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Hypoxia Signaling in Cardiovascular Diseases

Neha Gupta and Mohammad Zahid Ashraf

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Abstract

Cardiovascular diseases such as stroke, coronary artery disease, and thrombosis remain a global health burden. Understanding the mechanism of these diseases paves the way for development of prophylactics/therapeutics. It is well known at cellular levels; the pathophysiology of most of the cardiovascular disease involves a complicated yet coordinated signaling networks triggered in response to either cellular or tissue levels of hypoxic milieu. Information related to types of hypoxia and signaling mechanism associated to such complications if compiled and presented in a comprehensive manner shall prove relevant in proposing common therapeutic targets for wide array of cardiovascular complications. The relative functional roles of hypoxia-triggered signaling pathways are also an area of current research. Based upon these facts, this chapter discusses the types of hypoxia and role of hypoxia-mediated signaling pathways in various types of commonly occurring cardiovascular disorders.

Keywords: hypoxia, signaling, cardiovascular disorders, thrombosis, therapeutics

1. Introduction

Oxygen concentration below the tissue specific physiological levels is termed as 'Hypoxia'. Depending upon the cause of oxygen scarcity, hypoxia can be classified into Hypoxic hypoxia (occurs due to deficiency in oxygen exchange in lungs or arises due to reduced partial pressure of oxygen in air), Anemic hypoxia (arises when the transport of oxygen is affected), stagnant hypoxia (due to delayed blood renewal, or insufficient blood flow) or histotoxic hypoxia (body is not able to use the available oxygen) [1]. Among its various types, stagnant hypoxia and hypoxic hypoxia are most common types associated with pathophysiology of a variety of cardiovascular disorders (CVDs) such as hypoxic milieu developing in veins due to reduced blood flow promotes thrombus formation [2, 3], whereas, environmental hypoxia at

high altitude exposures also promotes a prothrombotic tendency [4, 5]. Physiological alterations are ultimately orchestrated as a myriad of changes at both cellular and molecular levels. These changes involving the activation of transcription factors (Hypoxia-inducible Factors-1, NF- κ B), their downstream signaling pathways, generation of reactive oxygen species and many other molecular adaptive responses in cells, also contribute toward the development of diseased phenotype. A better understanding of these signaling pathways would lead to the identification of putative targets for development of therapeutics and prophylactics to reduce the burden of CVDs. The current chapter discusses the hypoxia-associated pathophysiological changes toward disease progression and major transcription factors playing a role in hypoxic conditions, the signaling and molecular events involved in commonly occurring CVDs. Expanding the understanding of the hypoxia-associated molecular-signaling pathways and cross-talk between them will provide new avenues of therapeutic opportunity of the disease.

2. Master regulators of hypoxia responsive factors

2.1. Transcription factors

2.1.1. Nuclear factor (NF)- κ B

Nuclear factor (NF)- κ B is a eukaryotic transcription factor that mediates inflammatory processes through Rel family of proteins and was originally described as a nuclear factor required for immunoglobulin k light-chain transcription in B cells [6]. Normally, in most of the cells, NF- κ B lies in its inactive state by binding to the inhibitor I κ B and is retained in cytoplasm. Upon sensing an inflammatory stimulus, I κ B undergoes ubiquitin-mediated degradation and NF- κ B translocation takes place to the nucleus [7]. Inside the nucleus, NF- κ B regulates the transcription of a number of genes. NF- κ B plays a central role in inflammatory processes by orchestrating the expression of numerous factors (cytokines, adhesion molecules and enzymes) [8, 9].

Activation of NF- κ B also occurs in cardiovascular tissue with a concomitant increase in expression of *i*NOS (inducible nitric oxide synthase) protein. Increased NF- κ B activity in circulating neutrophils and raised plasma levels of NF- κ B, controlled gene products, soluble E-selectin and soluble vascular cell-adhesion molecule-1 (VCAM-1) are a response to hypoxia in patients of obstructive sleep apnea syndrome (OSAS) [10].

2.2. Hypoxia-inducible factor-1 (HIF-1)

HIF-1 is a heterodimeric transcription factor consisting of a constitutively expressed- β subunit and an α -subunit containing an oxygen dependent degradation (ODD) domain [11]. Under normoxic conditions, hydroxylation of ODD occurs in an oxygen dependent manner rendering α -subunit vulnerable to proteasomal degradation [12]. Therefore, HIF-1 is suppressed in normoxia, whereas under hypoxic conditions, HIF-1 is stable and active, capable to bind to the regulatory regions of its target genes and inducing their expression. HIF-1 is

the major regulator of oxygen homeostasis, for adaptation to hypoxia involving increasing tissue reperfusion, and oxygenation, thereby, overcoming initial hypoxic insult [13]. Even under normoxic conditions also HIF-1 regulates the shift to increased glycolysis and anaerobic metabolism at low oxygen tensions [13]. HIF-1 regulates a number of target genes (such VEGF-1, EPO). Furthermore, mammalian HIF-1 α has three isoforms viz. HIF-1 α , 2 α , and 3 α . HIF-1 α accumulation is the key regulatory subunit for assembly of HIF under low O₂ conditions. Regulation of HIF-1 α occurs post-translationally in response to low O₂ levels [14, 15].

2.3. Interaction between NF- κ B and HIF-1 pathways

Although, NF- κ B and HIF-1 has independent roles in gene regulation, their cross-talk plays equally important role in pathophysiology of a number of diseases. Structurally, there lies an active NF- κ B binding site, in the proximal promoter site of HIF-1 gene and NF- κ B, regulates the basal levels of HIF-1 gene expression [16]. Even under hypoxic conditions, HIF-1 transcription is upregulated through NF- κ B dependent mechanism [17]. Reports are there to show that hypoxia-induced transcription of NF- κ B depends upon the presence of HIF-1 and HIF-1 also directly, regulates neutrophil survival in hypoxia via NF- κ B modulation [18]. Higher expressions of HIF-1 are related to increased NF- κ B activity and an enhanced inflammatory response [18, 19]. Some of the common gene products are shared by HIF-1 α such as eNOS, a potent vasodilator whose bioavailability is increased by coordinated action of HIF-1 and NF- κ B. In OSAS even crosstalk of NF- κ B and HIF-1 also play a central role [20].

3. Hypoxia in various CVDs

3.1. Hypoxia in obstructive sleep apnea syndrome

OSAS have been recognized as a major health problem affecting developed countries. The disorder is characterized by obstruction of upper airways during sleep resulting in sleep fragmentation and excessive day time sleepiness. OSAS has shown to have a causal relationship with CVDs [21–23]. Although pathogenesis of CVDs in OSAS is multifactorial, the proposed mechanism by which OSAS predisposes to CVD includes sympathetic excitation, vascular endothelial dysfunction, metabolic dysregulation as well as oxidative stress and inflammation induced by cyclical intermittent hypoxia [24]. Evidences are there to show that inflammatory pathways mediate the pathobiology of cardiovascular complications in OSAS. The pattern of intermittent hypoxia in patients of OSAS can be either repetitive cycles of hypoxia/reoxygenation or it can be with prolonged periods of sustained hypoxia allowing for development of an adaptive response, associated with increased tissue perfusion and oxygenation whereas shorter intermittent hypoxic exposures may also activate inflammatory pathways [25, 26]. Intermittent hypoxia directly promotes the production of cytokines and inflammatory cells in OSAS patients. The inflammatory response in OSAS is regulated by NF- κ B and HIF-1 α . A rise in NF- κ B activity and its downstream product TNF- α has been observed in OSAS. Levels of TNF- α has also been found to be higher in serum samples of OSAS patients as compared to age and sex matched controls. OSAS patients also show elevated monocyte

NF- κ B activity [25]. In OSAS, patients with several nocturnal hypoxemia, HIF-1, can be viewed as a pro-inflammatory contributor to hypoxic response by promoting inflammatory cell survival [27, 28].

3.2. Venous thrombosis: role of valvular stasis-associated hypoxia

Venous Thrombosis involves the formation of a thrombus inside deep veins usually in legs. Such thrombus can break off and travels in circulation and may lodge at pulmonary vasculature leading to Pulmonary Embolism, which may cause death. As per current understanding the luminal thrombus in veins develops in the presence of increased stasis and hypoxia resulting from the outgrowth of a progressively occlusive thrombus extending from valve to lumen [2, 29]. Evidences for the role of stasis (reduced blood flow), include clinical scenario like long term immobilization due to hospitalization. Pressure of stasis in venous valves is supported by the observation that contrast media used in venography lingers in the veins for up to 60 min after the procedure in the elderly with a clear gradient of increasing stasis with age [30]. Further, pO_2 measurements in sinuses of dogs by Hamer et al. have established that prolonged stasis leads to severe hypoxia at venous valvular sinus. A steeply declining pO_2 gradient from 5 to 1 kPa was observed after 2 h of stasis [31]. However, the anatomical location of the severe hypoxia and thrombus initiation were same site [29]. Changes in blood flow pattern are attributed to generation of hypoxia. Role of HIF-1 α in venous thrombus is contradictory and interplayed. An earlier study revealed that HIF-1 α stimulates, vein recanalization and thrombus resolution [32] however, study by Gupta et al. suggest that HIF-1 α plays a role in thrombus development [33].

3.3. Pathways associated with ischemia-associated thrombosis

Reduced blood flow in veins (also called as stasis), is associated with reduced intravascular O_2 tension and thrombus progression. However, only reduced levels of O_2 have not been found sufficient to trigger fibrin clot formation. Although interplay of hypoxia with different cell types, majorly mononuclear phagocytes and polymorphonuclear leucocytes, can contribute, the association between hypoxia and hypoxemia has remained strong, despite extensive mechanistic explanations [3, 34]. In thrombotic episodes, hypoxemia is found severe in proximity to venous valve cusps and nascent thrombi develop on apparently intact endothelial surface at the parietal aspect of valve cusps during hypoxemia [3]. In addition, *in vivo* exposures to intermittent hypoxia/reoxygenation are also associated with thrombus formation. Under such settings, hypoxia/hypoxemia is sufficient to cause venous thrombosis. Stasis leads to ischemia that is associated with a myriad of changes in vascular microenvironment, increased vascular permeability [3].

In a mice model of hypoxia-induced thrombosis, administration of blocking Ab to tissue factor (TF) suppressed fibrin deposition [35]. This observation was also supported by the evidence generated when TF expression was analyzed in hypoxic murine lungs. Hypoxic exposure produced ~20 fold rise in TF transcripts in hypoxic lungs in comparison to normoxic ones [36]. In such cases, early growth receptor-1 (egr-1) has been identified as the primary driving motif for hypoxia-induced TF transcriptional upregulation. The biological importance of

egr-1 has also been validated in *in vivo* model system where egr-1 null animals when exposed to hypoxia showed a minimal rise in TF mRNA levels with no change in antigen levels in comparison to normoxia exposed controls [37]. Earlier evidences indicate that oxygen deprivation promotes egr-1 synthesis due to binding of ternary complex factor to serum response element (SRE) sites in egr-1 promoter region [38]. Egr-1 also plays a central role in monocyte expression of TF under hypoxia. Expression of egr-1 initiated mechanism in pathologic changes associated with hypoxia point toward novel strategies to prevent these events, that is, target egr-1 rather than directly targeting coagulation mechanism. These series of events producing exposure of TF in hypoxemic vasculature especially in mononuclear phagocytes and smooth muscle cells provide a new biologic context to consider mechanisms underlying and possible interventions to prevent hypoxia-induced thrombosis.

3.4. Hypoxia signaling in inflammation and tissue regeneration, with role in chronic obstructive pulmonary disease (COPD) (studies with zebrafish models)

Most of the *in vitro* studies have been complemented by *in vivo* model systems to obtain a more physiologically relevant setting to understand the inter-relationship of hypoxia and disease. Rodents are most widely used. Mice and rats are highly amenable to manipulation and are small enough to fit into hypoxic chambers for longer periods of time. With advent of technology and in present era, Zebra fish are also used as a new whole-organism model of disease to understand the complex physiology involved [39]. One of the primary reasons is that zebrafish have optically transparent larvae; an opportunity to visualize disease processes *in vivo* using fluorescence microscopy. In addition, high-throughput drug screening can be done easily by addition of small molecule compounds to the embryo in water [40]. An injury to blood vessel is often associated with tissue hypoxia when blood flow is restricted in localized milieu. Even, inflammation can occur and recruitment of immune cells at the injury site occurs and clearance of damaged cells takes place to prevent infection [41]. Innate immune cells (leucocytes) are the first one to respond to injury and sense change in local oxygen levels. This inflammatory response is highly regulated by HIF, signaling, contributing to the regulation of immune activity and lifespan of leucocytes, as timely resolution of inflammation is also necessary otherwise failure to timely resolution may result in inflammatory diseases such as COPD [42, 43]. Once inflammation is resolved, tissues thus regenerate and homeostasis is restored. In zebrafish models, cardiomyocytes regeneration is dependent upon HIF-1 α signaling by virtue of which cardiomyocytes can survive and regenerate with an injury of 20% of heart tissue thereby identifying HIF-1 α as a potential therapeutic target [44, 45].

3.5. Hypoxia in heart and cardiac dysfunction: role of reactive oxygen species (ROS)

Myocardial gene expression highly depends upon the levels of O₂. O₂ levels change either during isolated hypoxia or ischemia-associated hypoxia, as a result gene expression patterns are altered. In experiments, conducted with myocardial infarction-induced mice, HIF-1 α stability was found to reduce infarct size and decrease the number of apoptotic cells [46]. The possible explanation is an upregulation of cardiotrophin-1 (member of IL-6 family) by HIF-1 α in hypoxic environment. Further, impaired cardiac muscle contractility due to reduced calcium

ion uptake by cardiomyocytes along with certain amount of dilation in muscles was the additional factor involved [47–49]. This elevated HIF-1 α levels may lead to better cardiomyocyte survival under hypoxia.

In addition to the regulatory role of transcription factors, formation of ROS is another major event occurring under oxygen regulation conditions. ROS participates as a benevolent molecule in cell signaling processes and can induce irreversible cellular damage. Formation of ROS in heart or other tissues may occur by several mechanisms either by xanthine oxidase (XO), NAD(P)H, oxidases, and cytochrome P450, or by auto-oxidation of catecholamines and by uncoupling of NO synthase (NOS) [50–52]. Presence of unpaired e⁻ on NO facilitates its reaction with O₂⁻ to form peroxynitrites (ONOO⁻), an oxidant. Further, Formation of ROS is also induced by cytokine stimulus, growth factors such as angiotensin II (ATII), PDGF and TNF- α [50, 53]. As an adaptive response, production of ROS is counterbalanced by several enzymatic (such as superoxide dismutase (SOD), Catalase, Thioredoxin) and non-enzymatic mechanisms (intracellular oxidants such as vitamins E, C, β -carotene, ubiquinone liponic acid and glutathione) [54–56]. Deletion of Thioredoxin reductase leads to cardiac abnormalities and even cardiac death, secondary to severe dilated cardiomyopathy [57]. Activation of ROS occurs in response to various stressors and in failing heart as well (**Table 1**).

3.6. Hypoxia-mediated inflammation in atherosclerosis

Inflammation and hypoxia are integral parts in development of atherosclerosis. Data from recent reports suggest that HIF-1 α is involved in the pathogenesis of atherosclerosis. Smooth muscle cells extracted from coronary arteries showed that HIF-1 α increased activity was related to increased VEGF expression required for proliferation of smooth muscle cells (SMC) [70]. Moreover, hypoxia also produces HIF-1 α dependent increase in macrophage migration inhibitory factor (MIF)-required for escalation of migration increased proliferation of vascular SMCs during progression of atherosclerosis [71]. In developing atherosclerosis chronic inflammation and various types of cells (SMC, EC monocytes/macrophages, and T lymphocytes) are involved in plaque formation [72]. Even, the oxygen supply from the luminal blood strongly affects the cells of blood vessel wall [73]. In developed atherosclerosis, tissue hypoxia occurs at the plaque lesion and HIF-1 α expression occurs at the macrophage rich center of plaque [72, 74].

HIF-1 α also upregulates the expression of low density lipoprotein receptor related protein-1 (LRP1) associated with cholesterol independent progression of atherosclerosis [75]. In fact, bone marrow transplantation of muscle specific HIF-1 α deficient mice reduced the plaque burden in aorta of Ldlr^{-/-} mice. Furthermore, expression of inflammatory genes (M1 macrophage accumulation) was also suppressed in HIF-1 α deficient mice [76]. It is also known that tissue hypoxia in plaque lesion is not a consequence of increased plaque burden but a consequence of HIF-1 α signaling-mediated M1 macrophage activation [72, 77].

3.7. Congenital heart diseases (CHD): role of spatially differential hypoxia

CHDs are the major inborn abnormality with major role of environmental factors. The role of non-physiological hypoxia during early pregnancy also induces CHD. Reports are there to show that cells in the mouse heart tube are hypoxic while cardiac progenitor cells (CPCs) in the secondary heart field are normoxic. This spatial difference in the oxygenation of developing

Disease	ROS related mechanism	References
Heart failure function (In ischemic syndrome, heart failure is a sequelae of myocardial ischemia and necrosis is a major cause of death worldwide)	ROS contributes to the formation of oxidized LDL, the key molecular player in progression of atherosclerosis. Even the activation of MMPs by ROS contributes to plaque rupture initiating coronary thrombosis and occlusion	[58–60]
Myocardial infarction	ROS plays a role in necrosis and reperfusion, injury. Overexpression of SOD (an antioxidant molecule), reduces the infarct size. Evidences that ROS play an important role in myocardial infarction (MI). Around 20% of patients suffering from MI, often develop heart failure which is also determined by the healing and remodeling patterns of ventricles. The latter highly depends upon ROS. Even inhibition of XO with allopurinol diminishes ROS production in myocardium and attenuates maladaptive LV remodeling, leading to post MI cardiac function.	[61–65]
Cardiac hypertrophy (cardiac hypertrophy often serves as a maladaptive precursor to heart failure)	ROS activates either directly or indirectly many extracellular factors as well as downstream signaling pathways that mediate hypertrophic growth response to these factors. Molecules such as PKC, MAPKs, p38, JNK, ERK1/2, Akt, Tyrosine kinase, NF-kB. For instance, AgII-induced hypertrophy is mediated by induction of extracellular signal, whereas direct activation involves ROS-mediated activation of PKC via oxidation of cysteine residues.	[66–69]

Table 1. Different diseases associated to ROS signaling.

heart serves as a signal to regulate the expansion of CPC and cardiac morphogenesis. The response is also mediated by HIF-1 α , where HIF-1 α forms a complex with notch effector HES family bHLH transcription factor 1 (HES 1) and protein deacetylase sirtuin1 (SIRT1) at the ISL1 gene (islet gene) where ISL1 repression occurs in hypoxic heart tube or as a response to ectopic hypoxic response and prevents CHDs. Thus this is an example where spatial difference in physiological hypoxia maintains the homeostasis for CPCs and provides mechanistic explanation for non- congenital CHDs [78].

3.8. Pulmonary arterial hypertension (PAH)

PAH is clinically manifested as elevated BP in pulmonary artery with resulting right ventricular heart failure [79, 80]. Hypoxia is known to elicit pulmonary vasoconstriction and arterial remodeling [81, 82]. Hypoxic exposures are the commonly used murine models of PAH. Recently, pulmonary endothelial specific HIF-2 α deficient mice showed tolerance to hypoxia-induced PAH as compared to HIF-1 α deficient or control mice [83]. As a molecular mechanism HIF-2 α regulates NO production in pulmonary vasculature via induction of arginase-1, thereby indicating that HIF-2 α -Arginase-1 axes may be used as a therapeutic target to improve NO availability in PAH [83].

3.9. High-altitude hypoxia and thrombosis

An imbalance between tissue demand and actual oxygen supply also develops due to environmental hypoxia or reduced oxygen content in ambient air [4]. Such episodes are commonly

found on exposure to high altitude, mountain climbing or while traveling through air travel, (commercial flights). In commercial flights, when cabin pressure reduces and becomes equivalent to an altitude of 1.5–2.5 km hypoxia is often followed by reoxygenation in majority of such cases, serves as an exacerbating factor for thrombus development in veins [84, 85]. In an earlier study, such observations have been recorded with simulated mouse models where hypoxia-reoxygenation is known to promote thrombosis in mouse model of DVT thereby validating incidence of DVT under H/R conditions. The mechanistic explanation given is that hypoxia promotes the secretion of Weibel-Palade bodies, thereby initiating thrombosis in stenosis model [5]. In addition, a recent report also elucidated the possible early factors for hypoxia-induced venous thrombosis; however, in these cases, animals were exposed to hypoxia/normoxia post-thrombus induction (by ligation method) and the study has reported the role of novel regulators NLRP3-Caspase-1-IL-1 β signaling axis under the transcriptional regulation of HIF-1. Using the pre-clinical rat model for hypoxia-induced thrombosis, the investigators have clearly demonstrated that under hypoxic environments (as found at high altitude), NLRP3-Caspase-1-IL-1 α signaling axis could serve as therapeutic target to prevent thrombogenesis under hypoxic settings. Nonetheless, the translational potential of these pre-clinical observations were also made evident in patients of altitude induced venous thrombosis obtained from army soldiers posted at regions of High altitude [33]. In another parallel study, aimed to investigate the role of hypoxia-induced platelet hyper-reactivity, platelet specific novel regulator protein ‘calpain’ was found to be involved in promoting prothrombotic tendency on ascension to high altitude [86]. A genome wide expression analysis of genes in patients of high altitude-induced venous thrombosis revealed that the progression of venous thrombus formation is attributed to the differential expression of hypoxia responsive genes in response to environmental hypoxia [87].

4. HIF-1-independent responses

These responses become functional to promote ATP conservation by limiting energy consuming processes such as ribosome biogenesis ion channel activity. Such types of responses include mTORC1 & UPR pathways-mediated regulation of mRNA translation [88]. Responses include inhibition of protein synthesis by affecting the assembly of active eukaryotic initiation factor (eIF) 4F & eIF2-GTP-met-tRNA ternary complex. mTOR is a highly conserved serine/threonine kinase which integrates environmental stimuli to regulate metabolism, translation & structural organization in cell in response to growth factors and O₂ availability [89, 90].

mTOR occurs in two distinct complexes. mTORC1 (comprising of raptor and GBL/mLST8) and mTORC2 (raptor and GBL/mLST8). mTORC1 plays a role in ribosome biogenesis, mRNA translation, and nutrient import. mTORC2 regulates Akt catalysis and actin organization. Hypoxia regulates the translational activity via involvement of mTORC1 and C2-mediated action. The activity of mTORC1 is regulated by different types of kinases (upstream such as PI3K/Akt/MAPK) by phosphorylation of tuberous sclerosis complex (TSC) [90].

4.1. Biological manifestation of mTORC1 pathways in cardiovascular cells

Cells of cardiovascular system respond to hypoxic environments by exhibiting increased growth and program of vascular remodeling operating in tissues and cells (SMC, EC, fibroblasts), involving signaling pathways (mTORC1 mediated and its downstream targets) [91, 92].

In the cell types of pulmonary artery, adventitial fibroblasts proliferation occurs under reduced O₂ conditions [93]. Signaling pathways include MAPK, PKC. In fact, hypoxic exposure leads to mTORC1 activation as in aortic SMC [92]. Along with mTORC1 activation, P70^{S6K} activity and 4E-BP1 phosphorylation increase, thus affecting the rate of protein synthesis changing with hypoxic gradient [94].

Ischemia is characterized by exposure of cells to O₂ followed by O₂ availability that produce interesting effects on mTORC1 pathway. In experimental models of ischemia/reperfusion cells showed failure in response with mTORC1 inhibition. Additionally, reperfusion also resulted in increased mTORC1 signaling with increased P70^{S6K} and 4E-BP1 phosphorylation. mTORC1 signaling during ischemia imparts/contributes to withstand the associated stresses and help in recovery following ischemic insult [95].

5. Conclusion

Activation of hypoxia-induced signaling mechanisms form an integral component in development of widely known CVDs (**Figure 1**). These mechanisms are activated as an adaptive response toward hypoxia, and involve a coordinated action of Transcription

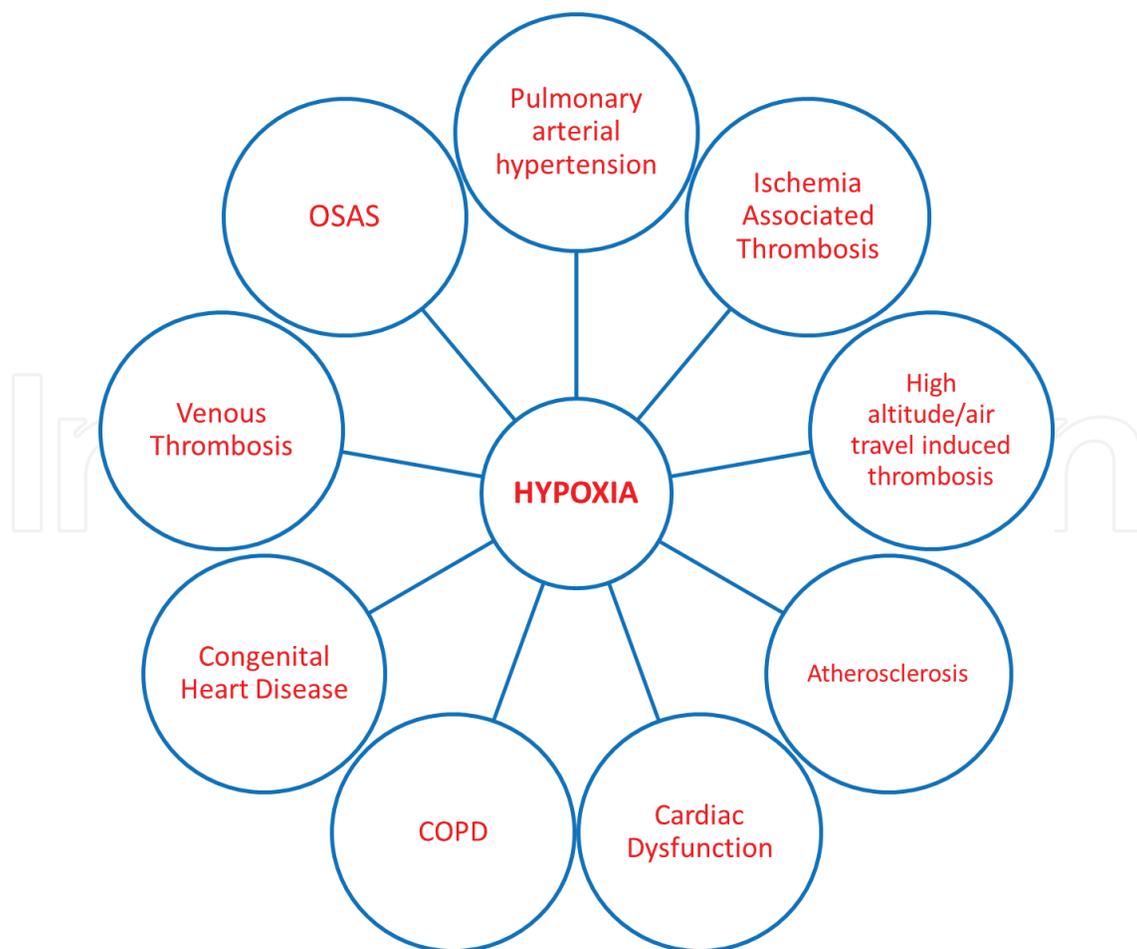


Figure 1. Commonly known CVDs with pathophysiology as a function of hypoxia signaling mechanisms.

factors (HIF-1, NF- κ B), reactive oxygen species and downstream effector molecules, which can serve as therapeutic targets to control the development of the related disease.

Conflict of interest

The authors declare no conflict of interest.

Author details

Neha Gupta^{1*} and Mohammad Zahid Ashraf^{2*}

*Address all correspondence to: nehaguptalifesciences@gmail.com and zashraf@jmi.ac.in

1 Department of Biosciences, Jamia Millia Islamia, New Delhi, India

2 Department of Biotechnology, Jamia Millia Islamia, New Delhi, India

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