

# Hypertension in Hypoxia

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## Introduction

Hypertension is a pathophysiological condition, when arterial blood pressure is elevated. The heart works harder to overcome the increased systemic pressure in order to maintain blood flow to cells and tissues. Over time, the additional strain on the heart and arteries slowly leads to deadly sequelae such as congestive heart failure, myocardial infarction, pulmonary embolism, cerebral aneurysm and kidney failure<sup>(1)</sup>. Primary hypertension is the most frequent, accounts about 90-95% incidences. It is associated with many factors such as sedentary lifestyle, stress, tobacco smoking, diabetes, high salt intake, potassium deficiency and sodium sensitivity, obesity, alcohol intake and vitamin D deficiency<sup>(2,3)</sup>. Other hand, secondary hypertension is less frequent, and is linked to mainly dysfunctions and disorders associated with central nervous system, kidneys, lungs, vascular and endocrine system<sup>(4)</sup>.

This review focuses on altitude-associated hypertension in the tourists, trekkers, and mountaineers who visit high altitude and normally reside near sea level. The acute physiological adjustments and early acclimatization that occur in the cardiovascular and pulmonary systems, ensures the oxygen delivery to the cells and tissues despite a significant reduction in the partial oxygen pressure. The review discusses also the high altitude tolerance and adaptations of the mountain dwellers living for generations. The review describes the pathogenesis of hypertension in general and molecular mechanisms of pulmonary hypertension associated with high altitude hypoxia and different disease conditions.

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## Pathophysiology of Hypertension

Hypertension is a common health problem, affecting about 33% populations worldwide associated with significant morbidity and mortality<sup>(5)</sup>. Hypertension is a chronic elevation of blood pressure (BP) that, in the long-term, causes organ dysfunction and damage. The absolute risk for hypertension even further increases in disease condition such as cardiovascular disease (CVD) when elevated BP coexists with other CVD risk factors, such as diabetes and dyslipidemia. The pathophysiology of hypertension involves a number of mechanisms that interact in complex fashion to influence BP and their derangement further plays a crucial role in developing a severe form. Many factors contribute to the raised blood pressure in hypertensive patients, including cardiac output and systemic vascular resistance, renin-angiotensin-aldosterone system, sympathetic nervous system, endothelial dysfunctions, and obesity and insulin resistance.

*Cardiac output and vascular resistance:* A balance between the cardiac output and peripheral vascular resistance normally maintains the BP. As the consequence a series of cardiovascular adjustments take place to increase blood volume during early primary hypertension. Firstly, as the result of increased blood volume circulating through the heart, cardiac output increases. As the systemic arteries sense the increase in blood volume, arterial constriction occurs, which finally leads to an increase in total peripheral resistance during hypertension.

At borderline hypertension BP is elevated due to raised cardiac output and not of increased vascular resistance, which is related to sympathetic hyperactivity. Other hand, the patients with essential hypertension show a normal cardiac output with an elevated peripheral resistance. This subsequent increase in peripheral arteriolar resistance might therefore prevent the elevated pressure being transmitted to the capillaries

where it would substantially affect homeostasis. The peripheral resistance is determined basically by smooth muscle cells of arterioles, not by large arteries or capillaries. The smooth muscle cells contraction is mainly regulated by the intracellular calcium concentration.

*Renin-angiotensin-aldosterone system:* This is one of the very important endocrine systems associated directly with regulation of BP. Renin plays a critical role in the pathogenesis of hypertension<sup>(6)</sup>, is secreted from kidney in response to reduced salt intake as well as the stimulation from sympathetic nervous system. Renin converts angiotensinogen to angiotensin I, a physiologically inactive substance which is rapidly converted to angiotensin II in the lungs by angiotensin converting enzyme. Angiotensin II is a potent vasoconstrictor and thus causes an increase in BP. Also, it stimulates the release of aldosterone, which results in reabsorption of sodium and water, leading to plasma volume expansion and also it acts through nongenomic mineralocorticoid receptor mediated responses<sup>(7)</sup> and hence increases in BP.

The circulating renin-angiotensin system may not be directly responsible for the increase in BP in primary hypertension as many hypertensive patients have been found to have low levels of renin and angiotensin II, and drugs that block the renin-angiotensin system are not particularly effective. The non-circulating "local" renin-angiotensin epicrine or paracrine systems have also been reported, which may have important roles in regulating regional blood flow as well as maintaining BP<sup>(8)</sup>.

*Autonomic nervous system:* Sympathetic nervous system has an important role in maintaining normal BP as its stimulation can cause both arteriolar constriction as well as dilatation. Patients with essential hypertension show the evidence of increased activity of muscle sympathetic nerve<sup>(9)</sup> and augmented cardiac and renal noradrenaline release from the sympathetic nerves<sup>(10, 11)</sup>. Hyperactivity

of sympathetic system has also been shown closely associated to hypertension-related end organ damage<sup>(12, 13, 14)</sup>. Interaction between the autonomic nervous system and the renin-angiotensin system along with other factors including sodium level and blood volume has also been suggested having significant association with hypertension<sup>(15)</sup>.

*Endothelial dysfunction:* Dysfunction of the endothelium has been correlated with hypertension. The endothelium senses biochemical signals from circulation and, in turn, releases vasodilator such as nitric oxide (NO) and the vasoconstrictor peptide, endothelin (ET)<sup>(16)</sup>. The role of NO has been described in patients with essential hypertension showing a determinant for the premature development of atherosclerosis<sup>(17)</sup>. Further, several studies have reported the influence of NO on stimulating soluble guanylyl cyclase activity in vascular smooth muscle cells<sup>(18)</sup> impairing BP and cellular events such as renal hemodynamics, vasodilation, leukocyte adhesion and cellular proliferation and thrombosis<sup>(19, 20)</sup>. Besides, ET-1 is also considered to be an important factor in the development of vascular dysfunction and cardiovascular complications beyond pulmonary arterial hypertension<sup>(21)</sup>.

*Obesity and insulin resistance:* Insulin resistance is another important risk factors in the development of hypertension in both normal and obese individuals<sup>(22, 23, 24)</sup>. Hypertension in diabetes patients is common and is characterized by increased peripheral vascular resistance and elevated BP<sup>(25, 26)</sup>. It is shown that the hypertension coexists with renal disease in type I diabetic patients. Further, in type II diabetics, the hyperinsulinemic insulin-resistant syndrome is frequently accompanied by hypertension, even in the absence of obesity<sup>(22, 23, 27)</sup>. It is also shown that hypertensive patients exhibited increased circulating insulin levels compared with normotensives of comparable glucose tolerance even after compromising the differences in body weight<sup>(27)</sup>. Other hand, the obese individuals have been observed

having the elevated sodium retention and volume expansion along with increased sympathetic nervous activity and stimulation of the rennin-angiotensin system<sup>(28)</sup>. Thus studies describe that several risk factors including obesity, glucose intolerance, diabetes mellitus, and hyperlipidaemia cluster together, leading to the complex pathophysiology of hypertension in patients.

### **Molecular Mechanism of Hypertension**

During hypertension, expression of many molecules including phospholipase C-inositol phosphate-diacylglycerol, mitogen-activated protein kinase, tyrosine kinases/phosphatases, RhoA/Rhokinase, transcription factors and NADPH and oxidase-derived reactive oxygen species (ROS) are changed in response to altered cellular functions<sup>(29, 30, 31)</sup>. Various prehypertensive peptides such as angiotensin-II and endothelin-1, which signal through membrane associated G protein-coupled receptors, are also associated with stimulation of the above signaling pathways<sup>(32, 33)</sup>. In addition, aldosterone, through their intracellular mineralocorticoid receptor, has also been shown to influence cardiac and vascular function in hypertensive patients<sup>(34)</sup>. The importance of aldosterone in the pathogenesis of hypertension has recently been supported by the findings of a mutation of the Kp channel<sup>(35)</sup>.

In hypertension, the bioavailability of vasodilator NO is reduced significantly, other hand vasoconstrictor ET-1 activity is increased<sup>(36)</sup>. Due to activation of guanylate cyclase by NO, there is an increase in cyclic GMP levels in smooth muscle cells, which leads to vasodilatation. It is reported that overproduction of endothelial nitric oxide synthase (eNOS), which synthesizes NO, in transgenic mice prevented pulmonary hypertension (PH) induced by hypoxia<sup>(37)</sup>. In eNOS-deficient mice, exposure to mild hypoxia even resulted a severe form of PH<sup>(38, 39)</sup>. The mechanism of action of NO-induced vasodilation is based on activation of Ca<sup>2+</sup>-dependent K<sup>+</sup> channels and increase the outward

potassium flow<sup>(40)</sup>. Cell membrane thus gets hyperpolarized and decreases the effect of the depolarizing signals and induces vasodilation.

Studies in human utilizing selective and nonselective ET-1 receptor antagonists demonstrated the crucial role of ET-1 in vasoconstriction<sup>(36, 41)</sup>. In hypertension modulating cardiovascular pathway, ET-1 activity has been linked commonly to aldosterone. Aldosterone has multiple actions through rapid nongenomic and genomic pathways involving mineralocorticoid-dependent as well as -independent signaling, in the heart, the vessels and other non epithelial tissues<sup>(42)</sup>. Besides, the angiotensin II signaling through receptor tyrosine kinases involves Ang II type1 receptor (AT1) mediated transactivation of these kinases in vascular remodeling<sup>(43)</sup>. Other hand, AT2 receptor stimulation has been reported promoting cardiovascular protection through anti-fibrotic and anti-inflammatory actions without having anti-hypertensive effects.

Other important mechanism also has been described in developing hypertension by activating factors such as G protein RhoA and its target protein Rho kinase via the inhibition of myosin light chain phosphatase activity<sup>(44, 45, 46)</sup>. RhoA is phosphorylated at Ser188 by PKG-I, which inhibits its membrane association and thus prevents activation of its downstream targets, such as Rho kinase<sup>(47, 48)</sup>. Thus, RhoA and Rho kinase contribute to sustained vasoconstriction and vascular functions by regulating various cell functions<sup>(49, 50)</sup>. RhoA-Rhokinase signaling pathway has been shown to be involved in various pulmonary vascular disorders under hypoxic conditions<sup>(51, 52, 53)</sup>. An increased RhoA and Rho kinase activity with concomitant increased Rho kinase expression was observed in pulmonary vascular smooth muscle exposed to chronic hypoxic conditions<sup>(54)</sup>. Rho kinase has been linked to endothelial nitric oxide synthase (eNOS) activity, as an increase in eNOS protein was observed in Rho kinase inhibitor-treated lungs during hypoxia

exposure, suggesting that an upregulation of eNOS is involved in inhibiting the pulmonary vasoconstriction<sup>(55)</sup>. Moreover, pulmonary arteries have been shown to have increased sensitivity to NO on exposure to chronic hypoxia<sup>(56, 57)</sup>.

Reactive oxygen species has been related to NO signaling, showing that the increase in both ROS and Rho kinase activities reduce synthesis of endothelium-derived NO<sup>(58, 59)</sup>, thereby increasing vasoconstriction leads to hypertension. NADPH oxidase (Nox) has been shown to be the major source for the generation of ROS in vascular smooth muscle cells<sup>(60)</sup>, endothelial cells<sup>(61)</sup>, and fibroblasts<sup>(62)</sup>. Increased expression of Nox4 (an isoform of Nox) in the vasculature of hypertensive patients may disrupt the NO signaling through a number of pathways<sup>(63)</sup>. In hypoxia-induced murine model of PH, an increase in Nox4 expression was reported in vascular smooth muscle cells, which clearly indicated a crucial role of Nox in PH pathophysiology<sup>(64)</sup>. Thus the studies suggest that all these molecules are interconnected to each other via different pathways and upon interaction lead to PH.

### Hypoxia and Hypertension

Hypoxia has critical impact on the pulmonary hypertension (PH). Pulmonary artery pressure gets elevated chronically in people living at high altitude, which supports the idea that hypoxia alone can cause PH<sup>(65)</sup>. A number of primary lung diseases are also known to be associated with chronic hypoxia, including chronic obstructive pulmonary disease (COPD), cystic fibrosis, diffuse interstitial fibrosis, bronchopulmonary dysplasia, radiation fibrosis, infiltrative lung tumors, and collagen vascular disease<sup>(66-72)</sup>. Neuromuscular and skeletal disorders such as scoliosis, Duchenne muscular dystrophy, and poliomyelitis may also impair ventilation and be associated with hypoxia-induced PH<sup>(66, 73)</sup>. Hypoxic condition has long been recognized to play a significant role in the pathogenesis and progression of

chronic renal disease. During hypoxia the hypoxia inducible factor (HIF) is elevated regulating several important cellular processes such as angiogenesis, vasotone, glucose metabolism and cell survival. In renal disorder, HIF activation is well described showing its role in disease progression. The hypoxia exposure also has been shown to promote significantly the renal injury by increasing hypertension<sup>(74)</sup>.

### High altitude Hypoxia and Hypertension

Native sea level dwellers when migrate to high altitude, develop increased pulmonary vascular resistance and hypertension due to adverse hypoxic exposure<sup>(75)</sup>. Further, they also develop hypoxia associated respiratory diseases including chronic obstructive pulmonary disease (COPD), interstitial lung disease, sleep disordered breathing and some rare neonatal disease<sup>(76)</sup>.

In normal condition, the mean pulmonary arterial pressure (mPAP) of an individual exists under 25 mm Hg (generally, 12 at resting condition and 16 mm Hg at exercise)<sup>(77)</sup> while in case of pulmonary hypertension (PH) it is increased above 25 mm Hg at rest and 30 mm Hg at exercise accordingly. The degree of PH ordinarily is modest at tolerable altitudes but may approach systemic levels when alveolar hypoventilation and systemic arterial hypoxemia are severe, as in chronic mountain sickness<sup>(78, 79)</sup>.

### Pathophysiology of Hypoxia induced Hypertension

Chronic hypoxia induces structural changes in pulmonary arteries, and in the biochemical and functional phenotypes of the vascular cells<sup>(80)</sup>. When alveolar hypoxia is prolonged, pulmonary vasoconstriction occurs and is compensated by a rise in pulmonary arterial pressure, which is further accompanied by structural changes in small peripheral pulmonary arteries, including increased thickness of arterial walls<sup>(81, 82)</sup>. Commonly such changes are occurred in patients with chronic

obstructive airways disorder<sup>(83)</sup>.

Another characteristic feature of hypoxic pulmonary hypertension is luminal vascular obstruction caused by smooth muscle cells proliferation, thrombosis and vasoconstriction. These changes reflect a homeostatic imbalance characterized by disproportion between secreted vasodilators and constrictors that affect growth and thrombosis. Furthermore, persistent structural alterations of the small pulmonary arterioles are believed to be associated with the complex pathophysiology of pulmonary vascular lesions (plexiform lesions) in patients suffering from severe PH<sup>(84, 85)</sup>.

### Molecular Mechanism of Hypoxia Regulation of Hypertension

In hypoxic hypertension, the thickening of pulmonary arteries (PA) is common<sup>(86, 87, 88)</sup>. The thickening of the arterial walls is believed to be caused by hypertrophy and increased accumulation of smooth muscle cells as along with increased deposition of extracellular matrix proteins such as collagen, elastin, fibronectin and tenascin<sup>(89, 90, 91)</sup>.

A number of the above such acclimatization mechanisms are regulated by hypoxia responsive genes, which ensure cellular and systemic functions under hypertensive conditions. Expression and activation of oxygen responsive transcription factors are regulated by alterations in partial pressure of oxygen (pO<sub>2</sub>) that may either be due to reduction in oxygen delivery or malfunctioning in oxygen utilization at cellular level. HIF-1 is believed to be the main transcription factor mediating these molecular responses, besides other transcription factors such as, early growth response-1 (Egr-1), nuclear factor kappa B (NF-κB) and nuclear factor of activated T cells (NFAT) are also involved.

HIF-1 is a heterodimer composed of an oxygen-regulated HIF-1α subunit and constitutively expressed HIF-1β subunit of the Per-Arnt-Sim (PAS) family proteins



(92, 93). These proteins bind to consensus DNA binding motifs within regulatory promoter regions, hypoxia-responsive elements (HREs) of hypoxia-responsive genes. HIF-1 $\alpha$  is rapidly degraded by the ubiquitin-proteasome system by specific prolyl hydroxylase-domain (PHDs) enzymes, which initiates its degradation via von Hippel-Lindau tumor suppressor protein (VHL) by a process that requires the presence of two sequences in HIF-1 $\alpha$  termed oxygen dependent degradation domains<sup>(94, 95, 96, 97)</sup>. The hydroxylation of proline residues 402 and 564 of the  $\alpha$ -subunit of HIF-1 facilitate interaction with the VHL tumor suppressor that targets HIF $\alpha$  for proteasomal degradation. In hypoxia, oxygen dependent proline and asparagine hydroxylation are inhibited and HIF- $\alpha$  accumulates. It binds to the constitutively expressed nuclear protein HIF-1 $\beta$ , translocates to the nucleus, associates with co-activators, docks with HREs in target genes and becomes transactivated to regulate transcription. HIF-1 $\alpha$  is the most ubiquitously expressed and is recognized as a master regulator of hypoxic signaling<sup>(98)</sup>.

In hypoxic hypertension, the HIF-1 $\alpha$  promotes the upregulation of ET-1. It has been demonstrated that the ET-1 transcription is significantly increased by hypoxia via recruitment of several nuclear factors including HIF-1, AP-1, GATA-2, CAAT-binding factor (NF-1) and CREB binding protein (p300/CBP)<sup>(99, 100, 101)</sup>. In an animal model with obstructive sleep apnea, a crucial role of HIF-1 and ET-1 in promoting hypertension has been described<sup>(102)</sup>. Another *in vivo* study using spontaneous hypertensive rats (SHR) shows an elevated hypertensive condition in response to hypoxic exposure with an increase in myocardial pre-pro ET-1 levels and ET-A receptor expression. HIF-1 $\alpha$  targeting ET-1 gene in SHR was also evident from the finding that myocardial HIF-1 activity was increased during hypertension. The role of ET in hypertension was also demonstrated by administration of bosentan, an ET receptor antagonist, to mice, which prevented both increase in BP and infarct

size. Thus study demonstrated that activation of ET system, mediated by HIF-1 activity, is responsible for the enhanced susceptibility cardiovascular problems, leading to hypertension and ischemic injury<sup>(103)</sup>. HIF has also been known to regulate expression of RhoA with concomitant downregulation of Rho kinase, in PH<sup>(104)</sup>.

The early growth response-1 (Egr-1) is a zinc finger-binding domain containing transcription factor also play important role in maintaining cellular functions in response to hypoxia. Egr-1 has strong binding affinity to a consensus DNA element to modulate the expression of genes involved in synaptic plasticity, cell growth and survival, extracellular matrix remodeling and thrombosis<sup>(105)</sup>. Nuclear localization of Egr-1 is enhanced under hypoxic conditions, which is necessary for synthesis of procoagulant tissue factor. It has been reported that Egr-1 activation under hypoxic condition is independent of HIF<sup>(106)</sup>. Also, other molecules including the members of the protein kinase C (PKC) family have been identified as the crucial initiators to Egr-1. PKC $\beta$  null mice revealed markedly decreased Egr-1 levels in response to hypoxia<sup>(107)</sup>. Furthermore, PKC $\alpha$  as well as the active downstream molecules such as Ras/Raf/ERK1/2 are implicated in Egr-1 gene induction in endothelial cells during hypoxia<sup>(108)</sup>. Thus studies show that the hypoxia induced Egr-1 expression is an important regulatory event that contributes to the pathogenesis of pulmonary thrombosis and vascular remodeling<sup>(109, 110)</sup>.

The NF- $\kappa$ B is an important mediator of inflammatory responses and is associated with induction of hypertension and vascular damage. NF- $\kappa$ B is a member of the Rel family of proteins and was first described as a nuclear factor in B cells<sup>(111)</sup>. NF- $\kappa$ B upregulates the transcription of several proinflammatory genes including tumor necrosis factor (TNF- $\alpha$ ), interleukin (IL-6 and IL-8), chemokines and surface adhesion molecule (intercellular adhesion molecule-1, ICAM-1)<sup>(112)</sup>. Activity of NF- $\kappa$ B and TNF- $\alpha$  level are also known to be increased in cells and animals exposed to

hypoxia treatment and also in hypertensive patients. TNF- $\alpha$  has been shown to play a major role in inflammation mediated vascular damage in hypertensive patients and animal models<sup>(113)</sup>.

The nuclear factor of activated T cells (NFAT) has been shown to be associated in the development of hypoxic hypertension<sup>(114)</sup> and cardiovascular function<sup>(115)</sup>. The NFAT transcription factor mediates binding of the Ca<sup>2+</sup>-activated phosphatase calcineurin and other regulatory functions necessary for nuclear translocation. It also contains nuclear localization and export sequences along with phosphorylation sites for a number of serine/threonine kinases. When intracellular Ca<sup>2+</sup> level increases, an increased calcineurin activity is observed<sup>(115, 116)</sup>. It was reported that systemic hypertension caused by hypoxia in mice is associated with NFATc3 activation in aorta and mesenteric arteries<sup>(114)</sup>. It was also reported that genetic ablation or pharmacological inhibition of NFATc3 prevents hypoxia induced hypertension, showing the importance of NFAT in hypoxia induced cardiovascular pathology<sup>(117, 118)</sup>.

### **Hypertension and Hypercoagulation at High Altitude**

The evidence of hypercoagulability states and pulmonary hypertension (PH) is common in travelers at high altitude under adverse hypoxic conditions<sup>(119)</sup>. For lowlanders, traveling in a short time at high altitudes (2500 to 5000 meters above sea level), can lead to acute health problems. Further, patients with PH when travel to high altitude, get pulmonary vasoconstriction which further causes increase in pulmonary artery pressure, which may worsen hemodynamics and also predispose to acute altitude illness<sup>(120)</sup>. During travel, basal metabolic rate (BMR) increases by approximately 17-27% for the first few weeks upon exposure to high altitude and gradually returns toward sealevel baseline<sup>(121)</sup>. Also, the highest oxygen uptake an individual can attain is decreased by approximately 20-30% during the

first weeks and gradually returns toward normal over the course of 1 year<sup>(122, 123)</sup>.

Hypercoagulation state is resulted due to complex interplay between the coagulation and fibrinolytic pathways. Hypoxia activates the transcription factor, Egr-1, leading to *de novo* transcription/translation of tissue factor, which results in vascular fibrin deposition. The procoagulant response is magnified by concomitant suppression of fibrinolysis by hypoxia-mediated upregulation of plasminogen activator inhibitor -1 (Pai-1). Interaction between fibrinolysis promoting and inhibiting factors like tissue plasminogen activator (tPA) and Pai-1 respectively, affect the fibrinolytic system. Thus, the hypertensive state leading to hypercoagulability may be evident from the travelers to the high altitude with elevated BP and thrombosis related complications including strokes and cardiac attacks.

Other hand, the people living at high altitudes for generations develops physiological adaptations to counter the extreme hypoxic conditions. A huge difference in pulmonary artery pressure was reported between individuals in response to hypoxia. Studies in the town of Leadville (3100 meters above sea level) in the Colorado Rockies showed that the degree of PH measured at right heart catheterisation varied from individual to individual, with some individuals demonstrating marked elevation of pulmonary arterial pressure<sup>(124)</sup>. These observations are consistent with differing genetic susceptibilities to hypoxia induced PH. Genetic factors have also been shown to be involved in the control of the pulmonary vascular response to hypoxia<sup>(125)</sup>. In Tibetan population, a greater increase in blood flow in brain was observed during exercise<sup>(126)</sup> as compared with lowlanders. The Tibetans exhibit less PH than the inhabitants of the Peruvian Andes, who in turn are less susceptible than recent immigrants to high altitude, such as Caucasian Americans, and the Han Chinese in Tibet. Tibetans who were born and raised at

high altitude were found to have higher capillary density in muscles as compared with Andean high altitude natives, Tibetans born and raised at low altitude, or lowlanders<sup>(127)</sup>, which could potentially improve perfusion and oxygen delivery, because each capillary would supply a smaller area of tissue, and oxygen would diffuse a shorter distance. It seems from these studies of people living at high altitude that it is genetically advantageous to exhibit a blunted cardiovascular response to chronic hypoxia, and that the susceptibility to hypoxia induced PH is bred out over many generations. Thus genes, which provide susceptibility to hypoxia induced PH could exist in high altitude populations. In Tibetan population living at high altitude, adaptation has been linked to EPAS1/HIF2A gene<sup>(128)</sup>. Between Han Chinese, Japanese population and Tibetan high altitude dwellers, EPAS1/HIF2A exhibited a significant signal for a cross population test for natural selection (XP-EHH)<sup>(129, 130)</sup>. In Tibetan population, it has also been shown that variation in EPAS1/HIF2A is associated with lower Hb concentration<sup>(131, 132)</sup>. Study also report common polymorphism in the gene for angiotensin converting enzyme and susceptibility to high altitude PH in highlanders from the Kyrgyz Republic in Central Asia<sup>(133)</sup>.

### Diagnosis

Pulmonary hypertension (PH) is often present with nonspecific symptoms like dyspnea on exertion, fatigue, syncope, anginal chest pain, hemoptysis (rupture of distended pulmonary vessels) and Raynaud's phenomenon, which are very difficult to be dissociated from those caused by a known underlying pulmonary or cardiac disorder. Cardiac output is decreased during exertional dyspnea, fatigue and syncope Reynaud's phenomenon occurs in approximately 2 percent of patients with primary pulmonary hypertension but is more common in patients with pulmonary hypertension related to connective tissue disease<sup>(134)</sup>. For diagnosis of PH, a high index of suspicion, a meticulous history and a

careful physical and medical examination including use of drugs and family history are necessary for the diagnosis of PH. PH patients have of right ventricular hypertrophy in electrocardiogram (ECG) or prominent pulmonary arteries on the chest radiograph.

Besides, 2D echocardiography with Doppler flow studies is also performed in patients with PH. Among other tests complete blood count, prothrombin time, partial thromboplastin time, hepatic profile and autoimmune panel are also followed in PH patients<sup>(135)</sup>. Hypoxia induced PH could also be checked by arterial blood gas analysis, as pulmonary function is highly reduced in this state.

### Treatment

Although many excellent antihypertensive agents are commercially available, millions of hypertensive patients do not have their BP under control and ultimately face the extreme problems of cardiovascular disease. Most of the hypertensive drugs for controlling PH are aimed at relatively few targets<sup>(136)</sup>. But still there exists lot many issues regarding treatment of hypertension including expensive drugs and therefore less availability and detection of hypertension itself is a big problem. Thus there is clear need of proper treatment for hypertensive patients and for this to be achieved several important therapeutic principles are to be considered. The use of diuretics including thiazides is considered as first line of therapy for hypertension. In addition, a beta-adrenoreceptor ( $\beta$ - blocker) is used for treating PH. If the response is still inadequate then calcium channel blocker is generally suggested to the patients. Finally, if this combination does not work or is not tolerated, an ACE inhibitor is then substituted. The pharmacological agents could be effective, potential drawbacks include the need for continuous i.v. infusion of vasodilators with potential side effects. The above drugs commonly target the pathways including renin-angiotensin system, adrenergic or adrenergic receptors, and calcium



channels.

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