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Review article

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Cardiovascular physiology and pathophysiology at high altitude

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Abstract

Oxygen is vital for cellular metabolism; therefore, the hypoxic conditions encountered at high altitude affect all physiological functions. Acute hypoxia activates the adrenergic system and induces tachycardia, whereas hypoxic pulmonary vasoconstriction increases pulmonary artery pressure. After a few days of exposure to low oxygen concentrations, the autonomic nervous system adapts and tachycardia decreases, thereby protecting the myocardium against high energy consumption. Permanent exposure to high altitude induces erythropoiesis, which if excessive can be deleterious and lead to chronic mountain sickness, often associated with pulmonary hypertension and heart failure. Genetic factors might account for the variable prevalence of chronic mountain sickness, depending on the population and geographical region. Cardiovascular adaptations to hypoxia provide a remarkable model of the regulation of oxygen availability at the cellular and systemic levels. Rapid exposure to high altitude can have adverse effects in patients with cardiovascular diseases. However, intermittent, moderate hypoxia might be useful in the management of some cardiovascular disorders, such as coronary heart disease and heart failure. The aim of this Review is to help physicians to understand the cardiovascular responses to hypoxia and to outline some recommendations that they can give to patients with cardiovascular disease who wish to travel to high-altitude destinations.

Sections

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Key points

- Acute exposure to high altitude stimulates the adrenergic system, increasing heart rate and cardiac output; although blood pressure remains stable, pulmonary artery pressure increases owing to hypoxic pulmonary vasoconstriction.
- Prolonged exposure to high altitude induces a decrease in maximal heart rate through desensitization of the adrenergic pathway, as a protective mechanism against environmental conditions of low oxygen availability.
- Long-term exposure to high altitude results in cardiac adaptations with no obvious dysfunction; stroke volume is slightly reduced owing to decreased left ventricular filling volume secondary to right ventricular overload.
- High-altitude natives can develop chronic mountain sickness, associated with erythropoiesis, pulmonary hypertension and right heart failure, although genetic adaptations to hypoxia have been found in Tibetan and Ethiopian populations.
- Patients with cardiovascular diseases can be at increased risk of adverse events at altitudes above 2,500 m, owing to hypoxaemia, high adrenergic activity and pulmonary hypertension.
- Intermittent, moderate hypoxia might be useful in the conditioning of patients with cardiovascular diseases, such as coronary heart disease and heart failure.

Introduction

The term hypoxia has arisen in the public sphere for two reasons in the past 5 years — the awarding of the Nobel Prize in Physiology or Medicine to Kaelin, Ratcliffe and Semenza in 2019 for "their discoveries of how cells sense and adapt to oxygen availability" and in the context of the coronavirus 2019 (COVID-19) pandemic. In the academic environment, hypoxia is an active topic of research. In April 2023, the search term 'hypoxia' produced more than 184,000 results in the PubMed database, with the first dating from 1945 (ref. 1). However, interest in the effects of oxygen deprivation on living organisms began in the mid-nineteenth century, when scientists working in high-altitude regions mainly used the terms anoxia or anoxaemia. A clear, clinical distinction between anoxia and hypoxia was first made by Carl Wiggers in 1941 (ref. 2). Hypoxia is a decrease in oxygen and is variable with time and localization in the body, whereas anoxia is the absence of oxygen. This contrast illustrates the concept of homeodynamics that defines living organisms as complex systems in a state of permanent instability, exposed to environmental and internal perturbations[3].

High-altitude environments are characterized by various physical constraints, including cold temperatures and an increased level of ultraviolet radiation. However, the most demanding condition is hypoxia owing to the progressive decline in barometric pressure (Fig. 1). The oxygen pressure in the inspired air (PiO_2) is given by the following equation: $PiO_2 = FiO_2 \times (Pb - P_{H_2O})$, in which FiO_2 is the fraction of oxygen in the inspired air, Pb is the barometric pressure and P_{H_2O} is the water pressure in the upper airways. P_{H_2O} does not vary with altitude and is equal to 47 mmHg for a body temperature of 37 °C. Similarly, FiO_2 does not depend on altitude and currently equals 0.2093 (20.93%), but this value has fluctuated since the formation of the Earth. For example, 300 million years ago, FiO_2 was around 0.30 (30%) and this relatively 'hyperoxic' environment favoured the development of large insects without a circulatory system transporting oxygen[4]. Conversely, 250–150 million years ago, FiO_2 fell to between 0.10 and 0.15 (10–15%). This relatively 'hypoxic' environment might have affected the size and metabolism of living organisms and could even partly explain the concomitant catastrophic mass extinction event at the end of the Triassic period[4,5]. FiO_2 then progressively rose to present-day values. The evolution of FiO_2 is interesting and might explain why living organisms have evolved various strategies to cope with hypoxia or hyperoxia.

High-altitude regions above 2,500 m are found in South America (Andean countries), North America (Rocky Mountains and Alaska), Europe (Alps and Pyrenees), Africa (Atlas and East African plateaux) and Asia (Himalayas and Tibetan plateau). Isolated peaks >4,000 m above sea level can be found in Antarctica, Indonesia and Japan. Worldwide, more than 40 million people live at altitudes above 2,500 m and are exposed to chronic hypoxia, whereas an undetermined number of people are exposed to acute hypoxia for leisure or work activities. Chronic intermittent hypoxia occurs when an individual spends a few days at high altitude followed by a few days at sea level, and this pattern is repeated regularly, as is the case for miners in South America. Billions of people who travel by air are potentially exposed to a pressurized cabin environment corresponding to a maximum altitude of 2,400 m. Therefore, a wide variety of exposure times — from a few minutes or hours to years — will trigger an array of physiological and pathological responses to hypoxia.

Physiological adaptations to hypoxia include cardiovascular, respiratory, metabolic, haematological and endocrine responses. In this Review, we focus on cardiovascular adaptations to both acute and chronic exposure to high altitude. We also discuss the effects of hypoxia in the setting of various cardiovascular diseases (CVDs) and outline some guidance for advising patients with CVD who wish to travel to high-altitude destinations (Box 1). In addition, we briefly explore the role of hypoxic preconditioning in health and disease.

Physiological responses

The physiological effects of hypoxia have been studied using either hypobaric hypoxia (using high-altitude environments or hypobaric chambers) or normobaric hypoxia (by breathing hypoxic gas mixtures). When PiO_2 is the same for each method, no physiologically significant differences between these experimental approaches have been observed[6].

Oxygen is vital for all human cells and, therefore, hypoxic conditions affect all physiological functions. Every cell can be considered to be an oxygen sensor owing to the presence of genetic sequences known as hypoxia-responsive elements. In acute hypoxia (minutes to hours), the activation of these elements triggers the expression of various factors, leading to the stabilization of hypoxia-inducible factors (HIF1, HIF2 and HIF3). In turn, HIFs induce the expression of messengers and hormones (such as erythropoietin, vascular endothelial growth factor and glucose transporters) involved in the physiological response to hypoxia[7]. Cell function can also be directly affected by hypoxia through the activation or inhibition of ion channels, such as K^+ channels for chemoreceptors and Ca^{2+} channels for smooth muscle cells[8]. Peripheral chemoreceptors are the first sensors to be challenged by a hypoxaemic stimulus, triggering immediate ventilatory (hyperventilation)

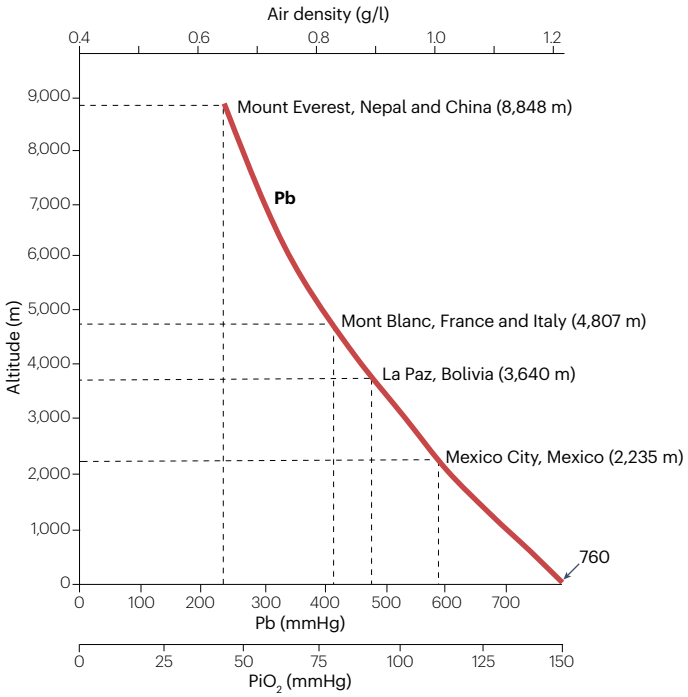

Fig. 1 | Altitude, barometric pressure, air density and inspired oxygen pressure. With increasing altitude, air density, barometric pressure (Pb) and inspired oxygen pressure (PiO_2) decrease. PiO_2 is given by the equation $PiO_2 = FiO_2 \times (Pb - P_{H_2O})$, in which FiO_2 is the fraction of oxygen in the inspired air and P_{H_2O} is the water pressure in the upper airways. P_{H_2O} does not vary with altitude and is equal to 47 mmHg for a body temperature of 37 °C. Similarly, FiO_2 does not vary with altitude and is equal to 0.2093 (20.93%).

and cardiac (tachycardia) responses via the medulla oblongata. The vascular response to hypoxia is variable, depending on the site of action. Hypoxia induces vasoconstriction in the pulmonary vessels and vasodilatation in the peripheral circulation (Fig. 2).

With prolonged exposure to hypoxia (days to weeks), other adaptive responses occur, such as downregulation of adrenergic receptors, changes in the acid–base balance leading to increased excretion of bicarbonates, stimulation of erythropoiesis via erythropoietin, changes in the secretion of various hormones (for example, an increase in catecholamine and corticosteroids) and inhibition of the renin–angiotensin–aldosterone system (RAAS). These integrated responses (Fig. 2) can preserve sufficient delivery of oxygen to all cells[9]. However, because maximal oxygen consumption during exercise irremediably decreases with increasing altitude, physical performance becomes impaired from ~800 m, at least in endurance-trained athletes[10]. Cognitive function also becomes impaired, but only at much higher altitudes (>6,000 m). Despite the rapid and integrated physiological response to hypoxia, if the stimulus is too severe or the metabolic demand too high, the balance between oxygen supply and consumption becomes altered and pathological events can occur. Conditions such as acute mountain sickness and pulmonary or cerebral oedema usually manifest during the first hours or days of exposure to altitude (mainly >2,500 m). The severity of these conditions can vary depending on the peripheral chemosensitivity of an individual to hypoxia[11] and the intensity of hypoxia-induced pulmonary hypertension[12].

With chronic exposure to hypoxia (months, years or lifetime), stabilized erythropoiesis generally contributes to permanent acclimatization to life in hypoxia. However, in some cases of chronic mountain sickness (CMS; also known as Monge disease), excessive erythropoiesis can lead to an increase in blood viscosity, thrombosis, pulmonary hypertension and heart failure in some natives of high-altitude environments[13].

Cardiovascular responses

The cardiovascular system has a major role in the integrated response to hypoxia (Table 1), involving two mechanisms: centrally mediated activation of the adrenergic system and a direct peripheral effect on the cells of the heart and blood vessels. Activation of medullary adrenergic centres is driven by input from the carotid chemoreceptors that are sensitive to hypoxaemia[14]. The whole sympathetic nervous system is activated, as evidenced by an increase in plasma and urine catecholamine concentrations[15]. An increase in arterial plasma catecholamine levels has been consistently observed with prolonged hypoxia[16]. Activation of the adrenergic system has also been demonstrated by increased activity in the peroneal adrenergic nerves[17].

G_s and G_i proteins that couple the β-adrenergic receptors to adenylate cyclase and activate or inhibit this enzyme, respectively, have been shown to have a crucial role in the downregulation of the adrenergic system in hypoxia (Fig. 3). In hypoxia, G_s activity is reduced, whereas G_i expression is increased, leading to inhibition of adenylate cyclase activity and, ultimately, a reduction in ion channel activity and heart rate[18]. β-Arrestin 2 could have an important role in regulating pathways involved in the desensitization and internalization of G-protein-coupled receptors observed in hypoxia and has been explored as a potential target for treating heart failure[19]. Interestingly, the heart is not the only organ in which hypoxia induces desensitization of G-protein-coupled receptors. Renal handling of calcium by parathormone, control of growth hormone secretion by hypothalamic factors, muscle lactate release and adipose tissue lipolysis are also affected, suggesting a general mechanism of adaptation to hypoxia[14].

The heart

Heart rate. The predominance of the adrenergic system at high altitude has been highlighted by a study of heart rate variability, in which hypoxia induced a decrease in R–R interval and an increase in the low-frequency to high-frequency ratio, an index of sympathovagal balance[20]. With acute exposure to high altitude, heart rate at rest and after moderate exercise increases and then progressively declines with acclimatization, but never returns to sea-level basal values[21]. The 'mirror' pattern of variation in resting heart rate and arterial oxygen saturation (SaO_2) illustrates the close relationship between hypoxaemia and adrenergic activation in acute and prolonged hypoxia (Fig. 4).

Although heart rate with moderate exercise initially increases at altitude, heart rate at maximal exercise is slightly reduced in acute hypoxia and decreases significantly with prolonged (>24 h) exposure to high altitude. The decrease in heart rate at maximal exercise has been observed in many studies conducted in the field and in simulated conditions[22] (Fig. 5). Both sympathetic and parasympathetic systems have been explored to find a physiological explanation for this decrease in maximal heart rate. The most convincing evidence is that β-adrenergic receptors are downregulated. This mechanism is well known in pharmacology — when an agonist is consistently elevated, the corresponding receptor is downregulated, leading to desensitization of the whole pathway as an adaptive phenomenon against excessive

Box 1

Recommendations for patients with cardiovascular diseases travelling to high-altitude regions

All patients
- Be aware of potential interactions between current medication and acetazolamide, if prescribed.
- Consider the presence of comorbidities.
- Consider the availability of medical facilities at destination.

Coronary artery disease
- Travel not advisable until at least 6 months after a cardiac event.
- Travel advisable if no electrocardiographic abnormalities are present during the stress test.
- Travel advisable if destination is ≤4,200 m above sea level (lower threshold if additional cardiovascular risks are present).
- No vigorous exercise at altitude.

Heart failure
- NYHA class I–II: travel advisable if destination is ≤3,500 m above sea level.
- NYHA class III: travel advisable if destination is ≤3,000 m above sea level.
- NYHA class IV: travel to high-altitude destinations is not advisable.

Arrhythmias
- For patients with serious ventricular arrhythmias, travel advisable if destination is ≤3,500 m above sea level.
- Travel advisable for patients with other arrhythmias.

Cyanotic heart disease or right-to-left shunt
- Travel not advisable, unless the patient has been surgically treated.

Systemic hypertension
- Travel not advisable for patients with uncontrolled or severe hypertension (>180/110 mmHg).
- Travel advisable for patients with stabilized hypertension.

Pulmonary hypertension
- Travel not advisable if destination is >2,000 m above sea level.
- If travel cannot be avoided, use of supplemental oxygen is required.

stimulation. Studies in animals[23–26] and in humans[27] have confirmed this hypothesis. Moreover, in a study of six healthy individuals, cardiac uptake of iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) was reduced after 1 week of exposure to an altitude of 4,350 m, supporting the hypothesis that hypoxia reduces adrenergic neurotransmitter reserve in the myocardium and alters endothelial cell function[28].

The parasympathetic system has been investigated in only a few studies, mainly through muscarinic receptor blockade by atropine or glycopyrrolate, suggesting that a hypoxia-induced increase in parasympathetic activity might contribute to the decrease in heart rate at exercise in prolonged hypoxia[29–31]. In animal models, the increase in parasympathetic effects on the heart has been related to the upregulation of muscarinic receptors[23,24,32], implying a decrease in centrally mediated activation of the parasympathetic system, as a mirror effect of adrenergic activation with downregulation of β-receptors. A causal link between the observed decrease in maximal heart rate and the decrease in exercise performance at altitude has been debated but has never been clearly demonstrated.

A model of myocardial oxygenation with exercise at increasing altitudes has demonstrated that the decrease in heart rate at maximal exercise is beneficial — by limiting cardiac oxygen consumption when oxygen availability is reduced, adequate myocardial oxygenation is maintained[22] (Fig. 6). This remarkable autoregulation of oxygen handling protects the heart from ischaemic events in extreme conditions in which arterial P_{O_2} is ~30 mmHg (Fig. 4). Indeed, no cases of myocardial infarction or angina pectoris have ever been reported in healthy individuals exercising at altitudes >8,000 m (ref. 33). The preservation of myocardial function in healthy people exposed to hypoxia can be considered in parallel with the use of β-blockers in patients with heart failure. Interestingly, a polymorphism in G-protein-coupled receptor kinase 5 (*GRK5*) that is common among African American individuals improves survival from heart failure, supporting the role of G proteins in the preservation of heart function at high altitude[34].

Cardiac dimensions and function. Cardiac output and stroke volume have been studied in various normobaric and hypobaric hypoxic conditions. Cardiac output increases at altitude, mainly owing to the increase in heart rate. Stroke volume decreases slightly, as measured during Operation Everest II when stroke volume decreased by 14% at rest and after moderate exercise (60 W) at 7,620 m[35]. This change is not due to a decrease in venous return to the heart, as argued by some researchers[36], because blood volume is maintained (the decrease in plasma volume is compensated for by an increase in red cell volume). The decline in stroke volume is actually caused by a slight reduction in the end-diastolic volume of the left ventricle as a consequence of increased pressure in the right ventricle linked to elevated pulmonary artery pressure (PAP). This mechanical effect of high right ventricular (RV) pressure on the interventricular septum can slightly impair left ventricular (LV) filling. However, these mechanisms do not significantly impair cardiac function. Acute moderate normobaric hypoxia (FiO_2 = 14.4%) has been shown to attenuate exercise-induced increases in stroke volume and cardiac output[37]. Stroke volume reached a plateau earlier in hypoxia than in normoxia[37], suggesting a slight impairment in cardiac filling related to a decrease in LV diastolic function[38] or to impaired RV function owing to elevated pulmonary vascular resistance[39].

In healthy individuals, cardiac inotropic function is not altered at altitude, even at extreme elevations, as shown by normal or even augmented LV ejection fraction[35,38]. Endurance athletes intermittently exposed (12 h per day for 13 days) to simulated altitude (2,500–3,000 m) showed a slight increase in the ratio of RV-to-LV diameter on echocardiography, suggesting minor RV dilatation without an alteration in contractile function[40]. Among healthy volunteers, LV mass (adjusted for changes in the body surface area) decreased by 11% after a 17-day trek to 5,300 m, but returned to pre-trek values after 6 months[41]. No change in LV or RV ejection fraction occurred, but a slight decrease in diastolic function was reported[41]. In Chilean soldiers[42] and miners[43] intermittently exposed to altitudes between 3,550 m and 4,600 m for 2.5–12.0 years, minor RV hypertrophy was observed and PAP was elevated (>25 mmHg in 4% of the military population). During a simulation of ascent to 8,848 m (Operation Everest III (COMEX '97)), cardiac function was assessed using a combination of M-mode and 2D echocardiography, with continuous and pulsed Doppler at 5,000, 7,000 and 8,000 m[44]. On ascent to altitude, aortic, left atrial and LV end-systolic diameter fell regularly. Mitral peak *E* velocity decreased, peak *A* velocity increased and the *E*/*A* ratio decreased. Systolic PAP showed a progressive and constant increase up to 40 mmHg at 8,000 m[44]. This study confirmed the elevation of PAP and the preservation of LV contractility at high altitude. A modification in LV filling pattern was observed, with decreased early filling and an increased contribution from atrial contraction, without elevation of LV end-diastolic pressure[38]. In another study, lowlanders arriving at high altitude (3,750 m) had an increase in mean PAP (13–22 mmHg) and altered RV and LV diastolic function, although RV systolic function was maintained[45]. After a 10-day period of acclimatization to high altitude, PAP (measured at 4,850 m) increased slightly (26 mmHg) without further changes in cardiac function. These observations confirm that healthy individuals exposed to mild hypoxia-induced pulmonary hypertension maintain systolic function, despite a slight impairment in ventricular filling mechanisms.

Cardiac electrical activity is not significantly modified by exposure to hypoxia in healthy individuals. However, a decrease in the amplitude of QRS and T waves on the electrocardiogram has been observed during moderate exercise in hypoxia, when compared with normoxia for the same heart rate[46]. These changes have no clinical implication but might reflect a slight hypoxia-induced decrease in ion exchange in cardiomyocytes.

Myocardial circulation. As discussed, the healthy myocardium shows remarkable adaptation to hypoxia via a reduction in maximal heart rate. In addition, hypoxia-induced coronary vasodilatation occurs, mediated by vasoactive metabolites (such as adenosine and nitric oxide (NO)) or by proton accumulation[47]. A coronary flow reserve of 35% was found at maximal exercise in 12 healthy individuals breathing 12% oxygen (equivalent to an altitude of 4,650 m), although 1% of energy demand was covered by anaerobic metabolism[48]. In another study, during moderate exercise (83 W) at 4,500 m, coronary reserve

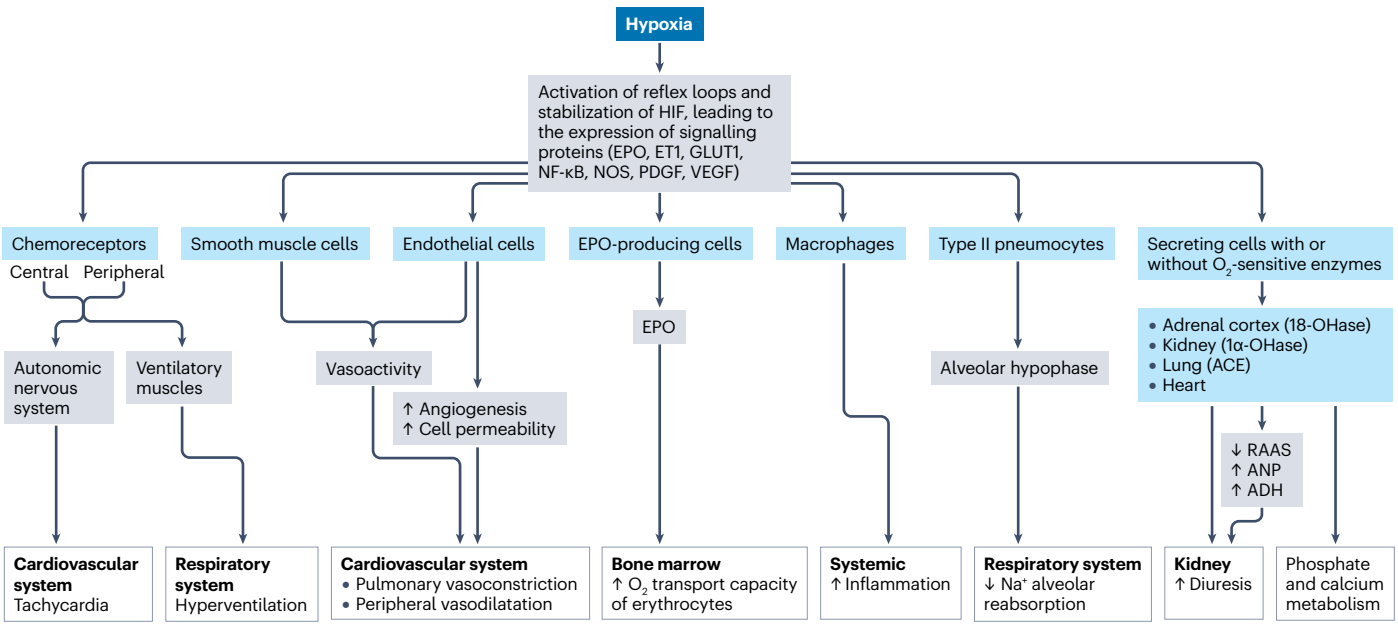

Fig. 2 | Physiological effects of acute hypoxia. Hypoxia induces the expression and translation of genes with hypoxia-responsive elements, which in turn trigger the expression of various factors that lead to the stabilization of hypoxia-inducible factors (HIFs). HIFs can induce the production of messengers or hormones involved in physiological reactions to hypoxia, such as erythropoietin (EPO), endothelin 1 (ET1), glucose transporters (such as GLUT1), nuclear factor-κB (NF-κB), nitric oxide synthases (NOS), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). Hypoxia also activates reflex loops, independently of HIF stabilization. Peripheral chemoreceptors are the first sensors of the hypoxaemic stimulus, triggering immediate ventilatory (hyperventilation) and cardiac (tachycardia) responses to hypoxia. The vascular response to hypoxia is variable, depending on the site of action. Hypoxia induces vasoconstriction in the pulmonary vessels and vasodilatation in the rest of the peripheral circulation. Other responses occur after prolonged exposure to hypoxia (hours to days), such as increased angiogenesis and endothelial cell permeability, stimulation of erythropoiesis via EPO, increased inflammation, decreased Na^+ alveolar reabsorption by pneumocytes and increased diuresis via inhibition of the renin–angiotensin–aldosterone system (RAAS) and stimulation of atrial natriuretic peptide (ANP) and antidiuretic hormone (ADH). 1α-OHase, 25-hydroxyvitamin D 1α-hydroxylase; 18-OHase, steroid 18-hydroxylase (also known as aldosterone synthase); ACE, angiotensin-converting enzyme.

Table 1 | Cardiovascular modifications induced by hypoxia

Parameter	Acute hypoxia	Prolonged hypoxia	Long-term high-altitude residence	Refs.
Adrenergic system	Activated	Activated and then downregulated	Activated or downregulated, depending on ethnic origin of the individual	14–18,20,23–27,171
Heart rate at rest	Increased	Return towards sea-level values	Depends on the ethnic origin of the individual	21
Maximal heart rate	Stable	Decreased	Lower than natives of sea-level regions	22
Cardiac output	Increased	Return to sea-level values	Depends on the ethnic origin of the individual	35,37,38
Stroke volume	Stable	Slightly decreased	Decreased in individuals with CMS	35,37,38
RV mechanics	Increase in RV volume	Increase in RV volume	Hypertrophy, especially in individuals with CMS	39,40,42,43,45
LV mechanics	Increase in systolic function	Slight decrease in LV filling, no change in LV ejection fraction	Decrease in LV filling	35,37,38,41,45
Blood pressure	Increase in parallel with heart rate	Increase in parallel with heart rate	Stable or increased	50–54,172
Pulmonary artery pressure	Increased	Increased	Increased	42,43,45,69–71
Cerebral circulation	Increased blood flow	Blood flow returns to normal	Stable	81,82
Renal circulation	Decreased renal blood flow and increased diuresis	Decreased effective renal blood flow	Decreased renal blood flow, especially in individuals with CMS	75–80
Myocardial circulation	Increased blood flow	Decreased coronary reserve	No data available	47–49
Muscular circulation	Increased blood flow	Increased blood flow	No data available	55,83–88,173

CMS, chronic mountain sickness; LV, left ventricular; RV, right ventricular.

was preserved among 10 healthy individuals, but was reduced by 18% in 8 patients with coronary artery disease (CAD)[49].

Systemic blood pressure

Centrally mediated activation of the adrenergic system has a vasoconstrictive effect on peripheral α-adrenergic receptors, which can lead to increases in peripheral vascular resistance and blood pressure. Moreover, an increase in heart rate and cardiac output can contribute to an increase in blood pressure independently of vascular resistance. Conversely, hypoxia has a direct relaxing effect on vascular smooth muscle cells, leading to vasodilatation and a decrease in vascular resistance. The overall effect depends on the time of exposure and the intensity of the hypoxic stimulus.

The effect of acute hypoxia on blood pressure illustrates these dichotomic responses between central and peripheral mechanisms. Hypoxia-induced activation of the autonomic nervous system is a potent activator of central sympathetic activity, triggered by augmented oxygen-related activity of the carotid chemoreceptors[50,51], which in turn induces a peripheral vasoconstrictor response via sympathetic-dependent contraction of vascular smooth muscle cells[51]. This centrally mediated mechanism is counterbalanced by the peripheral action of hypoxaemia, which stimulates the production and release of local vasodilatory factors such as endothelial NO[52–54], thereby promoting global vasodilatation in various (coronary, cerebral, splanchnic and skeletal) vascular beds[55]. In clinical tests performed to predict susceptibility to acute mountain sickness, a slight rise in systemic blood pressure was observed in hypoxia (FiO_2 = 11.5%), compared with normoxia, for the same level of exercise intensity[56–58]. However, a concomitant increase in heart rate also occurred, under the influence of hypoxia-dependent sympathetic activation, leading to an increase in cardiac output[59] and masking the effects of hypoxia on centrally and peripherally driven blood pressure. Therefore, during steady-state exercise at moderate intensity, despite the increase in blood pressure during hypoxia (versus normoxia) for a given power (watts), blood pressure was lower in hypoxia (versus normoxia) for a given heart rate, when 'clamping' the adrenergic drive[60]. This finding confirms the superior effect of peripheral vasodilatory mechanisms over centrally driven vasoconstriction on blood pressure. Adding physiological stress (such as exercise) to existing environmental stress leads to a further 'compensatory' systemic vasodilatation. These concomitant mechanisms seem to provide superior outcomes compared with exercise-induced or hypoxia-dependent vasodilatation alone[55].

Chronic exposure (months, years or lifetime) to high altitude requires multiple, additional physiological adaptations, which vary depending on the environment (such as altitude and climate) and the individual (genetics, lifestyle, socioeconomic factors and acclimatization)[61]. For example, in some studies, long term exposure to high altitude leads to a persistent increase in blood pressure[59,62–65], whereas in other studies, blood pressure remained stable[66] or even decreased[67]. In general, peripheral vasodilatation is crucial to preserve the blood flow to oxygen-demanding muscles in hypoxia in the presence of centrally driven vasoconstriction.

The peripheral circulation

Lungs. Within minutes of exposure to hypoxia, pulmonary vasoconstriction leads to a rapid increase in pulmonary vascular resistance and mean PAP[68,69]. Exercise aggravates the hypoxia-induced increase in pressure, which reaches 54 mmHg during maximal exercise at 8,848 m[70]. Pulmonary vasoconstriction involves inhibition of oxygen-sensitive K^+ channels, leading to depolarization of pulmonary artery smooth muscle cells and activation of voltage-gated Ca^{2+} channels, Ca^{2+} influx and vasoconstriction[71]. This process is immediately reversed by breathing

oxygen. However, lowlanders exposed to high altitude for 2–3 weeks develop pulmonary hypertension that is not completely reversed by breathing oxygen[70], suggesting vascular remodelling of the pulmonary arterioles. This process involves the proliferation of smooth muscle cells and thickening of the artery wall[72]. Pulmonary hypertension not only affects RV function[73] but also limits exercise performance[74].

Kidneys. The effects of acute hypoxia on renal plasma flow and glomerular filtration rate are limited. However, urine flow increases, probably through a combined effect of adrenergic stimulation and inhibition of the RAAS[75,76]. Hypocapnia and alkalosis, resulting from hypoxia-induced hyperventilation, have an important effect on renal physiology by inducing a large increase in bicarbonate excretion. In a study from the Global REACH 2018 expedition, renal blood flow decreased by 14% after 1 day of exposure to 4,330 m, but was restored after 1 week of acclimatization, whereas glomerular filtration rate remained lower than that at sea level[77]. With prolonged hypoxia, as haematocrit and blood viscosity increased, effective renal plasma flow decreased by 38% at 5,800 m (ref. 78) and by 39% at 6,542 m, whereas renal blood flow decreased by only 24% (ref. 79). In natives of high-altitude environments, a more severe reduction in renal plasma flow is observed, especially in patients with CMS[80].

Brain. Cerebral blood flow increases with acute hypoxia. However, because hypoxia induces hyperventilation, the resulting hypocapnia has a direct vasoconstricting effect on the cerebral circulation, and cerebral blood flow returns to normal sea-level values after a few hours or days of hypoxic exposure[81]. At 8,000 m, a decrease in the transient hyperaemic cerebrovascular response has been observed, suggesting impaired cerebral autoregulation that could have a role in the genesis of the acute neurological deficits observed at extreme altitude[82].

Skeletal muscle. Exercising promotes various muscular vasodilatory processes, particularly by blunting sympathetic α-adrenergic vasoconstriction and inducing the release of NO[55]. This response during exercise in hypoxic conditions compensates for the increased sympathetic vasoconstrictor activity directed towards skeletal muscle[83]. Although the specific mechanisms of this effect are not fully understood, they are thought to involve increased vasodilatation rather than reduced vasoconstriction in active locomotor muscles[55]. Other postulated mechanisms include augmented NO release, through β-adrenergic receptors in the exercising limb[84,85], directly from the endothelium[86] or via shear stress activation of endothelial cells[87]. Adenosine might also contribute to the regulation of skeletal muscle blood flow by stimulating prostaglandin and NO synthesis[88]. These processes might be modulated by exercise intensity, the severity and the duration of exposure to hypoxia, and by the mobilized muscle mass[55].

Adaptation in high-altitude natives

Cardiovascular adaptations to altitude in humans have been built through genetic modifications over millions of years of evolution. However, some individuals living at high altitude still manifest deleterious responses to hypoxia and develop conditions such as CMS. Strategies for adaptation to permanent living at high altitude differ according to the population and geographical region. Indigenous Tibetans, who have lived above 4,000 m for more than 40,000 years, seem to have the best profile of genetic adaptation to chronic hypoxia through changes in *HIF2* and *EGLN1* (also known as *PHD2*)[89]. This population has low SaO_2, but no excessive erythrocytosis or pulmonary hypertension. East African highlanders have haemoglobin and SaO_2 levels similar to those of sea-level natives[90], and their phenotypic adaptation to high altitude is still under investigation. Andeans, whose residence at high altitude dates to around 12,000 years ago, have a mixed genetic profile, with ethnic admixture with Europeans since the sixteenth century[91]. Therefore, this population does not have a clear genetic advantage for living at high altitude, with low SaO_2, high haemoglobin levels, elevated PAP and RV hypertrophy[92]. In a study of native residents of La Paz, Bolivia (3,500–4,100 m), pulmonary artery hypertension was reversed after prolonged residence at sea level or treatment with nifedipine[93].

A substantial proportion of the Andean population (15% in Cerro de Pasco, Peru; 4,300 m) develops CMS[13]. This condition is characterized by excessive erythropoiesis and, sometimes, pulmonary hypertension that can evolve towards right and global heart failure[94]. Patients with CMS from Cerro de Pasco have elevated mean PAP (34 mmHg) when compared with healthy high-altitude natives (25 mmHg) and sea-level residents (19 mmHg)[95]. These patients also have RV enlargement but do not develop impaired ejection fraction. However, the RV Tei index (myocardial performance index) was increased in patients with CMS and in healthy high-altitude residents, suggesting early impairment of RV function[95]. Moreover, patients with CMS seem to be at increased risk of developing cardiovascular events compared with their healthy counterparts[96]. In another study, a decrease in RV function at rest and during exercise was also found in patients with CMS from La Paz when compared with healthy high-altitude residents[97]. However, the researchers suggest that the lower resting values for RV function in patients with CMS could represent a physiological adaptation to chronic hypoxic conditions rather than impaired RV function.

In Peruvian high-altitude natives, peripheral chemoreceptors can develop hyperplasia with ageing, leading to a blunted ventilatory response to hypoxia[13,98]. Adrenergic activity was found to be increased, but β-adrenergic receptors were downregulated, similar to findings from sea-level natives exposed to prolonged hypoxia[99]. Plasma erythropoietin and soluble transferrin receptors are elevated, in line with excessive erythropoiesis, resulting in frequent episodes of sleep apnoea

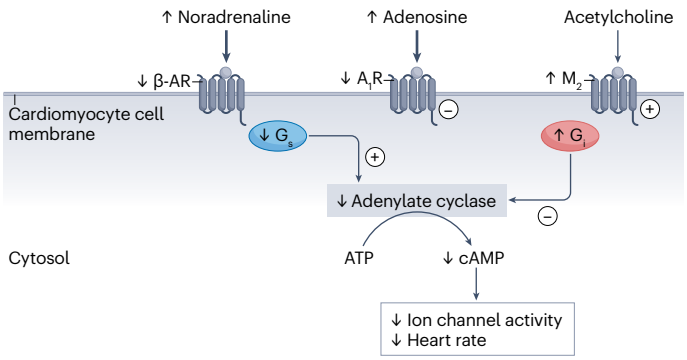

Fig. 3 | Effects of hypoxia on cardiomyocytes. Hypoxia induces an increase in the systemic levels of the agonists noradrenaline and adenosine. The increased noradrenaline and adenosine signalling in cardiomyocytes results in downregulation of β-adrenergic receptors (β-ARs) and the adenosine A_1 receptor (A_1R), upregulation of the muscarinic acetylcholine receptor M_2 (probably due to a decrease in acetylcholine release), a decrease in G_s protein activity and an increase in G_i protein expression and, ultimately, a decrease in adenylate cyclase activity and production of cAMP. The decrease in cAMP negatively influences the control of automatism, contraction and relaxation of cardiomyocytes. The arrows indicate an increase or decrease in concentration or activity observed in hypoxia versus normoxia.

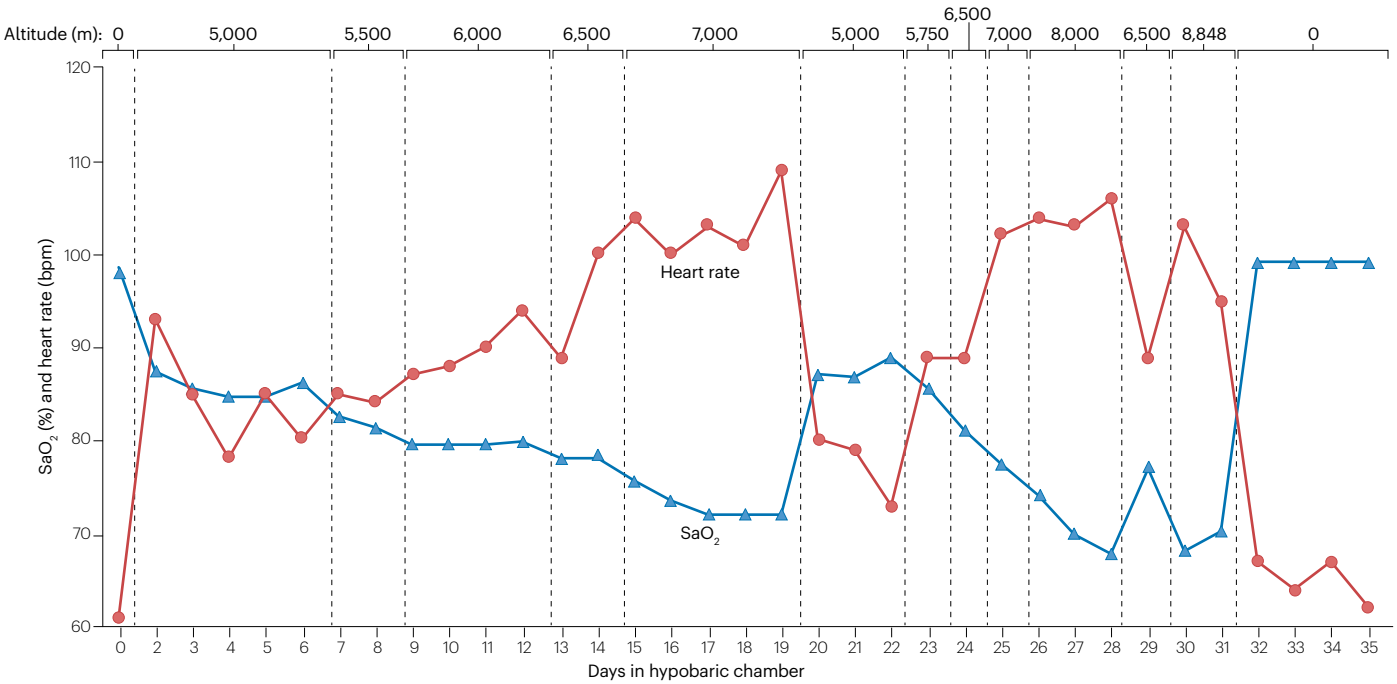

Fig. 4 | Heart rate and arterial oxygen saturation at rest during a simulation of ascent to 8,848 m. The graph shows the heart rate and arterial oxygen saturation (SaO_2) at rest in individuals exposed to simulated altitudes from sea level to 8,848 m in a hypobaric chamber during a simulation of an ascent of Mount Everest (Operation Everest III; COMEX '97)[44]. The variations in resting heart rate and SaO_2 mirror each other, illustrating the tight relationship between hypoxaemia and adrenergic activation in acute and prolonged hypoxia.

and nocturnal oxygen desaturation. These changes are reversed by administration of the carbonic anhydrase inhibitor acetazolamide[100].

Systemic arterial pressure has been studied in various high-altitude populations[101]. Native Tibetans have a higher prevalence of hypertension than Han Chinese people living at the same altitude, perhaps because of differences in genetics or nutrition[102]. Studies in Peruvian miners permanently living and working above 5,000 m showed normal blood pressure (continuously monitored over 24 h), despite a higher blood viscosity owing to a high haematocrit (>60%)[103]. Moreover, Andean natives with CMS do not have an excessive prevalence of hypertension[94]. This finding raises the question of whether the peripheral vasodilatory mechanisms that occur during acute hypoxia persist in chronic hypoxia. The data are scarce but indicate that these mechanisms are still present in native Tibetans, especially through augmented endothelial NO production[104]. However, the response might vary according to ethnicity, because NO-mediated cutaneous vasodilatation was found to be reduced in Peruvian high-altitude residents[104,105]. Other mechanisms of peripheral vasodilatation are still to be unravelled, but could include dampening of the vasodilatory effect of ATP or adenosine[16] and excessive blood viscosity[106].

Genetic studies of high-altitude populations have been developed with two objectives: first, to identify specific mutations that confer an evolutionary advantage for living at high altitude (comparing Andeans, Tibetans or Ethiopians with sea-level natives); and second, to characterize genetic risk factors among high-altitude natives who develop CMS. More than 1,000 genes encoding proteins involved in the circulatory system, angiogenesis, erythropoiesis and oxygen transport could be associated with adaptation or maladaptation to high altitude[89,107,108]. In genome-wide association studies, the specific allele frequency of several HIF pathway genes involved in the Tibetan pattern of adaptation, including *EPAS1* and *EGLN1*, has been identified that might contribute to the low haemoglobin concentration observed in Tibetans[109–111]. In Andeans, genetic studies suggest that positive selection has focused on the NO pathways and the cardiovascular system[112]. Studies of Ethiopian adaptation are scarce, but have identified HIF-mediated oxygen-sensing pathways[113], similar to those found in Tibetans and Andeans, suggesting convergent evolution in populations living at high altitude. The *VEGFA* gene has been implicated in cardiovascular maladaptation to hypoxia in Andeans[114], and *AEBP2*, which has a role in erythropoiesis, has also been proposed as a causal gene for CMS[115]. Other genes, such as the erythropoiesis regulator *SENP1* and the oncogene *ANP32D*, are also thought to be involved in the development of CMS in Andeans[116].

High altitude and cardiovascular disease

Acute altitude illnesses: is the heart involved?

One of the first descriptions of acute forms of mountain sickness, proposed by Ravenhill[117], mentioned a 'cardiac form of altitude illness' to describe what would later be called 'high-altitude pulmonary oedema' (HAPE) by Houston[118]. However, the heart is not involved in any manifestation of altitude illnesses — acute mountain sickness, HAPE or high-altitude cerebral oedema. From the circulatory viewpoint, hypoxia-induced vascular leak is a common feature of all forms of altitude illnesses, owing to increased capillary permeability, without any change in blood pressure. The increase in PAP owing to hypoxia-induced pulmonary vasoconstriction is one of the factors involved in the pathophysiology of HAPE, together with endothelial dysfunction, alveolar epithelial dysfunction and inflammatory processes[119]. Nobody has ever

died from heart problems at the summit of Mount Everest (8,849 m), despite extremely low arterial O_2 pressure (~30 mmHg) and high exercise intensities[33], probably because of the remarkable autoprotective physiological process discussed earlier.

Advice on pre-existing cardiovascular diseases

Very few robust scientific data are available about the risks of exposure to high or very high altitude in patients with chronic CVD. Most studies have included a small number of patients and were performed under very different conditions, in terms of both altitude and methodology. Studies of patients with cardiovascular conditions that involve travel to, or hiking in, high-altitude regions far from medical facilities are unethical. For this reason, among others, recommendations are mostly based on the consensus of experts and limit the highest advisable altitudes in the travel guidance for patients with pre-existing cardiovascular conditions[120–122] (Box 1).

Although the healthy heart is not directly involved in acute altitude illnesses, high altitudes can be challenging for those with CVD because exercising at a given intensity (such as walking uphill) is more demanding in hypoxia than at sea level. Because of the lower SaO_2 and the lower maximal exercise capacity ($\dot{V}O_2$ max) at altitude, the same physical activity requires a greater percentage of $\dot{V}O_2$ max and, therefore, a greater percentage of maximal heart rate and maximal cardiac output to deliver the same amount of oxygen to the myocardium[123]. Therefore, clinical symptoms that would not appear, or appear only during vigorous exercise, in normoxia could emerge during light-to-moderate exercise at high altitude.

A basic knowledge of the physiology of hypoxia, and the pathophysiology of CVD, will help clinicians to provide appropriate advice to their patients with CVD before travel to high-altitude regions[61]. In general, the risk factors for patients with CVD at high altitude are:

- Impaired oxygen delivery, leading to increased hypoxaemia (respiratory conditions, severe or insufficiently controlled heart failure and cyanotic congenital heart diseases).
- Pulmonary hypertension and right heart failure.
- Increased sympathetic activity (arrhythmias).
- Reduced ischaemic threshold, owing to a higher heart rate for a given power output at exercise (CAD).

To evaluate the risk associated with a travel to high altitude for a patient with CVD (Box 1), the physician should consider both the risk of complications of the cardiovascular pathology in hypoxia and comorbidities (such as chronic obstructive pulmonary disease, anaemia, diabetes mellitus and obstructive sleep apnoea), which are common in these patients. Furthermore, they should be aware that medical facilities are not easily accessible in isolated, high-altitude regions and inform their patients that treatment is, therefore, likely to be delayed. Physicians should also consider the medications being taken by the patient. For example, diuretics can lead to dehydration, and β-blockers will impair the physiological increase in heart rate at altitude and reduce physical performance. If acetazolamide is prescribed to limit the risk of high-altitude illness, interactions with other drugs, such as hypokalaemia with loop diuretics, should be avoided. Physicians should also give their patients general recommendations about altitude acclimatization; primarily that, for travel above 3,000 m, the daily gain in altitude should not exceed 400 m (refs. 56,58). Importantly, cardiovascular risks are increased when exposure to altitude is sudden, without progressive acclimatization.

Coronary artery disease. Patients with reduced coronary reserve could be assumed to be at increased risk of myocardial ischaemia at high altitude. However, no significant differences in symptoms, heart rate or systolic function have been observed in patients with ischaemic heart disease compared with healthy individuals at 3,454 m[124] or 4,200 m[125]. The 18% decrease in normal coronary reserve at 2,500 m[49] should be considered when interpreting these findings. In a study of nine patients with CAD exercising at 3,100 m, angina, ST segment depression or both occurred at the same product (heart rate × systolic blood pressure), but at lower workloads, than at sea level[126].

On the basis of these observations, patients with CAD who no longer show electrocardiogram abnormalities during an exercise test, at least 6 months after a cardiac event, can travel to altitudes up to 4,200 m (lower in the presence of comorbidities that increase cardiovascular risk). As a precaution, vigorous exercise at altitude in these patients is contraindicated. Interestingly, one study of healthy individuals exposed to an altitude of 4,559 m showed that acetazolamide increased the subendocardial viability ratio, estimated on the carotid artery using a PulsePen tonometer[127]. This finding suggests a decreased risk of subendocardial ischaemia at altitude in healthy people but remains to be confirmed in patients with ischaemic heart disease.

Heart failure. Some researchers have studied the effects of high altitude (up to 3,454 m) in patients with heart failure with ejection fraction

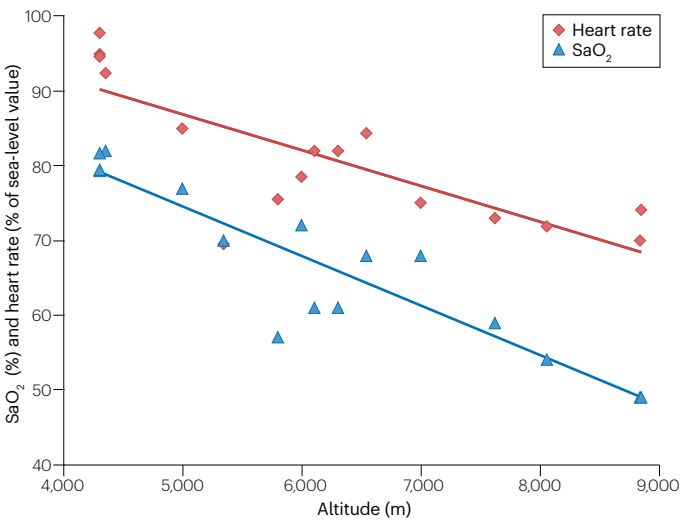

Fig. 5 | Parallel linear decrease in arterial oxygen saturation and heart rate at maximal exercise as a function of altitude. The graph shows the parallel linear decrease in arterial oxygen saturation (SaO_2) and heart rate (% of sea-level values) with increasing altitude during maximal exercise in individuals acclimated to hypoxia. The decrease in heart rate with increasing altitude has been observed in many studies conducted in the field and in simulated conditions. Both sympathetic and parasympathetic nervous systems are involved in this decrease in maximal heart rate. Downregulation of β-adrenergic receptors occurs, leading to desensitization of the pathway, as an adaptive phenomenon against excessive hypoxic stimulation. An increased parasympathetic effect on the heart might also contribute to the decrease in heart rate during exercise in prolonged hypoxia, via upregulation of the muscarinic receptors, which implies decreased centrally mediated activation of the parasympathetic system, as a mirror effect of adrenergic activation with downregulation of β-adrenergic receptors. Adapted from ref. 22, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

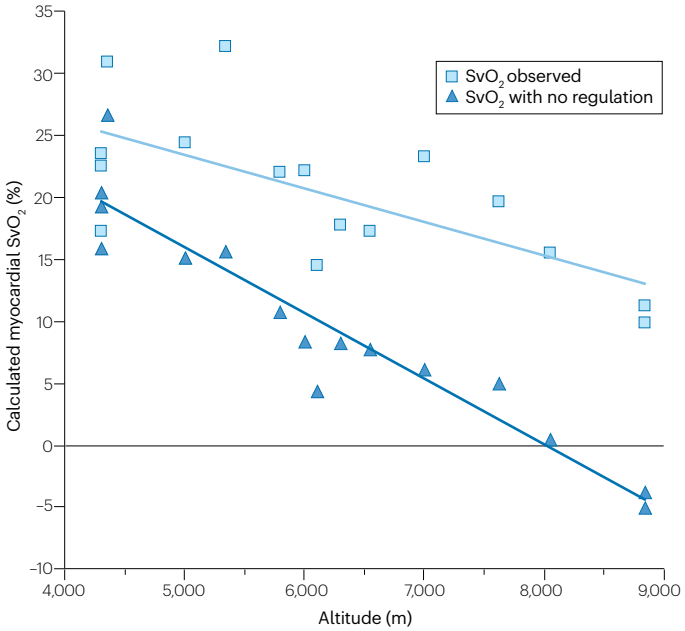

Fig. 6 | Myocardial venous oxygen saturation at maximal exercise with and without autoregulation of maximal heart rate. The graph shows the calculated values of myocardial venous oxygen saturation (SvO_2) during maximal exercise as a function of altitude. The dark blue triangles show SvO_2 values re-calculated using the observed SvO_2 data (light blue squares), assuming that the value of maximal heart rate at altitude is identical to that at sea level. The decrease in maximal heart rate with increasing altitude limits cardiac oxygen consumption when oxygen availability is reduced, protecting the heart against ischaemic events. In the hypothesis of no decrease in maximal heart rate (dark blue triangles), myocardial SvO_2 would become negative at 8,000 m and above. Adapted from ref. 22, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

<35%, with no cardiac events being reported[128–130]. On the basis of these studies, recommendations about travel to altitude for these patients depends on the NYHA score — no altitude for NYHA class IV, up to 3,000 m for NYHA class III and up to 3,500 m for NYHA classes I and II[122].

Arrhythmias. Although no specific data are available about the occurrence of arrhythmias at high altitude, it is reasonable to assume that the association between hypoxaemia and increase in adrenergic activity could induce arrhythmias. Therefore, recommendations limit altitude travel to 3,500 m for patients with serious ventricular arrhythmias[121].

Congenital heart diseases. Patients with cyanotic heart disease or right-to-left shunt (aggravated by pulmonary hypertension and increased right heart pressures) experience severe hypoxaemia at high altitudes. Therefore, travel to these regions should be avoided, unless the patient has been surgically treated[131]. Case reports of patients with patent foramen ovale suggest that right-to-left shunt might be aggravated at high altitude, and exercise-induced arterial oxygen desaturation could, therefore, be a risk factor for HAPE[132].

Systemic hypertension. As discussed earlier, the systemic circulation is exposed to the opposing effects of centrally mediated vasoconstriction and locally mediated vasodilatation. The overall effect on blood pressure largely depends on the duration of exposure and individual susceptibility[61]. Although some studies[133,134] have shown a greater increase in blood pressure at altitude in patients with hypertension than in healthy individuals, other studies have not[60,66]. To our knowledge, there is no evidence in the literature restricting travel to altitude in patients with stable hypertension. Recommendations to avoid high altitude apply only to patients with uncontrolled or severe hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg).

Pulmonary hypertension. Given that hypoxic pulmonary vasoconstriction occurs in all individuals exposed to high altitude, patients with pre-existing pulmonary hypertension are at high risk of right heart dysfunction or HAPE[135,136]. However, one randomized pilot study showed that patients with pulmonary hypertension can safely adapt to an altitude of 2,000 m[137]. The recommendation is to avoid travel to altitudes above 2,000 m and to use supplemental oxygen if such travel cannot be avoided.

Hypoxic preconditioning

Hypoxic preconditioning refers to exposure to moderate hypoxia with the aim of increasing resistance to subsequent severe hypoxia, and interest in the application of this technique in health and disease is growing[138]. Specific protocols that modulate stress level, duration of exposure and whether hypoxia is continuous or intermittent have revealed some positive effects of hypoxic preconditioning in a wide spectrum of pathologies, including age-dependent neurodegeneration[139], cerebral ischaemia[140,141], hypertension[142], obstructive sleep apnoea[143] and metabolic diseases[144,145]. Hypoxic preconditioning can be performed in actual high-altitude conditions, but individual control of physiological responses can be improved in simulated conditions, such as in normobaric rooms or tents.

Evidence for the beneficial effects of moderate hypoxia comes from epidemiological data in populations living permanently at moderate altitudes (~2,000–2,500 m), who have lower cardiovascular mortality that populations living at sea level[146–148]. Other chronic diseases, such as dyslipidaemia[149] and diabetes[150], also have a reduced prevalence at altitude; however, mortality from chronic obstructive pulmonary disease has been reported to be increased at high altitude[151].

Evidence for the benefits of hypoxic preconditioning for CVD is accumulating[152,153]. Among six male patients with CAD, myocardial perfusion was increased after progressive intermittent hypoxia (4,200 m

Glossary

Anoxia
The absence of oxygen from the tissues of a living organism.

Duration of exposure to hypoxia
Acute: minutes or hours; prolonged: days or weeks; chronic: months, years or lifetime.

Hypobaric hypoxia
Decrease in oxygen pressure owing to a decrease in barometric pressure.

Hypoxaemia
Decrease in oxygen pressure in blood compared with normal value at sea level (100 mmHg).

Hypoxia
Decrease in oxygen pressure in a given milieu (such as ambient air, lung alveoli, blood or cells).

Normobaric hypoxia
Decrease in oxygen pressure owing to a decrease in the fraction of oxygen in the inspired air.

over 14 days)[154]. Moreover, short-term intermittent hypoxia (14–10% oxygen over 21 days) increased aerobic capacity and exercise tolerance in 16 men aged 50–70 years with CAD[155]. Intermittent hypoxia (2,700 m over 22 days) increased cardiorespiratory capacity, exercise tolerance and quality of life in patients with severe heart failure[156]. Importantly, no adverse effects occurred among 45 patients with stable ischaemic LV dysfunction exposed to altitudes up to 3,000 m, although their maximal exercise capacity was reduced[128,130].

The underlying mechanisms of hypoxic preconditioning are not yet fully understood, but could involve several distinct processes and their potential interactions, through changes in HIF1 and its target genes[7]. Possible processes involved include neuroprotection and cardioprotection[157,158], NO synthesis and mitochondrial function[159], downregulation of apoptosis[160], erythropoietin-related protection[161,162], ROS formation[61] and upregulation of angiogenic growth factor[7,163–165].

The obstructive sleep apnoea syndrome, an existing pathological model of intermittent hypoxia, could help to adjust future modalities of hypoxic preconditioning. When apnoeas are brief (<60 s), recurrent cycles of hypoxia–reoxygenation lead to a marked decrease in SaO_2, an exacerbation of sympathetic activation and subsequent cardiovascular dysfunction[166]. By contrast, preliminary studies on the positive effects of intermittent hypoxia rely on a more moderate hypoxic stress during longer intervals, which could provide useful guidelines for further investigations[138,142,167,168]. Additional metrics could be used to accurately quantify the 'hypoxic load' experienced by patients or healthy individuals in a hypoxic environment. The most widely used assessment is to integrate the FiO_2 curve over time. Although simple to implement, this method does not represent tissue oxygenation at a cellular level during hypoxia. Although not perfect, a similar approach using the integration of SpO_2 over time would be closer to physiological reality and would eliminate the effects of chronic adaptation to hypoxia during hypoxic protocols[169].

Conclusions

Travel to high altitude exposes an individual to hypoxia. However, advances in high-altitude research have demonstrated that the cardiovascular system deploys some efficient mechanisms of acclimatization to oxygen deprivation, and the healthy heart adapts to hypoxia, even when severe, with preservation of systolic function and only minor impairment of LV and RV diastolic function. With acclimatization, desensitization of the adrenergic system, together with an increased parasympathetic influence, leads to a decrease in maximal heart rate and protection of the myocardium against potentially harmful energy disequilibrium. In the peripheral and pulmonary circulations, hypoxia induces vasodilatation and vasoconstriction, respectively, leading to minimal changes in systemic blood pressure but an increase in PAP that can contribute to high-altitude pulmonary oedema.

Permanent exposure to hypoxia, as in natives of high-altitude environments, can lead to CMS characterized by excessive polycythaemia, which is frequently associated with pulmonary hypertension and heart failure. Genetic studies have revealed protective adaptations of some populations (such as Tibetans and Ethiopians) to these pathological manifestations. Altogether, adaptation to hypoxic constraints is achieved through a balance between activation of compensatory mechanisms (such as hyperventilation, tachycardia and erythropoiesis) through upregulation mechanisms and inhibition of neurohormonal or humoral factors (such as G-protein-coupled receptors, NO and the RAAS), protecting the organism from high-energy-consuming processes[170] (Fig. 7). Although this complex system can fail and lead to pathological manifestations, it constitutes a remarkable example of homeodynamics that warrants further exploration, especially to unravel the molecular mechanisms underlying these adaptation processes.

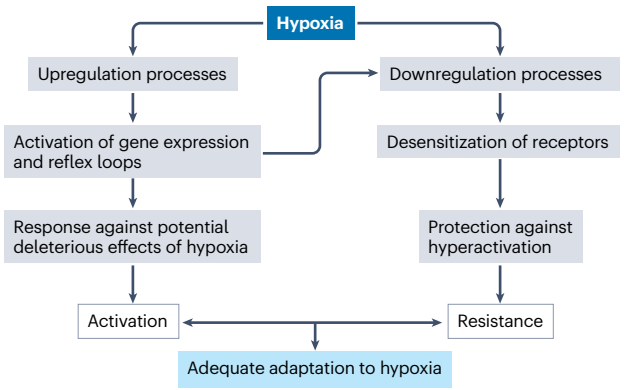

Fig. 7 | Processes of adaptation to hypoxia. Exposure of individuals to acute hypoxia activates the expression of genes and reflex loops (such as chemoreflex-induced hyperventilation or tachycardia) to maintain an adequate supply of oxygen to the cells. Although some of these reactions to hypoxia can be harmful, desensitization (downregulation) processes occur to limit the negative effects of some of the acute reactions to hypoxia. A balance between activation and resistance processes leads to adaptation to hypoxia. Adapted with permission from ref. 174, © 2017 Elsevier Masson SAS,all rights reserved.

Our improved understanding of the effect of altitude hypoxia on the cardiovascular system will allow better documented and evidence-based advice to patients with pre-existing CVDs. All CVDs are aggravated by increased adrenergic activity or associated with pulmonary hypertension, and hypoxaemia (right-to-left shunt) will also be exacerbated. Moderate altitude, up to 2,500 m, does not seem to be harmful for most patients with CVD. However, as altitude increases, patients will present an ischaemic threshold for a lower power output during exercise. Progressive acclimatization is necessary to avoid acute adverse effects on the cardiovascular system, and advice should be given in the context of disease severity and the expected level of exercise intensity. Intermittent exposure to moderate hypoxia might have a beneficial effect in patients with CAD or heart failure. However, future research is needed to define more precisely the indications, contraindications and modalities of pre-exposure to hypoxia in these patients.

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The authors contributed substantially to all aspects of the article.

Competing interests

The authors declare no competing interests.

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