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REVIEW

Impact of High Altitude on Cardiovascular Health: Current Perspectives

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Abstract: Globally, about 400 million people reside at terrestrial altitudes above 1500 m, and more than 100 million lowlanders visit mountainous areas above 2500 m annually. The interactions between the low barometric pressure and partial pressure of O_2, climate, individual genetic, lifestyle and socio-economic factors, as well as adaptation and acclimatization processes at high elevations are extremely complex. It is challenging to decipher the effects of these myriad factors on the cardiovascular health in high altitude residents, and even more so in those ascending to high altitudes with or without preexisting diseases. This review aims to interpret epidemiological observations in high-altitude populations; present and discuss cardiovascular responses to acute and subacute high-altitude exposure in general and more specifically in people with preexisting cardiovascular diseases; the relations between cardiovascular pathologies and neurodegenerative diseases at altitude; the effects of high-altitude exercise; and the putative cardioprotective mechanisms of hypobaric hypoxia.

Keywords: hypoxia, hypobaria, exercise, adaptation, acclimatization, conditioning

Introduction

Worldwide, about 400 million people reside at altitudes above 1500 m (~5000 ft)[1] and more than 100 million lowlanders visit areas above 2500 m (~8000 ft) annually.[2] Altitude ranges are commonly defined as high altitude (1500–3500 m; ~5000–11,500 ft), very high altitude (3500–5500 m; ~11,500–18,000 ft), and extreme altitude (>5500 m; >18,000 ft).[3] Figure 1 shows the altitude ranges of some of the world's major mountainous regions.

At 5052 m (16,575 ft) above sea level, the world's highest city is La Rinconada, Peru (population c. 50,000 in 2020). The highest major city, El Alto, Bolivia (population c. 940,000 in 2020) lies at 4150 m (13,615 ft). These and other sizeable cities are in very high-altitude regions (Figure 1).

Whereas highlanders are chronically exposed to altitude and its associated climatic conditions, high-altitude travelers with or without pre-existing diseases, including tourists, climbers and trekkers, mine and road workers, porters and pilgrims, experience less protracted high-altitude exposures of hours to weeks. Climate changes progressively with increasing altitude, characterized by decreasing barometric pressure and partial pressure of inspired O_2, declining ambient temperature and more intense ultraviolet solar radiation.[4] Although all these conditions may contribute to the development and progression of chronic and acute high-altitude illnesses, the reduced partial pressure of oxygen (hypobaric hypoxia) is considered

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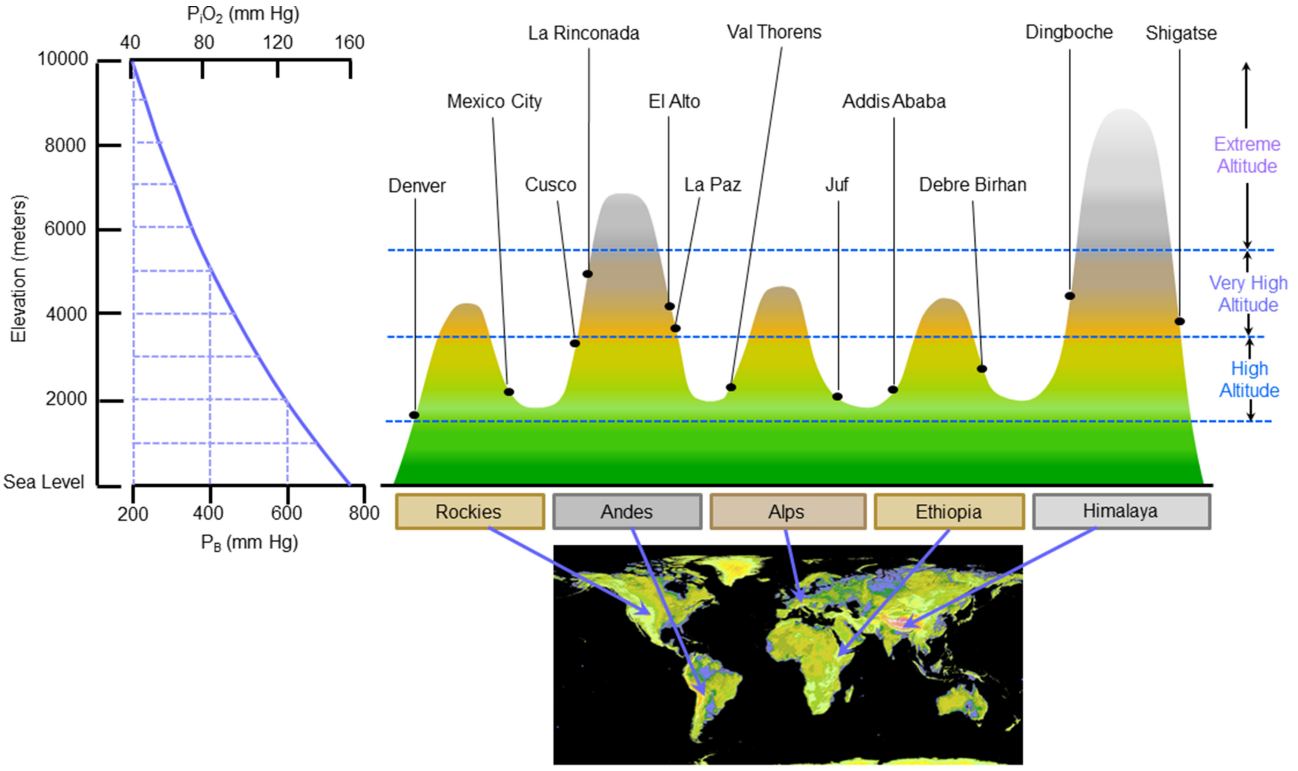

Figure 1 Partial pressure of inspired O_2 (P_IO_2) is decreased in mountainous regions. Representative cities in major mountain ranges are shown.
Notes: The map is courtesy of NASA/JPL-Caltech and adapted from NASA/JPL-Caltech. Aster Global Digital Elevation Map (GDEM) . Available at: https://asterweb.jpl.nasa.gov/images/GDEM-10km-colorized.png. Accessed February 28, 2021.[210]

the primary cause.[5–8] Genetic adaptations enable people to permanently live at altitudes up to 5000 m (~16,400 ft).[9,10] The highest altitude tolerable for prolonged sojourns is approximately 6000 m (~19,700 ft), which mine workers on Volcán Aucanquilcha, Chile endured for up to two years (West 1986). Appropriate acclimatization strategies allow short-term stays at altitudes higher than 7000 m (~23,000 ft) even for lowlanders, as demonstrated by many mountaineers.[11]

Besides genetic and lifestyle factors, chronic exposure to high-altitude environments may impact cardiovascular health, disease development and life-expectancy.[12–18] While acute ascent to high altitudes may adversely affect cardiovascular health in lowlanders, particularly in those with pre-existing diseases,[19,20] acclimatization diminishes this risk and hypoxia conditioning can even benefit and protect the cardiovascular system.[21,22] Not surprisingly, the interactions between the high-altitude climate, individual genetic, life-style and socio-economic factors, adaptation and acclimatization processes to various altitudes are extremely complex, restricting straightforward predictions of high-altitude sojourns on health-related outcomes concerning the cardiovascular system. Therefore, this review aims to interpret available epidemiological observations in high-altitude populations, present and discuss cardiovascular responses to acute and subacute high-altitude exposure in general and particularly in people with preexisting cardiovascular diseases, the relations between cardiovascular pathologies and neurodegenerative diseases at altitude, the effects of exercise at altitude and the putative cardioprotective mechanisms of adaptations to acute and chronic hypoxia.

Living at High Altitude: Epidemiological Considerations

Epidemiological data from populations permanently residing at high-altitude strongly indicate that environmental factors differently impact the development of cardiovascular diseases, depending on the altitude.[17,18,23,24] While, for instance, lower mortality from cardiovascular diseases, stroke, cancer, and Alzheimer's disease was reported in high altitude regions in the Swiss[18] and Austrian[24] Alps and the western United States[17,18,24,25] mortality from

pulmonary morbidities (eg, emphysema, COPD) seemed to increase in high altitude residents.[17,26] Thus, considering (patho) physiological responses to hypobaric altitude/hypoxia, here we distinguish moderate altitude (1500 to 2500 m)[27] and high altitude from 2500 m to about 5000 m, the highest permanent human residence.[28] Data on the altitude-dependent prevalence of risk factors for cardiovascular diseases, eg, systemic hypertension, dyslipidemia and diabetes mellitus, and cardiovascular disease mortality may provide insights regarding the benefits vs detriments of living at moderate and high altitude, and the underlying mechanisms.

Systemic Hypertension

Reports of the effects of altitude on the prevalence of systemic hypertension, usually defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, are conflicting. A survey of 1631 Tibet inhabitants living at three different altitude ranges between 2700 and 4505 m revealed a decrease in hypertension prevalence from 40.6% to 20.4% from the lowest to the highest range, associated with decreasing body mass index (BMI).[29] In contrast, systematic review of 8 cross-sectional studies totaling 16,913 individuals identified a close direct correlation between altitude and the prevalence of systemic hypertension in Tibet inhabitants, with a 2% increase in hypertension incidence per 100 m gain in altitude above 3000 m.[30] Concordant with these findings, another meta-analysis of 40,854 Tibetans living at ≥2400 m reported increases in systolic and diastolic blood pressures of 17 and 9.5 mmHg, respectively, per 1000 m gain in elevation.[31] However, in non-Tibetan, primarily Andean highlanders, blood pressure trended downward, albeit not significantly, with increasing altitude.[31]

The observed differences between Andean and Tibetan highlanders may represent the vascular consequences of divergent adaptation patterns.[32] In Andean highlanders, chronic mountain sickness and pulmonary artery hypertension are more prevalent, while systemic blood pressure and cerebral blood flow are lower than in Tibetan highlanders.[33] The mechanisms underlying these differences may primarily relate to regulation of gene expression, eg, activation of hypoxia-responsive gene transcription by hypoxia-inducible factors. Notably, a recent study suggested that conventional blood pressure measurement may underestimate hypertension prevalence in Andean highlanders, while ambulatory blood pressure monitoring unmasks hypertension.[34] Collectively these studies identify genetic adaptations, lifestyle and climatic factors as pivotal determinants of blood pressure responses to living at high altitude. Decreased appetite and caloric intake, and increased energy expenditure due to low ambient temperature, likely contribute to lower BMI and reduced risk of hypertension at high altitude.[4,29]

Dyslipidemia

Studies of residents of Lhasa, Tibet (3660 m) demonstrated high prevalence of hypertriglyceridemia in males and hypercholesterolemia in both sexes, and lower circulating high-density lipoprotein (HDL) cholesterol contents in females.[35] Similar findings were reported from the moderate-altitude (1500–2500 m) Yunnan-Kweichow Plateau in Southwestern China, with a higher prevalence of hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia in males, and slightly lower HDL cholesterol and higher LDL cholesterol values in females.[36] These authors attributed the prevalence of hyperlipidemia mainly to unhealthy living habits associated with obesity. By contrast, highly educated adults living in Riobamba, Ecuador (2754 m) had a lower prevalence of metabolic syndrome, hypercholesterolemia and hyperglycemia than lowlanders living on the Ecuadorian coast,[37] which may have been attributable to reduced appetite and self-reported lower energy intake at altitude. Socio-cultural and socio-economic factors explained inter-individual variation of hypercholesterolemia in the Swiss alpine population, while no specific altitude effects were detected.[38] Again, genetic, life-style, and socio-economic factors are probably more important than altitude-related low temperature and increased energy expenditure.

Diabetes

A cross-sectional study of 284,945 US residents revealed an inverse association (adjusted for multiple confounders) between altitude and diabetes prevalence.[39] Compared to low-altitude (0–499 m) residents, the odds ratio for diabetes was 0.95 (95% CI: 0.90–1.01) between 500 and 1499 m, and 0.88 (0.81–0.96) between 1500 and 3500 m. Notably, the inverse association was only true for men (0.84; 0.76–0.94), not women (1.09; 0.97–1.22).[39] Data from Tibetans living between 2900 and 4800 m suggested that altitude-related hypoxemia and polycythemia were closely associated with glucose intolerance and diabetes mellitus after adjusting for lifestyle.[40] As mentioned above, hyperglycemia was less prevalent in Ecuadorian Altiplano residents (~2770 m) than in

lowlanders.[37] As diabetes type 2 is closely associated with obesity, lower obesity prevalence (adjusted for multiple covariates including physical activity) with increasing altitude may largely explain the reduced diabetes risk in highlanders,[41] underscoring the importance of altitude and cold on caloric intake-expenditure balance and BMI.

Chronic Mountain Sickness (CMS)

Chronic mountain sickness (CMS), also known as Monge's disease, is a syndrome affecting about 5% to 10% of the 140 million people permanently living at high altitude.[42] It seems to be a consequence of progressive loss of ventilatory rate, increasingly observed with aging and resulting in excessive hypoxemia and polycythemia (Hb ≥19 g/dL for women and Hb ≥21 g/dL for men).[43] This syndrome is frequently associated with pulmonary hypertension, and in advanced cases, it may progress to cor pulmonale and congestive heart failure.[43] Periodic travel to lower altitudes is recommended for those with rather mild symptoms, but severe cases should move permanently to lower altitudes.[44]

Mortality from Cardiovascular Diseases

In contrast to the inconsistent findings regarding the altitude-dependent prevalence of risk factors for cardiovascular diseases, data on the cardiovascular mortality risk are more consistent, at least for the moderate altitude regions of the Alps. Increasing altitude was associated with lower coronary heart disease and stroke mortality rates for both sexes in Switzerland[18] and lower mortality from coronary artery disease, male colorectal cancer and female breast cancer in Austria.[24] Faeh and colleagues reported respective 22% and 12% reductions in mortality from coronary heart disease and stroke per 1000 m gain in elevation.[18] Adjusted analysis revealed that the decreased mortality probably was not due to reductions in classic cardiovascular risk factors but instead might be explained by geographic factors like altitude/hypoxia and/or the effects of solar radiation on Vitamin D. Accordingly, the Austrian study revealed reductions of coronary artery disease mortality at 1000–2000 m vs <250 m of 28% in men and 31% in women.[24] These findings are concordant with life expectancy increases of 1.2–3.6 years in men and 0.5–2.5 years in women residing in US counties with mean altitudes >1500 m vs residents of counties within 100 m of sea level.[17]

Detrimental effects of altitude residence on the risk of heart disease and mortality only rarely have been reported. Virues-Ortega and colleagues demonstrated increased overall mortality at higher altitudes, most pronounced over 3000 m, possibly due to more extreme climate conditions at those altitudes.[5] While risk factors for cardiovascular diseases are not uniformly affected by high altitude conditions, there is agreement on the beneficial effects of moderate if not extreme altitudes on the mortality risk from cardiovascular diseases. It thus seems likely that mild environmental stimuli (eg, hypoxia, cold, ultraviolet radiation) at moderate altitude will promote conditioning associated with favorable outcomes, vs the likely detrimental effects of more intense stimuli at extreme altitudes.[16] However, it is important to mention that altitude-related lifestyle behaviors very likely contribute to the observed beneficial effects of living at "moderate altitudes", ie, below 2000 m, on the cardiovascular and cerebrovascular systems.

Acute and Subacute Effects of High-Altitude Exposure

Individuals rapidly ascending from low to high altitudes (>2000 m) are at risk to develop acute mountain sickness (AMS), which is characterized by headache as the predominant symptom, commonly accompanied by nausea, lack of appetite, vomiting, insomnia, dizziness, and/or fatigue.[45] The AMS prevalence was shown to increase from 7% at 2200 m to 38% at 3500 m, and to 52% when rapidly ascending to 4559 m in the alpine regions,[45,46] and a similar risk has been derived from Chinese highland military medical records.[47] Usually, AMS symptoms resolve during the first days at altitude, but may in rare cases progress to life-threatening diseases such as high-altitude cerebral edema (HACE) and/or high-altitude pulmonary edema (HAPE). A HACE prevalence of 0.98% has been reported in a cohort of 1326 European individuals sojourning to 4000 m,[48] while Wu and colleagues found a prevalence of 0.28% among 14,000 Asian railroad workers who travelled from lowland China to Tibet (3500–5000 m).[49] In a population of unknown HAPE history, the HAPE incidence was 0.2% when climbing to 4500 m within 4 days, but increased to 6% when ascending to this altitude in only 1 to 2 days.[20] Besides hypoxia at high altitude, other risk factors like extreme temperatures must be considered. For instance, while military troops have developed appropriate acclimatization schedules for hypobaric hypoxia, the very low temperature, eg, down to – 55°C during the winter time in the Western Himalayas, still remains an important health

challenge, even in young, fit and healthy soldiers.[50] Adverse effects of acute high altitude exposure are largely avoidable by proper acclimatization, ie, low ascent rates, or the use of appropriate pre-acclimatization strategies.[45] A precise understanding of physiological responses to acute high altitude is required to optimize the individual acclimatization process and to avoid potentially associated risks to the cardiovascular system.

Declining partial pressure of oxygen, PO_2, parallels decreasing barometric pressure (P_B) with increasing altitude. For instance, at 2360 m, the altitude of Addis Ababa, Ethiopia, P_B and PO_2 are 75% of those at sea level, and at 5052 m, the altitude of La Rinconada, Peru they are only about 53% of the respective sea level pressures (Figure 1). As PO_2 in the inspired air (P_iO_2) declines, so does PO_2 in the alveoli (P_AO_2) and systemic arterial blood (P_aO_2), as does arterial oxygen saturation (S_aO_2). Hypoxemia activates peripheral chemoreceptor afferents of the carotid bodies increasing minute ventilation and, via sympathetic activation, heart rate[51] and, thus, cardiac output. Collectively, these ventilatory and cardiac responses partially counteract the diminished oxygen supply at high altitude.[21,51–55] Generally, the rising sensitivity of the peripheral chemoreceptors over days at altitude increases ventilation, but ventilatory acclimatization differs among individuals.[56] Hyperventilation improves oxygenation but lowers P_aCO_2 producing alkalemia. The resulting decrease of renal tubular H^+ secretion compensates for the respiratory alkalosis by enhancing urinary excretion of bicarbonate.[57,58] Elevated diuresis also causes hemoconcentration, on the one hand reducing plasma volume and lowering stroke volume and, on the other hand, increasing arterial oxygen content and oxygen delivery to tissues at a given cardiac output.[55,59] As acclimatization progresses, cardiac output returns to baseline but heart rate remains elevated because of the lower stroke volume (Figure 2).[55]

Hypoxic pulmonary vasoconstriction, another physiologic hallmark of acute high-altitude ascent, elevates pulmonary artery pressure, and this response reportedly is particularly profound in the elderly.[53,62] Systemic blood pressure also increases upon initial ascent to altitude, primarily due to pronounced sympathetic activation, at least in men.[59,61] While ventilation and heart rate, pulmonary and systemic blood pressures, and sympathetic activity remain elevated with acclimatization, stroke volume decreases, cardiac output returns to baseline, and arterial oxygen saturation improves (Figure 2).[55,59,62] Notably, all these responses vary considerably between individuals and do not completely compensate for the reduced P_iO_2, especially at extreme altitudes.

Despite all these changes, in healthy individuals, myocardial oxygen supply and left ventricular function are

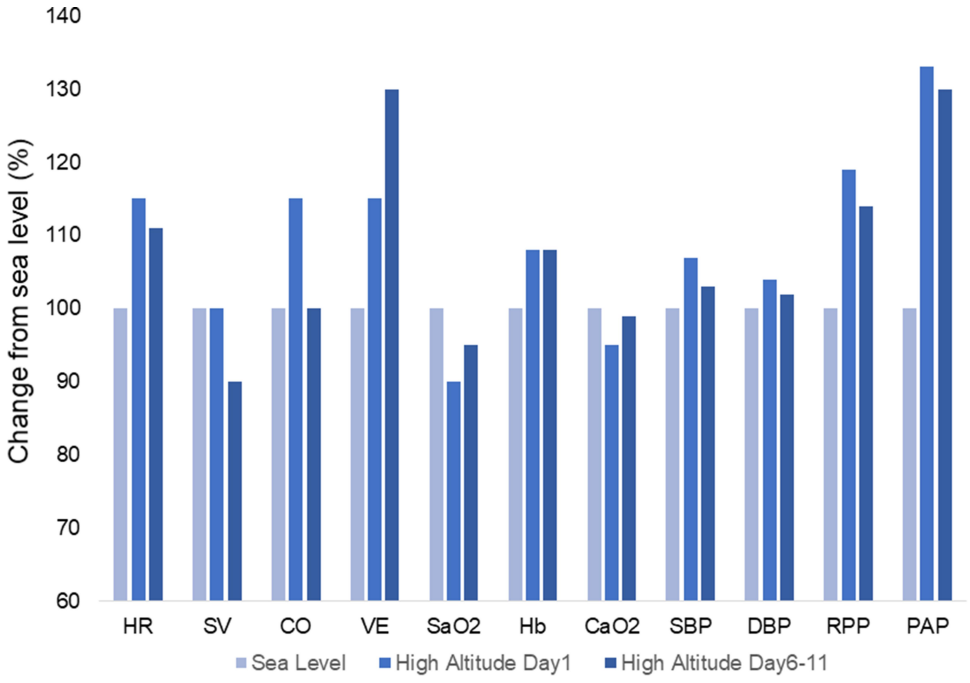

Figure 2 Changes of resting cardiovascular parameters when acutely exposed to high altitude and during acclimatization. **Notes:** Bbased on data reported in references [55] and [62–65]. From left to right.

Abbreviations: HR, heart rate; SV, stroke volume; CO, cardiac output; VE, minute ventilation; SaO_2, arterial oxygen saturation; Hb, hemoglobin concentration; CaO_2, arterial oxygen content; SBP, DBP, systolic and diastolic blood pressure; RPP, rate pressure product; PAP, pulmonary artery pressure.

maintained at rest and even during maximal exercise at high altitude.[55,66] Moreover, moderate and high altitude are also well tolerated by healthy elderly subjects,[21,67] but may become detrimental in those suffering from cardiovascular diseases.[19,60]

Cardiovascular Changes in Patients with Preexisting Cardiovascular Diseases

In cardiac patients, hypoxemia might be detrimental even at sea level, although there is very little evidence of aggravated cardiovascular diseases at least at low or moderate altitude. A list of recommendations from the European Society of Cardiology can serve as a basis for clinical practice.[68] However, as yet the biomedical literature provides no clinical evidence regarding the risk of all types of cardiovascular diseases at moderate or high altitude.[19,69,70] Nevertheless, the basic knowledge of the physiology of hypoxia and of the pathophysiology of cardiac or vascular diseases allows us to propose four simple guidelines to help practitioners make decisions and give appropriate advice to their cardiac patients with regard to altitude sojourns.

- Patients suffering from any diseases that may be aggravated by an overactivation of the adrenergic system (tachyarrhythmias) might be at risk at high altitude.
- Patients suffering from any diseases associated with pulmonary hypertension will be at high risk even at moderate altitude.
- Patients suffering from any diseases presenting, even at sea level, a certain degree of arterial hypoxemia (eg, increased right-to-left shunt) will be at risk at high altitude.
- For a given absolute power output during exercise, the heart rate (and therefore myocardial energy demand) increases with altitude, lowering the ischemic threshold in coronary patients.

The following advice can be given as a function of the preexisting disease.

Arrhythmias

Although rapid ascent to high altitude may increase the frequency of supraventricular and ventricular arrhythmias in patients with underlying heart disease,[60,71,72] no demonstrable clinical impact has been found.[73] However, it is reasonable to limit the access to altitude above 2500 m for patients with severe arrhythmias associated with underlying heart disease.

Pulmonary Hypertension

Preexisting pulmonary hypertension at sea level may deteriorate at even moderate altitude, regardless of the origin of the hypertension. Patients with congenital or acquired anomalies of the pulmonary circulation are also at high risk.[74,75] A transient hypoxic insult to the pulmonary circulation during the first postnatal week leaves a persistent imprint which, when activated by hypobaric hypoxia, predisposes to pulmonary hypertensive responses in adulthood.[76] Nevertheless, a recent pilot study showed that patients with pulmonary hypertension can safely adapt to a moderate altitude of 2048 m.[77]

Right-to-Left Shunt

Right-to-left atrium shunting through a patent foramen ovale (PFO) might be aggravated in hypoxic conditions due to increased pressures in the pulmonary artery and the right heart. PFO was found to be present in 56% of patients susceptible to HAPE vs 11% of non-susceptible subjects.[78,79] Patients with cyanotic congenital heart diseases may be at heightened risk at even moderate altitude.[80]

Coronary Artery Disease

It is reasonable to assume that in patients with a reduced coronary reserve, the decrease in oxygen availability due to altitude exposure will increase the risk of myocardial ischemia. However, the literature shows no evidence of increased incidence of acute myocardial ischemic events at low and moderate altitude.[60,72,81,82] In nine men with coronary artery disease, clinical or electrocardiographic signs of ischemia occurred at lower workloads at 3100 m than at 1600 m, although heart rate and heart rate x systolic blood pressure (rate pressure product, RPP) at the onset of angina were similar at the two altitudes.[72] These findings suggest that patients should limit their activity at high altitude by controlling their heart rate (70–85% of the ischemic threshold rate at lower altitude) rather than their workload. A rapid ascent and submaximal exercise proved to be safe at an altitude of 3454 m for low-risk patients with normal low-altitude exercise stress tests 6 months after revascularization for an acute coronary event.[83] Mortality from coronary heart disease, from 1990 to 2000, in men and women living at 259–1960 m decreased by 22% per 1000 m ascent. The

consistently protective effect of living at higher altitude on coronary heart disease and stroke mortality increased after adjustment for potential confounders.[18]

Congestive Heart Failure

Very few studies are available about heart failure at high altitude.[69,73,84] However, in 38 patients with a mean left ventricle ejection fraction of 35%, acute exposure to 3000 m in a hypobaric chamber induced no signs of myocardial ischemia, arrhythmias, or acute heart failure.[84] Altogether, it seems that up to 3000 m, there is no substantial increase in cardiovascular risk for patients with stable, compensated heart failure.[73,84,85] Corroborating this conclusion, a short-term high-altitude exposure at 3454 m was well tolerated in patients with stable heart failure.[83]

Systemic Hypertension

The systemic circulation at high altitude is affected by two opposing phenomena: local hypoxia-induced vasodilation and general sympathetic-induced vasoconstriction. The relative impact of these two factors on local perfusion and systemic arterial pressures varies considerably among subjects.[73,83,86,87]

In well-controlled hypertensive patients, no significant increase in systemic blood pressure is usually observed and no complications of systemic hypertension at high altitude have been reported.[87] Moreover, in 37 young adult men with stage 1 hypertension, completing a 20-day program of intermittent, normobaric hypoxia (inspired O_2 fraction 0.1; 4–10 daily cycles of 3 min hypoxia and 3 min room air breathing) lowered systolic and diastolic arterial pressures by 22 and 17 mm Hg, respectively.[88] Moreover, the decrease in systemic arterial pressure persisted at least 3 months after the hypoxia program in 85% of the subjects. Concordant with these results, no symptomatic episodes of hypertension were recorded in a cohort of 672 trekkers (60 of them with systemic hypertension), using conventional blood pressure measurements.[89] Therefore, no adverse effects are anticipated when patients with well-controlled hypertension are exposed to high altitude.

In summary, the literature is still sparse concerning cardiac diseases and tolerance to high altitude. However, it seems that patients with cardiac arrhythmias, pulmonary hypertension and right-to-left shunts should avoid an exposure to altitudes above 2500 m. In the case of coronary disease and congestive heart failure, the advice should depend on the functional state of the patient. Patients with well-controlled systemic hypertension are not at higher risk at high altitude.

Relation Between Cardiovascular Pathologies and Neurodegenerative Diseases at Altitude

Cardiovascular risk factors, such as total serum cholesterol or high systolic blood pressure,[90] are major risk factors for cognitive decline, the development of dementia and other age-related neurological diseases.[91–94] The brain's particular vulnerability to perfusion deficits and its specific blood supply requirements, including increased on-demand perfusion with neuronal activation, highly selective permeability across the blood brain barrier, and vulnerability of the cerebral microvasculature, necessitate a particularly delicate regulation of cerebral blood flow.[95]

Diminished oxygen supply to the brain – for example as a consequence of hypoxic conditions in high altitude – jeopardizes brain function and can acutely cause cognitive impairments,[96–101] mood alterations[102,103] and altitude-related conditions impacting the brain, such as acute mountain sickness or high altitude cerebral edema.[104] Severe hypoxia may even trigger parkinsonism-like symptoms[105–107] or global amnesia.[108] Brain deoxygenation at altitude reportedly is more pronounced during physical exercise[109] and more persistent than peripheral deoxygenation.[110]

Several systemic, brain-specific and cellular physiological adaptations are implemented to mitigate the detrimental consequences of hypoxia on the brain.[111–119] As described above, peripheral chemoreceptor-induced hyperventilation[120] and cardiac output[121,122] enhance systemic and brain oxygenation. Metabolic autoregulation and neurovascular coupling[95,123] acutely modulate the cerebral blood flow in response to hypoxia. This modulation can vary across different cerebral arteries; thus, Feddersen et al[124] reported increased blood flow velocity in anterior and middle cerebral arteries of ascending mountaineers, while blood flow velocity in the posterior cerebral artery declined. In rats, acute hypoxia exposure only transiently increases cerebral blood flow,[125] while chronic hypoxia triggers erythropoiesis[125] as well as angiogenesis[125] that increases brain capillary densities.[126,127] At the cellular level, responses to hypoxia are mediated by numerous biochemical adaptations[111] including downregulation of O_2-dependent reactions, promotion of glycolysis,[114]

protection of mitochondria,[115] boosting of antioxidant defense mechanisms[113,116] and attenuation of cell death.[117]

These effects of hypoxia exposure suggest its potential application to counteract age-related and pathological alterations of cerebral blood flow and cerebrovascular alterations. The role of aging-related cerebrovascular deterioration and cerebral blood flow dysregulation on cognitive dysfunction has been reviewed by Toth et al[95] and pathological alterations in neurovascular function are proposed to be key mechanisms in the pathogenesis of Alzheimer's disease.[128]

The cardiovascular adaptations to hypoxia, and in particular intermittent application of hypoxia (ie, hypoxia conditioning), improve cerebral blood flow and cerebrovascular function (Figure 3),[90,129] in a manner that enhances cerebral oxygenation.[130,131] Intermittent hypoxia also increases brain capillary densities, although to a smaller extent than chronic hypoxia.[132] Hypoxia-induced angiogenesis may particularly improve neurovascular coupling.[126,133]

In support of the application of hypoxia to improve brain function, several recent clinical trials have reported improved cognitive function following intermittent hypoxia therapies, for example, in generally healthy older adults[134–136] or those with mild cognitive impairment,[137,138] a risk factor for the subsequent development of dementia. Although experimental data on hypoxia conditioning in patients with age-related neurological diseases is limited, the potential of such therapeutic strategies in these diseases is becoming increasingly acknowledged.[119,139,140] Preclinical studies in rodents further emphasize this potential, for example, in models of Alzheimer's disease[141,142] and Parkinson's disease.[143]

Epidemiological studies on the effect of altitude of residence on brain function are conflicting, due in part to socioeconomic confounders. While reduced memory capacities were reported in young Tibetans living at 3650 m vs low altitude residents[144] and subtle impairments in speed of neurocognitive functions were reported in Andean high vs low altitude residents of different age groups,[145] no adverse cognitive effects were found in adolescent Bolivian high altitude (3700 m) residents.[146] Thielke et al[25] even report reduced Alzheimer's disease mortality at higher altitudes of residence (up to 1800 m) in California.

More research is required to define the effects of altitude of residence on cognitive functions, particularly in association with neurodegenerative diseases. Nevertheless, controlled hypoxia interventions are promising therapeutic approaches to mitigate age- or disease-related cognitive decline.

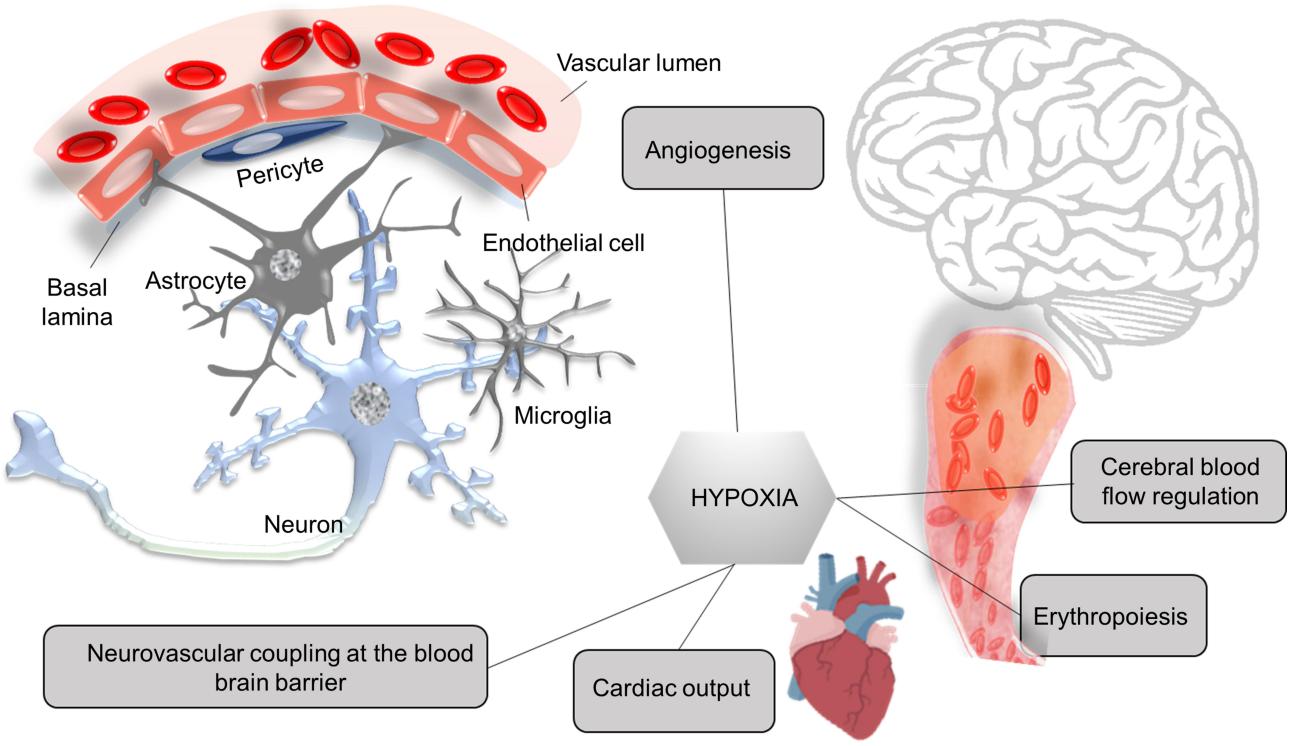

Figure 3 Hypoxia-evoked adaptations improve cardiovascular determinants of brain oxygenation.

Effects of Hypoxia on Aerobic Exercise, and Vice Versa

This section presents a brief description of the effects of hypobaric and normobaric hypoxia on responses to maximal and submaximal exercise, and then discusses some potential benefits and limitations of exercising in hypoxia.

Maximal Responses to Exercise in Altitude

At altitude, the decreased PO_2 and resultant hypoxemia[147] lower maximal oxygen uptake (VO_{2max}) by approximately 6–7% per 1000 m increase at altitude.[148] This altered O_2 intake is the main factor limiting aerobic performance at altitude vs sea level. Of interest, the decrement in endurance exercise performance is less severe in normobaric hypoxia imposed by reductions in the inspired fraction of oxygen (F_IO_2) than equivalent reductions in PO_2 due to decreased barometric pressure, ie, hypobaric hypoxia[149] since the intensity of the normobaric hypoxia stimulus may be lower, although this point is debated.[150,151] In either case, maximal cardiac output declines since both maximal stroke volume and heart rate are lower during hypoxia, whether due to decreased barometric pressure or F_IO_2.

Maximal heart rate (HR_{max}) declines at altitude.[152,153] It was argued that this decrease in HR_{max} is only observable above a threshold of 2000–3500m[147,154] corresponding to the altitude used in training and/or rehabilitation. However, this decrease was reported already at low altitude (<1000 m).[155] Of clinical interest, the decrease in HR_{max} is lower in normobaric than in hypobaric hypoxia.[156]

Submaximal Responses to Exercise at Altitude/in Hypoxia

During submaximal exercise, HR is greater and stroke volume lower at a given exercise intensity in hypoxia vs normoxia. Since resting HR increases while HR_{max} declines with altitude, HR reserve is attenuated, which the HR-based calculations of exercise intensity described below must take into account. The relationships between cardiac output, workload and VO_2 are preserved at all submaximal intensities, but reach their maxima at lower VO_2 and cardiac output[55] implying that altitude does not affect O_2 utilization efficiency. The mechanisms for the increased HR are still debated but sympathetic vasoconstrictor activity and the resultant higher vascular resistance likely predominate.

Therapeutic Exercising in Hypoxia for Cardiovascular Pathologies

Heart rate monitoring is very common and clinically safe for patients.[157] An important aspect when prescribing exercise in cardiovascular patients is the determination of exercise intensity. Generally, the recommended intensity is based on the percentage of HR_{max}[158,159] and is estimated as 60–70% of HR_{max} in patients. The hypoxic decrease in HR_{max} described above has clinical implications and requires adjustment of the exercise intensity at altitude since a given percentage of HR_{max} measured in normoxia would overestimate the target exercise intensity at altitude, with the risks of excessive fatigue or decreased adherence to training sessions.

Exercising in hypoxia, even at submaximal intensity, leads to a 'compensatory' vasodilatation, relative to the same exercise intensity in normoxia,[160] that, by augmenting blood flow, limits the decrement of oxygen delivery to the active muscles. Nitric oxide (NO) appears as the main vasodilator generated by the endothelium[161] even if several other vasoactive substances are also involved in this compensatory vasodilatation during hypoxic exercise. Of interest, this enhanced exercise hyperemia is greater at high altitude and augmented by increased exercise intensity.[160,162] By this mechanism, hypoxia may potentiate exercise-induced vascular adaptations such as vasodilation,[163] potentially benefiting patients with vascular dysfunction as in peripheral artery diseases.

Vasoconstriction in vascular beds of contracting muscles is blunted when exercise is performed in hypoxia, to the extent that vasodilation may prevail.[160] This functional sympatholysis may have additional effect with benefits for hypertensive subjects: the post-exercise hypotensive effect due to a reduction in total peripheral resistance is enhanced in hypoxia suggesting a larger hypotensive effect of exercise in hypoxia than in normoxia,[164] as suggested above.

Altogether, the health benefits of hypoxic exercise in cardiovascular patients are mediated by improved responsiveness of the vascular system, representing the balance of two opposing mechanisms: peripheral vasodilation and sympathetically mediated vasoconstriction. The effects of exercising at altitude in specific patients depend upon several factors, including the patient's predisposition to exercise, the intensity of the hypoxic dose (altitude, exposure duration, rate of ascent, intermittent

pattern) and attainment of adequate exercise intensity (but not limited to moderate intensity). Optimizing the benefits vs risks requires a patient-specific regimen and monitoring.

Cardioprotective Mechanisms of Hypobaric Hypoxia

By generating reactive oxygen species (ROS), intensifying sympathetic stimulation of the heart and lowering intracellular PO_2, systemic hypoxia mobilizes diverse gene programs expressing myriad cytoprotectants including antioxidant, anti-inflammatory and glycolytic enzymes, anti-apoptotic factors and Ca^{2+} transporters, which collectively defend cardiomyocytes from ischemic injury (Figure 4).

Defining hypobaric hypoxia's cardioprotective mechanisms at the cellular level requires invasive analyses of gene expression, proteins, metabolites and organelles, which are not ethically feasible in humans under most circumstances. Consequently, information on the molecular underpinnings of hypoxia-induced cardioprotection is gleaned from studies in animals, primarily rodents. Many such studies utilize intermittent, not sustained, hypoxia involving brief hypobaric exposures or cyclic exposures to normobaric, hypoxic gas. Although intermittent hypoxia's cardinal features differ from those of chronic hypoxia, information on intermittent hypoxia's cytoprotective mechanisms likely applies at least qualitatively to sustained hypoxia, too.

Reactive Oxygen Species Induction of Antioxidant Genes

Hypobaric hypoxia elicits ROS formation in humans. After 48 h at 4300 m altitude, lowlanders showed increased serum and urinary concentrations of the lipid peroxidation products F_2- and 8-isoprostanes.[165] In men exposed to 5500 m simulated altitude for 4 h, arterial O_2 saturation fell by 45%, serum concentrations of the ROS

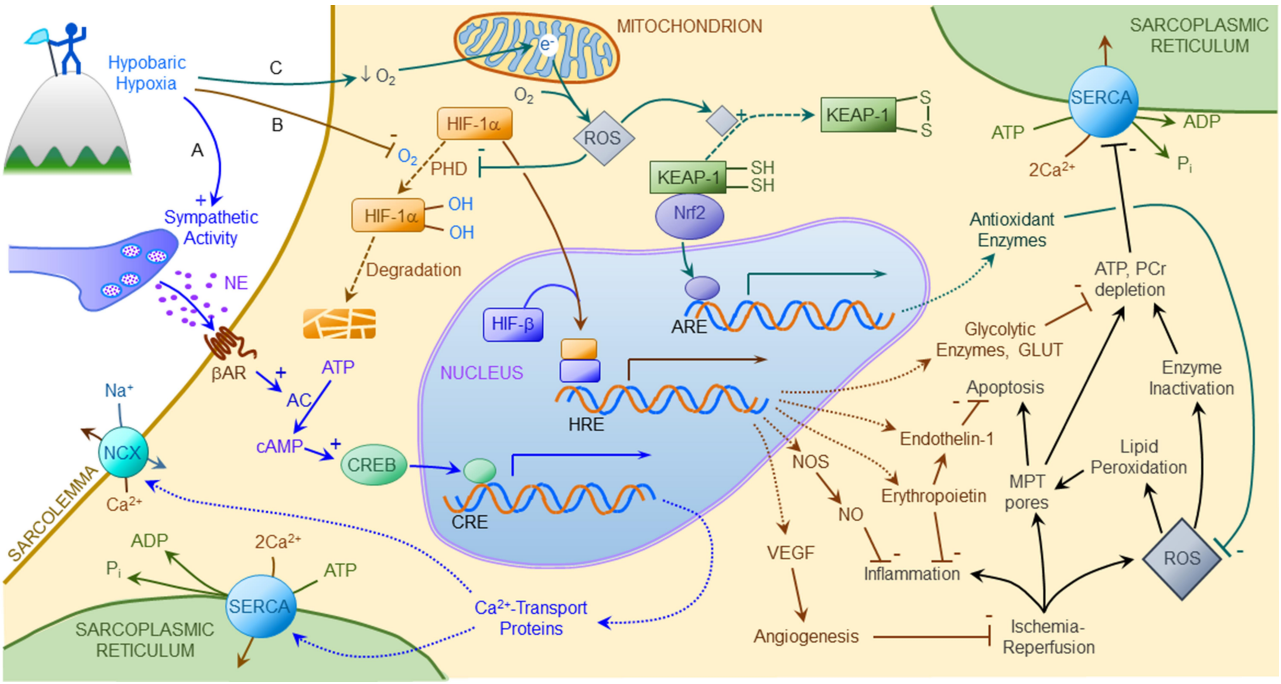

Figure 4 Hypobaric hypoxia induces cardioprotective gene expression. Hypoxia elicits cardioprotective adaptations by activating three gene programs: (A) β-adrenergic activation of cyclic nucleotide response element (CRE) binding protein (CREB) promotes transcription of genes encoding sarcoplasmic reticular Ca^{2+} ATPase (SERCA) and sarcolemmal Na^+/Ca^{2+} exchanger (NCX), thereby improving Ca^{2+} homeostasis in the face of ischemia-reperfusion. (B) Intracellular hypoxia attenuates O_2-dependent, prolyl hydroxylase (PHD) mediated degradation of the α subunit of hypoxia-inducible factor-1 (HIF-1), which translocates to the nucleus, binds HIF's β subunit, and activates hypoxia-response elements (HRE) promoting expression of genes encoding hypoxia-adaptive proteins including erythropoietin, vascular endothelial growth factor (VEGF), nitric oxide (NO) synthase (NOS), endothelin-1, glucose transporters (GLUT) and glycolytic enzymes. Erythropoietin and NO suppress inflammation, VEGF promotes coronary collateral formation, endothelin-1 suppresses apoptosis, and GLUT and glycolytic enzymes support anaerobic ATP and phosphocreatine (PCr) production during ischemia. (C) Cellular hypoxia causes electron (e^-) accumulation in the mitochondrial respiratory complexes. These electrons combine with residual O_2 forming reactive oxygen species (ROS) which oxidize sulfhydryl moieties in Keap1, allowing Nrf2 to activate antioxidant response elements (ARE) in genes encoding antioxidant enzymes, thereby bolstering cellular defenses against ROS overproduction. ROS also augment HIF-1-activated gene expression by blunting HIF-1α degradation. Collectively, these mechanisms increase cardiomyocyte resistance to ischemia-reperfusion induced Ca^{2+} overload, inflammation, mitochondrial permeability transition (MPT), ATP depletion and oxidative stress.

Abbreviations: AC, adenylyl cyclase; β-AR, β-adrenergic receptor; cAMP, cyclic AMP; P_i, inorganic phosphate.

products malondialdehyde and oxidized protein sulfhydryls increased,[166] and serum [glutathione]/[glutathione disulfide] concentration ratio, a measure of antioxidant capacity, fell. In a recent study in lowlanders spending two weeks at c 3300 m, serum concentrations of total ROS, protein carbonyls and lipid peroxides rose by 38%, 140% and 44%, respectively, while antioxidant capacity fell by 17% and serum pro-inflammatory cytokines tripled.[167]

Although intense ROS formation injures cardiomyocytes, moderate ROS formation during controlled hypoxia in rodents activates expression of antioxidant and anti-inflammatory genes, increasing cardiomyocyte resistance to ischemia. Research in hypoxia-conditioned rodents revealed robust antioxidant adaptations that paralleled ischemic tolerance. Jain et al exposed rats to extreme hypobaric hypoxia (9750 m simulated altitude; P_IO_2 c 57 mmHg) then grouped the animals according to their hypoxia endurance.[168] The myocardium of the most hypoxia-tolerant rats had greater activities of EPO, GLUT-1 and the antioxidant enzymes catalase, superoxide dismutase and heme oxygenase-1 vs myocardium of the least tolerant animals. Also in rats, two days hypobaric hypoxia (7620 m simulated altitude; P_IO_2 c 78 mmHg) induced myocardial lipid peroxidation and protein oxidation and depleted glutathione, but by 5 days, myocardial activities of antioxidant enzymes superoxide dismutase, glutathione S-transferase, glutathione peroxidase, heme oxygenase-1 and metallothionein all increased vs control myocardium.[169] Similarly, a program of 4 cycles of 4-days hypobaric hypoxia (4600 m simulated altitude; P_IO_2 c 90 mmHg) and 4-days normoxia elicited mitochondrial ROS formation and increased myocardial catalase, glutathione peroxidase and superoxide dismutase activities.[170,171] Hearts isolated from the hypoxia-conditioned rats demonstrated increased left ventricular function and decreased lipid peroxidation following ischemia-reperfusion, vs hearts from normoxic rats.[170] Similarly, hearts isolated from guinea-pigs completing a 28-day intermittent, hypoxia regimen (5000 m simulated altitude for 6 h/d; P_IO_2 c 112 mmHg) and subjected to ischemia-reperfusion or H_2O_2 exposure showed increased superoxide dismutase and catalase activities and improved contractile function which was abolished by the catalase inhibitor aminotriazole.[172]

Exposure of mice to 10 h hypobaric (4572 m) hypoxia (P_IO_2 = 118 mmHg) activated myocardial expression of genes encoding antioxidant enzymes catalase, glutathione peroxidase, metallothionein and microsomal glutathione S-transferase.[173] The 50% decrease in myocardial glutathione content following hypoxia indicated significant oxidative stress, which likely activated antioxidant gene expression. In dogs completing a 20-day program of cyclic, normobaric hypoxia-reoxygenation 24 h before occlusion-reperfusion of the left anterior descending coronary artery, infarct size was decreased by over 95% and post-ischemic ventricular tachyarrhythmias were sharply attenuated vs sham-conditioned dogs.[174] Oral intake of antioxidant *N*-acetylcysteine 2 h before each hypoxia session abrogated the cardioprotection, implicating ROS in the cardioprotective mechanism. Although the dogs were conditioned by intermittent, not chronic, hypoxia, these results are concordant with cardioprotection by ROS signaling in chronic hypoxia, too.

Although the molecular mediators of ROS-induced gene expression are not yet established, the ROS-responsive transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) is the most likely candidate. ROS disrupt the disulfide bonds linking Nrf2 to its repressor, Keap-1, thereby allowing Nrf2 migration from cytosol to nucleus, where its interactions with antioxidant response elements in the promoter regions activate genes encoding a host of antioxidant and anti-inflammatory proteins[175] including catalase, metallothionein, heme oxygenase-1, glutathione peroxidase, glutathione S-transferase and other elements of the cardiomyocyte's antioxidant armamentarium.[176] The effects of chronic, hypobaric hypoxia on Nrf2 are as yet unknown, and merit investigation.

Hypoxia-Inducible Gene Products

When exposed to chronic hypoxia, cardiomyocytes synthesize proteins that increase their tolerance to reduced O_2 availability. These proteins are products of an extensive gene expression program regulated by hypoxia-inducible factors (HIFs), the best-studied of which is HIF-1, a heterodimer of O_2-regulated α and constitutive β subunits. During normoxia, prolyl and arginyl hydroxylases hydroxylate HIF-1α, targeting it for proteasomal degradation which limits HIF-1-activated gene expression.[177] HIF-1α hydroxylation declines as cellular O_2 concentration falls, whereupon the subunit translocates to the nucleus and combines with the β subunit forming the transcriptionally active HIF-1 heterodimer. By inactivating prolyl hydroxylase, ROS stabilize HIF-1α and, thereby, augment hypoxia-activation of HIF-1's gene program.[178–180] HIF-1 activates hypoxia response elements in the promoters of

over 100 genes.[181] HIF-1 activates expression of [1] glucose transporters (GLUT) and the entire glycolytic enzyme sequence beyond hexokinase, thereby augmenting glucose catabolism and anaerobic ATP production; [2] vascular endothelial growth factor (VEGF) which, by activating angiogenesis, increases collateral O_2 delivery to ischemic myocardium; [3] nitric oxide synthase (NOS), which generates the anti-inflammatory metabolite nitric oxide, [4] endothelin-1 (ET-1), which activates anti-apoptotic signaling cascades[182] and gene expression;[183] and [5] erythropoietin (EPO), which activates red cell production in erythropoietic tissues, and also exerts anti-inflammatory actions in heart and brain, both of which are capable of synthesizing EPO.[184,185] Hypoxia-induction of this diverse gene program[181] increases survival and functional recovery of cardiomyocytes threatened by ischemia-reperfusion.

Chen et al evaluated coronary collateral density in patients with >70% occlusion of one or more conduit coronary arteries.[186] The patients with more extensive coronary collaterals had higher HIF-1α contents in circulating monocytes and leukocytes. The association of greater collateral density and, therefore, myocardial oxygenation with increased HIF-1α content argues that HIF-1α and its gene product VEGF were likely responsible for the increased collaterals.

Sojourns at high altitude elicit EPO production which initiates erythropoiesis to augment the blood's O_2-carrying capacity. Accordingly, circulating EPO concentrations increased within one day of ascent in healthy adults ascending from sea level to >3000 m.[187] Analysis of glycosylated EPO glycoforms pinpointed the kidneys as the major source of circulating EPO in human subjects at 3454 m (P_IO_2 c 137 mmHg).[188] Whether circulating EPO of renal origin contributes to hypoxia-induced cardioprotection, or if hypobaric hypoxia elicits myocardial EPO formation[184] in humans is unknown.

Sasaki et al studied rats acutely conditioned by 4 h normobaric hypoxia (F_IO_2 0.10) and 24 h reoxygenation, followed by permanent coronary artery occlusion.[189] Three weeks later, the hearts of the hypoxia-conditioned rats were found to have greater dobutamine-recruitable contractile reserve, which paralleled increased myocardial capillary and arteriolar density, blood flow and VEGF content vs hearts of non-hypoxic controls. In Jain et al's study, the myocardium of the most hypoxia-tolerant rats had greater activities of EPO and GLUT-1, as well as the aforementioned antioxidant enzymes, than myocardium of the least tolerant rats.[168] In Singh et al's study of hypobaric hypoxia conditioned rats,[169] the increased myocardial antioxidant enzymes at 5 d hypoxia were accompanied by increased HIF-1α content and expression of HIF-1's gene program products EPO, VEGF, GLUT-1 and nitric oxide synthase (NOS). A recent study in mice conditioned by 14 d continuous, normobaric hypoxia (F_IO_2 0.07) demonstrated increased myocardial expression of genes encoding VEGF, its receptor VEGF-R2, and RABEP2, a regulator of VEGF-R2 endosomal trafficking, vs normoxic mice. Myocardium of the hypoxic mice also demonstrated increased coronary collateral development and capillary density, and decreased myocardial infarct size following coronary artery occlusion.[190]

Hypobaric hypoxia is associated with increased circulating ET-1, as documented in healthy human subjects ascending to 3700–5000 m altitude.[191,192] Although a well-recognized vasoconstrictor, ET-1 at moderate concentrations suppresses cardiomyocyte apoptosis[182,183] by mobilizing signaling cascades that activate cytoprotective genes.[193,194] Human[195] and rat[196] cardiomyocytes synthesize and secrete ET-1 in response to hypoxia. HIF-1 activates cardiac ET-1 gene expression both directly[197,198] and via EPO.[199] Unlike moderate hypoxia, severe, deleterious hypoxia provokes ET-1 overproduction which activates cardiomyocyte apoptosis in a manner blunted by endothelin receptor antagonists[200] and likely contributes to the hypertensive response to severe hypoxia.[121]

Sympathetic Activity and Myocardial Ca^{2+} Management

Ascent to altitude elicits sympathetic activation of the heart.[60] Power spectral analysis of heart rate revealed increased sympathetic and decreased parasympathetic activities in lowlanders during 6-month sojourns at 4500–4800 m altitude.[201] Acute exposure of male lowlanders to 4000 m simulated altitude in a barochamber increased serum catecholamine concentrations.[202] Male lowlanders ascending to >3500 m showed persistently elevated sympathetic tone and serum catecholamines.[203]

During hypoxia, β-adrenergic activation increases heart rate and stroke volume to increase cardiac output, thereby maintaining blood pressure and O_2 delivery to the periphery. Cardiomyocytes isolated from rats completing an intermittent, hypobaric hypoxia program showed increased sarcoplasmic reticular Ca^{2+} ATPase activity and anti-apoptotic Bcl-2 content, and preserved sarcoplasmic reticular Ca^{2+} turnover following in vitro ischemia-reperfusion.[204] In

dogs, administration of the β_1-adrenoceptor antagonist metoprolol during a 20-day intermittent hypoxia regimen prevented the robust reductions of coronary occlusion-reperfusion-induced myocardial infarction and ventricular tachyarrhythmias.[205]

Increased cardiomyocyte Ca^{2+} turnover mediates the inotropic and lusitropic effects of β-adrenergic activity. Acutely, phosphorylation of molecular targets by cyclic AMP- and Ca^{2+}-calmodulin dependent protein kinases increases systolic sarcoplasmic reticular Ca^{2+} release to augment Ca^{2+} activation of the contractile machinery, and Ca^{2+} sequestration to effect diastolic relaxation. β-adrenergic activity induces genes encoding Ca^{2+}-transporting proteins (Figure 4) via interaction of cyclic nucleotide response element (CRE) binding protein (CREB) with CRE motifs in gene promoters.[206] Thus, hypoxia-reoxygenation of cardiomyocytes provoked CREB DNA-binding and expression of its target genes.[207] β-Adrenergically activated CREB promotes synthesis of the mitochondrial anti-apoptotic factor, Bcl-2,[208] sarcoplasmic reticular Ca^{2+} ATPase,[206] and sarcolemmal Na^+/Ca^{2+} exchanger.[209] Thus, β-adrenergic activation by hypoxia may elicit gene expression that preserves mitochondrial integrity and Ca^{2+} homeostasis under pathological conditions.

Summary

Preclinical studies have disclosed complex signaling cascades whereby hypoxia bolsters myocardial resistance to ischemia and reperfusion. β-Adrenergic activity, moderate ROS formation and intracellular hypoxia mobilize CREB, Nrf2 and HIF-1 to activate their respective gene programs. The myriad products of these genes augment anaerobic ATP production and membrane Ca^{2+} transport, suppress apoptosis, preserve mitochondrial integrity and confer powerful antioxidant and anti-inflammatory protection to blunt ischemia-reperfusion induced myocardial injury (Figure 4). Defining the extent to which these diverse mechanisms effect cardioprotection in humans is crucial to develop interventions harnessing these mechanisms to treat and prevent ischemic heart disease.

Disclosure

The authors disclose no conflicts of interest in this work.

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