



HAL
open science

Cardiovascular physiology and pathophysiology at high altitude

Jean-Paul Richalet, Eric Hermand, François Lhuissier

► **To cite this version:**

Jean-Paul Richalet, Eric Hermand, François Lhuissier. Cardiovascular physiology and pathophysiology at high altitude. *Nature Reviews Cardiology*, 2023, 10.1038/s41569-023-00924-9 . hal-04243067

HAL Id: hal-04243067

<https://hal.science/hal-04243067v1>

Submitted on 17 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Cardiovascular physiology and pathophysiology at high altitude

Jean-Paul Richalet, Eric Hermand & François J. Lhuissier

¹Hypoxie et Poumon, Université Sorbonne Paris Nord, INSERM U1272, Paris, France.

²Unité de Recherche Pluridisciplinaire Sport Santé Société, ULR 7369-URePSSS, Université Littoral Côte d'Opale, Université Artois, Université Lille, CHU Lille, Dunkirk, France.

e-mail: richalet@univ-paris13.fr

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.

33 **Key points**

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

50

51 **Introduction**

52 The term hypoxia has arisen in the public sphere for two reasons in the past 5 years — the awarding of
53 the Nobel Prize in Physiology or Medicine to Kaelin, Ratcliffe and Semenza in 2019 for "their
54 discoveries of how cells sense and adapt to oxygen availability" and in the context of the coronavirus
55 2019 (COVID-19) pandemic. In the academic environment, hypoxia is an active topic of research. In
56 April 2023, the search term 'hypoxia' produced more than 184,000 results in the PubMed database, with
57 the first dating from 1945 (ref. 1). However, interest in the effects of oxygen deprivation on living
58 organisms began in the mid-nineteenth century, when scientists working in high-altitude regions mainly
59 used the terms anoxia or anoxaemia. A clear, clinical distinction between anoxia and hypoxia was first
60 made by Carl Wiggers in 1941 (ref. 2). Hypoxia is a decrease in oxygen and is variable with time and
61 localization in the body, whereas anoxia is the absence of oxygen. This contrast illustrates the concept of
62 homeodynamics that defines living organisms as complex systems in a state of permanent instability,
63 exposed to environmental and internal perturbations³.

64 High-altitude environments are characterized by various physical constraints, including cold temperatures
65 and an increased level of ultraviolet radiation. However, the most demanding condition is hypoxia owing
66 to the progressive decline in barometric pressure (Fig. 1). The oxygen pressure in the inspired air (P_{iO_2}) is
67 given by the following equation: $P_{iO_2} = F_{iO_2} \times (P_b - P_{H_2O})$, in which F_{iO_2} is the fraction of oxygen in
68 the inspired air, P_b is the barometric pressure and P_{H_2O} is F_{iO_2} does not depend on altitude and currently
69 equals 0.2093 (20.93%), but this value has fluctuated since the formation of the Earth. For example, 300
70 million years ago, F_{iO_2} was around 0.30 (30%) and this relatively 'hyperoxic' environment favoured the
71 development of large insects without a circulatory system transporting oxygen⁴. Conversely, 250–150
72 million years ago, F_{iO_2} fell to between 0.10 and 0.15 (10–15%). This relatively 'hypoxic' environment
73 might have affected the size and metabolism of living organisms and could even partly explain the
74 concomitant catastrophic mass extinction event at the end of the Triassic period^{4,5}. F_{iO_2} then
75 progressively rose to present-day values. The evolution of F_{iO_2} is interesting and might explain why
76 living organisms have evolved various strategies to cope with hypoxia or hyperoxia.

77 High-altitude regions above 2,500 m are found in South America (Andean countries), North America
78 (Rocky Mountains and Alaska), Europe (Alps and Pyrenees), Africa (Atlas and East African plateaux)
79 and Asia (Himalayas and Tibetan plateau). Isolated peaks >4,000 m above sea level can be found in
80 Antarctica, Indonesia and Japan. Worldwide, more than 40 million people live at altitudes above 2,500 m
81 and are exposed to chronic hypoxia, whereas an undetermined number of people are exposed to acute
82 hypoxia for leisure or work activities. Chronic intermittent hypoxia occurs when an individual spends a
83 few days at high altitude followed by a few days at sea level, and this pattern is repeated regularly, as is
84 the case for miners in South America. Billions of people who travel by air are potentially exposed to a

85 pressurized cabin environment corresponding to a maximum altitude of 2,400 m. Therefore, a wide
86 variety of exposure times — from a few minutes or hours to years — will trigger an array of
87 physiological and pathological responses to hypoxia.

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

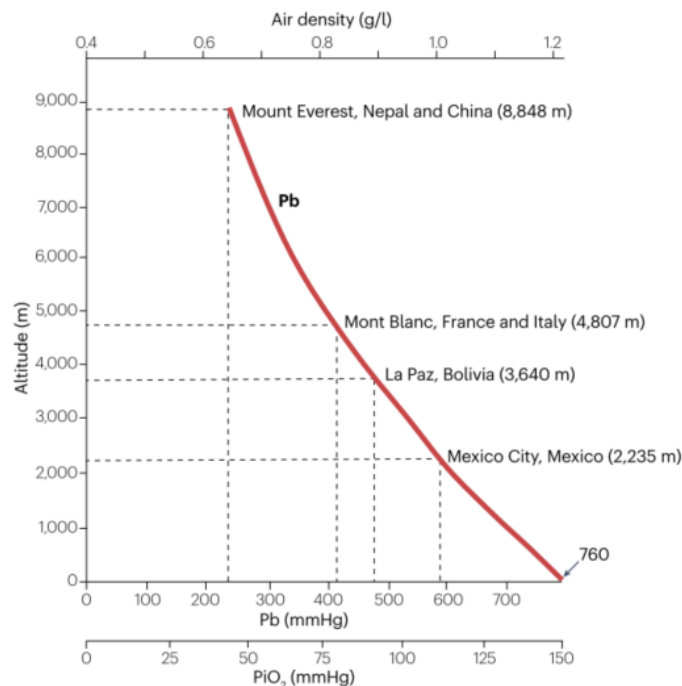


Fig. 1 | Altitude, barometric pressure, air density and inspired oxygen pressure. With increasing altitude, air density, barometric pressure (Pb) and inspired oxygen pressure (PiO₂) decrease. PiO₂ is given by the equation $PiO_2 = FiO_2 \times (Pb - P_{H_2O})$, in which FiO₂ is the fraction of oxygen in the inspired air and P_{H₂O} is the water pressure in the upper airways. P_{H₂O} does not vary with altitude and is equal to 47 mmHg for a body temperature of 37 °C. Similarly, FiO₂ does not vary with altitude and is equal to 0.2093 (20.93%).

94

95

96 **Physiological responses**

97 The physiological effects of hypoxia have been studied using either hypobaric hypoxia (using high-
98 altitude environments or hypobaric chambers) or normobaric hypoxia (by breathing hypoxic gas
99 mixtures). When PiO₂ is the same for each method, no physiologically significant differences between
100 these experimental approaches have been observed⁶.

101 Oxygen is vital for all human cells and, therefore, hypoxic conditions affect all physiological functions.
102 Every cell can be considered to be an oxygen sensor owing to the presence of genetic sequences known as
103 hypoxia-responsive elements. In acute hypoxia (minutes to hours), the activation of these elements

104 triggers the expression of various factors, leading to the stabilization of hypoxia-inducible factors (HIF1,
105 HIF2 and HIF3). In turn, HIFs induce the expression of messengers and hormones (such as
106 erythropoietin, vascular endothelial growth factor and glucose transporters) involved in the physiological
107 response to hypoxia⁷. Cell function can also be directly affected by hypoxia through the activation or
108 inhibition of ion channels, such as K⁺ channels for chemoreceptors and Ca²⁺ channels for smooth muscle
109 cells⁸. Peripheral chemoreceptors are the first sensors to be challenged by a hypoxaemic stimulus,
110 triggering immediate ventilatory (hyperventilation) and cardiac (tachycardia) responses via the medulla
111 oblongata. The vascular response to hypoxia is variable, depending on the site of action. Hypoxia induces
112 vasoconstriction in the pulmonary vessels and vasodilatation in the peripheral circulation (Fig. 2).

113 With prolonged exposure to hypoxia (days to weeks), other adaptive responses occur, such as
114 downregulation of adrenergic receptors, changes in the acid–base balance leading to increased excretion
115 of bicarbonates, stimulation of erythropoiesis via erythropoietin, changes in the secretion of various
116 hormones (for example, an increase in catecholamine and corticosteroids) and inhibition of the renin–
117 angiotensin–aldosterone system (RAAS). These integrated responses (Fig. 2) can preserve sufficient
118 delivery of oxygen to all cells⁹. However, because maximal oxygen consumption during exercise
119 irremediably decreases with increasing altitude, physical performance becomes impaired from ~800 m, at
120 least in endurance-trained athletes¹⁰. Cognitive function also becomes impaired, but only at much higher
121 altitudes (>6,000 m). Despite the rapid and integrated physiological response to hypoxia, if the stimulus is
122 too severe or the metabolic demand too high, the balance between oxygen supply and consumption
123 becomes altered and pathological events can occur. Conditions such as acute mountain sickness and
124 pulmonary or cerebral oedema usually manifest during the first hours or days of exposure to altitude
125 (mainly >2,500 m). The severity of these conditions can vary depending on the peripheral
126 chemosensitivity of an individual to hypoxia¹¹ and the intensity of hypoxia-induced pulmonary
127 hypertension¹².

128 With chronic exposure to hypoxia (months, years or lifetime), stabilized erythropoiesis generally
129 contributes to permanent acclimatization to life in hypoxia. However, in some cases of chronic mountain
130 sickness (CMS; also known as Monge disease), excessive erythropoiesis can lead to an increase in blood
131 viscosity, thrombosis, pulmonary hypertension and heart failure in some natives of high-altitude
132 environments¹³.

133

134 **Cardiovascular responses**

135 The cardiovascular system has a major role in the integrated response to hypoxia (Table 1), involving two
136 mechanisms: centrally mediated activation of the adrenergic system and a direct peripheral effect on the
137 cells of the heart and blood vessels. Activation of medullary adrenergic centres is driven by input from

138 the carotid chemoreceptors that are sensitive to hypoxaemia¹⁴. The whole sympathetic nervous system is
139 activated, as evidenced by an increase in plasma and urine catecholamine concentrations¹⁵. An increase in
140 arterial plasma catecholamine levels has been consistently observed with prolonged hypoxia¹⁶. Activation
141 of the adrenergic system has also been demonstrated by increased activity in the peroneal adrenergic
142 nerves¹⁷.

143 G_s and G_i proteins that couple the β -adrenergic receptors to adenylate cyclase and activate or inhibit
144 this enzyme, respectively, have been shown to have a crucial role in the downregulation of the adrenergic
145 system in hypoxia (Fig. 3). In hypoxia, G_s activity is reduced, whereas G_i expression is increased, leading
146 to inhibition of adenylate cyclase activity and, ultimately, a reduction in ion channel activity and heart
147 rate¹⁸. β -Arrestin 2 could have an important role in regulating pathways involved in the desensitization
148 and internalization of G-protein-coupled receptors observed in hypoxia and has been explored as a
149 potential target for treating heart failure¹⁹. Interestingly, the heart is not the only organ in which hypoxia
150 induces desensitization of G-protein-coupled receptors. Renal handling of calcium by parathormone,
151 control of growth hormone secretion by hypothalamic
152 factors, muscle lactate release and adipose tissue lipolysis are also affected, suggesting a general
153 mechanism of adaptation to hypoxia¹⁴.

154

155 **The heart**

156

157 **Heart rate.**

158 The predominance of the adrenergic system at high altitude has been highlighted by a study of heart rate
159 variability, in which hypoxia induced a decrease in R–R interval and an increase in the low-frequency to
160 high-frequency ratio, an index of sympathovagal balance²⁰. With acute exposure to high altitude, heart
161 rate at rest and after moderate exercise increases and then progressively declines with acclimatization, but
162 never returns to sea-level basal values²¹. The ‘mirror’ pattern of variation in resting heart rate and arterial
163 oxygen saturation (SaO₂) illustrates the close relationship between hypoxaemia and adrenergic activation
164 in acute and prolonged hypoxia (Fig. 4).

165 Although heart rate with moderate exercise initially increases at altitude, heart rate at maximal exercise is
166 slightly reduced in acute hypoxia and decreases significantly with prolonged (>24 h) exposure to high
167 altitude. The decrease in heart rate at maximal exercise has been observed in many studies conducted in
168 the field and in simulated conditions²² (Fig. 5). Both sympathetic and parasympathetic systems have been
169 explored to find a physiological explanation for this decrease in maximal heart rate. The most convincing
170 evidence is that β -adrenergic receptors are downregulated. This mechanism is well known in
171 pharmacology — when an agonist is consistently elevated, the corresponding receptor is downregulated,

172 leading to desensitization of the whole pathway as an adaptive phenomenon against excessive
173 stimulation. Studies in animals^{23–26} and in humans²⁷ have confirmed this hypothesis. Moreover, in a study
174 of six healthy individuals, cardiac uptake of iodine-123 metaiodobenzylguanidine (¹²³I-MIBG) was
175 reduced after 1 week of exposure to an altitude of 4,350 m, supporting the hypothesis that hypoxia
176 reduces adrenergic neurotransmitter reserve in the myocardium and alters endothelial cell function²⁸.

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

185 A model of myocardial oxygenation with exercise at increasing altitudes has demonstrated that the
186 decrease in heart rate at maximal exercise is beneficial — by limiting cardiac oxygen consumption when
187 oxygen availability is reduced, adequate myocardial oxygenation is maintained²² (Fig. 6). This
188 remarkable autoregulation of oxygen handling protects the heart from ischaemic events in extreme
189 conditions in which arterial P_{O_2} is ~30 mmHg (Fig. 4). Indeed, no cases of myocardial infarction or
190 angina pectoris have ever been reported in healthy individuals exercising at altitudes >8,000 m (ref. 33).
191 The preservation of myocardial function in healthy people exposed to hypoxia can be considered in
192 parallel with the use of β -blockers in patients with heart failure. Interestingly, a polymorphism in G-
193 protein-coupled receptor kinase 5 (*GRK5*) that is common among African American individuals improves
194 survival from heart failure, supporting the role of G proteins in the preservation of heart function at high
195 altitude³⁴.

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 $\leq 4,200$ 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 $\leq 3,500$ m above sea level.
- NYHA class III: travel advisable if destination is $\leq 3,000$ 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 $\leq 3,500$ 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.

196

197

198 Cardiac dimensions and function.

199 Cardiac output and stroke volume have been studied in various normobaric and hypobaric hypoxic
200 conditions. Cardiac output increases at altitude, mainly owing to the increase in heart rate. Stroke volume
201 decreases slightly, as measured during Operation Everest II when stroke volume decreased by 14% at rest
202 and after moderate exercise (60 W) at 7,620 m³⁵. This change is not due to a decrease in venous return to
203 the heart, as argued by some researchers³⁶, because blood volume is maintained (the decrease in plasma
204 volume is compensated for by an increase in red cell volume). The decline in stroke volume is actually
205 caused by a slight reduction in the end-diastolic volume of the left ventricle as a consequence of increased
206 pressure in the right ventricle linked to elevated pulmonary artery pressure (PAP). This mechanical effect
207 of high right ventricular (RV) pressure on the interventricular septum can slightly impair left ventricular
208 (LV) filling. However, these mechanisms do not significantly impair cardiac function. Acute moderate
209 normobaric hypoxia ($\text{FiO}_2 = 14.4\%$) has been shown to attenuate exercise-induced increases in stroke
210 volume and cardiac output³⁷. Stroke volume reached a plateau earlier in hypoxia than in normoxia³⁷,
211 suggesting a slight impairment in cardiac filling related to a decrease in LV diastolic function³⁸ or to
212 impaired RV function owing to elevated pulmonary vascular resistance³⁹.

213 In healthy individuals, cardiac inotropic function is not altered at altitude, even at extreme elevations,
214 as shown by normal or even augmented LV ejection fraction^{35,38}. Endurance athletes intermittently
215 exposed (12 h per day for 13 days) to simulated altitude (2,500–3,000 m) showed a slight increase in the
216 ratio of RV-to-LV diameter on echocardiography, suggesting minor RV dilatation without an alteration in
217 contractile function⁴⁰. Among healthy volunteers, LV mass (adjusted for changes in the body surface
218 area) decreased by 11% after a 17-day trek to 5,300 m, but returned to pre-trek values after 6 months⁴¹.

219 No change in LV or RV ejection fraction occurred, but a slight decrease in diastolic function was
220 reported⁴¹. In Chilean soldiers⁴² and miners⁴³ intermittently exposed to altitudes between 3,550 m and
221 4,600 m for 2.5–12.0 years, minor RV hypertrophy was observed and PAP was elevated (>25 mmHg in
222 4% of the military population). During a simulation of ascent to 8,848 m (Operation Everest III (COMEX
223 '97)), cardiac function was assessed using a combination of M-mode and 2D echocardiography, with
224 continuous and pulsed Doppler at 5,000, 7,000 and 8,000 m⁴⁴. On ascent to altitude, aortic, left atrial and
225 LV end-systolic diameter fell regularly. Mitral peak *E* velocity decreased, peak *A* velocity increased and
226 the *E/A* ratio decreased. Systolic PAP showed a progressive and constant increase up to 40 mmHg at
227 8,000 m⁴⁴. This study confirmed the elevation of PAP and the preservation of LV contractility at high
228 altitude. A modification in LV filling pattern was observed, with decreased early filling and an increased
229 contribution from atrial contraction, without elevation of LV end-diastolic pressure³⁸. In another study,
230 lowlanders arriving at high altitude (3,750 m) had an increase in mean PAP (13–22 mmHg) and altered
231 RV and LV diastolic function, although RV systolic function was maintained⁴⁵. After a 10-day period of
232 acclimatization to high altitude, PAP (measured at 4,850 m) increased slightly (26 mmHg) without further
233 changes in cardiac function. These observations confirm that healthy individuals exposed to mild
234 hypoxia-induced pulmonary hypertension maintain systolic function, despite a slight impairment in
235 ventricular filling mechanisms.

236 Cardiac electrical activity is not significantly modified by exposure to hypoxia in healthy individuals.
237 However, a decrease in the amplitude of QRS and T waves on the electrocardiogram has been observed
238 during moderate exercise in hypoxia, when compared with normoxia for the same heart rate⁴⁶. These
239 changes have no clinical implication but might reflect a slight hypoxia-induced decrease in ion exchange
240 in cardiomyocytes.

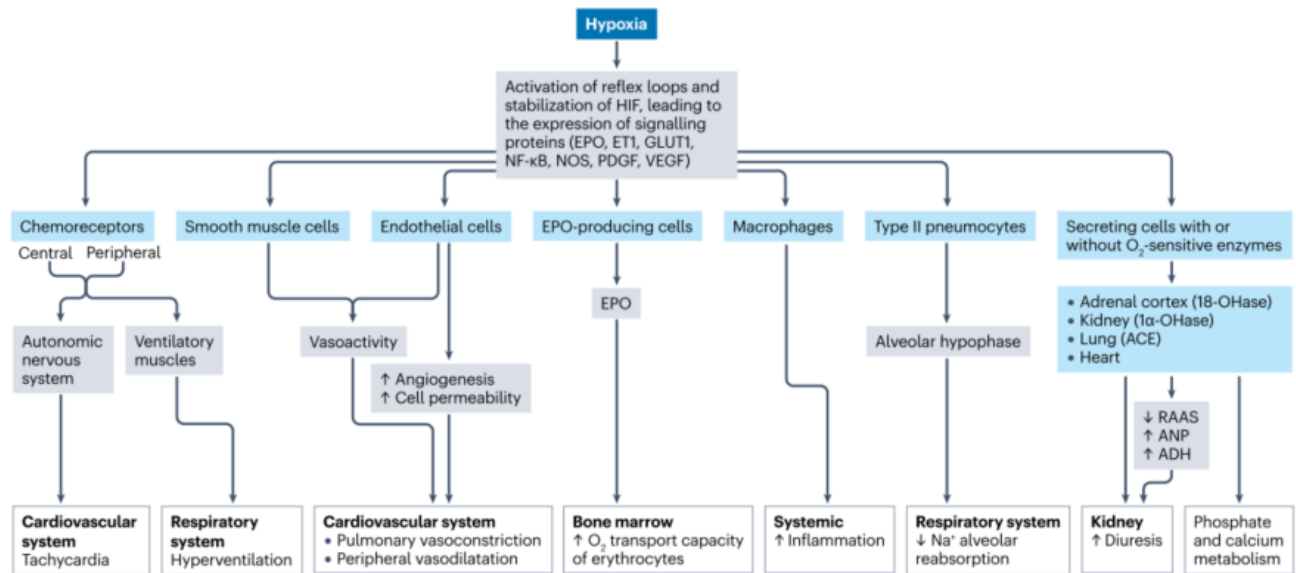


Fig. 2 | Physiological effects of acute hypoxia. Hypoxia induces the expression and translation of genes with hypoxia-responsive elements, which in turn trigger the expression of various factors that lead to the stabilization of hypoxia-inducible factors (HIFs). HIFs can induce the production of messengers or hormones involved in physiological reactions to hypoxia, such as erythropoietin (EPO), endothelin 1 (ET1), glucose transporters (such as GLUT1), nuclear factor- κ B (NF- κ B), 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.

241
242

243 **Myocardial circulation.**

244 As discussed, the healthy myocardium shows remarkable adaptation to hypoxia via a reduction in
245 maximal heart rate. In addition, hypoxia-induced coronary vasodilatation occurs, mediated by vasoactive
246 metabolites (such as adenosine and nitric oxide (NO)) or by proton accumulation⁴⁷. A coronary flow
247 reserve of 35% was found at maximal exercise in 12 healthy individuals breathing 12% oxygen
248 (equivalent to an altitude of 4,650 m), although 1% of energy demand was covered by anaerobic
249 metabolism⁴⁸. In another study, during moderate exercise (83 W) at 4,500 m, coronary reserve was
250 preserved among 10 healthy individuals, but was reduced by 18% in 8 patients with coronary artery
251 disease (CAD)⁴⁹.

252

253 **Systemic blood pressure**

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

260 The effect of acute hypoxia on blood pressure illustrates these dichotomic responses between central and

261 peripheral mechanisms. Hypoxia-induced activation of the autonomic nervous system is a potent activator
262 of central sympathetic activity, triggered by augmented oxygen-related activity of the carotid
263 chemoreceptors^{50,51}, which in turn induces a peripheral vasoconstrictor response via sympathetic-
264 dependent contraction of vascular smooth muscle cells⁵¹. This centrally mediated mechanism is
265 counterbalanced by the peripheral action of hypoxaemia, which stimulates the production and release of
266 local vasodilatory factors such as endothelial NO⁵²⁻⁵⁴, thereby promoting global vasodilatation in various
267 (coronary, cerebral, splanchnic and skeletal) vascular beds⁵⁵. In clinical tests performed to predict
268 susceptibility to acute mountain sickness, a slight rise in systemic blood pressure was observed in hypoxia
269 (FiO₂ = 11.5%), compared with normoxia, for the same level of exercise intensity⁵⁶⁻⁵⁸. However, a
270 concomitant increase in heart rate also occurred, under the influence of hypoxia-dependent sympathetic
271 activation, leading to an increase in cardiac output⁵⁹ and masking the effects of hypoxia on centrally and
272 peripherally driven blood pressure. Therefore, during steady-state exercise at moderate intensity, despite
273 the increase in blood pressure during hypoxia (versus normoxia) for a given power (watts), blood pressure
274 was lower in hypoxia (versus normoxia) for a given heart rate, when ‘clamping’ the adrenergic drive⁶⁰.
275 This finding confirms the superior effect of peripheral vasodilatory mechanisms over centrally driven
276 vasoconstriction on blood pressure. Adding physiological stress (such as exercise) to existing
277 environmental stress leads to a further ‘compensatory’ systemic vasodilatation. These concomitant
278 mechanisms seem to provide superior outcomes compared with exercise-induced or hypoxia-dependent
279 vasodilatation alone⁵⁵.

280 Chronic exposure (months, years or lifetime) to high altitude requires multiple, additional
281 physiological adaptations, which vary depending on the environment (such as altitude and climate) and
282 the individual (genetics, lifestyle, socioeconomic factors and acclimatization)⁶¹. For example, in some
283 studies, long term exposure to high altitude leads to a persistent increase in blood pressure^{59,62-65}, whereas
284 in other studies, blood pressure remained stable⁶⁶ or even decreased⁶⁷. In general, peripheral
285 vasodilatation is crucial to preserve the blood flow to oxygen-demanding muscles in hypoxia in the
286 presence of centrally driven vasoconstriction.

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.

287

288

289 **The peripheral circulation**

290 **Lungs.**

291 Within minutes of exposure to hypoxia, pulmonary vasoconstriction leads to a rapid increase in
 292 pulmonary vascular resistance and mean PAP^{68,69}. Exercise aggravates the hypoxia-induced increase in
 293 pressure, which reaches 54 mmHg during maximal exercise at 8,848 m⁷⁰. Pulmonary vasoconstriction
 294 involves inhibition of oxygen-sensitive K⁺ channels, leading to depolarization of pulmonary artery
 295 smooth muscle cells and activation of voltage-gated Ca²⁺ channels, Ca²⁺ influx and vasoconstriction⁷¹.
 296 This process is immediately reversed by breathing oxygen. However, lowlanders exposed to high altitude
 297 for 2–3 weeks develop pulmonary hypertension that is not completely reversed by breathing oxygen⁷⁰,
 298 suggesting vascular remodelling of the pulmonary arterioles. This process involves the proliferation of
 299 smooth muscle cells and thickening of the artery wall⁷². Pulmonary hypertension not only affects RV
 300 function⁷³ but also limits exercise performance⁷⁴.

301

302 **Kidneys.**

303 The effects of acute hypoxia on renal plasma flow and glomerular filtration rate are limited. However,
 304 urine flow increases, probably through a combined effect of adrenergic stimulation and inhibition of the
 305 RAAS^{75,76}. Hypocapnia and alkalosis, resulting from hypoxia-induced hyperventilation, have an
 306 important effect on renal physiology by inducing a large increase in bicarbonate excretion. In a study
 307 from the Global REACH 2018 expedition, renal blood flow decreased by 14% after 1 day of exposure to
 308 4,330 m, but was restored after 1 week of acclimatization, whereas glomerular filtration rate remained
 309 lower than that at sea level⁷⁷. With prolonged hypoxia, as haematocrit and blood viscosity increased,

310 effective renal plasma flow decreased by 38% at 5,800 m (ref. 78) and by 39% at 6,542 m, whereas renal
311 blood flow decreased by only 24% (ref. 79). In natives of high-altitude environments, a more severe
312 reduction in renal plasma flow is observed, especially in patients with CMS⁸⁰.

313

314 **Brain.**

315 Cerebral blood flow increases with acute hypoxia. However, because hypoxia induces hyperventilation,
316 the resulting hypocapnia has a direct vasoconstricting effect on the cerebral circulation, and cerebral
317 blood flow returns to normal sea-level values after a few hours or days of hypoxic exposure⁸¹. At 8,000
318 m, a decrease in the transient hyperaemic cerebrovascular response has been observed, suggesting
319 impaired cerebral autoregulation that could have a role in the genesis of the acute neurological deficits
320 observed at extreme altitude⁸².

321

322 **Skeletal muscle.**

323 Exercising promotes various muscular vasodilatory processes, particularly by blunting sympathetic α -
324 adrenergic vasoconstriction and inducing the release of NO⁵⁵. This response during exercise
325 in hypoxic conditions compensates for the increased sympathetic vasoconstrictor activity directed towards
326 skeletal muscle⁸³. Although the specific mechanisms of this effect are not fully understood, they are
327 thought to involve increased vasodilatation rather than reduced vasoconstriction in active locomotor
328 muscles⁵⁵. Other postulated mechanisms include augmented NO release, through β -adrenergic receptors
329 in the exercising limb^{84,85}, directly from the endothelium⁸⁶ or via shear stress activation of endothelial
330 cells⁸⁷. Adenosine might also contribute to the regulation of skeletal muscle blood flow by stimulating
331 prostaglandin and NO synthesis⁸⁸. These processes might be modulated by exercise intensity, the severity
332 and the duration of exposure to hypoxia, and by the mobilized muscle mass⁵⁵.

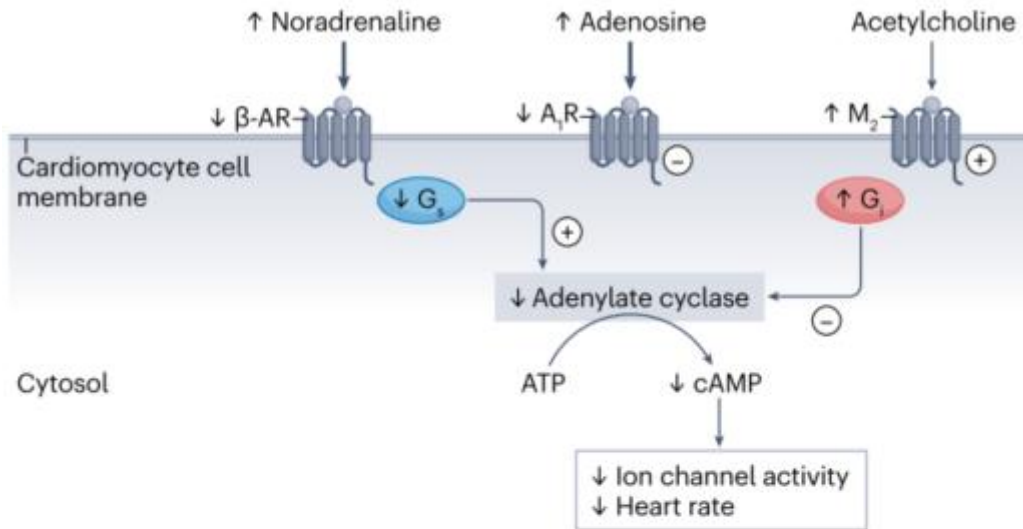


Fig. 3 | Effects of hypoxia on cardiomyocytes. Hypoxia induces an increase in the systemic levels of the agonists noradrenaline and adenosine. The increased noradrenaline and adenosine signalling in cardiomyocytes results in downregulation of β -adrenergic receptors (β -ARs) and the adenosine A_1 receptor (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.

333
334

335 **Adaptation in high-altitude natives**

336 Cardiovascular adaptations to altitude in humans have been built through genetic modifications over
 337 millions of years of evolution. However, some individuals living at high altitude still manifest deleterious
 338 responses to hypoxia and develop conditions such as CMS. Strategies for adaptation to permanent living at
 339 high altitude differ according to the population and geographical region. Indigenous Tibetans, who have
 340 lived above 4,000 m for more than 40,000 years, seem to have the best profile of genetic adaptation to
 341 chronic hypoxia through changes in *HIF2* and *EGLN1* (also known as *PHD2*)⁸⁹. This population has low
 342 SaO_2 , but no excessive erythrocytosis or pulmonary hypertension. East African highlanders have
 343 haemoglobin and SaO_2 levels similar to those of sea-level natives⁹⁰, and their phenotypic adaptation to
 344 high altitude is still under investigation. Andeans, whose residence at high altitude dates to around 12,000
 345 years ago, have a mixed genetic profile, with ethnic admixture with Europeans since the sixteenth
 346 century⁹¹. Therefore, this population does not have a clear genetic advantage for living at high altitude,
 347 with low SaO_2 , high haemoglobin levels, elevated PAP and RV hypertrophy⁹². In a study of native
 348 residents of La Paz, Bolivia (3,500–4,100 m), pulmonary artery hypertension was reversed after
 349 prolonged residence at sea level or treatment with nifedipine⁹³.

350 A substantial proportion of the Andean population (15% in Cerro de Pasco, Peru; 4,300 m) develops
351 CMS¹³. This condition is characterized by excessive erythropoiesis and, sometimes, pulmonary
352 hypertension that can evolve towards right and global heart failure⁹⁴. Patients with CMS from Cerro de
353 Pasco have elevated mean PAP (34 mmHg) when compared with healthy high-altitude natives (25
354 mmHg) and sea-level residents (19 mmHg)⁹⁵. These patients also have RV enlargement but do not
355 develop impaired ejection fraction. However, the RV Tei index (myocardial performance index) was
356 increased in patients with CMS and in healthy high-altitude residents, suggesting early impairment of RV
357 function⁹⁵. Moreover, patients with CMS seem to be at increased risk of developing cardiovascular events
358 compared with their healthy counterparts⁹⁶. In another study, a decrease in RV function at rest and during
359 exercise was also found in patients with CMS from La Paz when compared with healthy high-altitude
360 residents⁹⁷. However, the researchers suggest that the lower resting values for RV function in patients
361 with CMS could represent a physiological adaptation to chronic hypoxic conditions rather than impaired
362 RV function.

363 In Peruvian high-altitude natives, peripheral chemoreceptors can develop hyperplasia with ageing, leading
364 to a blunted ventilatory response to hypoxia^{13,98}. Adrenergic activity was found to be increased, but β -
365 adrenergic receptors were downregulated, similar to findings from sea-level natives exposed to prolonged
366 hypoxia⁹⁹. Plasma erythropoietin and soluble transferrin receptors are elevated, in line with excessive
367 erythropoiesis, resulting in frequent episodes of sleep apnoea and nocturnal oxygen desaturation. These
368 changes are reversed by administration of the carbonic anhydrase inhibitor acetazolamide¹⁰⁰. Systemic
369 arterial pressure has been studied in various high-altitude populations¹⁰¹. Native Tibetans have a higher
370 prevalence of hypertension than Han Chinese people living at the same altitude, perhaps because of
371 differences in genetics or nutrition¹⁰². Studies in Peruvian miners permanently living and working above
372 5,000 m showed normal blood pressure (continuously monitored over 24 h), despite a higher blood
373 viscosity owing to a high haematocrit (>60%)¹⁰³. Moreover, Andean natives with CMS do not have an
374 excessive prevalence of hypertension⁹⁴. This finding raises the question of whether the peripheral
375 vasodilatory mechanisms that occur during acute hypoxia persist in chronic hypoxia. The data are scarce
376 but indicate that these mechanisms are still present in native Tibetans, especially through augmented
377 endothelial NO production¹⁰⁴. However, the response might vary according to ethnicity, because NO-
378 mediated cutaneous vasodilatation was found to be reduced in Peruvian high-altitude residents^{104,105}.
379 Other mechanisms of peripheral vasodilatation are still to be unravelled, but could include dampening of
380 the vasodilatory effect of ATP or adenosine¹⁶ and excessive blood viscosity¹⁰⁶.

381 Genetic studies of high-altitude populations have been developed with two objectives: first, to identify
382 specific mutations that confer an evolutionary advantage for living at high altitude (comparing Andeans,
383 Tibetans or Ethiopians with sea-level natives); and second, to characterize genetic risk factors among

384 high-altitude natives who develop CMS. More than 1,000 genes encoding proteins involved in the
 385 circulatory system, angiogenesis, erythropoiesis and oxygen transport could be associated with adaptation
 386 or maladaptation to high altitude^{89,107,108}. In genome-wide association studies, the specific allele
 387 frequency of several HIF pathway genes involved in the Tibetan pattern of adaptation, including *EPAS1*
 388 and *EGLN1*, has been identified that might contribute to the low haemoglobin concentration observed in
 389 Tibetans^{109–111}. In Andeans, genetic studies suggest that positive selection has focused on the NO
 390 pathways and the cardiovascular system¹¹². Studies of Ethiopian adaptation are scarce, but have identified
 391 HIF-mediated oxygen-sensing pathways¹¹³, similar to those found in Tibetans and Andeans, suggesting
 392 convergent evolution in populations living at high altitude. The *VEGFA* gene has been implicated in
 393 cardiovascular maladaptation to hypoxia in Andeans¹¹⁴, and *AEBP2*, which has a role in erythropoiesis,
 394 has also been proposed as a causal gene for CMS¹¹⁵. Other genes, such as the erythropoiesis regulator
 395 *SENPI* and the oncogene *ANP32D*, are also thought to be involved in the development of CMS in
 396 Andeans¹¹⁶.

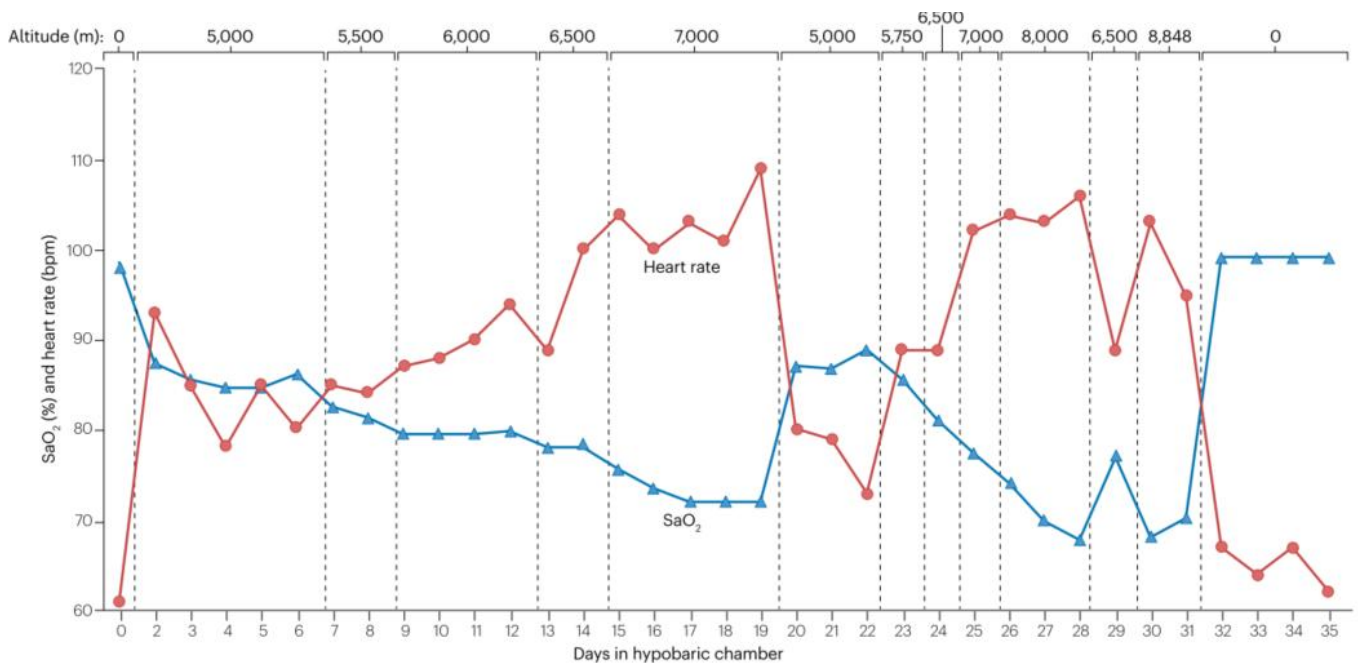


Fig. 4 | Heart rate and arterial oxygen saturation at rest during a simulation of ascent to 8,848 m. The graph shows the heart rate and arterial oxygen saturation (SaO₂) at rest in individuals exposed to simulated altitudes from sea level to 8,848 m in a hypobaric chamber during a simulation of an ascent of

Mount Everest (Operation Everest III; COMEX '97)⁴⁴. The variations in resting heart rate and SaO₂ mirror each other, illustrating the tight relationship between hypoxaemia and adrenergic activation in acute and prolonged hypoxia.

397
398

399 High altitude and cardiovascular disease

400 Acute altitude illnesses: is the heart involved?

401 One of the first descriptions of acute forms of mountain sickness, proposed by Ravenhill¹¹⁷, mentioned a
 402 'cardiac form of altitude illness' to describe what would later be called 'high-altitude pulmonary oedema'
 403 (HAPE) by Houston¹¹⁸. However, the heart is not involved in any manifestation of altitude illnesses —
 404 acute mountain sickness, HAPE or high-altitude cerebral oedema. From the circulatory viewpoint,

405 hypoxia-induced vascular leak is a common feature of all forms of altitude illnesses, owing to increased
406 capillary permeability, without any change in blood pressure. The increase in PAP owing to hypoxia-
407 induced pulmonary vasoconstriction is one of the factors involved in the pathophysiology of HAPE,
408 together with endothelial dysfunction, alveolar epithelial dysfunction and inflammatory processes¹¹⁹.
409 Nobody has ever died from heart problems at the summit of Mount Everest (8,849 m), despite extremely
410 low arterial O₂ pressure (~30 mmHg) and high exercise intensities³³, probably because of the remarkable
411 autoprotective physiological process discussed earlier.

412

413 **Advice on pre-existing cardiovascular diseases**

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

421 Although the healthy heart is not directly involved in acute altitude illnesses, high altitudes can be
422 challenging for those with CVD because exercising at a given intensity (such as walking uphill) is more
423 demanding in hypoxia than at sea level. Because of the lower SaO₂ and the lower maximal exercise
424 capacity (VO₂ max) at altitude, the same physical activity requires a greater percentage of VO₂ max and,
425 therefore, a greater percentage of maximal heart rate and maximal cardiac output to deliver the same
426 amount of oxygen to the myocardium¹²³. Therefore, clinical symptoms that would not appear, or appear
427 only during vigorous exercise, in normoxia could emerge during light-to-moderate exercise at high
428 altitude.

429 A basic knowledge of the physiology of hypoxia, and the pathophysiology of CVD, will help
430 clinicians to provide appropriate advice to their patients with CVD before travel to high-altitude regions⁶¹.

431 In general, the risk factors for patients with CVD at high altitude are:

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

437

438 To evaluate the risk associated with a travel to high altitude for a patient with CVD (Box 1), the

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

451

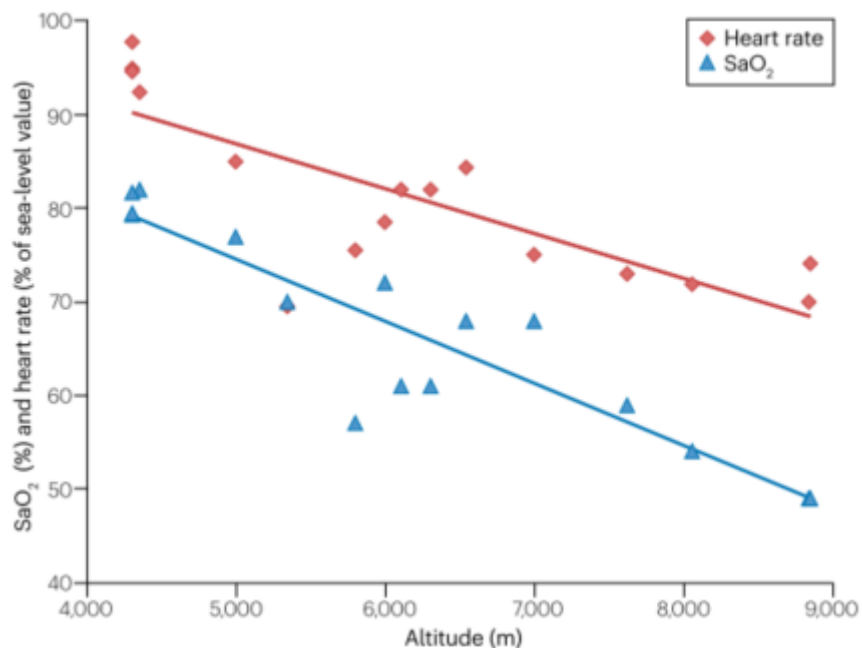


Fig. 5 | Parallel linear decrease in arterial oxygen saturation and heart rate at maximal exercise as a function of altitude. The graph shows the parallel linear decrease in arterial oxygen saturation (SaO₂) and heart rate (% of sea-level values) with increasing altitude during maximal exercise in individuals 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/>).

452

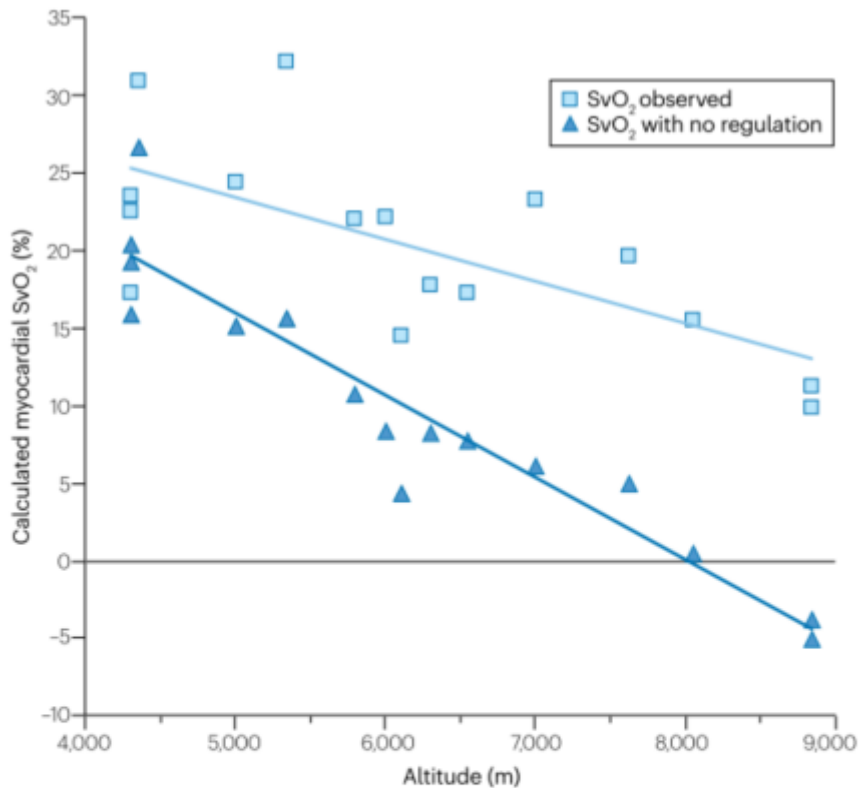


Fig. 6 | Myocardial venous oxygen saturation at maximal exercise with and without autoregulation of maximal heart rate. The graph shows the calculated values of myocardial venous oxygen saturation (SvO₂) during maximal exercise as a function of altitude. The dark blue triangles show SvO₂ values re-calculated using the observed SvO₂ 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 SvO₂ would become negative at 8,000 m and above. Adapted from ref. 22, CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

453

454

455 **Coronary artery disease.**

456 Patients with reduced coronary reserve could be assumed to be at increased risk of myocardial ischaemia
 457 at high altitude. However, no significant differences in symptoms, heart rate or systolic function have
 458 been observed in patients with ischaemic heart disease compared with healthy individuals at 3,454 m¹²⁴ or
 459 4,200 m¹²⁵. The 18% decrease in normal coronary reserve at 2,500 m⁴⁹ should be considered when
 460 interpreting these findings. In a study of nine patients with CAD exercising at 3,100 m, angina, ST
 461 segment depression or both occurred at the same product (heart rate × systolic blood pressure), but at
 462 lower workloads, than at sea level¹²⁶.

463 On the basis of these observations, patients with CAD who no longer show electrocardiogram
 464 abnormalities during an exercise test, at least 6 months after a cardiac event, can travel to altitudes up to
 465 4,200 m (lower in the presence of comorbidities that increase cardiovascular risk). As a precaution,
 466 vigorous exercise at altitude in these patients is contraindicated. Interestingly, one study of healthy

467 individuals exposed to an altitude of 4,559 m showed that acetazolamide increased the subendocardial
468 viability ratio, estimated on the carotid artery using a PulsePen tonometer¹²⁷. This finding suggests a
469 decreased risk of subendocardial ischaemia at altitude in healthy people but remains to be confirmed in
470 patients with ischaemic heart disease.

471

472 **Heart failure.**

473 Some researchers have studied the effects of high altitude (up to 3,454 m) in patients with heart failure
474 with ejection fraction <35%, with no cardiac events being reported¹²⁸⁻¹³⁰. On the basis of these studies,
475 recommendations about travel to altitude for these patients depends on the NYHA score — no altitude for
476 NYHA class IV, up to 3,000 m for NYHA class III and up to 3,500 m for NYHA classes I and II¹²².

477

478 **Arrhythmias.**

479 Although no specific data are available about the occurrence of arrhythmias at high altitude, it is
480 reasonable to assume that the association between hypoxaemia and increase in adrenergic activity could
481 induce arrhythmias. Therefore, recommendations limit altitude travel to 3,500 m for patients with serious
482 ventricular arrhythmias¹²¹.

483

484 **Congenital heart diseases.**

485 Patients with cyanotic heart disease or right-to-left shunt (aggravated by pulmonary hypertension and
486 increased right heart pressures) experience severe hypoxaemia at high altitudes. Therefore, travel to these
487 regions should be avoided, unless the patient has been surgically treated¹³¹. Case reports of patients with
488 patent foramen ovale suggest that right-to-left shunt might be aggravated at high altitude, and exercise-
489 induced arterial oxygen desaturation could, therefore, be a risk factor for HAPE¹³².

490

491 **Systemic hypertension.**

492 As discussed earlier, the systemic circulation is exposed to the opposing effects of centrally mediated
493 vasoconstriction and locally mediated vasodilatation. The overall effect on blood pressure largely depends
494 on the duration of exposure and individual susceptibility⁶¹. Although some studies^{133,134} have shown a
495 greater increase in blood pressure at altitude in patients with hypertension than in healthy individuals,
496 other studies have not^{60,66}. To our knowledge, there is no evidence in the literature restricting travel to
497 altitude in patients with stable hypertension. Recommendations to avoid high altitude apply only to
498 patients with uncontrolled or severe hypertension (systolic blood pressure >180 mmHg and/or diastolic
499 blood pressure >110 mmHg).

500

501 **Pulmonary hypertension.**

502 Given that hypoxic pulmonary vasoconstriction occurs in all individuals exposed to high altitude, patients
503 with pre-existing pulmonary hypertension are at high risk of right heart dysfunction or HAPE^{135,136}.
504 However, one randomized pilot study showed that patients with pulmonary hypertension can safely adapt
505 to an altitude of 2,000 m¹³⁷. The recommendation is to avoid travel to altitudes above 2,000 m and to use
506 supplemental oxygen if such travel cannot be avoided.

507

508 **Hypoxic preconditioning**

509 Hypoxic preconditioning refers to exposure to moderate hypoxia with the aim of increasing resistance to
510 subsequent severe hypoxia, and interest in the application of this technique in health and disease is
511 growing¹³⁸. Specific protocols that modulate stress level, duration of exposure and whether hypoxia is
512 continuous or intermittent have revealed some positive effects of hypoxic preconditioning in a wide
513 spectrum of pathologies, including age-dependent neurodegeneration¹³⁹, cerebral ischaemia^{140,141},
514 hypertension¹⁴², obstructive sleep apnoea¹⁴³ and metabolic diseases^{144,145}. Hypoxic preconditioning can be
515 performed in actual high-altitude conditions, but individual control of physiological responses can be
516 improved in simulated conditions, such as in normobaric rooms or tents.

517 Evidence for the beneficial effects of moderate hypoxia comes from epidemiological data in
518 populations living permanently at moderate altitudes (~2,000–2,500 m), who have lower cardiovascular
519 mortality than populations living at sea level^{146–148}. Other chronic diseases, such as dyslipidaemia¹⁴⁹ and
520 diabetes¹⁵⁰, also have a reduced prevalence at altitude; however, mortality from chronic obstructive
521 pulmonary disease has been reported to be increased at high altitude¹⁵¹. Evidence for the benefits of
522 hypoxic preconditioning for CVD is accumulating^{152,153}. Among six male patients with CAD, myocardial
523 perfusion was increased after progressive intermittent hypoxia (4,200 m over 14 days)¹⁵⁴. Moreover,
524 short-term intermittent hypoxia (14–10% oxygen over 21 days) increased aerobic capacity and exercise
525 tolerance in 16 men aged 50–70 years with CAD¹⁵⁵. Intermittent hypoxia (2,700 m over 22 days)
526 increased cardiorespiratory capacity, exercise tolerance and quality of life in patients with severe heart
527 failure¹⁵⁶. Importantly, no adverse effects occurred among 45 patients with stable ischaemic LV
528 dysfunction exposed to altitudes up to 3,000 m, although their maximal exercise capacity was
529 reduced^{128,130}.

530 The underlying mechanisms of hypoxic preconditioning are not yet fully understood, but could involve
531 several distinct processes and their potential interactions, through changes in HIF1 and its target genes⁷.
532 Possible processes involved include neuroprotection and cardioprotection^{157,158}, NO synthesis and
533 mitochondrial function¹⁵⁹, downregulation of apoptosis¹⁶⁰, erythropoietin-related protection^{161,162}, ROS
534 formation⁶¹ and upregulation of angiogenic growth factor^{7,163–165}. The obstructive sleep apnoea syndrome,

535 an existing pathological model of intermittent hypoxia, could help to adjust future modalities of hypoxic
536 preconditioning. When apnoeas are brief (<60 s), recurrent cycles of hypoxia–reoxygenation lead to a
537 marked decrease in SaO₂, an exacerbation of sympathetic activation and subsequent cardiovascular
538 dysfunction¹⁶⁶. By contrast, preliminary studies on the positive effects of intermittent hypoxia rely on a
539 more moderate hypoxic stress during longer intervals, which could provide useful guidelines for further
540 investigations^{138,142,167,168}. Additional metrics could be used to accurately quantify the ‘hypoxic load’
541 experienced by patients or healthy individuals in a hypoxic environment. The most widely used
542 assessment is to integrate the FiO₂ curve over time. Although simple to implement, this method does not
543 represent tissue oxygenation at a cellular level during hypoxia. Although not perfect, a similar approach
544 using the integration of SpO₂ over time would be closer to physiological reality and would eliminate the
545 effects of chronic adaptation to hypoxia during hypoxic protocols¹⁶⁹.

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.

546

547

548 **Conclusions**

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

558 Permanent exposure to hypoxia, as in natives of high-altitude environments, can lead to CMS
559 characterized by excessive polycythaemia, which is frequently associated with pulmonary hypertension
560 and heart failure. Genetic studies have revealed protective adaptations of some populations (such as

561 Tibetans and Ethiopians) to these pathological manifestations. Altogether, adaptation to hypoxic
562 constraints is achieved through a balance between activation of compensatory mechanisms (such as
563 hyperventilation, tachycardia and erythropoiesis) through upregulation mechanisms and inhibition of
564 neurohormonal or humoral factors (such as G-protein-coupled receptors, NO and the RAAS), protecting
565 the organism from high-energy-consuming processes¹⁷⁰ (Fig. 7). Although this complex system can fail
566 and lead to pathological manifestations, it constitutes a remarkable example of homeodynamics that
567 warrants further exploration, especially to unravel the molecular mechanisms underlying these adaptation
568 processes.

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

580

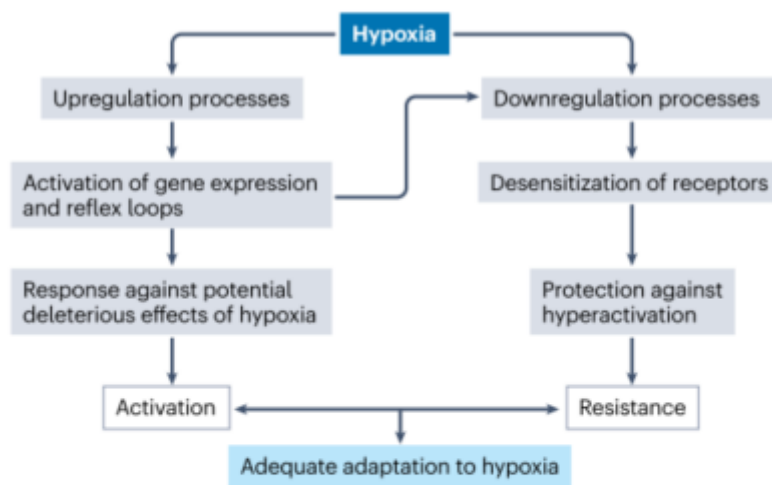


Fig. 7 | Processes of adaptation to hypoxia. Exposure of individuals to acute hypoxia activates the expression of genes and reflex loops (such as chemoreflex-induced hyperventilation or tachycardia) to maintain an adequate supply of oxygen to the cells. Although some of these reactions to hypoxia can 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.

581

582 **References**

- 583 1 Pace, N., Consolazio, W. V. & Lozner, E. L. The effect of transfusions of red blood cells on the
584 hypoxia tolerance of normal men. *Science* 102, 589–591 (1945).
- 585 2 Wiggers, C. J. Cardiac adaptations in acute progressive anoxia. *Ann. Intern. Med.* 14, 1237–1247
586 (1941).
- 587 3 Richalet, J.-P. The invention of hypoxia. *J. Appl. Physiol.* 130, 1573–1582 (2021).
- 588 4 Berner, R. A. Phanerozoic atmospheric oxygen: new results using the GEOCARBSULF model. *Am.*
589 *J. Sci.* 309, 603–606 (2009).
- 590 5 Payne, J. L. et al. The evolutionary consequences of oxygenic photosynthesis: a body size
591 perspective. *Photosynth. Res.* 107, 37–57 (2011).
- 592 6 Saugy, J. J. et al. Same performance changes after live high-train low in normobaric vs. hypobaric
593 hypoxia. *Front. Physiol.* 7, 138 (2016).
- 594 7 Semenza, G. L. Regulation of oxygen homeostasis by hypoxia-inducible factor 1. *Physiology* 24, 97–
595 106 (2009).
- 596 8 Sommer, N., Strielkov, I., Pak, O. & Weissmann, N. Oxygen sensing and signal transduction in
597 hypoxic pulmonary vasoconstriction. *Eur. Respir. J.* 47, 288–303 (2016).
- 598 9 Luks, A. et al. *Ward, Milledge and West's High Altitude Medicine and Physiology* 6th edn (CRC
599 Press, 2021).
- 600 10 Wehrlin, J. P. & Hallén, J. Linear decrease in VO₂max and performance with increasing altitude in
601 endurance athletes. *Eur. J. Appl. Physiol.* 96, 404–412 (2006).
- 602 11 Richalet, J.-P. & Lhuissier, F. J. Aging, tolerance to high altitude, and cardiorespiratory response to
603 hypoxia. *High Alt. Med. Biol.* 16, 117–124 (2015).
- 604 12 Dehnert, C. Identification of individuals susceptible to high-altitude pulmonary oedema at low
605 altitude. *Eur. Respir. J.* 25, 545–551 (2005).
- 606 13 León-Velarde, F. & Richalet, J.-P. Respiratory control in residents at high altitude: physiology and
607 pathophysiology. *High Alt. Med. Biol.* 7, 125–137 (2006).
- 608 14 Richalet, J.-P. in *Hypoxia: Translation in Progress* (eds Roach, R. C., Hackett, P. H. & Wagner, P.
609 D.) Ch. 23, 343–356 (Springer, 2016).
- 610 15 Escourrou, P., Johnson, D. G. & Rowell, L. B. Hypoxemia increases plasma catecholamine
611 concentrations in exercising humans. *J. Appl. Physiol.* 57, 1507–1511 (1984).
- 612 16 Calbet, J. A. L. Chronic hypoxia increases blood pressure and noradrenaline spillover in healthy
613 humans. *J. Physiol.* 551, 379–386 (2003).
- 614 17 Hansen, J. & Sander, M. Sympathetic neural overactivity in healthy humans after prolonged exposure
615 to hypobaric hypoxia. *J. Physiol.* 546, 921–929 (2003).
- 616 18 Kacimi, R. et al. Differential regulation of G protein expression in rat hearts exposed to chronic
617 hypoxia. *Am. J. Physiol. Heart Circ. Physiol.* 269, H1865–H1873 (1995).
- 618 19 Boussi, L. & Frishman, W. H. β -Arrestin as a therapeutic target in heart failure. *Cardiol. Rev.* 29,
619 223–229 (2021).
- 620 20 Cornolo, J., Mollard, P., Brugniaux, J. V., Robach, P. & Richalet, J.-P. Autonomic control of the
621 cardiovascular system during acclimatization to high altitude: effects of sildenafil. *J. Appl. Physiol.*
622 97, 935–940 (2004).
- 623 21 Vogel, J. A. & Harris, C. W. Cardiopulmonary responses of resting man during early exposure to
624 high altitude. *J. Appl. Physiol.* 22, 1124–1128 (1967).
- 625 22 Richalet, J. & Hermand, E. Modeling the oxygen transport to the myocardium at maximal exercise at
626 high altitude. *Physiol. Rep.* 10, e15262 (2022).
- 627 23 Kacimi, R., Richalet, J. P. & Crozatier, B. Hypoxia-induced differential modulation of adenosinergic

- 628 and muscarinic receptors in rat heart. *J. Appl. Physiol.* 75, 1123–1128 (1993).
- 629 24 León-Velarde, F. et al. Hypoxia- and normoxia-induced reversibility of autonomic control in Andean
630 guinea pig heart. *J. Appl. Physiol.* 81, 2229–2234 (1996).
- 631 25 León-Velarde, F. et al. Differential alterations in cardiac adrenergic signaling in chronic hypoxia or
632 norepinephrine infusion. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 280, R274–R281 (2001).
- 633 26 Voelkel, N. F., Hegstrand, L., Reeves, J. T., McMurty, I. F. & Molinoff, P. B. Effects of hypoxia on
634 density of beta-adrenergic receptors. *J. Appl. Physiol.* 50, 363–366 (1981).
- 635 27 Richalet, J. P. et al. Decreased cardiac response to isoproterenol infusion in acute and chronic
636 hypoxia. *J. Appl. Physiol.* 65, 1957–1961 (1988).
- 637 28 Richalet, J. P. et al. MIBG scintigraphic assessment of cardiac adrenergic activity in response to
638 altitude hypoxia. *J. Nucl. Med.* 31, 34–37 (1990).
- 639 29 Boushel, R. et al. Parasympathetic neural activity accounts for the lowering of exercise heart rate at
640 high altitude. *Circulation* 104, 1785–1791 (2001).
- 641 30 Clar, C., Dorrington, K. L., Fatemian, M. & Robbins, P. A. Effects of 8 h of isocapnic hypoxia with
642 and without muscarinic blockade on ventilation and heart rate in humans. *Exp. Physiol.* 86, 529–538
643 (2001).
- 644 31 Hartley, L. H., Vogel, J. A. & Cruz, J. C. Reduction of maximal exercise heart rate at altitude and its
645 reversal with atropine. *J. Appl. Physiol.* 36, 362–365 (1974).
- 646 32 Favret, F., Richalet, J.-P., Henderson, K. K., Germack, R. & Gonzalez, N. C. Myocardial adrenergic
647 and cholinergic receptor function in hypoxia: correlation with O₂ transport in exercise. *Am. J.*
648 *Physiol. Regul. Integr. Comp. Physiol.* 280, R730–R738 (2001).
- 649 33 Basnyat, B., Sill, D. & Gupta, V. Myocardial infarction or high-altitude pulmonary edema?
650 *Wilderness Environ. Med.* 11, 196–198 (2000).
- 651 34 Liggett, S. B. et al. A GRK5 polymorphism that inhibits β -adrenergic receptor signaling is protective
652 in heart failure. *Nat. Med.* 14, 510–517 (2008).
- 653 35 Reeves, J. T. et al. Operation Everest II: preservation of cardiac function at extreme altitude. *J. Appl.*
654 *Physiol.* 63, 531–539 (1987).
- 655 36 Grover, R. F., Weil, J. V. & Reeves, J. T. Cardiovascular adaptation to exercise at high altitude.
656 *Exerc. Sport Sci. Rev.* 14, 269–302 (1986).
- 657 37 Fukuda, T. et al. Effects of acute hypoxia at moderate altitude on stroke volume and cardiac output
658 during exercise. *Int. Heart J.* 51, 170–175 (2010).
- 659 38 Boussuges, A. et al. Operation Everest III (Comex '97): modifications of cardiac function secondary
660 to altitude-induced hypoxia: an echocardiographic and Doppler study. *Am. J. Respir. Crit. Care Med.*
661 161, 264–270 (2000).
- 662 39 Ghofrani, H. A. et al. Sildenafil increased exercise capacity during hypoxia at low altitudes and at
663 Mount Everest Base Camp: a randomized, double-blind, placebo-controlled crossover trial. *Ann.*
664 *Intern. Med.* 141, 169 (2004).
- 665 40 Brugniaux, J. V. et al. Living high-training low: tolerance and acclimatization in elite endurance
666 athletes. *Eur. J. Appl. Physiol.* 96, 66–77 (2006).
- 667 41 Holloway, C. J. et al. Cardiac response to hypobaric hypoxia: persistent changes in cardiac mass,
668 function, and energy metabolism after a trek to Mt. Everest Base Camp. *FASEB J.* 25, 792–796
669 (2011).
- 670 42 Brito, J. et al. Chronic intermittent hypoxia at high altitude exposure for over 12 years: assessment of
671 hematological, cardiovascular, and renal effects. *High Alt. Med. Biol.* 8, 236–244 (2007).
- 672 43 Richalet, J.-P. et al. Chilean miners commuting from sea level to 4500 m: a prospective study. *High*
673 *Alt. Med. Biol.* 3, 159–166 (2002).
- 674 44 Richalet, J.-P. Operation Everest III: COMEX '97. *High Alt. Med. Biol.* 11, 121–132 (2010).

- 675 45 Huez, S., Faoro, V., Guénard, H., Martinot, J.-B. & Naeije, R. Echocardiographic and tissue Doppler
676 imaging of cardiac adaptation to high altitude in native highlanders versus acclimatized lowlanders.
677 *Am. J. Cardiol.* 103, 1605–1609 (2009).
- 678 46 Coustet, B., Lhuissier, F. J., Vincent, R. & Richalet, J.-P. Electrocardiographic changes during
679 exercise in acute hypoxia and susceptibility to severe high-altitude illnesses. *Circulation* 131, 786–
680 794 (2015).
- 681 47 Deussen, A., Ohanyan, V., Jannasch, A., Yin, L. & Chilian, W. Mechanisms of metabolic coronary
682 flow regulation. *J. Mol. Cell Cardiol.* 52, 794–801 (2012).
- 683 48 Grubbström, J., Berglund, B. & Kaijser, L. Myocardial oxygen supply and lactate metabolism during
684 marked arterial hypoxaemia. *Acta Physiol. Scand.* 149, 303–310 (1993).
- 685 49 Wyss, C. A. et al. Influence of altitude exposure on coronary flow reserve. *Circulation* 108, 1202–
686 1207 (2003).
- 687 50 Hainsworth, R., Drinkhill, M. J. & Rivera-Chira, M. The autonomic nervous system at high altitude.
688 *Clin. Auton. Res.* 17, 13–19 (2007).
- 689 51 Bruno, R. M. et al. Sympathetic regulation of vascular function in health and disease. *Front. Physiol.*
690 3, 284 (2012).
- 691 52 Bilo, G. et al. Effects of selective and nonselective beta-blockade on 24-h ambulatory blood pressure
692 under hypobaric hypoxia at altitude. *J. Hypertens.* 29, 380–387 (2011).
- 693 53 Parati, G. et al. Effects of acetazolamide on central blood pressure, peripheral blood pressure, and
694 arterial distensibility at acute high altitude exposure. *Eur. Heart J.* 34, 759–766 (2013).
- 695 54 Parati, G. et al. Changes in 24 h ambulatory blood pressure and effects of angiotensin II receptor
696 blockade during acute and prolonged high-altitude exposure: a randomized clinical trial. *Eur. Heart J.*
697 35, 3113–3122 (2014).
- 698 55 Casey, D. P. & Joyner, M. J. Compensatory vasodilatation during hypoxic exercise: mechanisms
699 responsible for matching oxygen supply to demand. *J. Physiol.* 590, 6321–6326 (2012).
- 700 56 Richalet, J.-P., Larmignat, P., Poitrine, E., Letournel, M. & Canouï-Poitrine, F. Physiological risk
701 factors for severe high-altitude illness: a prospective cohort study. *Am. J. Respir. Crit. Care Med.*
702 185, 192–198 (2012).
- 703 57 Canouï-Poitrine, F. et al. Risk prediction score for severe high altitude illness: a cohort study. *PLoS*
704 *One* 9, e100642 (2014).
- 705 58 Richalet, J.-P. et al. Validation of a score for the detection of subjects with high risk for severe high-
706 altitude illness. *Med. Sci. Sports Exercise* 53, 1294–1302 (2021).
- 707 59 Vogel, J. A., Hansen, J. E. & Harris, C. W. Cardiovascular responses in man during exhaustive work
708 at sea level and high altitude. *J. Appl. Physiol.* 23, 531–539 (1967).
- 709 60 Winkler, L., Lhuissier, F. J. & Richalet, J.-P. Systemic blood pressure at exercise in hypoxia in
710 hypertensive and normotensive patients. *J. Hypertens.* 35, 2402–2410 (2017).
- 711 61 Mallet, R. T., Burtscher, J., Richalet, J.-P., Millet, G. P. & Burtscher, M. Impact of high altitude on
712 cardiovascular health: current perspectives. *Vasc. Health Risk Manag.* 17, 317–335 (2021).
- 713 62 Savard, G. K., Areskog, N. H. & Saltin, B. Cardiovascular response to exercise in humans following
714 acclimatization to extreme altitude. *Acta Physiol. Scand.* 154, 499–509 (1995).
- 715 63 Wolfel, E. E. et al. Oxygen transport during steady-state submaximal exercise in chronic hypoxia. *J.*
716 *Appl. Physiol.* 70, 1129–1136 (1991).
- 717 64 Wolfel, E. E. et al. O₂ extraction maintains O₂ uptake during submaximal exercise with beta-
718 adrenergic blockade at 4,300 m. *J. Appl. Physiol.* 85, 1092–1102 (1998).
- 719 65 Zhou, Q. et al. A randomly-controlled study on the cardiac function at the early stage of return to the
720 plains after short-term exposure to high altitude. *PLoS ONE* 7, e31097 (2012).
- 721 66 Keyes, L. E. et al. Blood pressure and altitude: an observational cohort study of hypertensive and

- 722 nonhypertensive Himalayan trekkers in Nepal. *High Alt. Med. Biol.* 18, 267–277 (2017).
- 723 67 Tremblay, J. C. et al. Endothelial function and shear stress in hypobaric hypoxia: time course and
724 impact of plasma volume expansion in men. *Am. J. Physiol. Heart Circ. Physiol.* 319, H980–H994
725 (2020).
- 726 68 Rieger, M. G. et al. Cardiopulmonary and cerebrovascular acclimatization in children and adults at
727 3800 m. *J. Physiol.* 600, 4849–4863 (2022).
- 728 69 Talbot, N. P., Balanos, G. M., Dorrington, K. L. & Robbins, P. A. Two temporal components within
729 the human pulmonary vascular response to approximately 2 h of isocapnic hypoxia. *J. Appl. Physiol.*
730 98, 1125–1139 (2005).
- 731 70 Groves, B. M. et al. Operation Everest II: elevated high-altitude pulmonary resistance unresponsive to
732 oxygen. *J. Appl. Physiol.* 63, 521–530 (1987).
- 733 71 Moudgil, R., Michelakis, E. D. & Archer, S. L. Hypoxic pulmonary vasoconstriction. *J. Appl.*
734 *Physiol.* 98, 390–403 (2005).
- 735 72 Stenmark, K. R., Fagan, K. A. & Frid, M. G. Hypoxia-induced pulmonary vascular remodeling:
736 cellular and molecular mechanisms. *Circ. Res.* 99, 675–691 (2006).
- 737 73 Richalet, J.-P. & Pichon, A. in *The Right Heart* (eds. Gaine, S. P., Naeije, R. & Peacock, A. J.) 117–
738 129 (Springer, 2014).
- 739 74 Naeije, R. et al. Pulmonary artery pressure limits exercise capacity at high altitude. *Eur. Respir. J.* 36,
740 1049–1055 (2010).
- 741 75 Hildebrandt, W., Ottenbacher, A., Schuster, M., Swenson, E. R. & Bärtzsch, P. Diuretic effect of
742 hypoxia, hypocapnia, and hyperpnea in humans: relation to hormones and O₂ chemosensitivity. *J.*
743 *Appl. Physiol.* 88, 599–610 (2000).
- 744 76 Olsen, N. V. et al. Effects of acute hypoxia on renal and endocrine function at rest and during graded
745 exercise in hydrated subjects. *J. Appl. Physiol.* 73, 2036–2043 (1992).
- 746 77 Steele, A. R. et al. Global REACH 2018: renal oxygen delivery is maintained during early
747 acclimatization to 4,330 m. *Am. J. Physiol. Renal Physiol.* 319, F1081–F1089 (2020).
- 748 78 Singh, M. V. et al. Blood gases, hematology, and renal blood flow during prolonged mountain
749 sojourns at 3500 and 5800 m. *Aviat. Space Environ. Med.* 74, 533–536 (2003).
- 750 79 Richalet, J. P. et al. Control of erythropoiesis in humans during prolonged exposure to the altitude of
751 6,542 m. *Am. J. Physiol.* 266, R756–R764 (1994).
- 752 80 Lozano, R. & Monge, C. Renal function in high-altitude natives and in natives with chronic mountain
753 sickness. *J. Appl. Physiol.* 20, 1026–1027 (1965).
- 754 81 Ainslie, P. N. & Subudhi, A. W. Cerebral blood flow at high altitude. *High Alt. Med. Biol.* 15, 133–
755 140 (2014).
- 756 82 Ter Minassian, A. et al. Doppler study of middle cerebral artery blood flow velocity and cerebral
757 autoregulation during a simulated ascent of Mount Everest. *Wilderness Environ. Med.* 12, 175–183
758 (2001).
- 759 83 Hanada, A., Sander, M. & González-Alonso, J. Human skeletal muscle sympathetic nerve activity,
760 heart rate and limb haemodynamics with reduced blood oxygenation and exercise. *J. Physiol.* 551,
761 635–647 (2003).
- 762 84 Casey, D. P. et al. Nitric oxide contributes to the augmented vasodilatation during hypoxic exercise.
763 *J. Physiol.* 588, 373–385 (2010).
- 764 85 Wilkins, B. W. et al. Exercise intensity-dependent contribution of β -adrenergic receptor-mediated
765 vasodilatation in hypoxic humans. *J. Physiol.* 586, 1195–1205 (2008).
- 766 86 Pohl, U. & Busse, R. Hypoxia stimulates release of endothelium-derived relaxant factor. *Am. J.*
767 *Physiol. Heart Circ. Physiol.* 256, H1595–H1600 (1989).
- 768 87 Kooijman, M. et al. Flow-mediated dilatation in the superficial femoral artery is nitric oxide mediated

- 769 in humans: FMD in the SFA is nitric oxide mediated. *J. Physiol.* 586, 1137–1145 (2008).
- 770 88 Mortensen, S. P., Nyberg, M., Thaning, P., Saltin, B. & Hellsten, Y. Adenosine contributes to blood
771 flow regulation in the exercising human leg by increasing prostaglandin and nitric oxide formation.
772 *Hypertension* 53, 993–999 (2009).
- 773 89 Azad, P. et al. High-altitude adaptation in humans: from genomics to integrative physiology. *J. Mol.*
774 *Med.* 95, 1269–1282 (2017).
- 775 90 Moore, L. G., Armaza, F., Villena, M. & Vargas, E. Comparative aspects of high-altitude adaptation
776 in human populations. *Adv. Exp. Med. Biol.* 475, 45–62 (2000).
- 777 91 Hunley, K., Gwin, K. & Liberman, B. A Reassessment of the impact of European contact on the
778 structure of Native American genetic diversity. *PLoS ONE* 11, e0161018 (2016).
- 779 92 Hultgren, H. N. & Miller, H. Human heart weight at high altitude. *Circulation* 35, 207–218 (1967).
- 780 93 Antezana, A. et al. Pulmonary hypertension in high-altitude chronic hypoxia: response to nifedipine.
781 *Eur. Respir. J.* 12, 1181–1185 (1998).
- 782 94 León-Velarde, F., Villafuerte, F. C. & Richalet, J.-P. Chronic mountain sickness and the heart. *Prog.*
783 *Cardiovasc. Dis.* 52, 540–549 (2010).
- 784 95 Maignan, M. et al. Pulmonary pressure and cardiac function in chronic mountain sickness patients.
785 *Chest* 135, 499–504 (2009).
- 786 96 Corante, N. et al. Excessive erythrocytosis and cardiovascular risk in Andean highlanders. *High Alt.*
787 *Med. Biol.* 19, 221–231 (2018).
- 788 97 Pratali, L. et al. RV contractility and exercise-induced pulmonary hypertension in chronic mountain
789 sickness. *JACC Cardiovasc. Imag.* 6, 1287–1297 (2013).
- 790 98 Severinghaus, J. W., Bainton, C. R. & Carcelen, A. Respiratory insensitivity to hypoxia in chronically
791 hypoxic man. *Respir. Physiol.* 1, 308–334 (1966).
- 792 99 Antezana, A., Richalet, J., Antezana, G., Spielvogel, H. & Kacimi, R. Adrenergic aystem in high
793 altitude residents. *Int. J. Sports Med.* 13, S96–S100 (1992).
- 794 100 Richalet, J.-P. et al. Acetazolamide for Monge’s disease: efficiency and tolerance of 6-month
795 treatment. *Am. J. Respir. Crit. Care Med.* 177, 1370–1376 (2008).
- 796 101 Aryal, N., Weatherall, M., Bhatta, Y. K. D. & Mann, S. Blood pressure and hypertension in adults
797 permanently living at high altitude: a systematic review and meta-analysis. *High Alt. Med. Biol.* 17,
798 185–193 (2016).
- 799 102 Sun, S. Epidemiology of hypertension on the Tibetan plateau. *Hum. Biol.* 58, 507–515 (1986).
- 800 103 Hanco, I. et al. Excessive erythrocytosis and chronic mountain sickness in dwellers of the highest
801 city in the world. *Front. Physiol.* 11, 773 (2020).
- 802 104 Coombs, G. B. et al. Global Reach 2018: nitric oxide-mediated cutaneous vasodilation is reduced
803 in chronic, but not acute, hypoxia independently of enzymatic superoxide formation. *Free Radic.*
804 *Biol. Med.* 172, 451–458 (2021).
- 805 105 Beall, C. M., Laskowski, D. & Erzurum, S. C. Nitric oxide in adaptation to altitude. *Free Radic.*
806 *Biol. Med.* 52, 1123–1134 (2012).
- 807 106 Tremblay, J. C. et al. Global Reach 2018: high blood viscosity and hemoglobin concentration
808 contribute to reduced flow-mediated dilation in high-altitude excessive erythrocytosis. *Hypertension*
809 73, 1327–1335 (2019).
- 810 107 Basak, N. & Thangaraj, K. High-altitude adaptation: role of genetic and epigenetic factors. *J.*
811 *Biosci.* 46, 107 (2021).
- 812 108 Beall, C. M. Andean, Tibetan, and Ethiopian patterns of adaptation to high-altitude hypoxia.
813 *Integr. Comp. Biol.* 46, 18–24 (2006).
- 814 109 Beall, C. M. et al. Natural selection on EPAS1(HIF2alpha) associated with low hemoglobin

- 815 concentration in Tibetan highlanders. *Proc. Natl Acad. Sci. USA* 107, 11459–11464 (2010).
- 816 110 Bigham, A. et al. Identifying signatures of natural selection in Tibetan and Andean populations
817 using dense genome scan data. *PLoS Genet.* 6, e1001116 (2010).
- 818 111 Simonson, T. S. et al. Genetic evidence for high-altitude adaptation in Tibet. *Science* 329, 72–75
819 (2010).
- 820 112 Sharma, V., Varshney, R. & Sethy, N. K. Human adaptation to high altitude: a review of
821 convergence between genomic and proteomic signatures. *Hum. Genomics* 16, 21 (2022).
- 822 113 Scheinfeldt, L. B. et al. Genetic adaptation to high altitude in the Ethiopian highlands. *Genome*
823 *Biol.* 13, R1 (2012).
- 824 114 Espinoza, J. R. et al. Vascular endothelial growth factor-A is associated with chronic mountain
825 sickness in the Andean population. *High Alt. Med. Biol.* 15, 146–154 (2014).
- 826 115 Gazal, S. et al. The genetic architecture of chronic mountain sickness in Peru. *Front. Genet.* 10,
827 690 (2019).
- 828 116 Zhou, D. et al. Whole-genome sequencing uncovers the genetic basis of chronic mountain
829 sickness in Andean highlanders. *Am. J. Hum. Genet.* 93, 452–462 (2013).
- 830 117 Ravenhill, T. H. Some experiences of mountain sickness in the Andes. *J. Trop. Med. Hyg.* 16,
831 313–320 (1913).
- 832 118 Houston, C. S. Acute pulmonary edema of high altitude. *N. Engl. J. Med.* 263, 478–480 (1960).
- 833 119 Richalet, J.-P., Jeny, F., Callard, P. & Bernaudin, J.-F. High altitude pulmonary edema: the
834 intercellular network hypothesis. *Am. J. Physiol. Lung Cell. Mol. Physiol.* <https://doi.org/10.1152/ajplung.00292.2022> (2023).
- 835 120 Donegani, E. et al. Pre-existing cardiovascular conditions and high altitude travel. *Travel Med.*
836 *Infect. Dis.* 12, 237–252 (2014).
- 838 121 Luks, A. M. & Hackett, P. H. Medical conditions and high-altitude travel. *N. Engl. J. Med.* 386,
839 364–373 (2022).
- 840 122 Parati, G. et al. Clinical recommendations for high altitude exposure of individuals with pre-
841 existing cardiovascular conditions: a joint statement by the European Society of Cardiology, the
842 Council on Hypertension of the European Society of Cardiology, the European Society of
843 Hypertension, the International Society of Mountain Medicine, the Italian Society of Hypertension
844 and the Italian Society of Mountain Medicine. *Eur. Heart J.* 39, 1546–1554 (2018).
- 845 123 Mollard, P. et al. Determinants of maximal oxygen uptake in moderate acute hypoxia in endurance
846 athletes. *Eur. J. Appl. Physiol.* 100, 663–673 (2007).
- 847 124 Schmid, J.-P. Safety and exercise tolerance of acute high altitude exposure (3454 m) among
848 patients with coronary artery disease. *Heart* 92, 921–925 (2006).
- 849 125 de Vries, S. T. et al. Impact of high altitude on echocardiographically determined cardiac
850 morphology and function in patients with coronary artery disease and healthy controls. *Eur. J.*
851 *Echocardiogr.* 11, 446–450 (2010).
- 852 126 Morgan, B. J., Alexander, J. K., Nicoli, S. A. & Brammell, H. L. The patient with coronary heart
853 disease at altitude: observations during acute exposure to 3100 meters. *J. Wilderness Med.* 1, 147–
854 153 (1990).
- 855 127 Salvi, P. et al. Changes in subendocardial viability ratio with acute high-altitude exposure and
856 protective role of acetazolamide. *Hypertension* 61, 793–799 (2013).
- 857 128 Agostoni, P. et al. Effects of simulated altitude-induced hypoxia on exercise capacity in patients
858 with chronic heart failure. *Am. J. Med.* 109, 450–455 (2000).
- 859 129 Schmid, J.-P. et al. Short-term high altitude exposure at 3454 m is well tolerated in patients with
860 stable heart failure. *Eur. J. Heart Fail.* 17, 182–186 (2015).
- 861 130 Vona, M. et al. Effects of altitude on effort tolerance in non-acclimatized patients with ischemic

- 862 left ventricular dysfunction. *Eur. J. Cardiovasc. Prev. Rehabil.* 13, 617–624 (2006).
- 863 131 Staempfli, R. et al. Cardiopulmonary adaptation to short-term high altitude exposure in adult
864 Fontan patients. *Heart* 102, 1296–1301 (2016).
- 865 132 Allemann, Y. et al. Patent foramen ovale and high-altitude pulmonary edema. *JAMA* 296, 2954–
866 2958 (2006).
- 867 133 Bilo, G. et al. Ambulatory blood pressure in untreated and treated hypertensive patients at high
868 altitude: the High Altitude Cardiovascular Research-Andes study. *Hypertension* 65, 1266–1272
869 (2015).
- 870 134 Wu, T.-Y. et al. Who should not go high: chronic disease and work at altitude during construction
871 of the Qinghai-Tibet railroad. *High Alt. Med. Biol.* 8, 88–107 (2007).
- 872 135 Hackett, P. H. et al. High-altitude pulmonary edema in persons without the right pulmonary artery.
873 *N. Engl. J. Med.* 302, 1070–1073 (1980).
- 874 136 Richalet, J.-P., Chenivesse, C., Larmignat, P. & Meille, L. High altitude pulmonary edema, Down
875 syndrome, and obstructive sleep apneas. *High Alt. Med. Biol.* 9, 179–181 (2008).
- 876 137 Lichtblau, M. et al. Altitude travel in patients with pulmonary hypertension: randomized pilot-trial
877 evaluating nocturnal oxygen therapy. *Front. Med.* 7, 502 (2020).
- 878 138 Verges, S., Chacaroun, S., Godin-Ribuot, D. & Baillieux, S. Hypoxic conditioning as a new
879 therapeutic modality. *Front. Pediatr.* 3, 58 (2015).
- 880 139 Burtscher, J., Mallet, R. T., Burtscher, M. & Millet, G. P. Hypoxia and brain aging:
881 neurodegeneration or neuroprotection? *Ageing Res. Rev.* 68, 101343 (2021).
- 882 140 Moncayo, J., de Freitas, G. R., Bogousslavsky, J., Altieri, M. & van Melle, G. Do transient
883 ischemic attacks have a neuroprotective effect? *Neurology* 54, 2089–2094 (2000).
- 884 141 Zhang, Y. et al. Hypoxia conditioning enhances neuroprotective effects of aged human bone
885 marrow mesenchymal stem cell-derived conditioned medium against cerebral ischemia in vitro. *Brain*
886 *Res.* 1725, 146432 (2019).
- 887 142 Serebrovskaya, T. V., Manukhina, E. B., Smith, M. L., Downey, H. F. & Mallet, R. T. Intermittent
888 hypoxia: cause of or therapy for systemic hypertension? *Exp. Biol. Med.* 233, 627–650 (2008).
- 889 143 Mateika, J. H. & Syed, Z. Intermittent hypoxia, respiratory plasticity and sleep apnea in humans:
890 present knowledge and future investigations. *Respir. Physiol. Neurobiol.* 188, 289–300 (2013).
- 891 144 Hobbins, L., Hunter, S., Gaoua, N. & Girard, O. Normobaric hypoxic conditioning to maximize
892 weight loss and ameliorate cardio-metabolic health in obese populations: a systematic review. *Am. J.*
893 *Physiol. Regul. Integr. Comp. Physiol.* 313, R251–R264 (2017).
- 894 145 Klug, L. et al. Normobaric hypoxic conditioning in men with metabolic syndrome. *Physiol. Rep.*
895 6, e13949 (2018).
- 896 146 Burtscher, M. Lower mortality rates in those living at moderate altitude. *Ageing* 8, 2603–2604
897 (2016).
- 898 147 Ezzati, M. et al. Altitude, life expectancy and mortality from ischaemic heart disease, stroke,
899 COPD and cancers: national population-based analysis of US counties. *J. Epidemiol. Community*
900 *Health* 66, e17 (2012).
- 901 148 Faeh, D., Gutzwiller, F. & Bopp, M. Lower mortality from coronary heart disease and stroke at
902 higher altitudes in Switzerland. *Circulation* 120, 495–501 (2009).
- 903 149 Lopez-Pascual, A., Arévalo, J., Martínez, J. A. & González-Muniesa, P. Inverse association
904 between metabolic syndrome and altitude: a cross-sectional study in an adult population of Ecuador.
905 *Front. Endocrinol.* 9, 658 (2018).
- 906 150 Woolcott, O. O. et al. Inverse association between diabetes and altitude: a cross-sectional study in
907 the adult population of the United States: diabetes at high altitude. *Obesity* 22, 2080–2090 (2014).
- 908 151 Coté, T. R., Stroup, D. F., Dwyer, D. M., Horan, J. M. & Peterson, D. E. Chronic obstructive

- 909 pulmonary disease mortality: a role for altitude. *Chest* 103, 1194–1197 (1993).
- 910 152 Anderson, J. D. & Honigman, B. The effect of altitude-induced hypoxia on heart disease: do
911 acute, intermittent, and chronic exposures provide cardioprotection? *High Alt. Med. Biol.* 12, 45–55
912 (2011).
- 913 153 Sanchis-Gomar, F., Viña, J. & Lippi, G. Intermittent hypobaric hypoxia applicability in
914 myocardial infarction prevention and recovery. *J. Cell Mol. Med.* 16, 1150–1154 (2012).
- 915 154 del Pilar Valle, M. et al. Improvement of myocardial perfusion in coronary patients after
916 intermittent hypobaric hypoxia. *J. Nucl. Cardiol.* 13, 69–74 (2006).
- 917 155 Burtscher, M. et al. Intermittent hypoxia increases exercise tolerance in elderly men with and
918 without coronary artery disease. *Int. J. Cardiol.* 96, 247–254 (2004).
- 919 156 Saeed, O. et al. Improved exercise performance and skeletal muscle strength after simulated
920 altitude exposure: a novel approach for patients with chronic heart failure. *J. Card. Fail.* 18, 387–391
921 (2012).
- 922 157 Cai, Z. et al. Complete loss of ischaemic preconditioning-induced cardioprotection in mice with
923 partial deficiency of HIF-1. *Cardiovasc. Res.* 77, 463–470 (2007).
- 924 158 Huang, T. et al. Hypoxia-inducible factor-1 α upregulation in microglia following hypoxia protects
925 against ischemia-induced cerebral infarction. *NeuroReport* 25, 1122–1128 (2014).
- 926 159 Belaidi, E., Beguin, P. C., Levy, P., Ribuot, C. & Godin-Ribuot, D. Prevention of HIF-1 activation
927 and iNOS gene targeting by low-dose cadmium results in loss of myocardial hypoxic preconditioning
928 in the rat. *Am. J. Physiol. Heart Circ. Physiol.* 294, H901–H908 (2008).
- 929 160 Park, A.-M., Nagase, H., Vinod Kumar, S. & Suzuki, Y. J. Acute intermittent hypoxia activates
930 myocardial cell survival signaling. *Am. J. Physiol. Heart Circ. Physiol.* 292, H751–H757 (2007).
- 931 161 Joyeux-Faure, M., Godin-Ribuot, D. & Ribuot, C. Erythropoietin and myocardial protection:
932 what's new? *Fundam. Clin. Pharmacol.* 19, 439–446 (2005).
- 933 162 Moore, E. & Bellomo, R. Erythropoietin (EPO) in acute kidney injury. *Ann. Intensive Care* 1, 3
934 (2011).
- 935 163 El'chaninova, S. A., Korenyak, N. A., Pavlovskaya, L. I., Smagina, I. V. & Makarenko, V. V. The
936 effect of interval hypoxic hypoxia on the vascular endothelial growth factor and basic fibroblast
937 growth factor concentrations in the peripheral blood. *Hum. Physiol.* 30, 705–707 (2004).
- 938 164 Maulik, N. & Das, D. K. Redox signaling in vascular angiogenesis. *Free Radic. Biol. Med.* 33,
939 1047–1060 (2002).
- 940 165 Ray, P. S., Estrada-Hernandez, T., Sasaki, H., Zhu, L. & Maulik, N. Early effects of hypoxia/
941 reoxygenation on VEGF, ang-1, ang-2 and their receptors in the rat myocardium: implications for
942 myocardial angiogenesis. *Mol. Cell Biochem.* 213, 145–153 (2000).
- 943 166 Dempsey, J. A., Veasey, S. C., Morgan, B. J. & O'Donnell, C. P. Pathophysiology of sleep apnea.
944 *Physiol. Rev.* 90, 47–112 (2010).
- 945 167 Mallet, R. T., Manukhina, E. B., Ruelas, S. S., Caffrey, J. L. & Downey, H. F. Cardioprotection
946 by intermittent hypoxia conditioning: evidence, mechanisms, and therapeutic potential. *Am. J.*
947 *Physiol. Heart Circ. Physiol.* 315, H216–H232 (2018).
- 948 168 Navarrete-Opazo, A. & Mitchell, G. S. Therapeutic potential of intermittent hypoxia: a matter of
949 dose. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 307, R1181–R1197 (2014).
- 950 169 Millet, G. P. et al. Commentaries on viewpoint: time for a new metric for hypoxic dose? *J. Appl.*
951 *Physiol.* 121, 356–358 (2016).
- 952 170 Richalet, J.-P. Oxygen sensors in the organism: examples of regulation under altitude hypoxia in
953 mammals. *Comp. Biochem. Physiol. A Physiol.* 118, 9–14 (1997).
- 954 171 Kanai, M., Nishihara, F., Shiga, T., Shimada, H. & Saito, S. Alterations in autonomic nervous
955 control of heart rate among tourists at 2700 and 3700 m above sea level. *Wilderness Environ. Med.*

956 12, 8–12 (2001).

957 172 Heistad, D. D. & Abboud, F. M. Dickinson W. Richards lecture: circulatory adjustments to
958 hypoxia. *Circulation* 61, 463–470 (1980).

959 173 Mortensen, S. P., González-Alonso, J., Damsgaard, R., Saltin, B. & Hellsten, Y. Inhibition of
960 nitric oxide and prostaglandins, but not endothelial-derived hyperpolarizing factors, reduces blood
961 flow and aerobic energy turnover in the exercising human leg: effect of triple blockade on exercise
962 hyperaemia. *J. Physiol.* 581, 853–861 (2007).

963 174 Richalet, J.-P. & Herry, J.-P. *Médecine de Montagne: Alpinisme et Sports de Montagne* 5th edn,
964 Vol. 72 (Elsevier Masson, 2017).

965