# Potential applications for human hypoxia models

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# CHAPTER II | HUMAN HYPOXIA MODELS IN AEROSPACE MEDICINE: POTENTIAL APPLICATIONS FOR HUMAN PHARMACOLOGICAL RESEARCH

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## ABSTRACT

Aerospace medicine required controlled terrestrial models to investigate influences of altered atmosphere conditions, such as hypoxia, on human health and performance. These models could potentially be expanded to encompass disease conditions or treatment targets regulated through hypoxia or hypercapnia. 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 model for studying diseases such as pulmonary hypertension, chronic obstructive pulmonary disease, obstructive sleep apnoea, migraine and kidney disease. This approach may be particularly useful in mechanism-oriented early-stage clinical studies. This review discusses the ability of hypoxia models from space medicine research to mimic or induce these conditions in a controlled laboratory setting as a tool for testing the efficacy and safety of new pharmaceutical interventions.


# INTRODUCTION

## Challenges in space and aeronautics environments

In space and in aeronautics, human beings are exposed to harsh environmental conditions that pose risks for health and performance. An important example is altered atmospheric pressure and composition. Even in pressurized aeroplane cabins, atmospheric pressure and oxygen partial pressure are significantly reduced. In spacecraft, atmospheric pressure and relative oxygen content vary profoundly between vehicles. Moreover, during extravehicular activities in free space or on another celestial body, pressure in the spacesuit is substantially reduced to reduce its stiffness and astronauts breathe pure oxygen.[1] Carbon dioxide concentrations in space- and aircraft cabins can increase significantly due to the closed environment.[2,3] These conditions pose risks for human health and performance in space but could also be tweaked to achieve desirable health effects.



## Terrestrial models in space medicine

Testing influences of atmospheric 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. Our study testing the interaction between simulated weightlessness through head-down tilt bedrest and elevated ambient carbon dioxide is prime example for this approach.[4] This review will discuss how this approach could be used in modelling disease conditions in clinical drug development with a particular focus on hypoxia.[5] 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.

## Understanding hypoxia: causes and effects

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, anaemia,

chronic vascular diseases, obstructive sleep apnoea (OSA), as well as lung diseases such as cystic fibrosis, asthma and chronic obstructive pulmonary disease (COPD).[6–9] Oxygen plays is crucial for tissues to generate energy and to maintain cellular functions.[10,11] Furthermore, hypoxia on a tissue level develops when capillaries are rarefied, poorly perfused or when the distance between capillaries and cells is increased, for example, by oedema 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.[12] 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.[13]



### Using hypoxia as a controlled human disease model

Experimentally induced hypoxia has the potential to serve as a 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. Furthermore, hypoxia could be utilized to validate potential treatment targets and pathways that are regulated through oxygen.

## SPACE MEDICINE DISCOVERIES: LESSONS FROM TERRESTRIAL MODELS IN WEIGHTLESSNESS ENVIRONMENTS

Weightlessness is a defining challenge in the space-related environmental conditions that astronauts must navigate. As they effortlessly float through their spacecraft, the physical demands on their bodies are significantly reduced, resulting in a state of immobility. Comparable to bedrest on Earth, prolonged periods of weightlessness lead to a decline in bone mass and muscle weakening. Consequently, spaceflight serves as a unique testing ground for drugs combating bone loss.

A pharmacological study involving 7 astronauts, with an average stay of 5.5 months on the International Space Station, revealed the superior effects of resistive exercise on bone health when combined with alendronate therapy compared to exercise alone.[14] Remarkably, classical anti-osteoporotic drugs also demonstrated positive effects on bones in ground-based bedrest immobilization studies.[15] These findings align with current guidelines for osteoporosis treatment, emphasizing the importance of a combination of pharmacological and nonpharmacological interventions.[16]

Beyond musculoskeletal challenges, spaceflight induces deconditioning of the circulatory system and cardiac atrophy, leading to orthostatic intolerance and fainting upon return to Earth. To address this, pharmacological countermeasures have been explored both in space and terrestrial models. For instance, a study administering 5 mg of the α-agonist drug midodrine orally to subjects following up to 16 days of head-down tilt bedrest reduced the risk of presyncope during tilt table testing from 75 to 28%.[17] Another study involving astronauts returning to Earth found that 10 mg of midodrine orally could reduce tachycardia while maintaining safety.[18] Clinical guidelines for syncope management now recommend midodrine for orthostatic hypotension.[19]



While immobility is a classic risk factor for thromboembolic events, space has seen only 1 symptomatic venous thrombosis, successfully treated with enoxaparin and subsequent apixaban, without progressing to pulmonary embolism.[20,21] Speculation surrounds the activation of natural thromboprotection mechanisms in space, although these have not been thoroughly investigated during in-flight conditions. Notably, a recent study uncovered a novel mechanism that shields bears in hibernation, individuals undergoing head-down bedrest and patients with spinal cord injuries—all enduring chronic immobilization—from thrombosis.[22] Both bear and human thrombocytes exhibit a joint antithrombotic phenotype marked by decreased heat shock protein (HSP) 47 expression. These promising findings may pave the way for innovative classes of antithrombotic drugs, warranting further testing and refinement on spaceflight-related research platforms.

All these examples demonstrate that knowledge and methodologies derived from studies on how the space or aeronautics environment affects human health can be exploited for terrestrial applications. We suggest that influences of atmosphere conditions on human beings deserve more attention in that regard.

## PHYSIOLOGICAL RESPONSE TO HYPOXIA

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 response to acute, intermittent 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 blood levels, which are conveyed to the central nervous system. The response restores homeostasis by increasing ventilation, optimizing pulmonary ventilation–perfusion ratio, adjusting cardiac function and raising the oxygen carrying capacity of the blood.[23,24] In addition to optimizing gas exchange, inadequate supply triggers hyperacute responses within seconds to minutes of vascular beds, which are initiated by mitochondria, acting as oxygen sensor.[25] A hypoxic vasomotor response leads to vasodilation and increases 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 over minutes to hours during which the master switch of cellular hypoxia defence, known as hypoxia-inducible factors (HIFs), are activated. HIFs regulate the expression of various hypoxia-sensitive genes such as erythropoietin (EPO), endothelin-1 (ET-1) and vascular endothelial growth factor (VEGF).[6,23,26] Nitrate oxide (NO) contributes to oxygen sensing by modulating the activity of proteins such as prolyl hydroxylase 2 (a key oxygen sensor in the HIF-1 pathway). Hypoxia upregulates NO synthases which increases NO production. NO goes on to inhibit prolyl hydroxylase 2, which prevents HIF-1α hydroxylation and degradation. NO is also crucial to the hypoxic response by regulating vasodilation and blood flow.[27] Nitrite acts as NO reservoir and is converted back to NO in oxygen-deficient conditions. Dietary nitrate, especially from beets, can affect nitrite levels, which provides an opportunity for therapeutic interventions in hypoxic related diseases.[28–30] The European Space Agency (ESA) suggests growing beets, spinach, lettuce and rocket salad (nitrate-rich vegetables) as a food source for long-term space missions.[29]

HIFs are rapidly broken down by prolyl-hydroxylase under normoxic conditions, but 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 oxygen delivery to cells and tissues.[31] HIF prolyl hydroxylase inhibitors such as roxadustat and molidustat stimulate EPO production in renal anaemia[32,33] HIF-1α can also induce glucose transporter genes to augment glucose transport and metabolism.[35] Furthermore, inflammatory stimuli trigger a metabolic shift in immune cells from





oxidative phosphorylation towards glycolysis.[35] HIF may also be activated hypoxia-independent under normoxic conditions for instance during severe systemic bacterial infection.[36,37] Similarly, HIF activation can occur in situations mimicking hypoxia, such as severe iron deficiency.[38] Whereas HIF-1α is the dominating HIF molecule during the first 24 h of hypoxia exposure, HIF-2α gains dominance thereafter.[39] HIF-2α upregulation contributes to serious systemic diseases such as pulmonary hypertension, pulmonary and cardiac fibrosis, and polycythemia.[40] Furthermore, HIF activates the transcription of genes which are pivotal for cancer genesis, progression and metastasis.[41] Studying high-altitude populations, such as Andeans, Ethiopians and Tibetans, reveals genetic adaptations to chronic hypoxia, including variations in erythrocyte homeostasis, angiogenesis, vasoregulation and immune response.[42,43] These adaptations, particularly the lower expression of the endothelin receptor type B gene, provide insights into hypoxia tolerance and offer valuable models for understanding and potentially treating cardiac diseases.[44,45] Additionally, HSP70, known for its protective effects under hypoxic conditions, may serve as a potential biomarker for hypoxia tolerance, with genetic variations in HSP70 genes influencing susceptibility to high-altitude illnesses.[46] Currently, HIF-1, HSP70 and NO are identified as potential biomarkers to gauge hypoxia tolerance in experimental animals and in humans.[47]

## LEVEL-RESPONSE RELATIONSHIP AND LIMITS OF HYPOXIA TOLERANCE

The time-dependent patterns of physiological responses to hypoxia observed during the acclimatization process at high altitude are shown in Figure 1. Hypoxia severity determines intensity and extent of the physiological response.[48,49]

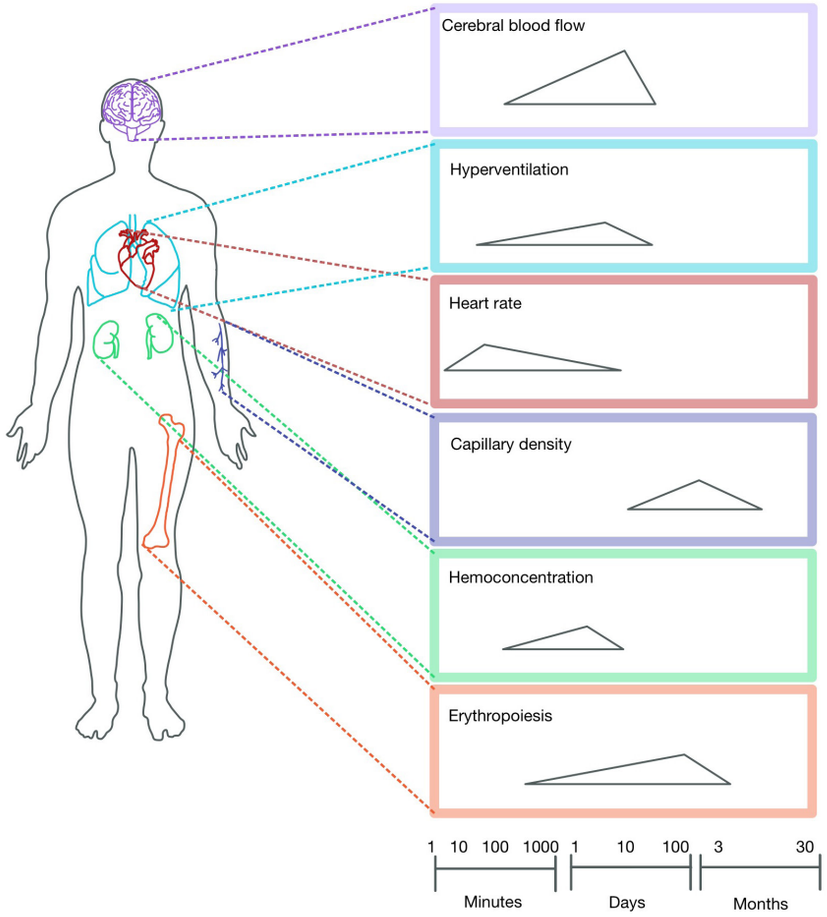
In mild hypoxia, the body initiates compensatory responses to mitigate the impact of oxygen deficiency. These responses include sympathetic nervous system activation, increased ventilation, peripheral vasodilation, increased cardiac output and enhanced oxygen extraction by tissues.

As hypoxia worsens to moderate levels, HIF activation affects genes involved in oxygen transport, angiogenesis and metabolism. Red blood cell production is increased to enhance oxygen-carrying capacity and cell metabolism increasingly shifts towards anaerobic energy generation with increased lactate production and subsequent metabolic acidosis.

In severe hypoxia with critical oxygen deficiency, breathing becomes

more laboured with increased respiratory effort. Anaerobic metabolism and lactate production further increase resulting in severe metabolic acidosis. Cognitive function becomes impaired, resulting in confusion, impaired judgement 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.

**FIGURE 1** **The time-dependent patterns of physiological responses to acute hypoxia observed during the acclimatization process at high altitude (modified from Burtscher *et al.*, 2022[50] and Mallet *et al.*, 2023[51]).**





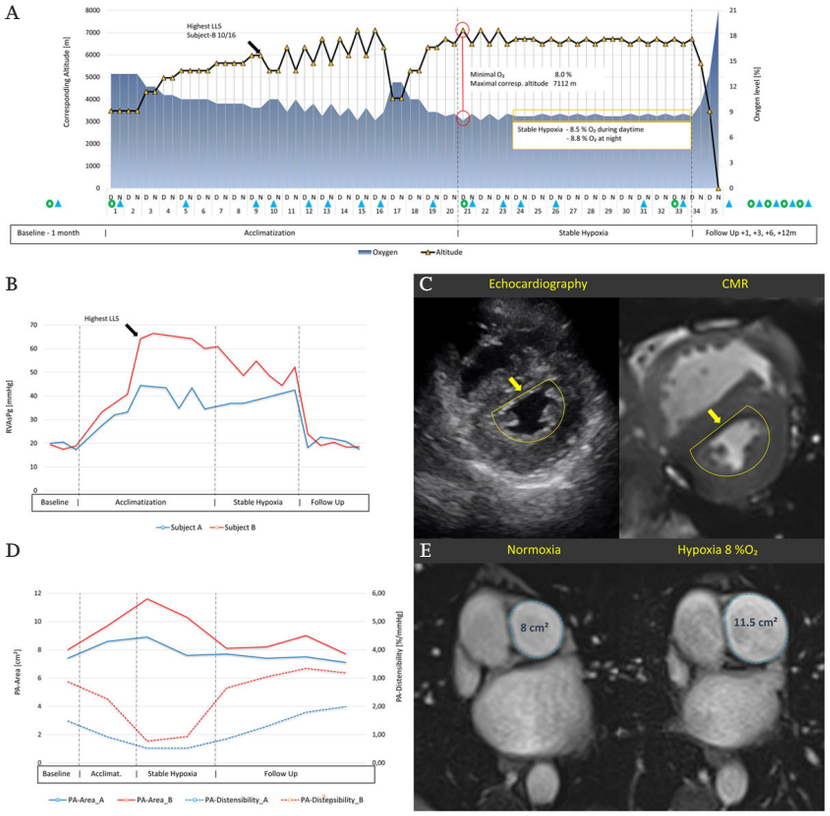

The limits of hypoxia tolerance at which the body's compensatory mechanisms are overwhelmed and critical physiological dysfunction and potentially irreversible damage ensues is referred to as defence zone. The defence zone lies around 35 mmHg of arterial oxygen partial pressure.[52] Furthermore, each organ exhibits a distinctive normoxic tissue oxygen partial pressure threshold, below which 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.[11,53] Interindividual variability in hypoxia tolerance results from genetic background, age, health status, physical fitness and acclimatization.[47]

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 at 8848 m in hypobaric chambers, have demonstrated safety and feasibility of exposing highly selected, healthy, young individuals, under well controlled conditions to extreme hypoxia over several weeks.[54,55] In these studies, subjects experienced increased ventilation–perfusion mismatch and higher pulmonary artery pressure with altitude and exercise. Despite substantial weight loss in a 40-day ascent and difficulties in achieving maximal altitude acclimatization, the subjects reached the summit in improved physiological conditions, thanks to controlled acclimatization and environmental factors. In our recent series of pilot trials, we have demonstrated the safety and feasibility of subjecting not only healthy (Figure 2), middle-aged individuals but also those with prior myocardial infarction to normobaric hypoxia approaching the human hypoxic limit (Figure 2).[56–59] Both kinds of study series pave the way for pharmacological studies using human hypoxia models.

## HYPOBARIC AND NORMOBARIC HYPOXIA

The two approaches to elicit ambient hypoxia are hypobaric hypoxia and normobaric hypoxia. These techniques have different characteristics that are important for practical use. 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. A large meta-analysis of high-altitude studies showed a linear decrease in arterial oxygen partial pressure by 1.6 kPa for every 1000 m of altitude ascended to 6000 m.[60]

**FIGURE 2** Experimental setup at the German Aerospace Center's :envihab facility, illustrating a 35-day exposure of two healthy professional mountaineers to severe sustained hypoxia. The study assessed pulmonary artery hypertension, echocardiographic images and cardiac magnetic resonance imaging (CMR): providing valuable insights into the impact of prolonged hypoxia on cardiovascular parameters (obtained from Hoffmann *et al.* 2020[56] and conducted at the German Aerospace Center).




In normobaric hypoxia, oxygen concentration is lowered by adding 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 characterized.[61,62] 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 cause 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. Through air pumps, pressure regulators and control systems, chamber pressure can be adjusted rapidly. Furthermore, hypobaric chambers are often used for research or training programmes that require large groups to be exposed to hypoxic conditions simultaneously. By contrast, normobaric hypoxia is easier to implement, but requires more time to adjust the oxygen concentrations. Nitrogen 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 excludes experimenters from hypoxia and is inexpensive.

## 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 various clinical research settings. Tonic chemoreceptor hyperactivity with subsequent sympathetic nervous system activation has been implicated in the pathogenesis of arterial hypertension.[63] Thus, peripheral chemoreceptor modulation could have therapeutic utility in this condition, particularly in patients not responding sufficiently to established therapies.[64] Our recent studies demonstrated that acute hypoxia during high-resolution functional magnetic resonance imaging can be used to trace peripheral chemoreceptor responses in human beings.[65] Because changes in $CO_2$ confound the response to hypoxic peripheral chemoreceptor stimulation, isocapnic hypoxia protocols have been proven useful in clinical research.[66]

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 signalling pathway. Indeed, hypoxia plays a major role in a multitude of human diseases, either as a result of the disease, such

as 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 tumour to more aggressive phenotypes.[67] These numerous implications create ample opportunity to utilize hypoxia in clinical testing.

## PULMONARY ARTERIAL HYPERTENSION

### Pathophysiological background of the disease

Pulmonary arterial hypertension is a serious, progressive vasculopathy of the lungs of different aetiologies. Increased arterial pulmonary pressure results from increased vascular resistance of pulmonary resistance 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.[68] Pulmonary arterial hypertension can also result from left heart failure, chronic thromboembolic disease or mixed or unknown origin. Because the latter diseases do not originate from the pulmonary system, they may be less suitable to be modelled by human hypoxia. This model is better suited for the types of pulmonary arterial hypertension caused primarily by impaired lung functions or hypoxia, such as COPD, interstitial lung disease, sleep-disordered breathing and chronic high-altitude exposure.

### Disease mechanisms modelled with experimental hypoxia

Systemic hypoxia at high altitude or in hypoxia chambers leads to hypoxic pulmonary vasoconstriction and increases 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.[56] Pulmonary arterial hypertension at altitude is not a disease per se, but it can progress to life-threatening high-altitude pulmonary oedema. 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.[56] Chronic sojourn at high altitude may eventually result in pulmonary arterial hypertension and, remodelling of the pulmonary vasculature and right heart failure. These similarities are what makes induced hypoxia an excellent tool to model this disease in a controlled manner.



Pulmonary arterial hypertension is caused by disbalance between vasodilatory and vasoconstrictive factors. Patients with pulmonary hypertension exhibit reduced levels of the key vasodilators NO, its second messenger cGMP and prostacyclin while vasoconstrictors endothelin-1 and thromboxane-A2 are increased. Additionally, reactive oxygen species production increased through induction of oxidase systems.[69]

### Open questions which can be addressed with human hypoxia models

Human hypoxia models could be particularly suitable when testing pharmacological interventions for pulmonary arterial hypertension associated with arterial hypoxia such as in high altitude or pulmonary disease. In this setting, hypoxia exposure recapitulates a fundamental pathogenic mechanism increasing pulmonary vascular resistance. Considering that home oxygen therapy is often effective in reducing dyspnoea and improving physical capacity in these conditions,[70] 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. However, hypoxia-exposure in healthy probands could also add useful information in early-stage clinical trial of drugs developed for pulmonary hypertension treatment not primarily caused by hypoxia.

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.[71] There are 120 million people worldwide who live above 2500 m. Because research at geographic altitude can be a logistical challenge, these conditions could be more safely simulated under highly controlled laboratory conditions.

### Limitations of pulmonary arterial hypertension hypoxia models

While 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 such as 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 failure, which can affect the whole cardio-circulatory system. Healthy

participants will maintain right heart function with higher cardiac outputs than pulmonary arterial hypertension patients.

## COPD

### Pathophysiological background of the disease

COPD encompasses inflammatory diseases that cause structural abnormalities to the airways and or pulmonary parenchyma,[72] usually caused by smoking or inhaled particulates.[73] Pronounced ventilation–perfusion inequalities within poorly ventilated, yet well-perfused alveoli, result in hypoxaemia and, in certain patients, hypercapnia.[74] 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 epithelial cell failure. Cough and dyspnoea represent the primary symptoms of this condition. Hypoxic respiratory epithelial cells in COPD lungs exhibit an increased sodium absorption, attributed to the upregulated expression of epithelial $Na^+$ channels, consequently leading to mucus thickening.[75] Paradoxically, the opposite effect has been observed in healthy individuals who developed high altitude pulmonary oedema. In these individuals, hypoxia reduced transepithelial sodium transport mediated by epithelial $Na^+$ channels, resulting in the accumulation of fluid in the alveoli.[76]

COPD is associated with systemic inflammation and numerous comorbidities, most notably cardiovascular disease.[77,78] Hypoxia plays a vital role in this process because the increase in the HIF cascade stimulates angiogenesis within atherosclerotic plaques.[77] 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.[7] 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 modelled with experimental hypoxia

By isolating hypoxia effects 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.[79] Type I respiratory failure, characterized by a ventilation–perfusion mismatch with normal or low arterial partial pressure of carbon dioxide levels and a reduced arterial partial pressure of oxygen ($PaO_2$), can be modelled using hypoxia in combination with hypocapnia or isocapnia. Type II respiratory failure, characterized by elevated arterial partial pressure of carbon dioxide levels and reduced $PaO_2$ levels, can be modelled using hypoxia and hypercapnia. Human hypoxia models facilitate refining ventilation techniques, evaluating the effectiveness of pharmaceutical interventions and tailoring personalized therapeutic approaches to the distinct stages and characteristics of respiratory failure.

### Open questions which can be addressed with human hypoxia models

Human hypoxia models could be applied to selectively assess hypoxia influences on atherosclerosis progression. Effects of different hypoxia levels and durations on COPD progression, exacerbations and the underlying mechanisms can also be explored.[80] Furthermore, treatment optimization 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

The model does 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 remodelling. Additionally, individual variations and comorbidities associated with COPD, including cardiovascular diseases, may influence the response to hypoxia and limit generalizability. While the ability of the model to isolate a single factor within this disease can be used as an advantage, as previously described, cautious interpretation and consideration of these limitations are still necessary when using the COPD hypoxia model.

## CENTRAL SLEEP APNOEA AND OSA

### Pathophysiological background of the diseases

In central sleep apnoea (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.[81] 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.[82] The repetitive episodes of hypoxia and hypercapnia trigger physiological responses, including sympathetic activation, systemic inflammation, oxidative stress and endothelial dysfunction.[83] 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.[84]



## Disease mechanisms modelled with experimental hypoxia

Above 2000 m, sleep in hypobaric and normobaric hypoxia produces a characteristic periodic breathing pattern, similar to CSA, which is called Cheyne–Stokes breathing. The apnoea hypopnoea index is directly proportionally associated with increasing sleeping altitude whereas mean oxygen saturation during sleep is inversely associated.[85]

Intermittent hypoxia, which mirrors repetitive hypoxia and reoxygenation cycles experienced by individuals with OSA during sleep can be used to model OSA. This model allows researchers to study 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.[86] 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.[87,88] Importantly, hypoxia models should replicate the intermittent nature of hypoxia during sleep and consider specific OSA characteristics, including upper airway obstruction and sleep architecture. Controlling 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 modelling tool, researchers can gain insights into the underlying disease 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

Animal and human models used to study OSA through intermittent hypoxia induction do not fully replicate all disease aspects.[89] Therefore, healthy human OSA models are continually improved through technological adjustments. To maximize construct validity, experiments should be conducted overnight on sleeping participants rather than during the waking hours.[90] Secondly, intermittent hypoxia models should include hypercapnia, which is present during obstruction in OSA. Thirdly, the therapeutic potential of these models depends on factors such as dose, duration and frequency. Acute mild hypoxia (9–16% inspired $O_2$) exposure with a lower number of cycles (3–15 episodes/day) leads to positive effects without inducing pathology. Conversely, chronic severe hypoxia (2–8% inspired $O_2$) combined with a higher number of cycles (48–2400 episodes/day) leads to increasing progression of pathological conditions.[91] Fourthly, intermittent hypoxia should mimic characteristic slow oxygen desaturation and rapid re-saturation 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. Dial-down CPAP during sleep can induce upper airway obstruction and negative intrathoracic pressure swings, thus creating an experimental model that closely simulates OSA.[92] However, this technique is labour-intensive, invasive and not without risks. 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 obstacles in the model, as it mainly emphasizes the lack of oxygen in OSA and may not fully understand the complexities of other factors like airway collapse and disrupted sleep patterns. Additionally, 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. These limitations should be considered when using OSA hypoxia models.

## MIGRAINE

### Pathophysiological background of the disease

Recurrent migraine is a common, debilitating and highly elusive disorder that is 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,[93] however, 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.[94]

### Disease mechanisms modelled with experimental hypoxia

Symptoms of acute mountain sickness, a disease of the brain which is developed by individuals who ascent to high altitudes too fast, are often migraine-like and include headache, nausea and vomiting.[95] An association between migraine and hypoxia has been suggested for patients with patent foramen ovale. 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.[96] Furthermore, hypoxia can trigger migraine.[97–99] Indeed, 6 h normobaric hypoxia at 12.6% oxygen triggered migraines in 80% of participants with > 16% presenting with aura.[97] Hypoxia was a more reliable migraine trigger than nitroglycerine, which is the current experimental standard.[99] Hypoxia offers safety advantages over the pharmacological models as it can be easily reversed, whereas nitroglycerine cannot be withdrawn such that rescue medications like triptans may be required.[100] However, only few studies with relatively small populations applied the hypoxia model. Possibly, migraine research could benefit from hypoxia, both as a dependable and physiologically accurate trigger for mechanistic and interventional studies.

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.[100] 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.[102] Furthermore, experimental hypoxia can be used to investigate the role of oxygen levels in modulating neurovascular function and neurotransmitter release, such as serotonin and calcitonin gene-related peptide, which are involved in migraine pathophysiology.[103] Hypoxia models can provide information regarding the interplay between hypoxia and migraine mechanisms including cerebral blood flow, vascular reactivity and neuroinflammatory processes.

### 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.[104] Investigating how hypoxia interacts with these triggers and influences migraine susceptibility can help uncover the complex interactions between multiple factors involved in migraine pathogenesis. Importantly, improving our ability to reliably trigger migraines safely would facilitate the clinical testing of any future migraine medications. Furthermore, studying the effects of hypoxia on sensory processing and perception may provide insights into the mechanisms underlying migraine-associated sensory hypersensitivity.[105]

### Limitations of the migraine hypoxia model

Migraine is a heterogeneous disorder with various triggers and individual variations, which may not be fully captured in experimental settings. Furthermore, translating findings from hypoxia models to clinical practice may be challenging. Severity, duration and frequency of hypoxia-induced migraine-like symptoms may differ from those experienced during spontaneous migraine attacks. Moreover, hypoxia models may not capture contributions of genetic factors, cortical excitability or neuroinflammatory processes on migraine. Genetic studies and advanced neuroimaging techniques could conceivably improve the model.

## KIDNEY FUNCTION

### Pathophysiological background of the disease

Renal oxygen sensors can translate a measure of plasma volume into a signal for tissue oxygen pressure, through the effects of sodium reabsorption on renal energy use and oxygen consumption. These processes are required for the regulation of EPO production.[106] However, in severe hypoxia below $pO_2$ 40 mmHg, glomerular filtration rate declines, leading to sodium retention and water retention.[107,108] Hence, renal function is often impaired in conditions associated with hypoxia such as OSA or COPD and predisposes to fluid and sodium retention.[109] A similar phenomenon has been described at high altitude, especially in altitude maladapted individuals.[110] Hypoxia effects on patients with impaired renal function can be studied in hypoxia models with implications risks of long air travel or dwelling at high altitude.

### Disease mechanisms 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, ischaemia or inadequate oxygenation.[111] Hypoxia can trigger cellular responses, including the activation of HIFs, which play a crucial role in adaptive mechanisms to maintain cellular homeostasis under low-oxygen conditions.[112] 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.[113] These models can simulate renal ischaemia–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.[114,115]

### Open questions which can be addressed with human hypoxia models

Human hypoxia models may help in elucidating 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. Additionally, human hypoxia models can help explore the potential benefits of oxygen-based therapies and interventions in kidney diseases.[116]

### Limitations of the kidney function hypoxia model

The kidney function hypoxia model may oversimplify complex pathophysiological processes involved in renal hypoxia. The kidney comprises multiple cell types, intricate blood supply and complex regulatory mechanisms. Second, experimental hypoxia may not fully replicate the conditions seen in human kidney diseases. Experimental models often involve controlled and acute hypoxia, whereas human kidney diseases are characterized by 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 such as inflammation, oxidative stress, immune responses and genetic factors. 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 diseases. The model may not fully capture this heterogeneity and may not be applicable to all kidney disease scenarios.

## CONCLUSIONS

Human hypoxia models that originated from aerospace medicine 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. 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. The models have not yet been used widely (Table 1) but we recommend their application as facilities for inducing hypoxia are available in aerospace medicine departments and often open for collaborative projects. 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 standardization and validation of the different published models.[117] 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 our head-down tilt bedrest studies conducted in collaboration with DLR, ESA and NASA, which produces musculoskeletal and cardiovascular deconditioning as well as cephalad fluid shifts resembling those produced by real weightlessness.[118]





**TABLE 1** Human hypoxia models used as platform for pharmacological interventions.

| Reference | Drug | Class | Biomarker | Design | Hypoxia inducer | Outcome |
|---|---|---|---|---|---|---|
| PULMONARY HYPERTENSION | | | | | | |
| Hall *et al.* (2021)[5] | GSK258688 | Recombinant angiotensin-converting enzyme-2 | PASP | n = 10 HV, 4000 m ± 10% (NH), 70 min, rest and exercise (phase 1 study) | Normobaric chamber | Dose was well tolerated but did not impact the acute HPV response in healthy volunteers. |
| Watt *et al.* (2000)[119] | Amlodipine | Calcium channel blocker | Pulmonary haemodynamics | n = 14 mountaineers, 12.5% $O_2$ (HH), 10 min, rest and exercise | NA | Increased heart rate, influenced HPV dose-dependently, increased breathlessness perception during exercise. |
| Pham *et al.* (2010)[120] | Bosentan | Endothelin (ET) A and ETB receptor blocker | PASP | n = 10 HV, 12% $O_2$ (NH), 90 min, rest and exercise | Normobaric chamber | Reduced hypoxia-induced PASP elevation during rest, but not during exercise. |
| Faoro *et al.* (2009)[121] | Bosentan | ETA and ETB receptor blocker | PVR | n = 11 HV, 12% $O_2$ (NH), 90 min, rest and exercise | Facial masks | Reduced hypoxia-induced PASP elevation during exercise during rest. |
| Ghofrani *et al.* (2004)[122] | Sildenafil | 5-phosphodiesterase (5-PDE) inhibitor | PASP | n = 14 mountaineers, 5400 m/10% $O_2$ (HH), 14 days, rest and exercise | Mount Everest/ facial mask | Reduced pulmonary hypertension both in rest and during exercise. |
| Ricart *et al.* (2005)[123] | Sildenafil | 5-PDE inhibitor | PASP | n = 14 HV, 5000m (HH), 90 min, rest and exercise | Hypobaric chamber | Reduced the hypoxia-induced increase in PASP, and after exercise. |
| Damy *et al.* (2015)[124] | Sildenafil | 5-PDE inhibitor | RVTG | n = 18 patients with CHF, 15% (NH), 2 h, rest and exercise | Facial masks | Reduces RVTG at rest and prevented hypoxia-induced increases, but not by exercise. |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | | | | |
| Burghuber (1987)[125] | Nifedipine | Calcium channel blocker | PAP, PVRI | n = 11 COPD patients with normal PAP, 13% $O_2$, 5% $CO_2$ and 72% $N_2$ (HH + HC), 10 min, rest | Facial masks | Acutely dilates the constricted vascular bed associated with hypoxia in these patients with COPD. |

| Reference | Drug | Class | Biomarker | Design | Hypoxia inducer | Outcome |
|---|---|---|---|---|---|---|
| DISORDERED SLEEP | | | | | | |
| Straus *et al.* (2021)[126] | Baclofen | GABA$_B$ agonist | Coefficient of variation of respiratory cycle total time | n = 14 HV, 12-14% $O_2$+ 6.2% $CO_2$, (NH + HC), NA, sleep | Tent | Baclofen destabilises breathing during sleep. |
| Beaudin *et al.* (2014)[90] | Celebrex | Selective COX-2 inhibitor | BP, CBF, and urinary prostanoids | n = 12 HV, IH, 6 h (1 min cycles), rest | Mask and normobaric chamber | COX-2 and COX-1 play distinct roles in regulating vascular responses to both acute and chronic intermittent hypoxia (IH). In addition, inhibiting COX-1 may alleviate cardiovascular and cerebrovascular issues in OSA. |
| | Indomethacin | Nonselective COX inhibitor | | | | |
| Foster *et al.* (2010)[127] | Losartan | Type I angiotensin II receptor | BP, CBF, and ventilation | n = 10 HV, IH, 6 h (1 min cycles), rest | NA | IH raises blood pressure through type I angiotensin II receptor activation, without affecting the cerebrovascular or ventilatory response to acute hypoxia. |
| HEART FAILURE | | | | | | |
| Pavelescu & Naeije (2012)[127,128] | Epoprostenol | Prostacyclin analog | PAP | n = 10 HV, 12% (NH), 1 h, rest | Tightly collar fitted helmet | At maximum tolerated doses in healthy volunteers, neither substance influenced cardiac function or demonstrated intrinsic positive inotropic effects. |
| | Sildenafil | 5-phosphodiesterase (5-PDE) inhibitor | | | | |
| MIGRAINE | | | | | | |
| Didier *et al.* (2022)[129] | Ketorolac | nonselective COX inhibitor | ASL-MRI | n = 6 HV, 9-13% $O_2$ (Isocapnic H), NA, rest | NA | CBF did not change globally or regionally with hypoxia stimulation and Ketorolac did not change CBF during hypoxia in any region. |

*Abbreviations: ASL-MRI, arterial spin labelling–magnetic resonance imaging; BP, blood pressure; CBF, cerebral blood flow; CHF, chronic heart failure; COX, cyclooxygenase; HC, hypercapnia; HH, hypobaric hypoxia; HPV, hypoxic pulmonary vasoconstriction; HV, healthy volunteers; IH, intermittent hypoxia; NH, normobaric hypoxia; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; RVTG, transtricuspid systolic pressure gradient*



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