Many pathological conditions, like sleep apnea (SA), preeclampsia, high altitude sickness, and chronic obstructive pulmonary disease, that cause intermittent or chronic hypoxia, are often associated with the development of either systemic or pulmonary hypertension.1 Mechanisms sensing hypoxia may be important contributors to the development of pulmonary hypertension and to tissue injury and repair associated with hypertensive disease and in integrated aspects of cardiovascular function. This review will focus on highlighting how some of the better documented oxygen-sensing mechanisms associated with vascular regulation could be influenced by poorly understood interactions between hypoxia and hypertension. It will also consider some of the identified integrated interactions between hypoxia and hypertensive disease processes that could contribute to the progression of disease processes, such as renal hypertension.

High altitude and chronic obstructive pulmonary disease are thought to promote pulmonary hypertension by exposing the pulmonary circulation to chronic hypoxia as a result of the low partial pressure of oxygen at high altitude and increases in the diffusion distance for oxygen, respectively.2,3 Although high altitude can initially promote increased systemic blood pressure, this change appears to reverse with time.4 Interestingly, hypobaric hypoxia conditions of high altitude were observed to prevent the development of hypertension and skeletal muscle arteriolar rarefaction in spontaneously hypertensive rats.5 Living at high altitude seems to lower blood pressure only in children,6 and it did not appear to attenuate hypertension in obese adults consuming high-fat diets.7 Based on studies in animal models of acute and chronic hypoxia, hypoxic pulmonary vasoconstriction (HPV) is initially activated. Eventually endothelial dysfunction associated with a loss of NO and increased reactive oxygen species (ROS), endothelin, serotonin, and contractile prostaglandins contribute to maintaining elevated pulmonary artery pressure through increased intracellular Ca2+ levels and rho kinase-associated myofilament Ca2+ sensitivity.8 Although the mechanisms involved in PO2 sensing and eliciting constriction are incompletely understood, there is consensus that hypoxia-evoked redox and ROS changes play a significant role in HPV and pulmonary hypertension development.8,9 Other than vasoconstriction, remodeling of pulmonary arterioles also has a significant role in increasing pulmonary arterial pressure. Numerous studies are ongoing to identify inflammatory and progenitor cell mechanisms involved in muscularization of resistance arteries, as well as adventitial fibroblast-promoted matrix remodeling and neointimal plexiform lesion formation.8 The emerging picture from these studies suggests that ROS and oxidant-associated redox signaling through mechanisms including hypoxia-inducible factor (HIF) and rho kinase could be promoting the remodeling that aggravates hypertension. Interestingly, therapies promoting guanylate cyclase activation under oxidant conditions or preventing cGMP degradation by treatment with sildenafil seem to be beneficial in attenuating many aspects of pulmonary hypertensive disease processes.10 The function of signaling mechanisms associated with HPV are thought to be important factors in modulating pulmonary hypertension development.8,9

**Vascular Oxygen-Sensing Mechanisms and HPV**

The sensing of hypoxia is a primary mechanism for regulating blood flow in the pulmonary circulation through HPV. The HPV response matches the perfusion of the pulmonary circulation to oxygen delivery by lung ventilation. Although the mechanism of HPV is not yet established, studies generally support roles for hypoxia modulating the generation of ROS and cellular oxidation-reduction (redox) signaling mechanisms regulating pulmonary arterial smooth muscle force.9,11–13 Several opposing theories exist for pulmonary artery oxygen sensors in HPV involving roles for mitochondria and/or Nox oxidases generating either increases or decreases in ROS under hypoxia, which function to regulate redox signaling mechanisms controlling the vasoconstriction to hypoxia that is observed. The redox theory for HPV proposed by Weir and Archer13 based primarily on studies in rat and mouse pulmonary arteries suggested that hypoxia was lowering the generation of mitochondrial-derived ROS, and this removed a peroxide-mediated vasodilator mechanism involving cytosolic NADPH and/or thiol oxidation opening voltage-regulated potassium channels. Studies by this group also demonstrated that Nox2-deficient mice showed a normal HPV response. Our studies in bovine pulmonary arteries...
detected evidence that hypoxia was promoting HPV by removing a peroxide-elicited relaxation. The relaxation removed by hypoxia appears to originate from both cGMP-dependent and cGMP-independent stimulation of protein kinase G as a result of peroxide promoting both a stimulation of soluble guanylate cyclase and a thiol oxidation–mediated dimerization activation of protein kinase G, respectively. Modulation of oxidases by small interfering RNA and pharmacological methods provided evidence that Nox4, but not Nox2 or mitochondria, was the source of peroxide controlling the HPV response seen in bovine pulmonary arteries. Hypoxia also causes an increase in NADPH in pulmonary arteries potentially through activating glucose-6-phosphate dehydrogenase (G6PD) or decreasing mitochondrial ROS. In contrast, Waypa and Schumacker reported evidence in cultured rat pulmonary artery smooth muscle cells for hypoxia promoting release of mitochondrial-derived peroxide, which was suggested to elicit vasoconstriction through increasing intracellular calcium levels and Rho kinase activity. Thus, several current theories for the mechanism of HPV include changes in the generation of ROS and cytosolic redox mechanisms in sensing changes in PO2 by pulmonary arterial smooth muscle, but controversy exists in defining the oxidase involved and in the direction of changes in ROS and redox elicited by hypoxia.

Differences in the effects of hypoxia on ROS generation by individual oxidases and their ability to influence specific redox-controlled signaling mechanisms in subcellular regions are potentially major factors contributing to the controversy in the HPV field. For example, contraction and hypoxia have metabolic actions that modulate NADPH/NADP+ and NADH/ NAD+ ratios in different subcellular regions. These changes in NADPH redox are likely to be major factors in determining local rates of ROS generation and the impact of oxidant conditions on redox-controlled signaling mechanisms regulating vascular function. For example, the generation of increased levels of superoxide by mitochondria under hypoxic conditions is potentially dependent on elevated levels of NADH in this organelle. Increases in cytosolic NADH and NADPH in pulmonary arteries under hypoxia could also be a factor in enhancing Nox oxidase activities or in regulating redox-controlled processes under hypoxia. Thus, although there seems to be redundancy in mechanisms potentially contributing to the HPV response, the most physiologically relevant conditions are likely to determine the processes involved. Other mechanisms that have been identified may have roles in adaptation and remodeling (see Figure 1).

The relatively hypoxic and low-pressure environment normally seen by pulmonary arteries compared with systemic arteries may create adaptations that contribute to the different responses to hypoxia in these vascular segments. Differences in mitochondria between rat pulmonary and renal arteries potentially influence the dissimilar effects of hypoxia on ROS production observed in these vessel segments. Elevated levels of NADPH and G6PD in pulmonary arteries compared with systemic arteries may be one key difference that creates distinctive redox responses to hypoxia in these vascular segments. For example, increased expression of G6PD and its generation of NADPH in pulmonary arteries may help maintain elevated levels of peroxide generation by Nox oxidases and prevent hypoxia from promoting cytosolic NADPH oxidation seen in coronary arteries.

Oxygen Sensors in Systemic Arteries and Metabolic Mechanisms Controlling Blood Flow

Metabolic regulation optimizes the delivery of oxygen by increasing blood flow in systemic circulations to meet the needs of tissue oxygen consumption. Multiple cell types potentially participate in what seem to be redundant mechanisms contributing to the metabolic control of blood flow. Metabolites produced by the tissues being perfused, such as adenosine, lactate, carbon dioxide, and ROS, are potential contributors to the metabolic regulation of blood flow. In addition, systemic arterial smooth muscle cells seem to have redox-regulated signaling mechanisms that promote vasodilation on exposure to hypoxia. Because the biosynthesis of some autacoids, including NO, prostaglandins, cytochrome P450-derived eicosanoids, and ROS, is oxygen dependent, these mediators often influence or modulate systemic and pulmonary responses to hypoxia.

Early studies documented that hypoxia elicited relaxation of systemic arteries via mechanisms independent of limitations in ATP and phosphocreatine generation needed for force generation. After removal of the effects of endothelium, NO, and prostaglandins, it is now well established that most systemic arteries show relaxation when exposed to severe hypoxia. Although an increase in mitochondrial ROS was observed when rat renal arteries were exposed to hyp-
oxia, this process may not be functioning as the oxygen sensor promoting relaxation in these arteries. Our studies suggest that contraction of bovine coronary arteries may reverse the effects of hypoxia from an increase to a decrease in mitochondrial superoxide. \(^{15,23}\) There appears to be a prominent ROS-independent mechanism through which hypoxia can relax systemic arteries. \(^{17}\) A contributing factor to how hypoxia promotes relaxation may be through inhibiting Rho kinase, a redox-regulated system that normally functions to enhance the actions of intracellular calcium on force generation by the contractile apparatus. \(^{24}\) Our studies in bovine coronary arteries detected that hypoxia promoted relaxation under conditions where it elicited cytosolic NADPH oxidation, a process that appears to coordinate multiple mechanisms of lowering intracellular calcium and opening K\(^+\) channels. \(^{11,17}\) This mechanism seems to originate from a metabolic stress that attenuates a pyruvate-regulated mitochondrial feedback mechanism maintaining glucose-6-phosphate and the generation of NADPH by G6PD. \(^{15,17}\) Pyruvate has been reported to inhibit functional increases in blood flow, \(^{25}\) suggesting a potential role of cytosolic NADPH oxidation in metabolic regulation. Interestingly, increasing generation of peroxide from mitochondria (by inhibition of electron transport) or from Nox2 (by thromboxane-prostanoid receptor activation or by stretch) was observed to attenuate hypoxia-induced relaxation of bovine coronary arteries as a result of peroxide stimulating extracellular signal–regulated kinase mitogen-activated protein kinase. \(^{23}\) Thus, elevated peroxide levels could potentially function as an inhibitor of systemic arterial relaxation to hypoxia.

**Interactions of Hypertension With Metabolic Regulation**

Limited information is available on the effects of hypertension on the metabolic regulation of blood flow. A study by Ely et al \(^{26}\) suggests that it can be preserved in a renal model of hypertension. However, hypertension may promote changes in the hypoxia-sensing mechanisms that are matching blood flow to the respiratory needs of the tissue. For example, the ability of exercise to increase skeletal muscle blood flow appears to be impaired by hypertension. \(^{27}\) In addition, a high-salt diet has been reported to initially attenuate vasodilator mechanisms associated with metabolic regulation and hypoxia-elicited relaxation of skeletal muscle resistance arteries. \(^{28}\) Thus, alterations in systemic blood flow regulation by hypoxia may influence the development and progression of hypertension.

**Changes in Potential Components of Oxygen-Sensing Mechanisms During Systemic and Pulmonary Hypertension**

Pulmonary \(^{8,29}\) and systemic \(^{30,31}\) hypertension are known to have major effects on many aspects of ROS signaling and systems that are also influenced by hypoxia. Although only limited information is available documenting the effects of pulmonary and systemic hypertension on HPV and metabolic regulation of blood flow, \(^{19,20,26,32}\) hypertensive disease processes could potentially have an effect on many of the components of hypoxia-sensing mechanisms controlling blood flow. There are many similarities between systemic \(^{31,33}\) and pulmonary \(^{34}\) hypertension, such as the roles of increased vasoconstriction, inflammation, and remodeling. Substantial evidence exists for changes in the activities of vascular oxidases, mitochondria, NO biosynthesis, and ROS metabolizing systems during systemic \(^{31}\) and/or pulmonary \(^{8}\) hypertension. For example, an Nox2 deficiency prevents the development of hypoxia-induced pulmonary hypertension. \(^{35}\) In addition, hypertension alters the properties of multiple oxidant-influenced signaling systems regulating vascular function, such as soluble guanylate cyclase regulation by NO, protein kinase C, rho kinase, systems generating vasoactive eicosanoids, and actions controlled by increased levels of hypertension mediators, such as angiotensin II and endothelin. \(^{8,31}\) Although many of these systems altered by hypertension are likely to be components of oxygen-sensing mechanisms, minimal consideration has been given to the roles of altered oxygen sensors in hypertensive disease processes. The model in Figure 1 highlights how some of the acute hypoxia-sensing mechanisms may participate during chronic hypoxia in activating changes that contribute to the development of pulmonary hypertension. However, the model in Figure 2 hypothesizes some relationships that could potentially be involved in how chronic hypoxia directly or indirectly influences vascular regulatory mechanisms contributing to changes seen in systemic hypertension. Activation of the HIF systems by hypoxia and/or increased ROS in hypertension appear to have important roles in modulating the expression of many proteins that contribute to altered vascular reactivity.
metabolic changes, and vascular remodeling seen in both systemic and pulmonary hypertension. Interestingly, pulmonary hypertension has been shown to deplete mitochondrial superoxide dismutase–associated activation of HIF-1α under aerobic conditions. This converts pulmonary arterial smooth muscle cells to a cancer cell-like metabolic phenotype lacking hypoxic regulation of potassium channels by mitochondrial ROS. Thus, alterations in oxygen-sensing mechanisms can regulate multiple processes contributing to the progression of hypertension.

Vascular Remodeling in Hypertension

High blood pressure is known to increase shear stress on the vessel wall, damage endothelium, and impair endothelial function. Increased shear stress and pressure elicit ROS generation in the endothelium and underlying vascular smooth muscle cells leading to remodeling of arteries in systemic, as well as pulmonary, hypertension. During remodeling smooth muscle cells are dedifferentiated and they start to proliferate and/or migrate. Smooth muscle contractile proteins are regulated by transcription factor serum response factor and cofactors myocardin and Krueppel-like factor 4. In differentiated states, smooth muscle cells express myocardin, which elevates the expression of contractile proteins, and during dedifferentiation cell cycle proteins are overexpressed.

Hypoxia evokes changes in vascular endothelial and smooth muscle cells phenotypes. Isolated fetal pulmonary artery smooth muscle cells show a myocardin serum response factor–mediated expression of contractile proteins, which is a process driven by protein kinase G. Pulmonary arteries exposed to hypoxia appear to show a similar myocardin serum response factor–mediated myocardin signaling in systemic arteries remain to be defined. Moreover, myocardin and serum response factor levels seem to be controlled by nuclear factor of activated T-cells and myocardin signaling is shifted from normal levels by Ca²⁺ and alterations in ROS, evoking aberrant transcription of genes, including microRNAs (miRNAs), promoting medial and intimal thickening remodeling of arteries. This will result in stiffening of the arterial wall and reduction in luminal diameter, which could create hypoxic conditions by decreasing organ blood flow. The model in Figure 3 highlights how conditions seen in hypertension can promote hypoxia, which activates regulatory processes that potentially contribute to the progression of hypertension.

New evidence suggests that hypoxia-induced decreases in miR-204 are a cause of pulmonary hypertension. Intriguingly, dehydroepiandrosterone partly blocks downregulation of miR-204 and reduces hypertension. Dehydroepiandrosterone inhibits G6PD, and it decreases HPV and hypoxia-induced pulmonary hypertension through mechanisms that may involve NADPH oxidation and/or increased cGMP signaling. Thus, miRNAs may contribute to hypoxia-driven redox transcriptional regulation of multiple proteins and cellular processes in hypertension. Furthermore, hypoxia also appears to stabilize HIF-1α in endothelial cells by increasing miR-424 during remodeling-associated angiogenesis. It is possible that smooth muscle cell remodeling controlled by miR-204 may also modulate redox signaling in a manner like miRNAs involved in angiogenesis. Interestingly, knockdown of dicer proteins involved in the synthesis of miRNAs is associated with decreased ROS production by decreasing p47phox. In contrast, Argonout, another enzyme involved in miRNA processing, is regulated by an ROS-sensitive p38 mitogen-activated protein kinase pathway. Although the previously mentioned signaling pathways activated by either increased blood pressure or hypoxia are rather complicated, as illustrated (Figure 3), it is likely that there

![Figure 3](https://hyper.ahajournals.org/Downloaded_from/ August 2012)
are cause and effect relationships between hypertension and hypoxia that need to be explored in future studies.

Roles for Localized Effects of Hypoxia on Integrated Mechanisms Promoting Hypertension

Secondary or renal hypertension—elicited renal dysfunction is an important contributing factor in the progression of this disease process. Evidence is emerging that heterogeneity in renal blood flow may result in hypoxia in medullary regions. Factors such as impairment of flow by angiotensin II–induced vasoconstriction, oxidative stress increasing oxygen use, and arterial-venous oxygen shunting may increase the extent of hypoxia, and this may contribute to renal dysfunction and the progression of hypertension through mechanisms highlighted in Figure 3. For example, hypoxia could further production of angiotensin, aldosterone, endothelin 1, and vasoconstrictive prostanooids. These hormones and autacoids are well-known stimulators of Nox oxidases, and they have the capacity to induce gene expression via redox-sensitive AKT kinase, mitogen-activated protein kinase, extracellular signal–regulated kinase, and c-Jun N-terminal kinase signaling pathways, which potentially contribute to elevated blood pressure levels.

Preeclampsia is thought to be caused by a shallowly implanted placenta that becomes hypoxic leading to secretion of inflammatory mediators from the placenta, which act on the vascular endothelium. Insufficient uteroplacental oxygenation in preeclampsia is responsible for events leading to the clinical manifestations of this disease. In vivo and in vitro models of placental hypoxia reproduce changes seen in preeclampsia. HIF-1α is increased by a fall in PO2, and this appears to contribute to the pathogenesis of both preeclampsia and intrauterine growth retardation. It was proposed that placental hypoxia releases cytotoxic factors produced at the maternal-fetal interface into the circulation to manifest the maternal symptoms associated with preeclampsia. Prolonged placental hypoxia or intermittent hypoxia leads to a perpetual cycle of compartmentalized uteroplacental tissue damage, release of antiangiogenic and vasoconstrictive factors that impair trophoblast invasion, and promotion of systemic vascular resistance resulting in the maternal syndrome via the increased release of soluble flt1 and endoglin. These soluble receptors bind vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor-β1 and β3 in the maternal circulation, evoking oxidative stress and endothelial dysfunction.

SA is characterized by repeated brief episodes of hypoxia and reoxygenation, which originate from causes including obesity, airway obstruction, and central nervous system dysfunction. Chronic SA evokes systemic and pulmonary hypertension. Chronic peripheral chemoreflex activation occurring during SA is potentially an important risk factor for hypertension, and the central coupling of respiratory and sympathetic activities has been proposed as a novel mechanism underlying the development of neurogenic hypertension. SA-induced intermittent hypoxia activates the renin-angiotensin system and increases the levels of endothelin 1, C-reactive protein, interleukin 6, nuclear factor-κB, tumor necrosis factor-α, intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin in blood. It also increases xanthine oxidase expression and lipid peroxidation. This indicates that inflammation and oxidative stress are promoted by intermittent hypoxia in SA. Inflammatory cytokines and renin angiotensin promote ROS production, which often evokes endothelial dysfunction in SA patients who resolve with continuous positive airway pressure treatment.

There is evidence for NADPH oxidase activation in multiple brain regions associated with oxidative brain injury and hypomorsolence in a murine model of SA. Therefore, increased nervous system oxidative stress could be a key factor in increasing sympathetic tone and peripheral resistance. There is also evidence of increased vascular NADPH oxidase-derived ROS and decreases in NO synthesis or bioavailability in SA. These changes can potentially mediate constriction of systemic arteries and the development of hypertension.

Concluding Remarks

Hypoxia or cycles of hypoxia and reoxygenation can contribute to the development of some forms of pulmonary and systemic hypertension through processes that appear to involve activation of oxygen sensors often associated with changes in oxidant signaling in various cells in the vasculature and other organ systems. Hypertension may also influence multiple aspects of hypoxia-sensing mechanisms promoting hypoxia and other processes that may be important factors in the progression of hypertensive disease process. However, the majority of mechanisms involved in these processes are poorly understood and remain to be defined.

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Disclosures

None.

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