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# Cardiovascular Adaptation to High-Altitude Hypoxia

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**Abstract**

High-altitude exposure has been well recognized as a hypoxia exposure that significantly affects cardiovascular function. However, the pathophysiologic adaptation of cardiovascular system to high-altitude hypoxia (HAH) varies remarkably. It may depend on the exposed time and oxygen partial pressure in the altitude place. In short-term HAH, cardiovascular adaptation is mainly characterized by functional alteration, including cardiac functional adjustments, pulmonary vascular constriction, transient pulmonary hypertension, and changes in cerebral blood flow (CBF). These changes may be explained mainly by ventilatory acclimatization and variation of autonomic nervous activity. In long-term HAH, cardiovascular adaptation is mainly characterized by both functional and structural alterations. These changes include right ventricle (RV) hypertrophy, persistent pulmonary hypertension, lower CBF and reduced uteroplacental and fetal volumetric blood flows.

**Keywords:** high altitude, hypoxia, cardiovascular adaptation, compensatory and pathologic adaptation

## 1. Introduction

High-altitude environment exerts a unique challenge to human life, which is chiefly characterized by lower partial pressure of $O_2$ ($PO_2$) relative to sea level at the same latitudes. The conventional definition of high-altitude hypoxia (HAH) is that arterial blood $O_2$ saturation ($SaO_2$) in body measurably begins to fall at altitudes >2500 m [1]. It is one of the hypoxemic types, which is due to a decrease in the amount of breathable oxygen caused by the low atmospheric pressure of high altitudes, and in turn low maximal oxygen uptake ($VO_2$ max), and the arterial partial pressure of $O_2$ ($PaO_2$) in the body [2]. Reduced oxygen availability at high altitude is associated with significant changes in cardiovascular function and increased the risk of cardiovascular disease. Human body has both short-term and long-term adaptations to altitude that allow it to partially compensate for the lowered amount of oxygen in the atmosphere [3]. In this chapter we present the physiologic and pathologic adaptation of cardiovascular system to short-term and long-term HAH and its underlying mechanisms.

## 2. Cardiovascular adaptation to high-altitude hypoxia

### 2.1. Cardiovascular adaptation to short-term high-altitude hypoxia and the underlying mechanisms

With ascent to high altitude, there is a nonlinear decrease in barometric pressure and a reduction in ambient partial pressure of oxygen ($PO_2$), and, subsequently a decrease in the $PO_2$ at every point along the oxygen transport cascade from inspired air to the alveolar space, arterial blood, the tissues, and venous blood. The higher the elevation attained, the greater the drop in $PO_2$ in the human body. These declines in oxygen tensions trigger a variety of physiologic responses in the cardiovascular system over a period of minutes to weeks after the initial altitude hypoxia exposure that enable the individual adapt to or compensate for the hypoxic environment.

At high altitude, in the short term, the low $PO_2$ of inspired air will typically concomitantly reduce $SaO_2$, so a compensatory adjustment may immediately take place to meet the large and consistent $O_2$ demand of the aerobic metabolism of tissues and cells. Initial lack of oxygen is sensed by the carotid bodies, which causes an increase in the breathing rate. Then the cardio-vascular functions are changed in response to the short-term HAH.

#### 2.1.1. Cardiac system

The main cardiac response to short-term HAH is the adjustment of cardiac function, which includes the changes in heart rate (HR) and cardiac output, left ventricular ejection fraction (LVEF), both ventricular systolic and diastolic function, and arterial blood pressure (ABP). At high altitude, an initial response is that the heart beats faster. Cardiac contractility and submaximal cardiac output also increase acutely during the first few days at altitude. This acute increase in cardiac output may largely be explained by the increased heart rate and may be offset by reduced stroke volume. For example, an earlier study demonstrated that acutely breathing an inspired fraction of $O_2$ of 0.12 caused 22% increase in cardiac output accompanied with 18% increase in heart rate and unchanged stroke volume, so the oxygen delivery to the tissues remained unchanged [4]. In addition, an evaluation of ventricular functions by Doppler echocardiography with tissue Doppler imaging (TDI) in volunteers exposed to acutely short-term (90 min) HAH reported that short-term HAH significantly increased HR, LVEF, isovolumic contraction wave velocity (ICV), acceleration (ICA), and systolic ejection wave velocity at the mitral annulus, indicating enhanced left ventricu-lar systolic function. However, there was no change in right ventricular area shortening fraction, tricuspid annular plane systolic excursion (TAPSE), ICV, and ICA at the tricuspid annulus, dem-onstrating preserved right ventricular systolic function. Furthermore, increase in isovolumic relax-ation time (IRT) at both annuli indicated altered diastolic function of both ventricles [5].

In response to a short-term high-altitude exposure, blood pressure is likely increased to a variable extent in many individuals. The changes in blood pressure may be dependent on individual conditions, the absolute altitude of exposure, and the duration of stay at altitude. A recent study has reported that after acute exposure to 3700 m, diastolic blood pressure and mean arterial blood pressure rose gradually and continually in healthy male young adults [6]. Further analysis showed that higher blood pressure accompanied poor sleeping quality and higher incidence of acute mountain sickness. In addition, systolic blood pressure also

significantly increased after high-altitude exercise [6]. Significant rise in systolic and diastolic blood pressure in the initial phase of exposure to altitude was also reported in other studies [7, 8].

There are several possible mechanisms involved in short-term HAH-mediated cardiac dysfunction. One of the important mechanisms is the changes of autonomic nervous system including parasympathetic nervous system and sympathetic nervous system (SNS). A functional approach to assess the role of parasympathetic nerves by muscarinic blockade reported that tachycardia after 8 hours of exposure to hypoxia can be prevented by muscarinic blockade, which indicated that a muscarinic effect was involved in the tachycardia after short-term HAH [9]. Acute exposure to high altitude induced a statistically significant increase in heart rate associated with a shift of sympathovagal balance towards more sympathetic and less parasympathetic activity, which suggests a depression of autonomic functions and a relative increase in sympathetic activity at higher hypoxic levels [10]. These adaptations consist of significantly increased sympathetic activation as evidenced by heightened circulating catecholamine levels (such as norepinephrine) [11–14]. Mazzeo et al. reported a different catecholamine response between acute and chronic high-altitude exposure [13]. In response to acute exposure to 4300 m (4 hours), the arterial plasma epinephrine levels but not norepinephrine levels were significantly increased. However, both epinephrine and norepinephrine concentrations were increased after 21 days of chronic exposure [13]. These findings provide evidence for a differential adaptive response between sympathetic neural activity and that of the adrenal medulla during high-altitude exposure.

The increase in sympathetic tone may be a natural response by acute nonadapted subjects to counteract the effects of hypoxia. Indeed, short-term altitude exposure can directly or indirectly affect the vascular tone of systemic resistance vessels and enhances ventilation and sympathetic activity through the activation of peripheral chemoreceptors [15]. The peripheral chemoreceptors mainly include carotid bodies and aortic chemoreceptor, which are served as hypoxia sensors in the arterial walls. Carotid bodies act as sensitive monitors of arterial $O_2$ tension ($PaO_2$), whereas aortic chemoreceptors mainly monitor arterial $O_2$ content ($CaO_2$). So, carotid bodies evoke stronger respiratory responses than aortic chemoreceptors [16]. A study in humans exposed to hypoxia demonstrated that carotid bodies are chiefly responsible for ventilatory and vascular response, whereas aortic chemoreceptors mainly mediated the tachycardic response [17]. Another study indicated that hyperventilation induced by hypoxic stimulation of carotid bodies decreased vagal traffic to the heart through Hering-Breuer reflex, which plays an important indirect role in tachycardic response to hypoxia [18]. Meanwhile, hypoxic stimulation of carotid bodies also directly activated SNS to accelerate HR through increasing circulating catecholamine [19]. In addition, hypoxic activation of peripheral chemoreceptors was addressed to reset the baroreflex control of both HR and sympathetic nervous system (SNS) activity to higher levels, so that HR and sympathetic vasoconstriction were increased, which were independent of breathing rate and tidal volume [20].

### 2.1.2. Pulmonary vascular system

Pulmonary circulation is the important portion of the cardiovascular system responsible for the gas exchange. Short-term HAH can immediately trigger hypoxic pulmonary vasoconstriction

(HPV), which, in conjunction with increased cardiac output, leads to an enhanced pulmonary vascular resistance and a rise in pulmonary artery pressure. An investigation reported that human pulmonary vascular tone rose rapidly to reach a maximum within 5 min and was then maintained for the duration of the altitude exposure. This acute hypoxic pulmonary vasoconstriction (HPV) was reversed to baseline values within 5 min after breathing oxygen [21]. HPV is intrinsic to the pulmonary vascular smooth cells and independent of the endothelium, as demonstrated in experiments with endothelium-denuded pulmonary arteries (PAs) [22]. In short-term HAH, it was confirmed that small resistance pulmonary arteries (<200 μm) were highly sensitive to the alveolar $O_2$ tension. There is a functional "$O_2$-sensing unit" in the pulmonary artery smooth muscle cell (PASMC) mitochondria, which can detect falls in alveolar $O_2$, leading to produce a mediator to modulate the function of effector proteins. During hypoxia, the production of the mediator is low, which causes the inhibition of specific $O_2$-sensitive $K^+$ channels resulting in depolarization of PASMCs and activation of voltage-gated L-type $Ca^{2+}$ channels. $Ca^{2+}$ influx is thereby increased and cytosolic $Ca^{2+}$ elevated, resulting in activation of the PASMCs' contractile machinery and development of HPV [23]. Given the fact that there is a lack of voltage-gated L-type $Ca^{2+}$ channels in endothelium, it is most likely that HPV is endothelium-independent and intrinsic to pulmonary smooth muscle cells. However, endothelium-dependent and -independent mechanisms could modulate this response. Hypoxia may enhance pulmonary artery resistance through endothelin (ET) and sympathetic stimulation, whereas HPV may be attenuated by increased release of NO, hyperventilation improving alveolar $PO_2$, and respiratory alkalosis [24].

High-altitude pulmonary edema (HAPE) is not an uncommon form of acute altitude illness that occurs in otherwise healthy mountaineers at altitudes typically above 2500 m. The initial cause of HAPE is a shortage of oxygen caused by the lower air pressure at high altitudes. The mechanisms underlying this oxygen shortage-induced HAPE are poorly understood, but one of the critical mechanisms is an excessive rise in pulmonary vascular resistance or hypoxic pulmonary vasoconstriction leading to increased microvascular pressures. This enhanced hydrostatic stress causes dynamic changes in the permeability of the alveolar capillary barrier and induces a high-permeability noninflammatory lung edema. Previous report indicated that decreased nitric oxide release and enhanced endothelin levels following acute high-altitude exposure may be the major determinants of exaggerated hypoxic pulmonary vasoconstriction in HAPE-susceptible individuals [25]. In addition, other hypoxia-mediated changes of sympathetic nervous activity, endothelial function, and altered levels of other vasoactive mediators such as endothelin and angiotensin II may also contribute additionally to HAPE susceptibility. Although higher pulmonary arterial pressure is associated with the development of HAPE, pulmonary hypertension may not in itself be sufficient to explain the development of high-altitude pulmonary edema. Development of pulmonary hypertension can occur in the absence of HAPE in humans at high altitude.

### 2.1.3. Cerebrovascular system

The brain is the most oxygen-dependent organ in the body. In response to acute exposure to high altitude, cerebral blood flow (CBF) rises significantly to ensure an adequate supply of $O_2$ to meet the brain tissues' large and consistent demand [26–28]. The mechanisms underlying the regulation of CBF during short-term HAH are complex and depend partly on the degree of hypoxia per se and on the partial pressures of arterial oxygen ($PaO_2$) and arterial carbon

dioxide ($PaCO_2$) [29]. Upon ascent to high altitude, a severe drop in $PaO_2$ (to <40–45 mmHg) induces a cerebral vasodilation, which suggests that altitude-mediated reduced $PaO_2$ may act as a cerebral vasodilator. However, the fall in $PaCO_2$ following hyperventilation caused by hypoxic-induced activation of peripheral chemoreceptor also produces cerebral vasoconstriction. Therefore, the changes in CBF at high altitude are highly related to the balance of $PaO_2$/$PaCO_2$ in the circulation. Indeed, it has been demonstrated that the low $PaO_2$-to-$PaCO_2$ ratio explains 40% of the increase in brain blood flow upon arrival at high altitude (5050 m) [26]. The increased CBF is mainly due to heightened hypoxic-induced dilatation in the cerebral circulation prior to ventilatory adjustments [26]. A number of mechanisms are proposed to contribute to the cerebral vasodilation. One of the mechanisms is that hypoxia may increase adenosine and nitric oxide level, which causes an increase in arterial diameter [27]. In addition, the cerebral dilatation can be also regulated through other factors (such as hypoxia inducible factor). Furthermore, the fact that acute altitude exposure-mediated increased CBF and cerebral vasodilation can be reversed by supplemental oxygen suggests a direct hypoxic effect. With increasing altitude, increased CBF is believed to be one compensatory mechanism serving to maintain normal oxygen flux to the brain in the face of arterial hypoxemia. However, the profound hypoxemia experienced by climbers at extreme altitude (>5500 m) is known to be related with cerebral dysfunction. Previous investigation has shown that hypoxia-mediated cerebral vascular dysfunction and cerebral edema is one of the major cause of deaths over 8000 m on Everest [30].

High-altitude cerebral edema (HACE) is a medical condition in which the brain swells with fluid because of ascending to a high altitude. It occurs when the body fails to acclimatize while ascending to a high altitude. HACE can be prevented by ascending to heights slowly to allow the body more time to acclimatize. The major cause of HACE is oxygen deprivation. It is most often a complication of acute mountain sickness or high-altitude pulmonary edema. The current leading theory of its pathophysiology is that HACE is likely a result of vasogenic edema [31]. High-altitude hypoxia increases vascular permeability, which passes through the vasogenic endothelium in the brain. The leaking may be caused by increased pressure, or it may be caused by inflammation that makes the endothelium vulnerable to leaking. It has been reported that activation of vascular endothelial growth factor (VEGF) by hypoxia-inducible factor may be one of the major causes leading to overperfusion of microvascular beds, endothelial leakage, and hence edema [31]. In addition, high-altitude hypoxia can alter cerebral vasodilation coupled with a possible impairment of the autoregulation of cerebral blood flow and disruption of the integrity of the blood brain barrier possibly by hypoxia-mediated release of certain neuromodulators such as VEGF and calcitonin gene-related peptide (CGRP). Furthermore, the increased sympathetic nervous activity at high altitude may also play a role in the development of cerebral edema.

## 2.2. Cardiovascular adaptation to long-term HAH and the underlying mechanisms

Acute short-term exposure to high altitude has been recognized as a type of cardiovascular stress, and results in an immediate increase in heart rate, cardiac output, and a transient rise in the blood pressure but without significant changes in the ejection fraction. However, long-term

exposure to high altitude or people who reside at high altitude show compensate change in cardiovascular system that has allowed them to adapt to high-altitude chronic hypoxia.

### 2.2.1. Cardiac system

In long-term HAH, the changes in cardiac function are different from those in acute short-term HAH. Similar to the short-term HAH, heart rate and arterial blood pressure may remain increased, but stroke volume is decreased and the cardiac output returns to baseline after a longer hypoxic exposure [4]. In long-term HAH, the heart must preserve adequate contractile function in spite of lowered oxygen tension in the cardiac circulation. Suarez et al. had conducted studies in young men during acclimation to a simulated altitude in a chamber for 40 days and their results showed that left ventricular systolic function indices including ejection fraction, ratio of peak systolic pressure to end systolic volume, and mean normalized systolic ejection rate at rest and exercise, were sustained in all subjects at high altitude despite reduced preload, pulmonary hypertension and severe hypoxemia, which means remarkably preserved contractility and excellent tolerance of the normal myocardium to long-term HAH [32]. Another study also demonstrated that cardiac contractility remained normal during exposure to altitude-induced hypoxia with preservation of LV ejection fraction and LV percent fractional shortening [33].

Cardiac adaptation to long-term HAH is characterized by a variety of functional adjustments to maintain homeostasis with minimum expenditure of energy. Such adjustments may help to protect the heart from development of ischemic heart disease. An epidemiological study reported that men residing at high altitude resulted in protection against death from ischemic heart disease [34]. The epidemiological observations on the cardioprotective effect of high altitude were confirmed in various experimental models [35–37]. It has been reported that the hearts of animals adapted to long-term HAH develop better functional recovery following ischemia and produce smaller cardiac infarction. In addition, it has also been reported that adaptation to HAH could protect the heart against ischemia-induced arrhythmias [38]. However, the cardioprotective effect of adaptation to HAH is age-dependent. For example, a recent experiment with rats at stimulated altitude of 5000 m from 7-week-old to their entire lifetime [39] showed that cardiac tolerance to acute hypoxia was significantly increased in up to 18 months-old rats, but it was lost in senescent rats (25 months-old). Similarly, people living at high altitude in the Andeans lost their adaptation and have higher incidence of pulmonary hypertension in their aged life.

The mechanisms underlying cardiac functional changes in response to long-term HAH remain far from being understood. However, recent studies in animals and man have highlighted the role of both sympathetic and parasympathetic nervous system in cardiac adaptation following long-term HAH. The role of the parasympathetic system in regulation of heart rate has been examined in humans from the response to muscarinic blockade. A study in human after exposing to an altitude of 5260 m for 9 weeks found that muscarinic blockade increased HR both at rest and during exercise, which suggested that enhanced parasympathetic activity involves in the altered HR during long-term HAH [40]. Meanwhile, another study in animals reported that the muscarinic receptor density in animals native to high altitude was significantly higher than in those living at low altitude. After 5 weeks of relocation to sea level the

muscarinic receptor density concomitantly declined to the level in sea level animals [41]. In addition, similar to the short-term HAH, the sympathetic nervous system also plays a key role in the regulation of HR and cardiac function during long-term HAH, but the pattern is different from those in short-term HAH. Previous studies in long-term HAH subjects reported that plasma norepinephrine level increased more significantly than epinephrine levels [13, 14, 42, 43]. Although the resting heart rate remains increased, the maximal heart rate (the heart rate at maximal exercise) is reduced at long-term HAH. In view of the evidence of elevated systemic catecholamine levels after long-term HAH, the lower maximal heart rate suggests a change in adrenergic receptor density. Indeed, several studies in animals have shown the change in adrenergic receptor density in response to long-term HAH. For example, a study in rats exposed to 21 days of hypobaric hypoxia found that there was a significant reduction in β-adrenergic receptor density [44]. Another study in rats following 21 days of exposure to a simulated altitude of 5500 m also reported a downregulation of α- and β-adrenergic receptor density in ventricular tissues [45]. Furthermore, studies in humans using isoprenaline as an indirect measure of density of β-adrenergic receptors demonstrated a downregulation of β-adrenergic receptors at high altitude [46]. It has been reported that prolonged HAH exposure could also alter peripheral and central adrenergic receptor expression, leading to changes in cardiac function [47, 48]. Taken together, sustained long-term HAH exposure causes progressive enhancement of both sympathetic and parasympathetic activity, resulting in alteration of cardiovascular function.

In addition to cardiac functional adaptation, cardiac structural adaptation also occurs following long-term HAH exposure. One of the changes in response to sustained HAH is development of right ventricle (RV) hypertrophy. Long-term high altitude-induced RV hypertrophy is a beneficial adaptation that helps to counteract the increased afterload caused by persistent pulmonary hypertension and maintain a normal cardiac output [49]. During the compensated phase of hypertrophy, a study using an isolated preparation of the RV working heart demonstrated that mechanical performance was almost doubled compared with the control group, while the index of contractility remained unchanged, which means that the elevated ventricular performance is merely the result of the increased muscle mass. Meantime, the markedly improved ability of the RV maintaining cardiac output against increased pulmonary resistance was observed [49]. Hypertrophic RV is associated with significant changes of cardiac protein profiling [50]. Experimental results in rats exposed to intermittent high-altitude hypoxia have shown that the concentration of collagenous and noncollagenous proteins was significantly increased both in hypertrophic RV and nonhypertrophic LV [51]. Cardiac enlargement may be the result of both an increase in the number of individual cell elements (hyperplasia) and an increase in their volume (hypertrophy).

### 2.2.2. Pulmonary vascular system

The most common effect of long-term sustained HAH exposure is the development of pulmonary hypertension. Previous studies have reported a prevalence of high-altitude pulmonary hypertension between 5% and 18% of the population living at high altitude [52]. High-altitude pulmonary hypertension is characterized by increased pulmonary vascular resistance secondary to hypoxia-induced pulmonary vasoconstriction and vascular remodeling. The pulmonary

vascular adaptations involve all elements of the vessel wall and include endothelial dysfunction, extension of smooth muscle into previously nonmuscular vessels and adventitial thickening. Long-term high-altitude-induced pulmonary hypertension was not completely reversed by oxygen breathing, suggesting that pulmonary arteries structural remodeling plays a pivotal role in pulmonary hypertension during long-term HAH [53]. Pulmonary arteries (PAs) remodeling involves cellular hypertrophy and hyperplasia in all three structural layers of PAs, namely adventitia, media, and intima. In addition, long-term HAH also causes other structural changes, such as the migration of medial smooth muscle cells (SMCs) into the intima, fibroblast proliferation and increased collagen deposition in the adventitia, more extracellular matrix proteins secreted by endothelial cells, and the appearance of SM-like cells in previously nonmuscularized vessels of the alveolar wall. All these changes eventually result in a reduction of the vascular lumen diameter and an increase in pulmonary vascular resistance [54].

The molecular mechanisms underlying the pathogenesis of high altitude-induced pulmonary hypertension are not fully understood, but several hypoxia-mediated signaling pathways are thought to play a key role. In the pulmonary vasculature, some membrane-bound receptors and signaling proteins are sensitive to hypoxia and play important role in the vascular medial proliferation. For example, a recent study in a sheep model of in utero high-altitude long-term hypoxia exposure demonstrated pulmonary vascular remodeling similar to that seen in other animal models of pulmonary hypertension [55]. The results indicated that pulmonary arteries of long-term HAH-exposed fetuses exhibited medial wall thickening and distal muscularization associated with an increased epidermal growth factor receptor (EGFR) protein expression in the pulmonary arteries. Furthermore, it has been demonstrated that the proliferation of fetal ovine pulmonary vascular smooth muscle cell was attenuated by inhibition of EGFR with a specific EGFR protein tyrosine kinase inhibitor [55]. These findings suggest that EGFR plays a role in fetal ovine pulmonary vascular remodeling following long-term HAH and that inhibition of EGFR signaling may reverse high altitude-induced pulmonary vascular remodeling. Similar to EGFR, platelet-activating factor (PAF) and PAF receptor have also been implicated in the pathogenesis of long-term HAH-induced pulmonary remodeling and hypertension in different animal models [56, 57]. In those studies, high PAF and PAF receptor expression levels in the pulmonary arteries have been reported in the long-term hypoxia-exposed animals [56, 57]. Furthermore, PAF receptor antagonists attenuated hypoxia-induced pulmonary hypertension and pulmonary vascular remodeling [56], suggesting that PAF receptor-mediated signaling also plays a key role in pulmonary vascular remodeling.

Accumulating evidence indicates that intrinsic changes in the ionic balance and calcium homeostasis of pulmonary arterial smooth muscle cells (PASMCs) caused by long-term hypoxia have a profound effect on PA remodeling. The membrane depolarization of PASMCs following the hypoxic inhibition of $O_2$ sensitive $K^+$ channels activated $Ca^{2+}$ influx and elevated cytoplasmic ionized $Ca^{2+}$ via voltage-gated $Ca^{2+}$ channels. Changes in the transport of $K^+$ and $Ca^{2+}$ through their respective ion channels modulate these processes by affecting cell volume, membrane potential, gene transcription, apoptosis, and cell-cycle progression. The adaptation of these ion channels at high altitude appears to involve in pulmonary arteries remodeling [58].

Although PASMCs are the major components of arteries that actively involve long-term HAH-mediated sustained vasoconstriction and enhanced medial hypertrophy, endothelial cells, on

the other hand, can sense humoral and hemodynamic changes incurred by high-altitude hypoxia, triggering their production of vasoactive and mitogenic factors that then affect PASMCs' function and growth [54, 59, 60]. Endothelin (ET)-1 is an important mediator of hypoxia-induced pulmonary vasoconstriction and vascular remodeling [61]. Chronic hypoxia increases ET-1 gene transcription and peptide synthesis in cultured endothelial cells. ET-1 and its receptors are selectively upregulated in patients with primary pulmonary hypertension and in humans exposed to high altitude [61]. Rats exposed to chronic hypoxia exhibit increased pulmonary artery pressure associated with an increase in ET-1 peptide levels. Moreover, hypoxic pulmonary vascular remodeling can be prevented and reversed by administration of ET receptor antagonist [61], suggesting a key role of ET-1 and its receptor-mediated signaling in chronic hypoxia-induced pulmonary hypertension and vascular remodeling.

### 2.2.3. Cerebrovascular system

Upon ascent to high altitude, cerebral blood flow (CBF) rises substantially. However, as HAH-exposed time is increased, the increased CBF will return to near sea level values within 1–3 weeks, which displays clear time-dependent changes during acclimatization. In general, high-altitude native residents have lower CBF values compared to sea level natives. The major mechanism underlying the reduction in CBF of high-altitude residents is the reported elevation in hematocrit and consequently increased arterial oxygen content ($CaO_2$), suggesting an inverse relationship between CBF and $CaO_2$. There are at least four reflex mechanisms that regulate CBF: (1) hypoxic ventilator response; (2) hypercapnic ventilatory response; (3) hypoxic cerebral vasodilation; and (4) hypocapnic cerebral vasoconstriction [62]. On initial arrival at high altitude, hypobaric hypoxia changes the mediators of CBF because of a decrease in arterial oxygen tension, which is an independent mediator of cerebral arteriolar dilatation. In addition, hypoxemia can trigger hyperventilation associated decrease in arterial carbon dioxide tension, which will cause cerebral arterial constriction because of an associated increase in periarteriolar pH. Therefore, over a few days period at a constant altitude, the influence of the arterial oxygen tension-induced threshold for cerebral vasodilation is attenuated and the degree of hypocapnia is enhanced. Furthermore, during a prolonged stay at altitude, the hematocrit also increases, resulting in an increased arterial oxygen content at an unchanged oxygen tension. This change will tend to decrease CBF. Therefore, cerebral hemodynamics during acclimatization to altitude is the result of these homeostatic mechanisms. In addition to these reflex responses, CBF is also regulated by some other hypoxia-induced changes. For example, high-altitude hypoxia-induced changes of cerebral capillary density, hypoxia-induced factor (HIF), nitric oxide, endothelin-1, reactive oxygen species (ROS), and neurotransmitters may be responsible for the falling CBF during long-term HAH [29].

### 2.2.4. Uteroplacental vascular system

Pregnancy is associated with a significant increase in uterine blood flow that optimizes the delivery of oxygen and nutrients to the developing fetus. The greater fall in uteroplacental vascular resistance preferentially directs blood flow to this vascular bed, raising the uterine blood flow from 20–50 ml/min in the nonpregnant state to 450–800 ml/min in the near-term pregnant stage [63]. The adaptations in the uterine circulation to pregnancy are complex and

are mainly achieved through the remodeling of uterine vasculature, enhanced vasodilator response, blunted vasoconstrictor response, and reduced pressure-dependent myogenic reactivity. At sea level pregnant uterine artery diameter doubles due to the vascular growth and remodeling as well as due to alterations in vasoreactivity, and changes in the active and passive properties of the uterine artery vascular wall. The molecular mechanisms prompting uterine vascular growth and enlargement of the vascular diameter are not fully understood. However, one of the major mechanisms underlying pregnancy-mediated decreased uterine vascular resistance may be regulated through hormonal stimuli. It has been reported that estradiol is likely a key player because of its angiogenic properties and stimulatory effects on nitric oxide-mediated vasodilation [64]. Estrogen receptors (ERs) have been identified in uterine artery vascular smooth muscle and their expressions are significantly increased in pregnant uterine arteries as compared with nonpregnant uterine arteries [65]. The pregnancy-associated increased ER expression may directly upregulate vascular endothelial growth factor (VEGF), MAP kinase, and eNOS expression and their activities, leading to promote uterine vascular growth and vasodilation [65]. The decreased uterine vascular resistance can also be regulated by contractile agonists or related proteins. For example, pregnancy decreases PKC activity but increases ERK kinase activity in uterine arteries, leading to decrease in uterine artery contractility [66, 67]. In addition, myogenic tone and distensibility are additional factors that can alter uterine arterial intraluminal diameter and uterine vascular resistance. It has been reported that pregnancy significantly downregulates pressure-dependent myogenic tone and increases the pressure-dependent passive uterine arterial diameter. The reduced myogenic tone is mediated by an increase in the inhibitory effect of ERK and a decrease in the PKC signal pathway [68].

High-altitude hypoxia has profound effects on uteroplacental circulation including altered uteroplacental and fetal volumetric blood flows, resulting in fetal intrauterine growth restriction. It has been demonstrated that high-altitude hypoxia decreases the pregnancy-associated rise in uterine blood flow [69]. Reduced uterine blood flow and inadequate perfusion of the placenta have been attributed to the increased incidence of preeclampsia and fetal intrauterine growth restriction [1]. One of the mechanisms that contributes to the decreased uterine blood flow may be a significant inhibition of pregnancy-associated increase in uterine vascular growth. It has been reported that there is only half as much pregnancy-mediated increase in uterine arterial DNA synthesis in chronic hypoxic vs. normoxic animals [70]. The proliferative response to serum stimulation in cultured uterine arterial smooth muscle cells is also attenuated by hypoxia exposure [70]. In addition, high-altitude hypoxia also can alter pregnancy-associated responses to contractile proteins and vasodilator-mediated signaling pathways. Experimental studies in sheep, that experienced long-term high-altitude exposure during pregnancy, showed significant increase in the pressure-dependent myogenic tone of resistance-sized uterine arteries by suppressing the ERK1/2 activity and increasing the PKC signaling pathway [65]. Furthermore, high-altitude hypoxia exposure selectively downregulated estrogen-$\alpha$ receptor expression in uterine arteries of pregnant animals and inhibited the steroid hormone-mediated adaptation of ERK1/2 and PKC signaling pathways to cause an increase in the myogenic tone of uterine arteries in pregnancy [65]. These observations provide a novel molecular mechanism underlying high altitude-induced decrease in

uterine blood flow by inhibition of estrogen/receptor-mediated signaling in pregnancy. The large-conductance $Ca^{2+}$-activated $K^+$ (BKca) is abundantly expressed in vascular smooth muscle cells. Previous studies have suggested that BKca channel is involved in the regulation of uterine circulation and the increase in uterine blood flow during pregnancy [71]. The BKca channel in vascular smooth muscle is a major effector in response to hypoxia. Studies in pregnant sheep model of long-term high-altitude (3801 m) exposure provide novel evidence that long-term high-altitude hypoxia during pregnancy adversely affects the uterine circulation via downregulating BKca channel function in uterine vasculatures [72]. High-altitude hypoxia during gestation significantly inhibited pregnancy-associated upregulation of BKca channel activity and attenuated BKca channel current density in pregnant uterine arteries [72]. This was mediated by a selective downregulation of BKca channel β1 subunit expression in the uterine arteries. In accordance, high-altitude hypoxia impaired the role of the BKca channel in regulating pressure-induced myogenic tone of uterine arteries that was enhanced in pregnant animals acclimatized to high altitude. These results suggest that selectively targeting BKca channel may be another key mechanism in the maladaptation of uteroplacental circulation caused by high-altitude hypoxia, which may contribute to the decreased uterine blood flow and fetal intrauterine growth restriction associated with maternal hypoxia. The molecular mechanisms underlying high-altitude hypoxia-mediated alteration of targeting gene expression in pregnant uterine arteries are not completely understood. However, recent studies suggest that epigenetic mechanism plays an important role in regulation of gene expression in adaptation to high altitude [73]. The results showed that chronic hypoxia increased estrogen receptor $\alpha$ subunit (ER-$\alpha$) promoter DNA methylation at both specific protein-1 and upstream stimulatory factor binding sites, decreased specificity protein-1 and upstream stimulatory factor binding to the promoter, and suppressed ER-$\alpha$ expression in uterine arteries of pregnant animals [73]. Furthermore, the studies provide novel evidence that hypoxia-mediated DNA methylation plays a causal role in ER-$\alpha$ gene repression and ablation of estrogen-mediated adaptation of uterine arterial BKca channel activity, resulting in increased uterine arterial myogenic tone in pregnancy [73].

There are significant differences in uterine arterial adaptation to pregnancy between the long- and short-resident high-altitude populations. The weight of the babies born to Tibetan residents at high altitude is more than that of those born to Han women living at the same altitude, which is associated with a higher uterine flow velocity and larger uterine arterial diameters [1]. The uterine arterial diameters in Andean pregnant women are also most doubling increased at high altitude whereas there are about half as much increase in European pregnant women [74]. As a result, Andean pregnant women have much higher uterine blood flows and birth weights of their babies than Europeans at high altitude. However, the values are the same at low altitude in both Andean and European women, which suggests a much higher protective effect of Andean ancestry at high altitude. The questions why long-resident high-altitude populations (such as Tibetan and Andean women) have higher resistant to the adverse effects of high-altitude hypoxia than the short-resident populations (such as Han and European women) are not fully understood. However, recent reports suggest that genetic background may play a key role in the altitude-related changes in birth weight and uterine blood flow [1].

## 3. Conclusion

The adaptation of the cardiovascular system to altitude is variable, depending on individual predisposition, the actual elevation, the rate of ascent, and the duration of exposure. In acute short-term exposure to HAH, the initial response is increasing sympathetic activity and hyperventilation resulting in increases in systemic vascular resistance, blood pressure, heart rate, and cardiac output. Pulmonary vasoconstriction leads to pulmonary hypertension. However, in response to acute HAH, cerebral blood flow (CBF) rises significantly to ensure an adequate supply of $O_2$ to meet the brain tissues' large and consistent demand. The sympathetic excitation results from acute HAH, partly through chemoreceptor reflexes and partly through altered baroreceptor function. In long-term HAH exposure or resident at high altitude, cardiovascular system progresses a compensatory adaptation. The cardiovascular system may promote adaptational changes in cardiovascular structure, remodeling, and functional proteins through different molecular mechanisms including epigenetic regulatory and/or genetic factor-mediated mechanisms. However, cardiovasculatures may progress a pathologic adaptation and develop a maladaptation syndrome known as high-altitude pulmonary edema, cerebral edema, chronic mountain sickness, pulmonary hypertension, heart failure, and fetal intrauterine growth restriction. In conclusion, cardiovascular system progresses a compensatory and pathologic adaptation to HAH. Understanding those adaptation processes will help us to reduce the development of adverse changes and simultaneously preserve the beneficial signs of the process of adaptation.

## Author details

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