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Mini Review

High Altitude Exposure and Cardiovascular Circulation: Friends or Foe?

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ABSTRACT

Cardiovascular function encounter changes on exposure to altitude. The fall in arterial blood oxygen saturation, due to low quantity of breathable oxygen, caused by low atmospheric pressure at high altitude, is known as High altitude hypoxia (HAH). The human body is capable of adapting to HAH via short- and long-term mechanisms. HAH affects the vascular tone of the pulmonary and systemic vessels thereby increasing ventilation, which is the first notable change at high altitude (HA). Exposure to altitude increases cerebral and coronary blood flow and causes pulmonary hypertension. Pulmonary hypertension, is associated with a rise in pulmonary vascular resistance secondary to vasoconstriction induced by hypoxia and vascular remodeling. Initially exposure to HA decreases systolic blood pressure which increase when the sympathetic nervous system is activated. The increase in blood pressure and sympathetic nervous system activation, leads to an increase in heart rate and cardiac output, which falls to normal few days after acclimatization, but the increased heart rate is retained, while the stroke volume remains decreased. The adaptation of the cardiovascular system to chronic exposure to hypoxia involves both structural and functional changes. These include; persistent pulmonary hypertension, right ventricle (RV) hypertrophy, decrease in CBF and reduced fetal and uteroplacental volumetric blood flows. This review focuses on the adjustment of the cardiovascular system to high altitude exposure.

Keywords: *Cardiovascular adaptation, Hypoxia, Circulation, High Altitude, Hypertension*

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INTRODUCTION

Humans are faced with unique challenges at high-altitude environments including cardiac stress (Naeije, 2010). High altitude (HA) is generally defined as greater than 2500 meters above sea level (mASL) approximately 8200ft (Leon-Velarde and Reeves, 1999) which is associated with lower partial pressure of O2 (PO2) relative to sea level. A recent estimation revealed that ≈83million people live at >2500 mASL, which includes populations mainly from South America, Central Asia, and Eastern Africa (Beall, 2014). These highlanders are chronically exposed to relative hypoxia, which has important consequences on the cardiovascular system and blood pressure (BP) regulation (Beall, 2014).

High-altitude hypoxia (HAH) is conventionally defined by the fall in arterial blood O_2 saturation (SaO_2) in the body at altitudes >2500 m (Moore *et al*., 2011). The hypoxemic type, caused by the high altitudinal low atmospheric pressure, due to decreased breathable oxygen quantity, resulting to low maximal oxygen uptake (VO_2 max), and arterial partial pressure of O2 (PaO2) in the body (Naeije, 2010). Oxygen availability decrease at high altitude leads to significant changes in cardiovascular system functions and increased risk of cardiovascular diseases. Low amount of atmospheric oxygen can be partially compensated for, by both long-term and short-term adaptations to altitude by the human body (Wagner, 2000). The first notable physiologic change at HA is hyperventilation. Several endocrine changes are induced by HA such as activation or inhibition of hormonal systems (Jean *et al*., 2010). Red blood cells are important players in the transport of oxygen in the body and are regulated by

erythropoietin. Prolonged exposure to HA leads to increased erythropoietin production resulting in increase in hemoglobin concentration increase (Naeije, 2010).

Adults at high altitude experience cardiovascular death as a leading cause of non-traumatic deaths (Burtscher and Ponchia, 2010). Exposure to high altitude causes the resting heart rate to increase relative to sea level. Also, in contrast, maximal heart rate is decreased (Bärtsch and Gibbs, 2007). The increased stroke volume observed with exercise at sea level is decreased at HA (Bärtsch and Gibbs, 2007, Boushel *et al*., 2001, Boos *et al*., 2014). Subsequently, while resting cardiovascular yield is higher at HA, versus ocean level, at top exercise it is relatively lower (Bärtsch and Gibbs, 2007, Boos *et al*., 2014, Naeije, 2010). These variables related to the huge diminishing in blood vessel oxygen content act to restrict top exercise limit and oxygen utilization (Bärtsch and Gibbs, 2007, Naeije, 2010). Other cardiovascular reactions remember an expansion for resting brachial artery systolic blood pressure (SBP) and 24hours arterial blood pressure (BP), which in relation to the rise in resting pulse, could be potential embroiling factors in cardiovascular danger (Bilo *et al*., 2015). Systemic hypertension is influenced by environmental factors such as high-altitude, genetics, race and geographic location. Studies have focused on the acute and subacute hemodynamic changes in lowlanders who are suddenly exposed to HA. Although, little is known about the definite pathophysiologic mechanisms of chronic hypertension at HA, differences in the characteristics of chronic hypertension between various HA settings, or the efficacy of anti-hypertensive agents in chronic highlanders. People living in low-income countries, such as the majority of highlanders, demonstrate higher prevalence of non-communicable diseases, including hypertension (Islam *et al*., 2014). Although, the current extent of hypertension is considered as a global public health issue by the World Health Organization (WHO, 2017), the real burden of hypertension and its complications in HA locations worldwide is not well defined. Given the large number of highlanders around the world, and the well-established role of hypertension in cardiovascular risk, hypertension at HA is a highly relevant clinical and public health problem that requires increased awareness and study. This review presents the physiologic and pathologic variation of cardiovascular framework to present moment and long haul HA and its basic systems.

High Altitude Exposure and the Cardiovascular Function

Heart rate: Acute hypoxia prompts increment in cardiovascular yield (which falls at rest and on workout with acclimatization), heart rate (at rest and on work out), and myocardial contractility for the initial days on introduction (Riley and Gavin, 2017).

The electrocardiogram at HA shows dynamically expanded adequacy of P wave, right QRS axis deviation, and indications of RV over-burden and hypertrophy (Riley and Gavin, 2017). In some cases, an electrocardiogram may stay unaltered up to outrageous elevations (Naeije, 2010). Elevation and exercise might be identified with supraventricular and ventricular untimely pulsates, there is no proof of an expanded instance of hazardous arrhythmias in either typical subjects or patients with coronary illness (Bartsch and Gibbs, 2007).

One of the earliest responses to high altitude is increment in heart rate (HR). The increase is identified with increased sympathetic activity and vagal withdrawal (Riley and Gavin, 2017). In a study of 139 healthy men, HR increased by 20.44 beats per min at an altitude of 3700m compared with 500m (Rao *et al*., 2015). Although, the underlying mechanism for this increase, particularly during exercise, is not understood; undoubtedly, increased sympathetic activity and circulating catecholamines play essential roles in increasing HR at rest but few studies reported that preliminary administration of beta blockers can overcome this increase (Mirrakhimov and Winslow, 2011). In other studies, only an obstruction of both sympathetic and vagal activities simultaneously can totally overcome the rise in HR induced by hypoxia at rest (Siebenmann *et al*., 2015). Therefore, it is possible that both vagal withdrawal and an increase in sympathetic activity are responsible for the rise in resting HR with altitude. Chronic exposure to altitude leads to enhancement in parasympathetic activity, causing reduction in maximum HR. During exercise HR is also decreased from sea-level values (Boushel *et al*., 2001). However, at rest, there are discordant data on whether HR is normalized or remain slightly elevated with acclimatization (Siebenmann and Lundby, 2015). Vagal withdrawal (which is important at rest) appears to play a more central role during exercise-induced tachycardia in hypoxia.

In a study by Siebenmann *et al*. (2015), observations showed that propranolol had no effect on exercise-induced tachycardia at altitude. Also, a combination of beta-adrenergic and muscarinic blockade only caused partial reversal of HR which suggests that other factors are involved (Siebenmann *et al*., 2015). They also observed that cardiac alpha adrenoceptors may respond to elevated levels of circulating catecholamines to control HR at HA. Animal studies also showed that pulmonary stretch receptors may play a role in regulating HR at high altitude, although the mechanisms of this is not fully understood and may simply be through an increase in sympathetic activity (Mirrakhimov and Winslow, 2011). Further studies are required on these possibilities, particularly the role cardiac alpha receptors play in the regulation of HR in hypoxia. There is possibility also that endothelin-1 (ET-1) plays a role in the control of HR HA. Receptors for ET- 1 (a potent vasoconstrictor peptide) are present in cardiomyocytes (Riley and Gavin, 2017). Plasma ET-1 is elevated with ascent to altitude (Riley and Gavin, 2017). Activation of the ET-1 b-type receptors in cardiomyocytes triggers a leak of calcium ions from the sarcoplasmic reticulum, delivering positive inotropic and chronotropic effects (Kohan *et al*., 2011; Karppinen *et al*., 2014). Parasympathetic activity is enhanced with chronic exposure to HA, leading to a decrease in maximum HR. The change in HR during exercise is also decreased from sea-level values (Boushel *et al*., 2001). However, there are conflicting data at rest if HR is normalized or maintains slightly elevated with acclimatization (Siebenmann and Lundby, 2015). Heart rate variability (HRV) is another area of interest of late for some studies. Reduction in HRV is a common finding at HA as a result of increased sympathetic activity (Karinen *et al*., 2012). In an investigation by Karinen *et al*., (2012)

observations revealed that HRV parameters could be used as a predictor of acute mountain sickness (AMS). A study by Mairer *et al*. (2013) showed a contradicting observation that HRV indices were not associated with the prediction of AMS (Mairer *et al*., 2013). Older subjects showed less adaptation and a decreased cardiovascular response to HA, suggesting that age may affect the increase in HR (Richalet and Lhuissier, 2013). Altitude simulation has recently allowed researchers to look at how different environmental components of altitude, such as hypoxia and hypobaria, affect HR. One such study found that post-exercise resting HR was 50% higher in hypobaric hypoxia compared with normobaric hypoxia (Di Pasquale *et al*., 2015). This example shows that both the hypobaric and hypoxic components of high altitude environment are responsible for our physiological response and not hypoxia alone.

Cardiac output and Stroke volume: Acute exposure to HA increases cardiac output (CO) to preserve O2 delivery to tissues. Although, maximal cardiac output remains the same (Ke *et al*., 2017) and maximum oxygen utilization (VO2 max) falls by 1% per 100 m above 1500m. The increase in cardiovascular yield is clarified by the increment in heart rate which might be counterbalanced by decreased stroke volume, which is discernible right off the bat. The role of stroke volume (SV) in CO increase with altitude remains controversial Siebenmann and Lundby (2015) which suggest that SV remains the same in acute hypoxia, while the results from studies on the subject are varied (ranging from a decrease (Sime *et al*., 1974) to increase in SV (Rao *et al*., 2015). An investigation by Rao *et al*., (2015) uncovered a significant increase in SV with acute exposure to HA from 64.65mL at 500m to 68.09mL at 3700m in 139 healthy males. They hypothesize that the reason for this increase in SV is likely due to increased venous return due to enhanced sympathetic activity on vasculature. Following this acute increase in SV, evidence shows that chronic reduction in SV following acclimatization, returns CO to normal physiological levels. While ejection fraction is increased after time, ruling it out as the cause of SV reduction during (Siebenmann and Lundby, 2015), SV reduction during acclimatization may be as a result of altered filling of the ventricles (Stembridge *et al*., 2016) which is likely due to decreased preload, as a result of pulmonary vasoconstriction (Siebenmann and Lundby, 2015). Blood volume rises with acclimatization due to polycythemia, which would alter venous return and CO, this is counteracted by the vascularization of tissues involved in venous return to normal levels (Mirrakhimov and Windslow, 2011). Maximum achievable CO decreases with chronic HA exposure (Wagner, 2000; Calbet, 2003). The leading theory for this is that muscle function is decreased at altitude, limiting its need for increased blood flow. Another theory is reduced myocardial function due to hypoxemia with the support of in vitro experiments. In vivo experiments have shown that myocardial function is maintained up to 5000m (Stembridge *et al*., 2016).

Blood pressure: Blood pressure (BP) changes during both acute and chronic altitude exposure are properly defined. Initially, there is a decrease in systolic BP due to hypoxic vasodilation, which is quickly (within a few hours) counteracted by the sympathetic nervous system activation, which raises systolic blood pressure (SBP) above sea-level values. Systemic hypertension is well documented (even in HA natives) in chronic HA exposure (Mirrakhimov and Windslow, 2011). A study by Lang *et al*. (2016) revealed that diastolic BP did remained unchanged between sea level and altitude in mildly hypertensive patients (Lang *et al*., 2016). Chronic intermittent exposure to HA causes no long-term effect on BP (Vinnikov *et al*., 2016). The increased SBP is evident even after moderate HA exposure. A study of 46 healthy people showed an increase in 24-hour ambulatory BP after an exposure to just 2035m (Torlasco *et al*., 2015). There is enhancement in BP response of hypertensives to exercise at HA (Lang *et al*., 2016). This systemic vasoconstriction is crucial in the maintenance of arterial O2 concentrations (Bender *et al*., 1988), although, the increase in SBP is linear with plasma noradrenaline concentration (Mirrakhimov and Windslow, 2011) which shows the importance of sympathetic activity in this response. Similar to HR, simultaneous alpha and beta blockade does not reverse it, which implies that other mechanisms must partially be responsible (Bartsch and Gibb, 2007). Compensatory polycythemia is a possibility, which elevates blood volume and the role of the renin-angiotensin system. Despite the crucial changes that have been observed, the effects of HA on the renin-angiotensin aldosterone system (RAAS) and the resulting effect on BP are widely ignored by some studies. Studies on RAAS at HA revealed acute decline in plasma levels of renin, aldosterone, and angiotensin II, but increase to normal levels with acclimatization (Maher *et al*., 1975; Keynes *et al*., 1982; Parati *et al*., 2014; Lang *et al*., 2016). The activity of renin and aldosterone also reduces (Lang *et al*., 2016; Riley and Gavin, 2017). The mechanism for the reduction in these components of RAAS is not known since the increase in sympathetic activity seen at HA in conjunction with renal artery vasoconstriction would be expected to increase plasma renin levels. Also, there are peculiarities in the levels of angiotensin-converting enzyme (ACE) at HA; a study revealed that peripheral ACE increases with acute altitude exposure (Kamikomaki and Nishioka, 2004) despite several studies showing that trans-pulmonary ACE activity decreases (Li *et al*., 2016). It is known that RAAS inhibition is a way to regulate the increase in BP at HA, although it may not be as effective as it is at sea level (Parati *et al*., 2014; Lang *et al*., 2016). Sympathetic regulation may be more effective (Bilo *et al*., 2011).

High Altitude Exposure and the Cardiovascular Circulation

The vascular tone of the systemic and pulmonary vessels is influenced by hypoxia, which elevates ventilation and sympathetic activities by means of incitement of the peripheral chemoreceptors (Bärtsch and Gibbs, 2007). Associations happen between the immediate impacts of hypoxia on blood vessels and the chemoreceptor-intervened reactions in the systemic and pulmonary circulation. Regulation of local oxygen conveyance as per the necessities of the tissues is accomplished by several mechanisms (Singel and Stamler, 2005; Lundberg and Weitzberg, 2005). One of such mechanisms is the arrival of ATP from red blood cells and the

production of nitric oxide (NO) by different approaches to control local oxygen conveyance as indicated by the necessities of the tissue. Extended stay at high altitude decreases these mechanisms when blood oxygen content is elevated on account of ventilatory acclimatization, a rise in hematocrit related with plasma volume decrease, and an increment in red blood cell mass because of erythropoiesis. Peripheral chemoreceptor afferent action rises hyperbolically as hypoxia builds (Marshall, 1994). Exposure ranging from several days to weeks elevate the sensitivity of the peripheral chemoreceptors to hypoxia, resulting in further improvement of ventilation (ventilatory acclimatization). Presumably, this is responsible for the further increment in sympathetic activity archived by micro-neurography following 3 weeks at 5200m (Hansen and Sander, 2003) and raised catecholamines in urine and plasma (Mazzeo *et al*., 1991). Blood pressure is reduced during the first few hours of exposure to HA which results from the nullification of sympathetic vasoconstriction in the systemic circulation by hypoxic vasodilatation. The blood pressure and systemic vascular opposition is elevated for about 3 to a month due to expanding sympathetic activities and diminished tissue hypoxia related with acclimatization. Oxygen administration does not fully reverse the increased blood pressure (Bärtsch and Gibbs, 2007) which suggests the involvement of additional mechanism.

Coronary Circulation: On intense introduction to hypoxia, the epicardial coronary arteries widens. A rise in resting myocardial blood flow makes up for the decreased blood oxygen content and adds to the upkeep of cardiovascular capacity (Koepfli *et al*., 2004), while work-out instigated coronary flow reserve is maintained at least to 4500 m (Wyss *et al*., 2003). In a study, healthy young indicated no myocardial ischemia on work out during a recreated climb to the culmination of Mount Everest (8840 m) more than 40 days (Malconian *et al*., 1990). Following 10 days at 3100 m (Bärtsch and Gibbs, 2007), coronary blood flow is diminished which is in contrast with at sea level and in relation to the drop in left ventricular work because of the rise in oxygen content of arterial blood with acclimatization. Hence, myocardial oxygen extraction per volume of blood rises to keep up myocardial oxygenation.

Pulmonary Circulation: Pulmonary hypertension is the most well-known impact of long-term exposure to HAH. Components of the vascular walls and endothelial dysfunction, expansion of smooth muscle into formerly non-muscular vessels and adventitial thickening are involved in pulmonary vascular adaptations.

Oxygen breathing does not completely reverse HA induced pulmonary hypertension from chronic exposure to HA, this suggests that pulmonary arterial structural remodeling is crucial in pulmonary hypertension during chronic exposure to HA (Ke *et al*., 2017). Several scientific investigations have detailed the pervasiveness of HA pulmonary hypertension somewhere in the range of 5% and 18% of the populace living at high height (Xu and Jing, 2009). High-altitude pulmonary hypertension is described by an ascent in pulmonary vascular obstruction auxiliary to hypoxia-instigated pulmonary vasoconstriction and vascular remodeling. Pulmonary arteries (PAs) redesigning includes cell hypertrophy and hyperplasia in each of the three structural layers of PAs, specifically adventitia, media, and intima. Also, chronic exposure to HA causes other structural alterations, for example; relocation of medial smooth muscle cells (SMCs) into the intima, fibroblast multiplication and an increment in collagen deposition in the adventitia, increment in extracellular matrix proteins secretion by endothelial cells, and the presence of SM-like cells in formerly non-muscular vessels of the alveolar wall. These changes lead to a decrease in vascular lumen distance across and an ascent in pulmonary vascular opposition (Stenmark *et al*., 2006). The molecular mechanisms fundamental to the pathogenesis of high altitude-instigated pulmonary hypertension are not completely understood, yet a few hypoxia-mediated signaling pathways are considered as players. Membrane-bound receptors in pulmonary vessels and signaling proteins are responsive to hypoxia and are significant in vascular medial multiplication. Recently, an examination utilizing sheep model of in utero exposure to chronic HAH shows that pulmonary vascular redesigning was like that seen in other animal models of pulmonary hypertension (Sheng *et al*., 2009). The outcome demonstrates that pulmonary arteries of fetuses introduced to chronic HAH displayed medial wall thickening and distal muscularization attributed to a rise in epidermal growth factor receptor (EGFR) protein expression in the pulmonary arteries. In a study, it was revealed that EGFR was crucial in fetal ovine pulmonary vascular redesigning following chronic HAH introduction and EGFR signaling restraint may invert high altitude-instigated pulmonary vascular redesigning. EGFR, Platelet-activating factor (PAF) and PAF receptor have likewise been indicated in the pathogenesis of chronic exposure to HAH-instigated pulmonary redesigning and hypertension in various animal models (Ono *et al*., 1992, Bixby *et al*., 2007). High PAF and PAF receptor expression levels in pulmonary arteries have been reported in exposure to chronic hypoxia in animal models (Ono *et al*., 1992; Bixby *et al*., 2007). Changes in ionic homeostasis of pulmonary arterial smooth muscle cells (PASMCs) brought about by chronic exposure to HAH have pronounced effects on PA redesigning. Membrane depolarization of PASMCs following O2 sensitive K+ Channels inhibition ignites Ca2+ influx subsequently elevating cytoplasmic ionized Ca2+ through voltage-gated Ca2+ channels. These adjustments in potassium and calcium ion transport regulates these processes by altering membrane potential, apoptosis, gene transcription, cell-cycle progression and cell volume. These adaptations are involved in pulmonary arterial remodeling. PASMCs, despite being a major component of arteries actively involved in the mediation of maintained vasoconstriction and promotion of medial hypertrophy, however, endothelial cells can detect humoral and hemodynamic changes resulting from exposure to chronic HAH, thereby triggering the release of vasoactive and mitogenic factors that influences the growth and function of PASMCs (Emery, 1994, Gerasimovskaya *et al*., 2005, Stenmark *et al*., 2006).

Exposure to chronic hypoxia builds gene transcription and peptide synthesis of Endothelin (ET)-1, a key player in hypoxia-instigated pulmonary vasoconstriction and vascular redesigning in cultured endothelial cells (Chen and Oparil,

2000). Patients with primary pulmonary hypertension have selectively upregulated ET-1 and its receptors and when exposed to HA (Chen and Oparil, 2000). Administration of ET receptor antagonist can prevent and reverse hypoxic pulmonary vascular redesigning which suggests the importance of ET-1 and its receptor-mediated signaling in chronic hypoxia-instigated pulmonary hypertension and vascular redesigning (Chen and Oparil, 2000).

Cerebral circulation: With exposure to high altitude, there is a rise in cerebral blood flow (CBF). However, increased exposure to altitude leads to a fall to near sea level of the increased CBF within 1-3 weeks. This shows that time is an important factor during acclimatization. Generally, natives of HA have lower CBF values which is in contrast to sea level locals. The basic system in the decrease in CBF of high-altitude occupants is because of the rise in hematocrit thus, an increment in arterial blood oxygen content (CaO2), this proposes an opposite connection between CBF and CaO2. Some of the mechanisms responsible for the regulation of CBF are hypoxic ventilator response, hypercapnic ventilatory response, hypoxic cerebral vasodilation and hypocapnic cerebral vasoconstriction (Ainslie and Subudhi, 2014).

Initial exposure to HA causes hypobaric hypoxia changes in arbiters of CBF, on account of a decrease in arterial oxygen tension, which is an autonomous mediator of cerebral arteriolar dilatation. Also, hypoxemia can excite hyperventilation related decline in blood vessel (arterial) carbon dioxide tension, this causes cerebral arterial tightening because of a related increment in periarteriolar PH. Consequently, over a couple of days of steady introduction to HA, the effect of arterial oxygen tension-incited limit for cerebral vasodilation is lessened and the degree of hypocapnia is enhanced. Thus, prolonged exposure to HA increases the hematocrit, which results in a rise in the arterial oxygen composition at an unaltered oxygen pressure. Notwithstanding these reflex reactions, CBF is likewise constrained by some other hypoxia-prompted changes for example, high-height hypoxia-initiated changes of cerebral slim thickness, hypoxia incited factor (HIF), nitric oxide, endothelin-1, receptive oxygen species (ROS), and synapses might be answerable for the falling CBF during long haul HAH (Ainslie and Ogoh, 2010).

This change will generally diminish CBF. Accordingly, cerebral hemodynamics during acclimatization to elevation is the consequence of these homeostatic components. Notwithstanding these reflex reactions, CBF is likewise regulated by some other hypoxia-prompted 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 might be answerable for the diminishing CBF during long-term HAH (Ainslie and Ogoh, 2010).

Uteroplacental circulation: Pregnancy, a condition associated with a notable increment in uterine blood flow which raises the oxygen conveyance and supplements to the developing fetus. Uteroplacental vascular resistance falls greatly which causes preferential direction of blood flow to this vascular bed, thus an increment in the uterine blood flow from 20–50 ml/min in the non-pregnant state to 450–800 ml/min during pregnancy (Palmer *et al*., 1992). Uterine circulation adaptations to pregnancy are perplexing and predominantly accomplished through the repair of the uterine vasculature, reduced vasoconstrictor response, improved vasodilator response and diminished pressure-dependent myogenic reactivity. At sea level, the uterine distance across during pregnancy doubles because of adjustments in vasoreactivity, adjustments in the active and passive properties of the uterine artery and vascular growth and refurbishment. Although, the underlying molecular mechanism for uterine vascular development and expansion of the vascular diameter are not completely perceived. However, hormonal stimuli might be one of the significant components responsible for pregnancy-interceded diminished uterine vascular resistance. Estradiol has been reported to be a vital participant in light of its angiogenic properties and stimulatory impacts on nitric oxide-interceded vasodilation (Burton *et al*., 2004).

Estrogen receptors (ERs) have been recognized in uterine artery vascular smooth muscle with notable increment in their expressions in pregnant uterine arteries which is in contrast with non-pregnant uterine arteries (Chang *et al*., 2010). Pregnancy-related increment in ER assessment may directly increase vascular endothelial growth factor (VEGF), mitogen-activated protein (MAP) kinase, and endothelial nitric oxide synthase (eNOS) expression and their activities prompting improved uterine vascular development and vasodilation (Chang *et al*., 2010). Diminished uterine vascular obstruction can likewise be controlled by contractile agonists or associated proteins. Also, myogenic tone and distensibility are extra factors that can adjust uterine arterial intraluminal diameter and uterine vascular resistance. It has been accounted for that pregnancy significantly decrease pressure-dependent myogenic tone, increasing the pressure-dependent passive uterine arterial diameter. The decreased myogenic tone is interceded by an increment in the inhibitory impact of extracellular-signal regulated kinase (ERK) and a decline in the protein kinase C (PKC) signalling pathway (Xiao *et al*., 2006).

Exposure to high-altitude has profound impacts on uteroplacental circulation which includes alterations in uteroplacental and fetal blood flow volume, which results in fetal intrauterine development limitation. In an investigation by Julian *et al*. 2008, HAH decreases pregnancy-associated uterine blood flow increase (Julian *et al*., 2008). Decreased uterine blood flow and insufficient perfusion of the placenta has been ascribed to the rise in the cases of preeclampsia and fetal intrauterine development limitation (Moore *et al*., 2011). One of the systems that adds to the diminished uterine blood flow might be a critical restraint of pregnancy-related increment in uterine vascular development. The proliferative reaction to serum stimulation in cultured uterine arterial smooth muscle cells is also diminished by hypoxia introduction (Rockwell *et al*., 2006).. Also, HAH can modify pregnancy-associated reactions to contractile proteins and vasodilator-intervened signaling pathways. Report has indicated that, long-term exposure of sheep to high-altitude during pregnancy demonstrated noteworthy increment in the pressure-dependent myogenic tone of resistance-sized uterine

arteries by subduing the ERK1/2 activity and an increment in the PKC signaling pathway (Chang *et al*., 2010). Furthermore, HAH exposure specifically downregulates estrogen-α receptor expression in the uterine arteries of pregnant animals and hindered steroid hormone-intervened adaptation of ERK1/2 and PKC signaling pathways raising the myogenic tone of the uterine arteries in pregnancy (Chang *et al*., 2010). Huge-conductance Ca2+-activated K+ (BKca) is richly expressed in vascular smooth muscle cells. The BKca channel, a significant effector in reaction to hypoxia in vascular smooth muscle has been proposed to be associated in the control of uterine circulation and uterine blood flow increment during pregnancy (Rosenfold *et al*., 2005). Proof from pregnant sheep model exposed to long-term HA (about 3801 m) proved that, long-term HAH during pregnancy adversely influences the uterine circulation by decreasing BKca channel function in uterine vasculatures (Hu *et al*., 2012). During human development, HAH significantly restrains pregnancy-related increase of BKca channel action and diminishes BKca channel current density in pregnant uterine arteries (Hu *et al*., 2012).

This was mediated by a selective decline of BKca channel β1 subunit appearance in the uterine arteries. Likewise, high-altitude hypoxia impeded the part of BKca channel in controlling pressure-instigated myogenic tone of uterine arteries which was improved in pregnant animals accustomed to HA. These outcomes propose that specifically focusing on BKca channel might be another key component in the maladaptation of uteroplacental circulation brought about by HAH, which may add to the diminished uterine blood flow and fetal intrauterine development limitation related with maternal hypoxia. The molecular mechanisms underlying HA hypoxia-intervened modification of targeting gene expression in pregnant uterine arteries are not totally perceived. Although, studies recommend that epigenetic system assumes a critical function in the control of gene expression in adaptation to HA (Chen *et al*., 2015).

Chronic hypoxia is responsible for the increment in estrogen receptor α subunit (ER-α), promotes DNA methylation at both upstream stimulatory factor binding sites and specific protein-1, diminished specificity protein-1 and upstream stimulatory factor binding to the promoter, and reduce ER-α expression in uterine arteries of pregnant animals (Chen *et al*., 2015). Additionally, proof shows that hypoxia-interceded DNA methylation assumes an irregular function in ER-α gene repression and deletion of estrogen-mediated adaptation of uterine arterial BKca channel activity, leading to an increment in uterine arterial myogenic tone during pregnancy (Chen *et al*., 2015). Noteworthy contrasts can be seen in the uterine arterial adaptation to pregnancy dependent on the term of exposure to HA. Birth weight of children destined to Tibetan occupants at high altitude is higher than that of destined to Han ladies living at a similar elevation, which is related with an increase uterine flow velocity and increased uterine arterial diameters (Moore *et al*., 2011).

Andean pregnant women have almost doubled increase in their uterine arterial diameters at HA while, European pregnant ladies have about half as much increment (Niermeyer *et al*., 2007). Thus, Andean pregnant ladies have higher uterine blood flow and birth weight than Europeans at HA. However, at sea level, the values are equivalent in both Andean and European ladies, this recommends a higher defensive impact of Andean family line at high altitude. Reports suggest that genetics are crucial in altitude-associated modifications in birth weight and uterine blood flow (Moore *et al*., 2011).

Conclusion

Cardiovascular adaptation to altitude varies, depending on individual predisposition, pace of climb and term of exposure. The initial response to HAH exposure is hyperventilation and increase in sympathetic activity (which results partly from chemoreceptor reflexes and baroreceptor function) leading to increase in heart rate, systemic vascular resistance, blood pressure, cardiac output and pulmonary hypertension associated with pulmonary vasoconstriction. A great part of the individual inconstancy is needy upon the seriousness of related pulmonary hypertension, which is frequently gentle yet might be extreme in an extent of cases. In response to HAH, CBF increases to guarantee satisfactory supply of oxygen to the cerebral tissues.

Cardiovascular adaptation includes changes in vascular structures, redesigning and functional proteins through various molecular mechanisms such as epigenetic regulatory as well as genetic factor instigated mechanisms. Adaptations to HAH involves both compensatory and pathologic mechanisms. Maladaptation such as; pulmonary hypertension, pulmonary edema, heart failure, cerebral edema, chronic mountain sickness, and fetal intrauterine growth restriction develops from pathologic adaptations.

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