular responses involved in renal hypoxia-related diseases.

Furthermore, experimental hypoxia models allow researchers to investigate the effects of hypoxia on renal blood flow, glomerular filtration rate, tubular function, and electrolyte handling. These models can simulate renal ischemia-reperfusion injury, a common cause of acute kidney injury, and elucidate the mechanisms underlying renal tissue damage, inflammation, and impaired renal function in hypoxic conditions.

Open questions which can be addressed with human hypoxia models

Human hypoxia models offer valuable opportunities to address several open questions regarding kidney function and hypoxia-related diseases. These models can help elucidate the cellular and molecular responses of the kidneys to hypoxic stress in real-time, providing insights into the adaptive mechanisms and potential therapeutic targets. Furthermore, human hypoxia models can aid in studying the interplay between hypoxia and other factors contributing to kidney disease progression, such as oxidative stress, inflammation, and metabolic disturbances.

By utilizing human hypoxia models, researchers can investigate the effects of controlled oxygen levels on specific renal cell types, including proximal tubular cells, podocytes, and endothelial cells [101]. This can enhance our understanding of the impact of hypoxia on cellular metabolism, cell death pathways, and cellular communication within the renal microenvironment. Additionally, human hypoxia models can help explore the potential benefits of oxygen-based therapies and interventions in kidney diseases [102].

Limitations of the kidney function hypoxia model

Despite its utility, the kidney function hypoxia model has several limitations that should be acknowledged. First, the model oversimplifies the complex pathophysiological processes involved in renal hypoxia. The kidney is a highly intricate organ with multiple cell types, intricate blood supply, and complex regulatory mechanisms. The model's simplified representation may not fully capture the intricacies of these processes and their interactions.

Second, the model relies on experimental hypoxia models, which may not perfectly replicate the conditions seen in human kidney diseases. Experimental models often involve controlled and acute hypoxia, whereas human kidney diseases often involve chronic and multifactorial hypoxia. Therefore, extrapolating findings from experimental models to human conditions should be done cautiously.

Third, the model primarily focuses on the role of hypoxia in kidney dysfunction, overlooking other contributing factors. Kidney diseases are multifactorial, and hypoxia is just one piece of the puzzle. Other factors such as inflammation, oxidative stress, immune responses, and genetic factors also play significant roles in kidney disease development and progression. Neglecting these factors in the model may limit its ability to provide a comprehensive understanding of kidney dysfunction.

Lastly, the model's generalizability may be limited. Human kidney diseases exhibit considerable heterogeneity, and the response to hypoxia can vary among individuals and disease subtypes. The model may not fully capture this heterogeneity and may not be applicable to all kidney disease scenarios.

APPLICATIONS OF SPACE MEDICINE MODELS IN CLINICAL RESEARCH

Human hypoxia models, which are the focus of this review, offer a tool for studying various physiological processes and diseases. These models have gained popularity, particularly for replicating hypoxic conditions in healthy humans and studying the effects of hypoxia on the body in a controlled manner. One promising application of hypoxia models is in cancer research, as tumor cells are known to thrive in low-oxygen environments. Similarly, hypoxia models could aid in the study of cardiovascular and neurological diseases, which are also characterized by a decrease in oxygen supply to tissues. Furthermore, by understanding how the body responds to hypoxia in extreme environments such as high altitudes and space travel, researchers could develop new ways to improve human health in the future. There is a need for more standardisation and validation of the different published models [103]. Overall, healthy human hypoxia models offer significant potential for advancing our understanding of various diseases and physiological processes. However, other human models developed for space medicine may also have applications for human drug development. A good example are head-down tilt bedrest studies, which produces musculoskeletal and cardiovascular deconditioning as well as cephalad fluid shifts resembling those produced by real weightlessness [104].

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