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Oxygen-Sensing Proteins and Arterial Stiffness: A Narrative Review

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ABSTRACT

Arterial stiffness has emerged as a robust, independent predictor of cardiovascular morbidity and mortality, reflecting both functional and structural alterations within the vascular wall. While conventional risk factors such as aging, hypertension, diabetes, and dyslipidemia are well-established contributors, recent advances underscore the critical role of oxygen-sensing mechanisms in vascular biology. Oxygen-sensing proteins including hypoxia-inducible factors (HIFs), prolyl hydroxylase domain enzymes (PHDs), heme oxygenases, mitochondrial electron transport chain components, and soluble guanylate cyclase serve as molecular sentinels that detect fluctuations in oxygen tension and orchestrate adaptive cellular responses. These pathways regulate angiogenesis, nitric oxide bioavailability, vascular smooth muscle tone, extracellular matrix remodeling, and inflammatory signaling processes intricately linked to arterial compliance. Dysregulation of oxygen-sensing proteins leads to impaired redox homeostasis, endothelial dysfunction, maladaptive vascular remodeling, and chronic low-grade inflammation, which collectively accelerate arterial stiffening. Moreover, emerging evidence suggests a bidirectional interplay: progressive arterial stiffness impairs oxygen delivery to peripheral tissues, thereby perpetuating hypoxia and further activating maladaptive oxygen-sensing cascades. Experimental studies in animal models, along with clinical investigations in patients with hypertension, chronic kidney disease, diabetes, and chronic hypoxic states, provide compelling insights into these associations. This narrative review synthesizes current evidence on the role of oxygen-sensing proteins in the pathophysiology of arterial stiffness, bridging mechanistic understanding with translational perspectives. Special emphasis is placed on molecular crosstalk between HIF signaling, mitochondrial function, and vascular remodeling. Furthermore, we discuss potential therapeutic avenues, including pharmacological modulation of HIF pathways, enhancement of nitric oxide signaling, and strategies targeting mitochondrial dysfunction, which may offer novel opportunities to attenuate arterial stiffening and reduce cardiovascular risk. By integrating experimental and clinical insights, this review highlights the promise of oxygen-sensing proteins as biomarkers and therapeutic targets in vascular aging and disease.

KEYWORDS: Oxygen-sensing proteins; arterial stiffness; hypoxia-inducible factors; prolyl hydroxylase; vascular remodeling; endothelial dysfunction; cardiovascular risk; redox signaling.

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INTRODUCTION

Cardiovascular diseases represent a significant global health burden, with hypoxia, or oxygen deprivation, being a critical contributing factor. The evolutionary success of aerobic organisms, particularly higher life forms, is intrinsically linked to oxygen, highlighting its fundamental role in survival and physiological function. Hypoxia-inducible factors serve as a central molecular switch in the cellular response to oxygen fluctuations, demonstrating remarkable conservation across diverse species [1]. This intricate regulatory system orchestrates the transcription of numerous genes vital for processes such as erythropoiesis, angiogenesis, and metabolic adaptation, ensuring cellular and systemic homeostasis during periods of reduced oxygen availability [2]. The duration of hypoxic exposure can vary significantly, ranging from acute, transient episodes lasting seconds to minutes, to chronic conditions extending over hours or days, such as those encountered at high altitudes [3]. This variability in hypoxic presentation, encompassing acute, chronic, continuous, intermittent, generalized, localized, hypo- or normobaric forms, profoundly impacts cardiovascular function through mechanisms involving autonomic nervous system activity, direct vascular tone alterations, and humoral changes. This review aims to synthesize current knowledge regarding the multifaceted roles of oxygen-sensing proteins in the pathogenesis of arterial stiffness, a key indicator of cardiovascular health, considering the diverse manifestations of hypoxia and their physiological consequences. This understanding is crucial, as hypoxia can trigger both adaptive and maladaptive cardiovascular responses, mediated largely by these oxygen-sensing proteins [4].

OXYGEN-SENSING PATHWAYS AND PROTEINS

The Nobel Prize-winning discoveries by Kaelin Jr., Ratcliffe, and Semenza elucidated how cells sense and adapt to varying oxygen levels, highlighting the pivotal role of hypoxia-inducible factors in this process. These factors, particularly HIF-1α and

HIF-2α, are central to a complex signaling network that governs cellular responses to hypoxia, thereby influencing a wide array of physiological and pathophysiological processes, including those in the cardiovascular system [1]. Cellular oxygen sensitivity is finely tuned by two principal classes of enzymes, collectively known as HIF-hydroxylases [5]. These enzymes, including prolyl hydroxylase domain enzymes and factor inhibiting HIF, modulate HIF stability and transcriptional activity by catalyzing the hydroxylation of specific proline and asparagine residues within the HIF-α subunit [1]. This post-translational modification, crucial for HIF-α degradation under normoxic conditions, is suppressed during hypoxia, leading to HIF-α stabilization, dimerization with HIF-β, and subsequent binding to hypoxia-response elements in target gene promoters. Although structurally similar, HIF-1α and HIF-2α exhibit distinct functional roles, with HIF-1α predominantly driving glycolysis and angiogenesis during acute hypoxia, while HIF-2α promotes vascular maturation during chronic hypoxic states [1]. This functional divergence suggests that while HIF-1α might contribute significantly to disease progression and persistence in conditions like pulmonary hypertension, HIF-2α could be a crucial driving factor in the early stages. Furthermore, the interplay between HIF-1α and HIF-2α extends to their roles in cardiovascular pathologies beyond pulmonary hypertension, with HIF-1α implicated in atherosclerosis, myocardial ischemia/reperfusion injury, and cardiomyopathy, while prolonged activation can exacerbate chronic heart failure. Conversely, maintaining HIF pathway activation within a normal physiological range has been shown to improve metabolic and cardiovascular markers, including enhanced glucose tolerance, reduced cholesterol and blood pressure, and decreased inflammatory burden [1]. However, non-hypoxic conditions, such as the presence of growth factors, hormones, or cytokines, can also modulate HIF-α subunits at various levels, regulating a plethora of signaling pathways that influence cellular metabolism, proliferation, survival, and angiogenic responses [6]. Under normoxic conditions, HIF-α subunits undergo hydroxylation by prolyl hydroxylase enzymes, which utilizes oxygen and α-ketoglutarate as substrates, marking them for proteasomal degradation via the von Hippel–Lindau tumor suppressor protein [7]. This process is pivotal, as the inhibition of prolyl hydroxylase activity under hypoxic conditions prevents HIF-α hydroxylation, thereby allowing its stabilization and subsequent activation of hypoxia-responsive genes [8, 9]. This intricate regulatory mechanism, involving the oxygen-dependent hydroxylation of HIF-α by PHDs, ensures that HIF-α is rapidly degraded in the presence of sufficient oxygen but accumulates under hypoxic conditions to initiate adaptive transcriptional programs [10, 11]. Beyond these classical roles, HIF-1α is also critical in regulating macrophage glycolysis and immune escape pathways, while elevated lactate levels can further promote HIF-2α accumulation, leading to pulmonary artery endothelial cell damage [12]. This intricate interplay underscores the multifaceted roles of HIF isoforms in cellular metabolism and immune responses, particularly within the context of chronic inflammatory diseases such as pulmonary arterial hypertension, where glycolysis and macrophage polarization are significantly altered. For instance, HIF-1α upregulates factors such as nuclear factor kappa B, VEGF, and reactive oxygen species, contributing to endothelial cell dysfunction and atherosclerotic progression, while also promoting macrophage-mediated inflammation and foam cell formation [13]. Similarly, HIF-2α, though often associated with adaptive responses, can also contribute to pathological processes by influencing vascular remodeling and inflammatory cascades [13]. Further investigation reveals that under normoxic conditions, other molecular mechanisms, such as bacterial lipopolysaccharide stimulation, can induce HIF-1α accumulation via reactive oxygen species production and succinate accumulation, thereby promoting the expression of inflammatory cytokines like IL-1β [14]. This illustrates that HIF-1α stabilization is not solely dependent on oxygen deprivation but can also be triggered by inflammatory stimuli, thereby linking inflammatory processes to HIF-mediated responses [15]. Specifically, prolyl hydroxylase domain–containing proteins mediate the hydroxylation of HIF-α subunits, which then undergo polyubiquitination by the von Hippel-Lindau tumor suppressor E3 ubiquitin ligase complex and subsequent degradation via the 26S proteasome [16, 17]. Under conditions of inflammation or reduced oxygen concentration, such as in tumors, HIFs are stabilized, dimerize with ARNT, and translocate to the nucleus to regulate transcription by binding to hypoxia response elements in the promoters of target genes [18]. This transcriptional activity orchestrates cellular adaptation to hypoxia through the induction of genes involved in angiogenesis, erythropoiesis, and glucose metabolism [19]. Furthermore, inflammatory stimuli, including cytokines like TNF-α and IL-1β, can independently induce HIF-1α stabilization and activation through NF-κB pathways, even under normoxic conditions [16].

HYPOXIA-INDUCIBLE FACTORS (HIFS) IN VASCULAR BIOLOGY

The diverse roles of hypoxia-inducible factors in vascular biology encompass both physiological adaptation and pathological development, primarily mediated through their differential regulation and target gene activation [1]. For instance, HIF-1α is a central mediator in the inflammatory response of macrophages, with its activation by agents such as LPS or IFN-γ leading to the production of proinflammatory cytokines like TNF-α and IL-6 [20]. This mechanism highlights how HIF-1α bridges inflammatory signals with cellular responses, influencing processes such as metabolism, cell cycle, angiogenesis, and chemoresistance [18]. Moreover, NF-κB, a transcription factor strongly activated by inflammatory stimuli and also sensitive to hypoxia, directly interacts with the HIF pathway; canonical NF-κB activity promotes HIF-1α mRNA transcription, further enhancing HIF activity during chronic inflammation [21]. Conversely, while HIF has been shown to regulate NF-κB activity in neutrophils, this appears to be a cell-type specific interaction, suggesting a nuanced regulatory crosstalk between these two critical transcription factors [22]. The complexity of HIF-1α regulation extends beyond oxygen availability and inflammatory signals, as evidenced by its modulation through interactions with various co-activators and co-repressors that fine-tune its transcriptional activity. For example, in hypoxic conditions, the HIF-α subunit translocates to the nucleus where it dimerizes with HIF-β, subsequently activating the transcription of numerous target genes vital for angiogenesis, such as vascular endothelial growth factor [23]. This induction of VEGF by HIF-1 ensures increased blood flow to hypoxic tissues and promotes the formation of new blood vessels, a critical adaptive response to oxygen deprivation [24]. However, beyond its role in angiogenesis, HIF-1α is also directly induced by inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β (IL-1β), which not only increase its accumulation but also enhance its transcriptional activity [25, 26]. This positive feedback loop between inflammation and HIF-1α further exacerbates pathological conditions, contributing to chronic inflammation and tissue damage [10]. This interplay demonstrates a critical link between inflammation and hypoxia, suggesting HIF-1α as a potential therapeutic target in various inflammatory diseases, including those affecting vascular integrity [16]. Moreover, this intricate feedback loop between

HIF-1α and inflammatory cytokines like TNF-α can lead to a sustained inflammatory state, especially under chronic hypoxic conditions, by promoting the differentiation of monocytes into macrophages and further cytokine secretion [27, 28]. The intricate relationship between hypoxia and inflammation is further exemplified by the co-activation of HIF-1 and nuclear factor κB, both crucial in driving chronic inflammation in various pathologies, including cancerous tumors and sites of infection or injury [29, 30].

PROLYL HYDROXYLASE DOMAIN PROTEINS (PHDS) AND OXYGEN SENSING

HIF prolyl-4-hydroxylases (HIF-P4Hs) serve as key oxygen sensors, whose activity is contingent upon molecular oxygen, iron, and 2-oxoglutarate [31]. In normoxic conditions, these enzymes hydroxylate specific proline residues on HIF-α subunits, marking them for proteasomal degradation [22]. Conversely, under hypoxic conditions, the reduced availability of oxygen inactivates these hydroxylases, thereby stabilizing HIF-α subunits and allowing their translocation into the nucleus where they can activate transcription of hypoxia-responsive genes [32, 24]. This regulatory mechanism underscores their fundamental role in governing the adaptive cellular response to varying oxygen concentrations, thereby influencing a cascade of physiological and pathophysiological processes, including angiogenesis and metabolic reprogramming [33]. Indeed, the oxidation of specific cysteine residues within the catalytic site of PHDs, particularly PHD2, can be promoted by increased mitochondrial reactive oxygen species, further modulating HIF1α stability independent of direct oxygen tension [19]. This intricate relationship between reactive oxygen species and PHD activity highlights a critical non-hypoxic mechanism influencing HIF-1α levels and cellular oxygen sensing [33]. Moreover, intracellular succinate, a metabolic intermediate, has been shown to inhibit PHDs, thereby stabilizing HIF-1α and amplifying pro-inflammatory gene transcription, even under normoxic conditions [34]. This inhibition is achieved through succinate's competitive binding with 2-oxoglutarate at the active site of PHDs, thereby impeding their enzymatic function [34]. This metabolic regulation of HIF-1α through succinate-mediated PHD inhibition represents a crucial link between cellular metabolism and inflammatory responses [19]. This intricate metabolic control of HIF-1α stabilization is further complicated by the activity of HIF-P4H-1, an isoform whose inhibition has been shown to downregulate pro-inflammatory genes and upregulate proapoptotic genes, suggesting a therapeutic avenue for inflammatory diseases and cancer [31]. Beyond the PHDs, another crucial oxygen-dependent hydroxylase, Factor Inhibiting HIF-1, modulates HIF-1α activity by hydroxylating an asparagine residue, thereby diminishing its transcriptional capacity [35, 36]. This hydroxylation by FIH-1 prevents the recruitment of coactivators like p300 and CBP, further refining the hypoxic response by regulating the strength of HIF-dependent gene expression [37]. When oxygen concentrations fall below critical thresholds, FIH-1's hydroxylation reactions are impaired, leading to the accumulation of HIF-α subunits and their subsequent interaction with HIF-β, which ultimately impacts gene expression [38]. Conversely, during hypoxia, the reduced activity of FIH-1, similar to PHDs, contributes to HIF-α stabilization and enhanced transcriptional activation through augmented co-activator complex formation [39]. It is also important to consider that the sensitivity of PHDs to oxygen varies between different tissues and HIF proteins, contributing to the diverse cellular responses to hypoxia [28].

OTHER OXYGEN-SENSING MECHANISMS IN THE VASCULATURE

Beyond the canonical HIF pathway, other oxygen-sensing mechanisms play pivotal roles in vascular homeostasis, integrating diverse signals to adapt cellular function to oxygen availability. For instance, the activity of the asparaginyl hydroxylase Factor Inhibiting HIF extends beyond its canonical role in modulating HIF activity, as it interacts with various signaling pathways, including Notch and IκBα, impacting diverse cellular functions like metabolism [40]. Furthermore, reactive oxygen species, often generated in response to hypoxia or other stressors, can directly modify various proteins, altering their activity and signaling cascades, thereby contributing to the cellular response to altered oxygen levels [38]. Specifically, FIH-1, a member of the 2-oxoglutarate-dependent oxygenase superfamily, hydroxylates asparagine residues in the C-terminal transactivation domain of HIF-α isoforms, thereby reducing their interaction with transcriptional coactivators such as p300/CBP and attenuating HIF-mediated gene expression [40]. This mechanism is particularly sensitive to oxygen concentrations, with FIH-1 requiring higher oxygen levels for optimal activity compared to the PHDs, suggesting that it primarily regulates HIF activity under moderate hypoxia or normoxia [1, 28]. This differential oxygen sensitivity between FIH-1 and PHDs allows for a nuanced regulation of HIF transcriptional activity across varying hypoxic gradients [41, 40]. Under normoxic conditions, the dual hydroxylation modifications of HIF-1α by both PHDs and FIH-1 serve to concurrently suppress protein abundance and transcriptional activity, thus ensuring the strict expression of hypoxia-inducible genes exclusively within hypoxic environments [1]. Moreover, FIH-1 exhibits differential activity towards HIF-1α and HIF-2α, with a more pronounced inhibitory effect on HIF-1α, contributing to distinct functional outcomes of these two HIF isoforms [42]. Additionally, FIH-1 possesses a broader substrate specificity, hydroxylation non-HIF targets such as ankyrin repeat domain-containing proteins, further highlighting its diverse regulatory roles beyond HIF pathway modulation [43]. For example, FIH hydroxylates asparagine residue 803 in the C-terminal transactivation domain of HIF-1α, repressing its transcriptional activity under normal oxygen tension [44]. This post-translational modification is crucial for preventing unwarranted HIF-1α activation during normoxia, ensuring that the hypoxic response is tightly regulated and only initiated when oxygen levels are critically low [40]. This asparagine hydroxylation by FIH-1 hinders the binding of critical co-activators, such as p300 and CBP, to the C-terminal transactivation domain of HIF-α, thereby attenuating its transcriptional potency [38, 45]. This mechanism ensures that the full transcriptional potential of HIF-α is only realized when oxygen availability is critically low, a condition under which FIH-1's activity is significantly reduced [40].

ARTERIAL STIFFNESS: PATHOPHYSIOLOGY AND CLINICAL SIGNIFICANCE

Arterial stiffness, a hallmark of vascular aging and a strong predictor of cardiovascular events, arises from complex alterations in the structural and functional properties of arterial walls.

Mechanisms of Arterial Stiffening: These alterations involve complex modifications to the extracellular matrix, including the accumulation of advanced glycation end-products and increased cross-linking of collagen, which collectively diminish arterial compliance. Elastin degradation and vascular smooth muscle cell dysfunction also contribute significantly to this process, leading to a loss of elasticity and increased pulse wave velocity [46, 20]. Furthermore, chronic inflammation and oxidative stress exacerbate arterial stiffening by promoting vascular remodeling and impairing endothelial function, ultimately contributing to the pathogenesis of various cardiovascular diseases. The interplay between these mechanisms establishes a vicious cycle, where increased stiffness further compromises endothelial integrity and promotes additional detrimental changes within the arterial wall. The heightened stiffness, in turn, amplifies the mechanical stress on the endothelium, potentially accelerating atherosclerotic plaque formation and destabilization. Moreover, age-related increases in arterial stiffness are closely associated with heightened blood pressure, decreased inotropic responsiveness, and impaired diastolic filling, further contributing to the development of heart failure [47, 48]. This cascade of events highlights the systemic impact of arterial stiffening, extending its pathological reach beyond the vascular system to affect overall cardiovascular function. Consequently, understanding the molecular mechanisms driving arterial stiffening, particularly those related to oxygen sensing, is crucial for developing effective therapeutic strategies. Emerging evidence suggests that chronic intermittent hypoxia, often seen in conditions like sleep apnea, can directly induce endothelial dysfunction and arterial stiffening through mechanisms involving oxidative stress and inflammation [49]. Elevated blood pressure, a direct consequence of compromised arterial elasticity, further perpetuates a harmful cycle of vascular damage, inflammation, and calcification [50]. These changes contribute to an increased arterial wall thickness and a gradual rise in arterial stiffness, particularly noticeable after the age of 50, affecting a significant portion of the geriatric population [51, 52].

Clinical Implications of Increased Arterial Stiffness: Increased arterial stiffness is an independent predictor of cardiovascular morbidity and mortality, rivaling traditional risk factors such as left ventricular hypertrophy in prognostic value [53, 54]. Its presence signifies an accelerated vascular aging process, leading to a decline in the buffering capacity of arteries against pulsatile blood flow and thereby increasing the risk of adverse cardiovascular events [55, 56]. This reduced compliance elevates systolic blood pressure and pulse pressure, consequently augmenting left ventricular afterload and myocardial oxygen demand, which can precipitate myocardial ischemia [57]. Moreover, the accelerated propagation of the forward pressure wave due to aortic sclerosis results in an earlier return of reflected waves during systole, thereby reducing diastolic coronary artery perfusion and myocardial oxygen delivery [58]. This phenomenon contributes to increased central blood pressure and an elevated risk of heart failure [59]. Furthermore, chronic intermittent hypoxia, such as that experienced in obstructive sleep apnea, directly contributes to increased arterial stiffness by inducing sympathetic activation, inflammation, and oxidative stress, thereby increasing the risk of cardiovascular morbidity [60, 49]. Indeed, studies indicate that obstructive sleep apnea, characterized by intermittent hypoxia, leads to endothelial dysfunction and vascular remodeling, further exacerbating arterial stiffening and cardiovascular risk [49]. Such pathological increases in aortic stiffness can cause reflected waves from the periphery to return in phase with cardiac systole, thereby augmenting central systolic pressure and increasing the hemodynamic load on the left ventricle [61]. This augmented load, in turn, can induce left ventricular hypertrophy and increase myocardial oxygen demand, predisposing individuals to conditions such as heart failure with preserved ejection fraction and coronary artery disease. Moreover, increased arterial stiffness is also associated with a heightened risk of cognitive impairment and stroke due to compromised cerebral blood flow and microvascular damage. The measurement of aortic stiffness, particularly via pulse wave velocity, serves as a non-invasive indicator of maladaptive changes in aortic properties and is a promising marker for subclinical cardiovascular disease [61].

ROLE OF OXYGEN-SENSING PROTEINS IN ARTERIAL REMODELING AND STIFFNESS

Oxygen-sensing proteins play a critical role in mediating the cellular and molecular responses that influence arterial structure and function, particularly in pathological conditions involving hypoxia [62]. These proteins act as crucial transducers of oxygen levels, initiating intricate signaling cascades that modulate gene expression and protein activity, ultimately influencing vascular tone, remodeling, and the extracellular matrix composition. Specifically, hypoxia-inducible factors are paramount among these, orchestrating a comprehensive transcriptional response that encompasses angiogenesis, erythropoiesis, and glucose metabolism, all of which indirectly influence arterial wall mechanics. Beyond HIFs, other oxygen-sensitive pathways, including those involving prolyl hydroxylase domain enzymes and various redox-sensitive signaling molecules, contribute to the complex regulation of vascular smooth muscle cell phenotype and extracellular matrix turnover, thereby influencing arterial stiffness.

HIF-1α and Vascular Smooth Muscle Cell Function: Hypoxia-inducible factor 1-alpha (HIF-1α) serves as a central regulator in vascular smooth muscle cells, mediating cellular adaptations to low oxygen environments that directly impact arterial remodeling and stiffness. Its activation promotes neointimal proliferation, medial hypertrophy, and pro-inflammatory signaling, contributing significantly to atherosclerosis and arterial thrombus formation [1]. This underscores HIF-1α's pivotal role in promoting processes that stiffen arterial walls, reduce their elasticity, and increase the risk of cardiovascular events, especially as a consequence of chronic hypoxic conditions [10]. Furthermore, HIF-1α upregulates genes involved in extracellular matrix remodeling, such as lysyl oxidase, which promotes collagen cross-linking and contributes to the stiffening of the arterial wall [63]. The master regulator, HIF-1α, also mediates pathological processes like vascular inflammation, oxidative stress, and the elaboration of matrix metalloproteinases, all of which are implicated in arterial stiffening and abdominal aortic aneurysm formation [64]. The activation of HIF-1, for instance, has been shown to induce phenotypic transformations in vascular smooth muscle cells, which are directly involved in the progression of arterial diseases [65]. In normoxic conditions, HIF-1α is typically degraded; however, under hypoxic stress, it becomes stabilized and translocates to the nucleus to heterodimerize with HIF-1β, thereby activating target gene expression [65]. This activation triggers the transcription of numerous genes critical for cellular adaptation to hypoxia, including those influencing cell proliferation, metabolic shifts, and angiogenesis [2]. Indeed, HIF-1α's involvement in vascular smooth muscle cell phenotypic modulation highlights its significance in arterial wall mechanics, as its knockdown can reverse hypoxia-induced phenotypic changes [66]. For instance, iron deficiency, a widespread nutritional state,

can activate HIF-1 signaling, leading to adverse phenotypic transformations in VSMCs that exacerbate conditions like aortic dissection severity [65]. Such activation can also lead to increased synthesis of extracellular matrix proteins and enzymes that cross-link these proteins, thereby directly contributing to the mechanical stiffening of the arterial wall. This intricate interplay underscores the potential of HIF-1α as a therapeutic target for mitigating arterial stiffness and associated cardiovascular pathologies.

PHDs and Extracellular Matrix Homeostasis: Beyond HIF-1α, prolyl hydroxylase domain enzymes act as crucial oxygen sensors that regulate the stability of HIF-1α, and also directly influence extracellular matrix homeostasis, impacting arterial stiffness. These enzymes regulate the hydroxylation of HIF-α subunits, marking them for proteasomal degradation under normoxic conditions, and thus their inhibition can stabilize HIF-1α, even in the presence of adequate oxygen [67]. This delicate balance between HIF-1α stabilization and degradation, primarily governed by PHDs, thus dictates the transcriptional response to hypoxia and subsequently influences the synthesis and degradation of extracellular matrix components [20]. Consequently, dysregulation of PHD activity can lead to aberrant HIF-1α accumulation, promoting vascular smooth muscle cell proliferation and extracellular matrix remodeling, both of which are critical contributors to increased arterial stiffness [6, 20]. Specifically, PHD2 is the most crucial isoform in this process, with its optimal activation occurring under normoxia and moderate hypoxia, ensuring proper HIF-α degradation [42]. However, under severe or prolonged hypoxia, PHD activity is significantly reduced, leading to HIF-α stabilization and the subsequent activation of its downstream genetic program, which includes genes involved in extracellular matrix remodeling [68]. Moreover, the destabilization of HIF-1α through PHD activity is critical for maintaining vascular smooth muscle cell integrity and preventing the structural degradation observed in conditions like aortic dissection, where iron deficiency can exacerbate HIF-1α-mediated damage [65]. Furthermore, certain inhibitors of prolyl hydroxylase, such as desferrioxamine, can stabilize HIF-1α, leading to increased activity of matrix metalloproteinases, which may contribute to the degradation of arterial extracellular matrix components [64]. Conversely, some studies indicate that pharmacological blockade of PHDs can preserve mitochondrial integrity and induce hypoxia tolerance in ischemic muscle, suggesting a context-dependent role [69]. The primary mechanism involves PHDs, which are iron- and α-ketoglutarate-dependent dioxygenases that hydroxylate HIF-α on conserved proline residues in the presence of oxygen, initiating its degradation via the von Hippel-Lindau protein and an E3 ubiquitin ligase complex [70, 1]. This hydroxylation by HIF-P4Hs is highly oxygen-dependent, making these enzymes direct sensors of cellular oxygen tension and central to the regulation of HIF-α stability. Indeed, inhibiting HIF-P4H enzymes prevents HIF degradation, thereby offering a novel approach to activate the endogenous hypoxia response, particularly in conditions like chronic kidney disease [71]. The activity of PHDs is not solely dependent on oxygen levels but is also influenced by other factors such as cellular redox state and the availability of co-factors like iron and 2-oxoglutarate, with disruptions to these elements inhibiting PHD activity and stabilizing HIF-1α [72]. This interplay underscores the intricate regulation of HIF-1α by PHDs and highlights how perturbations in PHD function can significantly impact arterial remodeling and stiffness. The implications of PHD dysregulation extend to a broader range of vascular pathologies, including atherosclerosis and hypertension, where aberrant extracellular matrix deposition and arterial stiffening are prominent features.

Interaction between Oxygen Sensing and Endothelial Dysfunction: Endothelial dysfunction, characterized by an imbalance in vasoactive substances and impaired nitric oxide bioavailability, is intimately linked with altered oxygen sensing mechanisms, particularly those involving HIFs and PHDs. Dysregulated oxygen sensing pathways contribute to endothelial cell dysfunction through various mechanisms, including compromised vasodilation and increased inflammatory responses [48]. Specifically, HIF-1α upregulation in endothelial cells can promote atherosclerosis by increasing nuclear factor kappa B, vascular endothelial growth factor, and reactive oxygen species, thereby impairing endothelial function [13]. Conversely, maintaining appropriate PHD activity is essential for endothelial homeostasis, as PHDs not only regulate HIF-α stability but also modulate inflammatory pathways by hydroxylating components of the NF-κB signaling cascade [10]. This intricate relationship highlights how molecular oxygen-sensing proteins are critical for preserving endothelial integrity and mitigating arterial stiffness [73]. The ensuing dysfunction often manifests as reduced nitric oxide production and increased endothelin-1 synthesis, both contributing to impaired vasorelaxation and enhanced vasoconstriction, thereby exacerbating arterial stiffness. Moreover, the critical role of oxygen in regulating endothelial function is underscored by studies indicating that changes in oxygen levels directly impact nitric oxide availability and the subsequent regulation of vascular tone [74]. This delicate balance is further complicated by the interaction of hypoxia-inducible factors with endothelial nitric oxide synthase (eNOS) and angiotensin II type 1 receptors, influencing blood pressure regulation and vascular remodeling [48]. Reduced nitric oxide bioavailability, often stemming from endothelial dysfunction and inflammation, plays a causal role in many cardiovascular diseases [75]. Specifically, hypoxia contributes to endothelial dysfunction by reducing nitric oxide bioavailability through mechanisms like tetrahydrobiopterin depletion and subsequent eNOS uncoupling, where the enzyme generates superoxide instead of nitric oxide [76]. Furthermore, chronic hypoxia can destabilize HIF-1α in endothelial cells, leading to lower levels of NO and promoting the development of pulmonary hypertension [6]. Conversely, intermittent hypoxia, a hallmark of conditions like obstructive sleep apnea, induces vascular dysfunction through inflammation and oxidative stress, further impairing protective NO signaling [49]. Moreover, chronic hypoxia also induces the transcription of genes such as Glut-1, VEGF, and iNOS, which enable cells to adapt to low-oxygen environments, while endothelial dysfunction originating from cellular injury is closely associated with the initiation and progression of atherosclerosis [1]. This intricate interplay between oxygen sensing and endothelial function highlights the complex mechanisms through which hypoxia, both acute and chronic, significantly impacts cardiovascular health by modulating NO bioavailability and inflammatory pathways [76, 77]. However, the precise mechanisms linking hypoxia-induced endothelial dysfunction to the development and progression of arterial stiffness remain areas of active investigation, particularly concerning the long-term effects of altered NO bioavailability and chronic inflammation. Further research is needed to delineate the specific cellular and molecular pathways that mediate the impact of varying oxygen tensions on endothelial integrity and the biophysical properties of arterial walls.

THERAPEUTIC IMPLICATIONS AND FUTURE DIRECTIONS

Given the critical role of oxygen-sensing proteins in regulating arterial stiffness and endothelial function, targeting these pathways presents promising therapeutic avenues for cardiovascular diseases.

Targeting Oxygen-Sensing Pathways for Arterial Stiffness: Strategies involving the manipulation of HIF-P4H activity or the direct modulation of HIF-1α signaling are currently under investigation as potential pharmacological interventions to mitigate arterial stiffening. For instance, pharmacological agents designed to inhibit PHD activity could stabilize HIF-1α, thereby enhancing adaptive responses to hypoxia and potentially reversing adverse arterial remodeling. However, selective targeting of specific PHD isoforms is crucial to avoid off-target effects and ensure therapeutic specificity. Conversely, in contexts where chronic hypoxia necessitates long-term adaptations, strategies aimed at selectively modulating HIF-2α activation might be more beneficial, given its role in promoting vascular maturation and sustained metabolic efficiency [1]. The delicate balance between HIF-1α and HIF-2α activation is critical, as sustained HIF-1α can exacerbate chronic heart failure, while maintaining HIF signaling within a normal range can improve metabolic and cardiovascular traits. Sustained activation of HIF-1α signaling, however, can promote oxidative stress, inflammation, and fibrosis, whereas HIF-2α can mitigate these deleterious effects by promoting pexophagy and activating antioxidant enzyme genes. Therefore, future therapeutic approaches should aim for a nuanced modulation of HIF pathways, possibly through HIF-PHIs or gene therapies, to harness their protective effects while mitigating potential detrimental outcomes in cardiovascular disease.

Challenges and Opportunities in Clinical Translation

Translating these mechanistic insights into effective clinical interventions requires overcoming significant hurdles, including the development of highly specific compounds with favorable pharmacokinetic profiles and minimal off-target effects. Current efforts largely focus on developing drugs that regulate HIF-α or its co-factors and downstream effectors, with particular attention to improving PHD inhibitors through enhanced oral absorption, faster onset of action, and improved safety profiles. Furthermore, the development of small molecule inhibitors specifically targeting HIF-α subunits, such as PT2385 for HIF-2α, presents a promising therapeutic strategy, though careful consideration of potential off-target effects and drug resistance is imperative [1]. For example, roxadustat, a PHD inhibitor, has been approved for anemia associated with chronic kidney disease, highlighting the clinical viability of targeting HIF pathways [20]. However, the therapeutic scope of targeting specific HIF-α subunits extends beyond anemia, as evidenced by HIF-2α inhibitors such as PT2385 and MK-6482, which demonstrate efficacy in treating renal cell carcinoma by disrupting HIF-2α/HIF-1β dimerization. These advancements suggest the potential for developing highly selective HIF-modulating therapies that could be repurposed for cardiovascular applications, provided further research clarifies their precise roles in arterial stiffness. Moreover, the intricate spatiotemporal dynamics of hypoxia-inducible factors within the cardiovascular system, encompassing their acute and chronic manifestations, underscore the complexity of hypoxia-induced signaling and necessitate a thorough understanding for effective therapeutic intervention. In vivo studies are essential to validate the efficacy and safety of these HIF-targeting compounds for arterial stiffness, moving beyond the predominantly in vitro observations [1]. Better preclinical models, combined with meticulously controlled clinical trials and relevant endpoints, are indispensable for realizing meaningful progress in the development of novel HIF-based therapies [20]. One promising avenue involves the development of subtype-selective small-molecule inhibitors that can differentiate between the highly similar HIF-1α and HIF-2α, thereby avoiding broad, potentially detrimental, systemic effects [1]. This challenge is being addressed by identifying and exploiting structural differences, such as a concealed hydrophobic cavity within the HIF-2α PAS-B domain, which can be targeted by small molecules to achieve selective inhibition [1]. This approach allows for a more refined therapeutic intervention, minimizing off-target effects associated with pan-HIF inhibition and opening doors for personalized medicine in cardiovascular disease. For instance, several prolyl hydroxylase domain inhibitors, such as roxadustat, daprodustat, vadadustat, molidustat, and enarodustat, have either been approved for clinical use or are in advanced clinical trials for treating anemia in chronic kidney disease, based on their capacity to activate erythropoiesis and iron metabolism through HIF stabilization [78, 1]. Such selective targeting strategies are crucial for maximizing therapeutic benefits while mitigating potential risks associated with systemic HIF activation, particularly in complex conditions like arterial stiffness where HIFs play diverse, sometimes opposing, roles. The sustained activation of HIF signaling pathways, when maintained within a physiological range, has been shown to subtly enhance the expression of erythropoietin and vascular endothelial growth factor, contributing to improved metabolic and cardiovascular profiles [1]. However, careful consideration of the risk-benefit ratio of systemic versus tissue-selective HIF inhibitors is vital, especially given the myriad roles of HIFs and their potential influence on extrapulmonary manifestations in patients with cardiovascular conditions [6]. For example, balancing moderate HIF-1α activity with enhanced HIF-2α expression could be a promising therapeutic strategy for cardiovascular and overnutrition diseases, as it may lead to stable angiogenesis and increased erythropoietin production [1]. However, the complexity of HIF isoform-specific roles and the potential for off-target effects necessitate further research to identify optimal therapeutic windows and selective strategies that avoid detrimental impacts on metabolism or other physiological processes [71]. Indeed, the nuanced modulation of HIF-P4Hs with orally administered small molecules, such as roxadustat, vadadustat, molidustat, and daprodustat, represents a viable approach for systemic HIF stabilization, particularly evident in their successful application for renal anemia and promising results in metabolic dysfunction and cholesterol regulation [47]. However, despite these benefits, concerns persist regarding potential adverse cardiovascular effects, such as thrombotic events and tumorogenesis, observed with some HIF-PHI treatments, necessitating further long-term clinical trials to ascertain their overall safety and efficacy [79, 13].

CONCLUSION

This narrative review has elucidated the intricate connections between oxygen-sensing proteins, primarily the hypoxia-inducible factors and their associated prolyl hydroxylases, and their profound implications for arterial stiffness. We have highlighted how

these molecular mechanisms contribute to vascular remodeling and dysfunction, emphasizing the need for a deeper understanding of their precise roles in the pathogenesis of cardiovascular diseases. Future research should therefore focus on developing highly selective HIF modulators that can precisely target specific isoforms or pathways to achieve therapeutic benefits without inducing undesirable side effects. This involves unraveling the complex interplay between HIFs and various physiological systems, including their rhythmic fluctuations and metabolic adaptations, to develop more targeted interventions.

REFERENCES

1. Zhao Y, Xiong W, Li C, Zhao R, Lu H, Song S, et al. Hypoxia-induced signaling in the cardiovascular system: pathogenesis and therapeutic targets. Signal Transduction and Targeted Therapy. Springer Nature; 2023 Nov 20;8(1).
2. Garcia-Rojas EYL, Villanueva C, Bond RA. Hypoxia Inducible Factors as Central Players in the Pathogenesis and Pathophysiology of Cardiovascular Diseases. Frontiers in Cardiovascular Medicine. Frontiers Media; 2021 Aug 10;8.
3. Das KK, Majid DSA, Prabhakar NR. Editorial: Vascular pathophysiology in hypoxia. Vol. 14, Frontiers in Physiology. Frontiers Media; 2023
4. Bilo G, Gatterer H, Torlasco C, Villafuerte FC, Parati G. Editorial: Hypoxia in cardiovascular disease. Frontiers in Cardiovascular Medicine. 2022 Aug 5;9.
5. Malacrida S, Giannella A, Ceolotto G, Reggiani C, Vezzoli A, Mrakic-Sposta S, et al. Transcription Factors Regulation in Human Peripheral White Blood Cells during Hypobaric Hypoxia Exposure: an in-vivo experimental study. Scientific Reports. 2019 Jul 9;9(1).
6. Pullamsetti SS, Mamazhakypov A, Weißmann N, Seeger W, Savai R. Hypoxia-inducible factor signaling in pulmonary hypertension. Journal of Clinical Investigation. American Society for Clinical Investigation; 2020 Sep 3;130(11):5638.
7. Semenza GL. Clinical investigation of hypoxia-inducible factors: getting there. Journal of Clinical Investigation. 2024 Feb 1;134(3).
8. Hirota K. HIF-α Prolyl Hydroxylase Inhibitors and Their Implications for Biomedicine: A Comprehensive Review. Biomedicines. Multidisciplinary Digital Publishing Institute; 2021 Apr 24;9(5):468.
9. Poloznikov AA, Nersisyan SA, Hushpulian DM, Kazakov EH, Tonevitsky AG, Kazakov SV, et al. HIF Prolyl Hydroxylase Inhibitors for COVID-19 Treatment: Pros and Cons. Front Pharmacol. 2021 Jan 29;11:621054.
10. Chen P, Chiu W, Hsu P, Lin S, Peng I, Wang C, et al. Pathophysiological implications of hypoxia in human diseases. Journal of Biomedical Science. BioMed Central; 2020 May 11;27(1).
11. Jaśkiewicz M, Moszyńska A, Króliczewski J, Cabaj A, Bartoszewska S, Charzyńska A, et al. The transition from HIF-1 to HIF-2 during prolonged hypoxia results from reactivation of PHDs and HIF1A mRNA instability. Cellular & Molecular Biology Letters. 2022 Dec 1;27(1).
12. Zhao S, Liu J, Wu Q, Zhou X. Role of histone lactylation interference RNA m6A modification and immune microenvironment homeostasis in pulmonary arterial hypertension. Frontiers in Cell and Developmental Biology. Frontiers Media; 2023 Sep 12;11.
13. Chou Y, Pan S, Lin S. Pleotropic effects of hypoxia-inducible factor-prolyl hydroxylase domain inhibitors: are they clinically relevant? Kidney Research and Clinical Practice. 2022 Nov 21;42(1):27.
14. Jacquemin C, Orch WE, Diaz O, Lalande A, Aublin-Gex A, Jacolin F, et al. Pharmacological induction of the hypoxia response pathway in Huh7 hepatoma cells limits proliferation but increases resilience under metabolic stress. Cellular and Molecular Life Sciences. 2024 Jul 30;81(1).
15. Wan JJ, Yi J, Wang FY, Zhang C, Dai A. Expression and regulation of HIF-1a in hypoxic pulmonary hypertension: Focus on pathological mechanism and Pharmacological Treatment. International Journal of Medical Sciences. 2023 Nov 15;21(1):45.
16. Lin N, Simon MC. Hypoxia-inducible factors: key regulators of myeloid cells during inflammation. Journal of Clinical Investigation. American Society for Clinical Investigation; 2016 Sep 5;126(10):3661.
17. Lin N, Shay JES, Xie H, Lee DSM, Skuli N, Tang Q, et al. Myeloid Cell Hypoxia-Inducible Factors Promote Resolution of Inflammation in Experimental Colitis. Frontiers in Immunology. 2018 Nov 5;9.
18. Triner D, Shah YM. Hypoxia-inducible factors: a central link between inflammation and cancer. Journal of Clinical Investigation. 2016 Aug 14;126(10):3689.
19. Corcoran SE, O'neill L. HIF1α and metabolic reprogramming in inflammation. Journal of Clinical Investigation. American Society for Clinical Investigation; 2016 Aug 28;126(10):3699.
20. Knutson AK, Williams AL, Boisvert WA, Shohet RV. HIF in the heart: development, metabolism, ischemia, and atherosclerosis. Journal of Clinical Investigation. American Society for Clinical Investigation; 2021 Aug 31;131(17).
21. Taylor CT, Colgan SP. Regulation of immunity and inflammation by hypoxia in immunological niches. Nature reviews Immunology. Nature Portfolio; 2017 Oct 3;17(12):774.
22. Taylor CT, Doherty G, Fallon PG, Cummins EP. Hypoxia-dependent regulation of inflammatory pathways in immune cells. Journal of Clinical Investigation. American Society for Clinical Investigation; 2016 Jul 24;126(10):3716.
23. Monaci S, Coppola F, Filippi I, Falsini A, Carraro F, Naldini A. Targeting hypoxia signaling pathways in angiogenesis. Frontiers in Physiology. 2024 Apr 25;15.
24. Sadia K, Ashraf MZ, Mishra A. Therapeutic Role of Sirtuins Targeting Unfolded Protein Response, Coagulation, and Inflammation in Hypoxia-Induced Thrombosis. Frontiers in Physiology. Frontiers Media; 2021 Nov 5;12.
25. Heikal L, Ghezzi P, Mengozzi M, Ferns GA. Assessment of HIF-1α expression and release following endothelial injury in-vitro and in-vivo. Molecular Medicine. 2018 May 16;24(1).
26. Malkov MI, Lee CT, Taylor CT. Regulation of the Hypoxia-Inducible Factor (HIF) by Pro-Inflammatory Cytokines. Cells. Multidisciplinary Digital Publishing Institute; 2021 Sep 7;10(9):2340.

27. Choromańska B, Myśliwiec P, Kozłowski T, Łuba M, Wojskowicz P, Dadan J, et al. Cross-Talk Between Nitrosative Stress, Inflammation and Hypoxia-Inducible Factor in Patients with Adrenal Masses. Journal of Inflammation Research. 2021 Nov 1;6317.
28. Li RL, He LY, Zhang Q, Liu J, Lu F, Duan HX, et al. HIF-1α is a Potential Molecular Target for Herbal Medicine to Treat Diseases. Drug Des Devel Ther. 2020 Nov 16;14:4915-4949.
29. Korbecki J, Simińska D, Gąssowska-Dobrowolska M, Listos J, Gutowska I, Chlubek D, et al. Chronic and Cycling Hypoxia: Drivers of Cancer Chronic Inflammation through HIF-1 and NF-κB Activation: A Review of the Molecular Mechanisms. International Journal of Molecular Sciences. Multidisciplinary Digital Publishing Institute; 2021 Oct 2;22(19):10701.
30. Pham K, Parikh K, Heinrich EC. Hypoxia and Inflammation: Insights From High-Altitude Physiology. Frontiers in Physiology. Frontiers Media; 2021 May 26;12.
31. Ullah K, Rosendahl AH, Izzi V, Bergmann U, Pihlajaniemi T, Mäki JM, et al. Hypoxia-inducible factor prolyl-4-hydroxylase-1 is a convergent point in the reciprocal negative regulation of NF-κB and p53 signaling pathways. Scientific Reports. 2017 Dec 4;7(1).
32. Taylor CT, Scholz CC. The effect of HIF on metabolism and immunity. Nature Reviews Nephrology. Nature Portfolio; 2022 Jun 20;18(9):573.
33. Rodríguez DA, Watts D, Gaete D, Sormendi S, Wielockx B. Hypoxia Pathway Proteins and Their Impact on the Blood Vasculature. International Journal of Molecular Sciences. Multidisciplinary Digital Publishing Institute; 2021 Aug 25;22(17):9191.
34. Huang H, Li G, He Y, Chen J, Yan J, Zhang Q, et al. Cellular succinate metabolism and signaling in inflammation: implications for therapeutic intervention. Frontiers in Immunology. 2024 Jun 11;15.
35. Guo Y, Xiao Z, Liu Y, Gao Y, Zhu Q, Hu L, et al. Hypoxia-inducible factors in hepatocellular carcinoma (Review). Oncology Reports. Elsevier BV; 2019 Nov 1.
36. Hammarlund EU, Flashman E, Mohlin S, Licausi F. Oxygen-sensing mechanisms across eukaryotic kingdoms and their roles in complex multicellularity. Science. American Association for the Advancement of Science; 2020 Oct 22;370(6515).
37. Lamadema N, Burr S, Brewer AC. Dynamic regulation of epigenetic demethylation by oxygen availability and cellular redox. Free Radical Biology and Medicine. Elsevier BV; 2018 Dec 17;131:282.
38. Laird M, Ku JC, Raiten J, Sriram S, Moore MK, Li Y. Mitochondrial metabolism regulation and epigenetics in hypoxia. Frontiers in Physiology. 2024 Jun 10;15.
39. Gonzalez FJ, Xie C, Jiang C. The role of hypoxia-inducible factors in metabolic diseases. Nature Reviews Endocrinology. Nature Portfolio; 2018 Oct 1;15(1):21.
40. Wu Y, Li Z, McDonough MA, Schofield CJ, Zhang X. Inhibition of the Oxygen-Sensing Asparaginyl Hydroxylase Factor Inhibiting Hypoxia-Inducible Factor: A Potential Hypoxia Response Modulating Strategy. Journal of Medicinal Chemistry. American Chemical Society; 2021 May 24;64(11):7189.
41. Kang GS, Jo HJ, Lee YR, Oh T, Park HJ, Ahn G. Sensing the oxygen and temperature in the adipose tissues – who's sensing what? Experimental & Molecular Medicine. Springer Nature; 2023 Nov 1;55(11):2300.
42. Otero-Albiol D, Carnero A. Cellular senescence or stemness: hypoxia flips the coin. Journal of Experimental & Clinical Cancer Research. BioMed Central; 2021 Jul 29;40(1).
43. Río AG del, Prieto-Fernández E, Egia-Mendikute L, Antoñana-Vildosola A, Jiménez-Lasheras B, Lee SY, et al. Factor-inhibiting HIF (FIH) promotes lung cancer progression. JCI Insight. 2023 Sep 14;8(20).
44. Martin CB, Chaplin VD, Eyles SJ, Knapp MJ. Protein Flexibility of the α-Ketoglutarate-Dependent Oxygenase Factor-Inhibiting HIF-1: Implications for Substrate Binding, Catalysis, and Regulation. Biochemistry. 2019 Sep 9;58(39):4047.
45. Chee NT, Lohse I, Brothers SP. mRNA-to-protein translation in hypoxia. Molecular Cancer. BioMed Central; 2019 Mar 30;18(1).
46. Thöni V, Mauracher D, Ramalingam A, Fiechtner B, Sandbichler AM, Egg M. Quantum based effects of therapeutic nuclear magnetic resonance persistently reduce glycolysis. iScience. 2022 Nov 9;25(12):105536.
47. Röning T, Magga J, Laitakari A, Halmetoja R, Tapio J, Dimova EY, et al. Activation of the hypoxia response pathway protects against age-induced cardiac hypertrophy. Journal of Molecular and Cellular Cardiology. 2021 Dec 14;164:148.
48. Yu J, Wang S, Shi W, Zhou W, Niu Y, Huang S, et al. Roxadustat prevents Ang II hypertension by targeting angiotensin receptors and eNOS. JCI Insight. 2021 Aug 17;6(18).
49. Arnaud C, Billoir E, Melo AF de, Pereira SA, O'Halloran KD, Monteiro EC. Chronic intermittent hypoxia-induced cardiovascular and renal dysfunction: from adaptation to maladaptation. The Journal of Physiology. 2023 Oct 26;601(24):5553.
50. Kim H. Arterial stiffness and hypertension. Clinical Hypertension. BioMed Central; 2023 Dec 1.
51. Thijssen DHJ, Carter SE, Green DJ. Arterial structure and function in vascular ageing: are you as old as your arteries? The Journal of Physiology. Wiley; 2015 Jul 3;594(8):2275.
52. Hamczyk MR, Campo L del, Andrés V. Aging in the Cardiovascular System: Lessons from Hutchinson-Gilford Progeria Syndrome. Annual Review of Physiology. Annual Reviews; 2017 Sep 21;80(1):27.
53. Hooglugt A, Klatt OC, Huveneers S. Vascular stiffening and endothelial dysfunction in atherosclerosis. Current Opinion in Lipidology. Lippincott Williams & Wilkins; 2022 Oct 7;33(6):353.
54. Feola M. An Update on the Role of Arterial Stiffness in Heart Failure and the Treatment of Dyslipidemia. Journal of Clinical Medicine. 2023 May 4;12(9):3270.
55. Climie RE, Alastruey J, Mayer C, Schwarz A, Laučytė-Cibulskienė A, Voicehovska J, et al. Vascular ageing: moving from bench towards bedside. European Journal of Preventive Cardiology. 2023 Feb 4;30(11):1101.

56. Peña L del MG, Romero-Orjuela SP, Rabeya F, Castillo VD, Echeverri D. Age and vascular aging: an unexplored frontier. Frontiers in Cardiovascular Medicine. Frontiers Media; 2023 Nov 9;10.
57. Wang L, Wang Y, Jiao T, Xu L, Ji E, Tapu SR, et al. Effects of CPAP treatment on arterial stiffness and inflammatory factors in patients with coronary heart disease complicated with OSA. Research Square (Research Square). 2024 Sep 2.
58. Wang L, Wang Y, Jiao T, Xu L, Ji E, Tapu SR, et al. Effects of continuous positive airway pressure treatment on arterial stiffness and inflammatory factors in patients with coronary heart disease complicated with obstructive sleep apnea. Research Square (Research Square). 2024 Nov 15.
59. Lee CJ, Yoon M, Ha J, Oh J, Park S, Lee S, et al. Comparison of the Association Between Arterial Stiffness Indices and Heart Failure in Patients With High Cardiovascular Risk: A Retrospective Study. Frontiers in Cardiovascular Medicine. 2021 Nov 15;8.
60. Marcon D, Faconti L, Farukh B, McNally R, Fava C, Pengo MF, et al. Does Treatment for Obstructive Sleep Apnoea Improve Arterial Stiffness? Evidence from Randomized Clinical Trials on Carotid-femoral Pulse Wave Velocity. Artery Research. 2020 Nov 13;27(1):1.
61. Angoff R, Mosarla R, Tsao CW. Aortic Stiffness: Epidemiology, Risk Factors, and Relevant Biomarkers. Frontiers in Cardiovascular Medicine. Frontiers Media; 2021 Nov 8;8.
62. Conde SV. (Mal)adaptative responses of arterial chemoreceptors: O2-dependent and -independent mechanisms. The Journal of Physiology. 2023 Dec 1;601(24):5463.
63. Wahl D, Clayton ZS. Peripheral vascular dysfunction and the aging brain. Aging. 2024 May 22;16(10):9280.
64. Liu W, Zhang W, Wang T, Wu J, Zhong X, Gao K, et al. Obstructive sleep apnea syndrome promotes the progression of aortic dissection via a ROS- HIF-1α-MMPs associated pathway. International Journal of Biological Sciences. 2019 Jan 1;15(13):2774.
65. Chen Y, Xu L, Wang Z, Shun Y, Shen X, Xie X, et al. Iron deficiency affects oxygen transport and activates HIF1 signaling pathway to regulate phenotypic transformation of VSMC in aortic dissection. Molecular Medicine. 2024 Jun 17;30(1).
66. Zhou X, Luo C, Fan J, Gao G, Wang T, Zhang H, et al. Myocardin Reverses Hypoxia-Inducible Factor-1α Mediated Phenotypic Modulation of Corpus Cavernosum Smooth Muscle Cells in Hypoxia Induced by Cobalt Chloride. The World Journal of Men s Health. 2022 Feb 18;41(2):363.
67. Luo Y, Teng X, Zhang L, Chen J, Liu Z, Chen X, et al. CD146-HIF-1α hypoxic reprogramming drives vascular remodeling and pulmonary arterial hypertension. Nature Communications. 2019 Aug 7;10(1).
68. Strowitzki MJ, Ritter AS, Kimmer G, Schneider M. Hypoxia-adaptive pathways: A pharmacological target in fibrotic disease? Pharmacological Research [Internet]. Elsevier BV; 2019 Jul 31;147:104364.
69. He X, Zeng H, Roman RJ, Chen J. Inhibition of prolyl hydroxylases alters cell metabolism and reverses pre-existing diastolic dysfunction in mice. International Journal of Cardiology. 2018 Aug 24;272:281.
70. Zou W, Shah YM. A PHD in immunosuppression: oxygen-sensing pathways regulate immunosuppressive Tregs. Vol. 129, Journal of Clinical Investigation. American Society for Clinical Investigation; 2019. p. 3524.
71. Koivunen P, Kietzmann T. Hypoxia-Inducible Factor Prolyl 4-Hydroxylases and Metabolism. Trends in Molecular Medicine. Elsevier BV; 2018 Nov 1;24(12):1021.
72. Hu J, Wang W, Zhang F, Li P, Boini KM, Yi F, et al. Hypoxia inducible factor-1α mediates the profibrotic effect of albumin in renal tubular cells. Scientific Reports. 2017 Nov 14;7(1).
73. Liao C, Zhang Q. Understanding the Oxygen-Sensing Pathway and Its Therapeutic Implications in Diseases. American Journal Of Pathology. Elsevier BV; 2020 Apr 24;190(8):1584.
74. Green HLH, Brewer AC. Dysregulation of 2-oxoglutarate-dependent dioxygenases by hyperglycaemia: does this link diabetes and vascular disease? Clinical Epigenetics. BioMed Central; 2020 Apr 28;12(1).
75. Ao O. Prolyl hydroxyl Binding Protein (PHD) and its Linkage to Changes in MyD88/p65 Pathway in Renal Injury Induced by Nitric Oxide Deficiency and High Salt Diet. Journal of pharmacology & clinical research. 2017 Jul 12;3(2).
76. Janaszak-Jasiecka A, Siekierzycka A, Płoska A, Dobrucki IT, Kalinowski L. Endothelial Dysfunction Driven by Hypoxia—The Influence of Oxygen Deficiency on NO Bioavailability. Biomolecules. Multidisciplinary Digital Publishing Institute; 2021 Jul 3;11(7):982.
77. Recoquillon S, Gómez-Guzmán M, Rodier M, Koffi C, Nitiéma M, Gagnadoux F, et al. Non-muscular myosin light chain kinase triggers intermittent hypoxia-induced interleukin-6 release, endothelial dysfunction and permeability. Scientific Reports. 2017 Oct 16;7(1).
78. Miao M, Wu M, Li Y, Zhang L, Jin Q, Fan J, et al. Clinical Potential of Hypoxia Inducible Factors Prolyl Hydroxylase Inhibitors in Treating Nonanemic Diseases. Frontiers in Pharmacology. Frontiers Media; 2022 Feb 24;13.
79. Bartnicki P. Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors as a New Treatment Option for Anemia in Chronic Kidney Disease. Biomedicines. Multidisciplinary Digital Publishing Institute; 2024 Aug 18;12(8):1884.