# Hypoxic Pulmonary Vasoconstriction and Chronic Lung Disease

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Hypoxic vasoconstriction in the lung is a unique and fundamental characteristic of the pulmonary circulation. It functions in health and disease states to better preserve ventilation-perfusion matching by diverting blood flow to better ventilated regions when local ventilation is compromised. As more areas of lung become hypoxic either with high altitude or global lung disease, then hypoxic pulmonary vasoconstriction (HPV) becomes less effective in ventilation-perfusion matching and can lead to pulmonary hypertension. HPV is intrinsic to the vascular smooth muscle and its mechanisms remain poorly understood. In addition, the pulmonary vascular endothelium, red cells, lung innervation, and numerous circulating vasoactive agents also affect the strength of HPV. This review will discuss the pathophysiology of HPV and address its role in pulmonary hypertension associated with World Health Organization Group 3 diseases. When sustained beyond many hours, HPV may initiate pulmonary vascular remodeling and lead to more fixed and less oxygen-responsive pulmonary hypertension if the hypoxic stimulus is maintained.

Hypoxic pulmonary vasoconstriction (HPV) is a fundamental attribute of the pulmonary circulation, which has fascinated cardiopulmonary physiologists and clinicians since its definitive description in the cat in 1946[1] and in humans 1 year later.[2] It was immediately appreciated that this response to local alveolar hypoxia and hypercapnia, either alone or in combination generally occurring as result of regional hypoventilation, acts to redirect pulmonary blood flow to areas of better ventilation with their higher alveolar $PO_2$ and lower $PCO_2$. In this fashion, HPV and hypercapnic pulmonary vasoconstriction (HCPV) are potent mechanisms to better match regional perfusion (Q) to alveolar ventilation ($V_A$) and so enhance gas exchange efficiency. If an area of regional hypoventilation is small in relation to the total pulmonary vascular bed, there is little to no increase in pulmonary artery (PA) pressure.[3] When there is more global alveolar hypoxia, such as at high altitude or more extensive hypoxia with or without hypercapnia in diffuse parenchymal and airways disease, HPV still operates to optimize $V_A$/Q matching. However, with more of the vasculature undergoing constriction it is less effective in this function and results in increased pulmonary vascular resistance (PVR) and pulmonary hypertension (PH).[3]

The presence and contribution of HPV to $V_A$/Q matching and PH in chronic lung diseases (World Health Organization [WHO] Group 3) and the extent to which it might be modified as part of treatment in this setting is not easily assessed. This is due to the fact that other changes in the vasculature in these conditions also increase vascular resistance. Depending on the disease and its duration and severity, these include physical destruction and loss of vascular bed with a decrease in total perfused cross-sectional area, hyperinflation such as with emphysema, reduction in local tonic vasodilator generation and/or increase in vasoconstrictor mediator production, and remodeling of existing vessels with increased smooth muscle mass and perivascular thickening leading to luminal narrowing.

In this review, the present understanding of HPV in the normal and diseased lung will be discussed with the goal of understanding its contribution to WHO Group 3 PH and its potential to be targeted therapeutically or be altered by treatments for these conditions.

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## CHARACTERIZATION OF HPV

Increases in PVR and PA pressure on ascent to high altitude or exposure to normobaric hypoxia universally occur in humans and other mammals. HPV can be detected with elevations in altitude as low as 1600-2500 m or with reductions in $F_IO_2$ to 0.15-0.18.[4,5] The magnitude of HPV (Figure 1) can vary almost 5-fold among healthy individuals,[6] and among species (Figure 2) in part related to total pulmonary vascular smooth muscle[6,7] and with duration of hypoxia (Figure 3) from minutes to several days.[7-9] HPV is the earliest mechanism that elevates PA pressure and PVR with hypoxic or high-altitude exposure. Ultimately, other mechanisms (perhaps partly in reaction to the first elevation of pressure initiated by HPV along with greater cardiac output) such as activation of pressure-independent hypoxia-sensitive inflammatory and proliferative pathways[10] may contribute to sustained PVR elevation and vascular remodeling. The process of remodeling is initiated as early as several hours at the level of new gene transcription, such as for collagen and other growth factors,[11] and is generally established within days to weeks of continuous alveolar hypoxia.[12-14]

The ability to reverse the acute effects of HPV by restoration of normoxia progressively diminishes with sustained

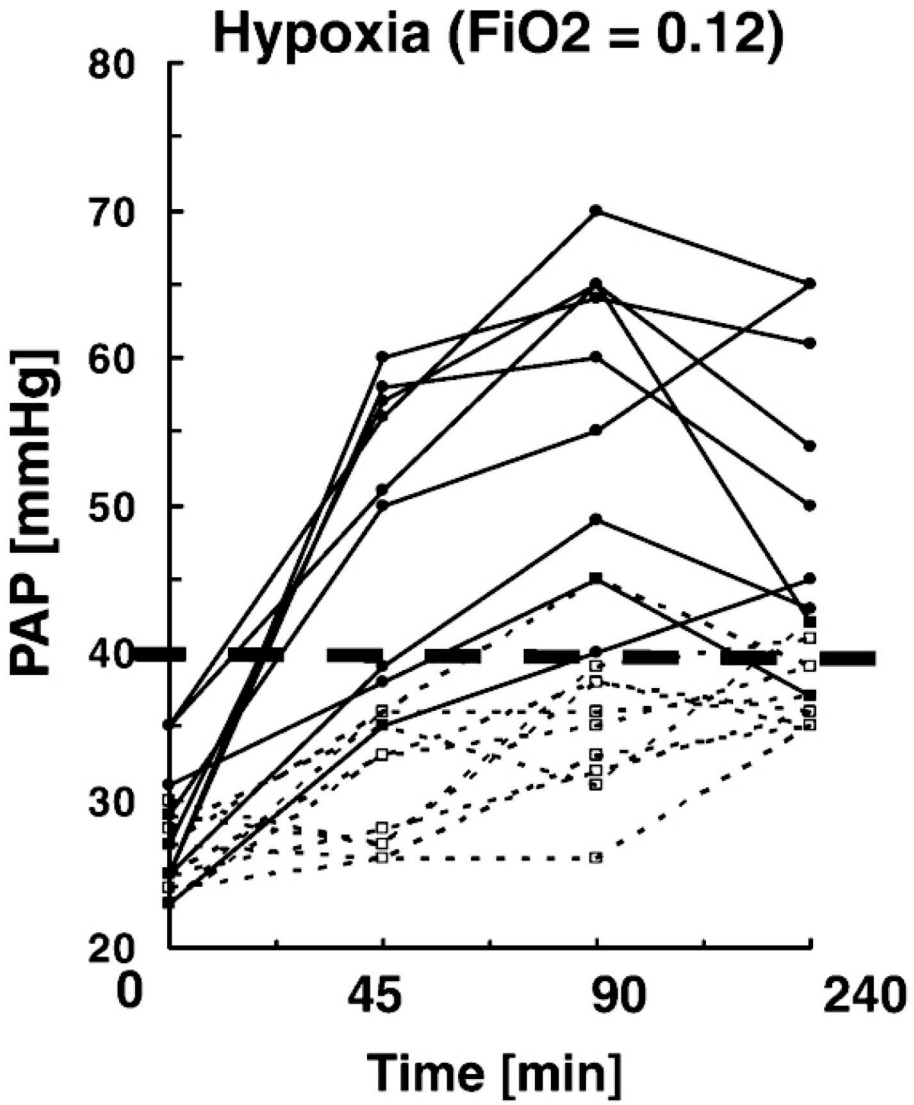


Figure 1. HPV variability as assessed by PA systolic pressure response in normal humans to 4 hours of moderate hypoxia. Subjects noted by solid lines are subjects susceptible to HAPE and show exaggerated HPV, while subjects without HAPE susceptibility (interrupted lines) have lower HPV. (Grunig et al. *J Am Coll Cardiol,* 2000.)

hypoxic exposure. This decline in reversibility has been demonstrated as early as 8 hours[9] and progressing through 1 to 3 days,[15,16] (Figure 4) and becomes more pronounced after 1 to several weeks of hypoxic exposure.[8,17,18] Although changes in inspired oxygen remain widely used to assess HPV, changes in arterial oxygenation and acid-base status always follow an alteration in inspired oxygen, so that systemic effects such as changes in central nervous system (CNS) and autonomic nervous activity might also contribute to the final pulmonary vascular response. It would be useful to employ a truly selective HPV inhibitor or stimulator in vivo rather than use changes in inspired oxygen, but all available pulmonary vasoactive agents have actions elsewhere in the circulation and brain, making them less than ideal for this purpose.

Lowland species with stronger acute HPV tend to develop greater PH with chronic hypoxia than animals with weaker HPV.[12] Whether humans with stronger HPV develop greater PH with chronic hypoxia or other conditions predisposing to PH has never been studied, but such a characteristic might underlie those often labeled as having "out-of-proportion" hypertension in the face of subsequent development of obstructive sleep apnea, heart failure, emphysema, and fibrotic lung disease. These conditions are more prevalent in older patients, and the impact of aging on HPV is also unknown.

The critical $PO_2$ at the level of the pulmonary arteriolar smooth muscle which initiates HPV in a lung region or the whole lung is a summation of the effects of alveolar $PO_2$ as set by inspired $PO_2$ and the ventilation-perfusion ($V_A/Q$) ratio, the bronchial arterial $PO_2$, and the mixed venous $PO_2$.[3] Because the bronchial arterial circulation perfuses the vaso vasorum of the pulmonary arteries and arterioles, systemic arterial $PO_2$ will also influence HPV. Separate perfusion of the bronchial artery in the sheep with deoxygenated blood, while alveolar $PO_2$ and systemic $PO_2$ were held constant, led to an increase in PA pressure.[19] In animal studies in which it is possible to control and hold systemic arterial and alveolar $PO_2$ constant, reductions in mixed venous $PO_2$ sensed in the PA cause vasoconstriction.[20,21] The importance of mixed venous $PO_2$ as a factor in HPV may be magnified with exercise, when mixed venous $PO_2$ falls to very low tensions as a result of high tissue oxygen extraction and greater arterial hypoxemia than at rest, but of the 3 contributions mixed venous $PO_2$ likely has the least influence.

## MECHANISMS OF ACUTE HPV

HPV is a complex process with elements of its expression arising from multiple points in the neuro-cardiopulmonary axis, with variation in intensity and mechanisms over time.[22] In addition to the intrinsic hypoxic response of the pulmonary vasculature that can be elicited in isolated pulmonary vascular smooth muscle cells and vessels, there are numerous extrinsic modulating influences sensitive to oxygen in vivo that include the vascular endothelial cells, red cells, chemoreceptors, autonomic nervous system, and lung innervation. The pulmonary circulation response to hypoxia is characterized by contraction of smooth muscle cells of the small pulmonary arterioles and veins of diameter less than 900 $\mu$m; the veins account for approximately 20% of the total increase in PVR.[23,24] At a regional level within the lung vasculature the magnitude of HPV may not be equivalent in all areas or static over time.[25-28] As a consequence of this

unevenness of regional HPV, some areas of the vasculature may be more perfused than others if they have a lower HPV response. This appears to be the case in those with a stronger global HPV response and susceptibility to high altitude pulmonary edema (HAPE).[26,27] Although it is not generally thought that hypoxia acts at the microvascular or acinar level, pulmonary capillary endothelial cells respond to hypoxia with membrane depolarization,[29] and this signal is propagated upstream and possibly downstream to resistance arterioles and venules. As yet, no evidence has been found for capillary constriction with hypoxia,[30] despite evidence that other vasoconstrictors are active at this level and in surrounding parenchymal perivascular cells that contain actin and myosin microfilaments.[31]

HPV in intact animals and humans appears to be fully expressed within 6 to 8 hours and has several temporal components. The first occurs within 5 minutes with a half-time of about 30-90 seconds.[32-35] A second phase of greater pressure elevation (almost double) is evident in humans and plateaus at 2 hours.[35] In animal studies, further elevation of pressure develops over the next 6 to 8 hours.[32] This has been confirmed in studies of isolated pulmonary arteries, lungs, or vascular smooth muscle cells showing a third phase taking upward of 8 hours.[36] The mechanisms behind these differing time phases and differences between in vivo and isolated lung and vessel investigations have not been well studied, but the isolated vessel studies suggest the first phase is intrinsic calcium-dependent smooth muscle contraction, with the later phases representing the summation of numerous other modulating influences acting on the smooth muscle[22,36] in a calcium concentration-independent fashion as discussed below. All of these differing hypoxic responses are fully and immediately reversible with return to normoxia if hypoxia is not extended beyond several hours.

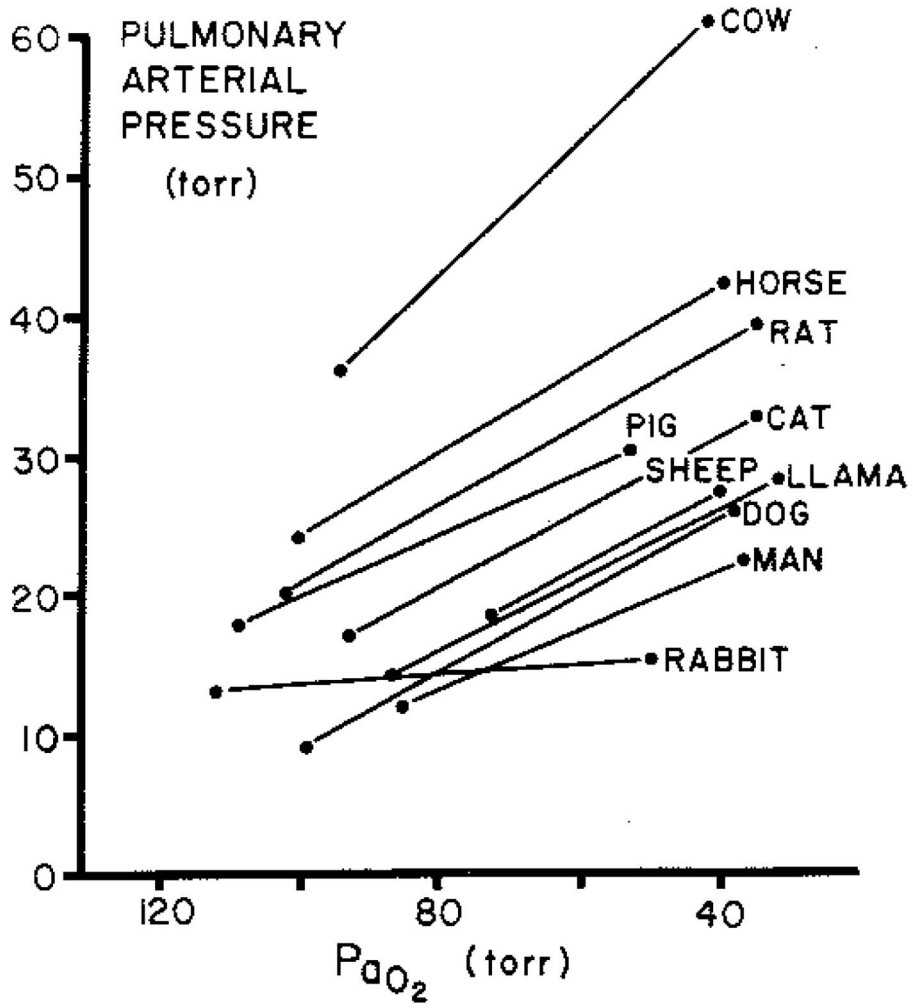


Figure 2. HPV in a variety of mammals showing baseline differences in normoxic mean PA pressure and increases with acute hypoxia. (Reeves et al. *Int Rev Physiol*, 1979.)

### *HPV at the Level of the Vascular Smooth Muscle*

There are several mechanisms involved in HPV that are activated in parallel or sequentially, leading to a critical increase of intracellular calcium and/or an enhanced calcium sensitivity of the actin-myosin that initiates contraction,[13,22] a response opposite to that which occurs in the systemic vasculature. Intracellular calcium concentration is increased by hypoxia-mediated inhibition of several potassium channels, leading to membrane depolarization and extracellular calcium entry through L-type channels, and a release of calcium from the sarcoplasmic reticulum (SR), with further influx through store-operated calcium channels (SOCC), receptor-operated calcium channels (ROCC), and transient receptor potential channel 6 (TRPC6). Figure 5 depicts the very complicated multiple pathways by which intracellular calcium in pulmonary vascular smooth muscle is quickly altered by hypoxia to initiate HPV. In addition, sensitivity to calcium of the contractile elements is enhanced via a hypoxia-induced increase in Rho-kinase activity.[37] The change in oxygen tension that stimulates these components of HPV is signaled by an alteration in the redox status of the smooth muscle cells.[13,38] Whether an increase or a decrease of reactive oxygen species (ROS) is responsible for HPV signal transduction is still under debate, but a stronger case is emerging that hypoxia increases mitochondrial ROS generation as an upstream signal for HPV.[38] It is clear that high-altitude exposure increases stable circulating markers of ROS production, and persons with higher HPV appear to generate more ROS and less bioactive vasodilating nitric oxide (NO) species across the lung.[39]

### *Endothelium-Dependent Modulation of HPV*

The pulmonary vascular endothelium generates a variety of vasoactive medi-

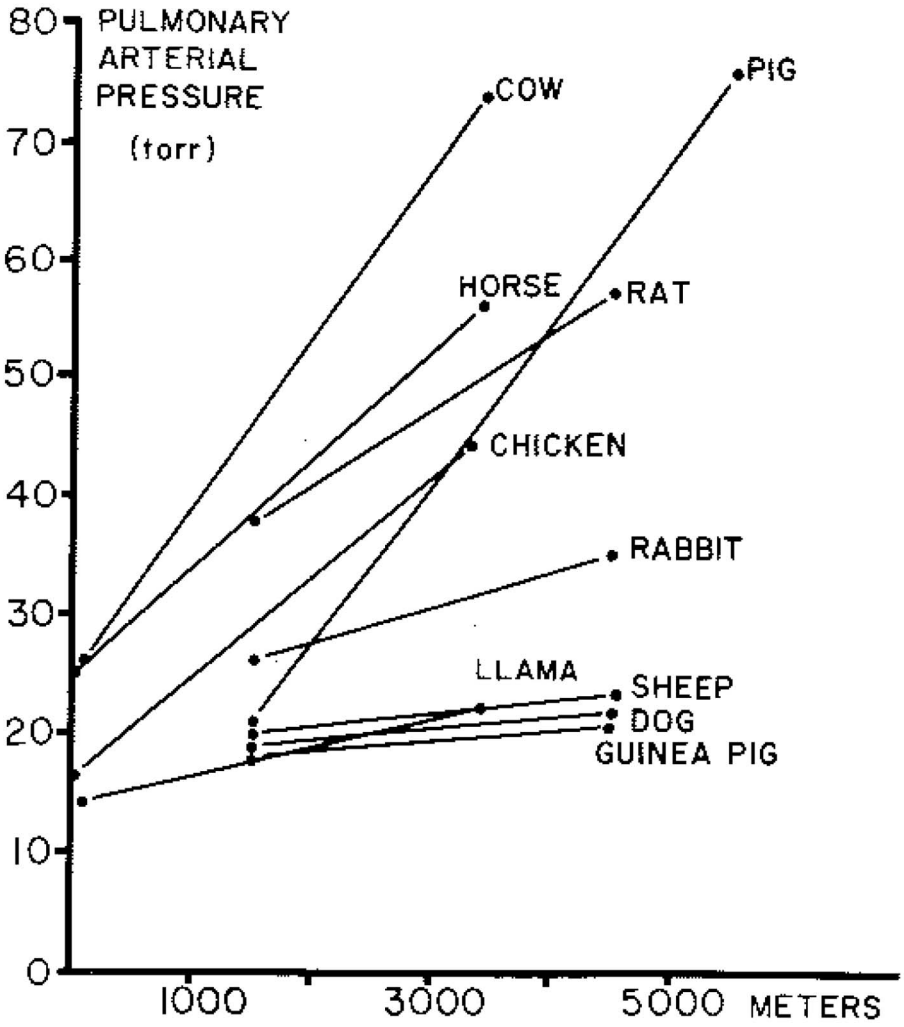


Figure 3. Species variability in severity of PH during exposure to chronic hypoxia. (Reeves et al. *Int Rev Physiol*, 1979.)

ators that act in a paracrine fashion on the surrounding vascular smooth muscle cells. These include NO and prostacyclin as vasodilators, and endothelin-1 acting as a vasoconstrictor via binding to endothelin-A receptors and a vasodilator by binding to endothelin-B receptors causing NO release.[36] Isolated human PA endothelial cells exposed to 3% oxygen produce more hydrogen peroxide and thus may also be a source for ROS that initiate HPV.[40] The endothelium also produces carbon monoxide (CO) via heme-oxygenase-2,[41] which is upregulated by hypoxia.[42,43] CO dilates vessels by activating guanylate cyclase to generate cyclic guanosine monophosphate (GMP) in a manner similar to NO. Hydrogen sulfide ($H_2S$), a strong reducing agent, generated in hypoxia is vasoconstricting in the pulmonary circulation by several not yet fully quantified mechanisms.[44] It should be noted that many of these "gaso-transmitters" alter the concentrations of each other, making it difficult to assess the contribution of each to HPV modulation.[45,46]

### *Erythrocyte-Dependent Modulation of HPV*

Red cells may contribute to HPV and pulmonary pressures in several ways. Although hypoxia-mediated decrease in deformability might reduce flow and increase measured vascular resistance,[47,48] direct measurements of human and other mammalian red cells over a range of $PO_2$ from 120 to 47 mm Hg show no evidence of significant deformability changes.[49] With elevations in hematocrit with altitude, pulmonary vascular pressures increase. This is partly due to increased blood viscosity and direct increases in lung vascular resistance as shown by hemodilution studies at high altitude in patients with chronic mountain sickness[50] and in animal studies.[51] Red cell-mediated changes in PVR with hypoxia represent a balance between those effects that are vasodilating and others that are vasoconstricting. Direct endothelial cell NO scavenging by oxyhemoglobin[52] and ROS generation by hypoxic red cells[53] will enhance HPV. In contrast, the oxygenation dependent behavior of red cells and hemoglobin that lead to s-nitrosothiol release[54] and NO generation from nitrite with hemoglobin desaturation[55] will blunt HPV. Additionally, deoxygenated red cells also release adenosine triphosphate (ATP), which activates endothelial cell NO production via purinergic receptor binding[56] and so act in a vasodilating fashion. Finally, recent evidence that red cells themselves express the endothelial isozyme of nitric oxide synthase (eNOS) and are able generate NO that escapes intracellular hemoglobin binding[57] needs to be considered. Similar to the various and sometimes competing interactions of endothelial cell vasoactive mediators on HPV, the contribution of red cells is similarly complicated and the net result on PVR may vary depending on the degree and duration of hypoxia.

### *Neurohumoral-Dependent Modulation of HPV*

The lung vasculature is innervated by sympathetic noradrenergic fibers from the large conduit arteries and veins down to 50 $\mu$m vessels in larger species such as man and dogs, but much less so in smaller species.[58] In addition to release of norepinephrine with sympathetic activation causing vasoconstriction via alpha-1 adrenergic receptors on vascular smooth muscle, there is release of other opposing vasodilating neurotransmitters such as neuropeptide Y and vasoactive intestinal peptide.[58] Additionally, there is opposing NO-dependent vasodilating parasympathetic innervation.[59] Arterial $PO_2$ is gauged by the peripheral chemoreceptors, which project afferents to the medullary cardiovascular control areas in the brain stem in addition to the respiratory control center, activating both

parasympathetic and sympathetic outflow to the lung. Denervation of the carotid bodies and loss of afferent input from the peripheral chemoreceptors increases HPV.[60,61] The efferent arc of this response is not well defined but is conveyed by the vagus nerve. Vagotomy reduces HPV.[62,63] Studies using atropine and propranolol suggest that vasodilating parasympathetic activity is more dominant than sympathetic activity in HPV inhibition.[63,64] Other data suggest a stronger sympathetic contribution.[65]

In regard to neurohumoral mediation of HPV, susceptibility to HAPE is characterized by a very exaggerated HPV[66] and a much greater generalized sympathetic nervous system activation to hypoxia.[67,68] However, not all studies find evidence for neural modulation of HPV.[69] The reason for this discrepancy is not clear, but those studies finding no effect on HPV have employed receptor blocking drugs rather than neural pathway interruption. It is entirely possible that peripheral chemoreceptor-mediated modulation of HPV may involve other neurotransmitter release via the lung innervation besides catecholaminergic or cholinergic agonists as described above. In humans, the association of stronger hypoxic ventilatory response (HVR), which is almost wholly a peripheral chemoreceptor mediated response, with weaker HPV supports the majority of the animal work.[70]

The pulmonary vasculature expresses adrenergic and cholinergic receptors, as well as other receptors, including those for thyroxine, angiotensin II, adenosine, natriuretic peptides, and estrogen. Thus it can respond to circulating vasoactive mediators with dilation by epinephrine via beta-2 receptors,[58] estrogens[71] and natriuretic peptides,[72] and constriction with angiotensin,[73] adenosine,[74] and thyroxine.[75] The full neurohumoral component of the lung vascular response to hypoxia is often neglected in discussions of HPV.

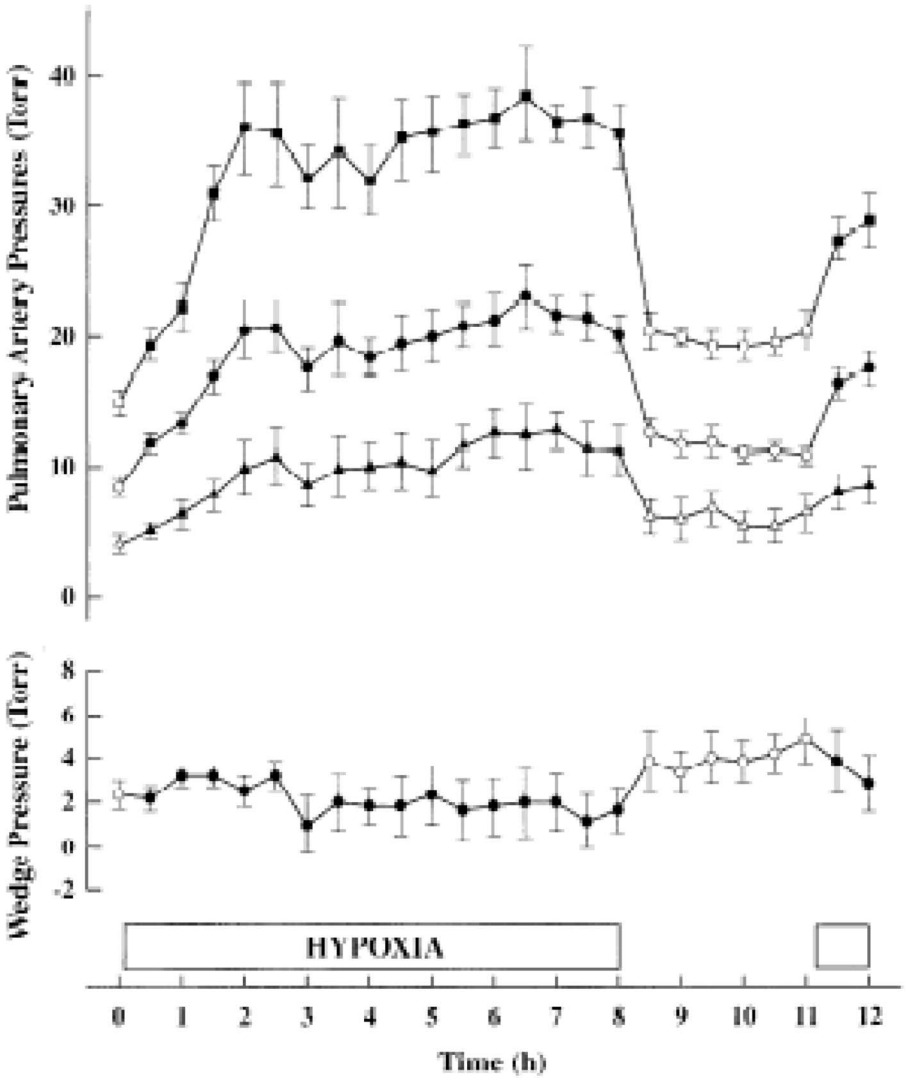


Figure 4. Time course in PA pressure (systolic, mean, and diastolic) and wedge pressure in humans with acute hypoxia showing lack of complete resolution of HPV with return to normoxia after 8 hours. (Dorrington et al. *J Appl Physiol*, 1997.)

### *Other Modulating Influences on HPV*

Individual genetic background[76-78] and a history of familial susceptibility to HAPE or PH[79-81] also contribute to the strength of HPV. Acid-base status and carbon dioxide have a considerable influence on HPV, with alkalosis and hypocapnia both diminishing HPV and hypercapnia increasing HPV.[82,83] Thus subjects with stronger ventilatory responses to hypoxia will not only maintain higher alveolar $PO_2$, but also will have less HPV due to their greater hypocapnic alkalemia at any given altitude or $F_IO_2$. Increasing lung volume by positive end-expiratory pressure in the range of 8-10 $cmH_2O$ does not reduce HPV.[84] Pre-existing high arterial wall tension also diminishes HPV.[85] Lastly, animal studies with low-grade infection or inflammation show that circulating and locally produced inflammatory leukotrienes, thromboxanes and cytokines, (ie, tumor necrosis factor, interleukin-6),[86-89] or activation of their receptors in the vasculature[90] appear to modulate HPV (both negatively and positively).

### *Hypoxia-Regulated Gene Transcription Factors and HPV*

The study of HPV continues to identify new sensing, signaling, and effector mechanisms and pathways. The most recent are the hypoxia-inducible factors (HIFs), transcription factors that alter the gene expression over 1000 genes involved in promoting tolerance to hypoxia.[91] Additionally, HIF activates a number of inflammatory signaling molecules such as nuclear factor kappa beta.[10] In this fashion, hypoxia and inflammation may be inextricably linked in chronic lung diseases. In 2 rat strains with differing pulmonary hypoxic

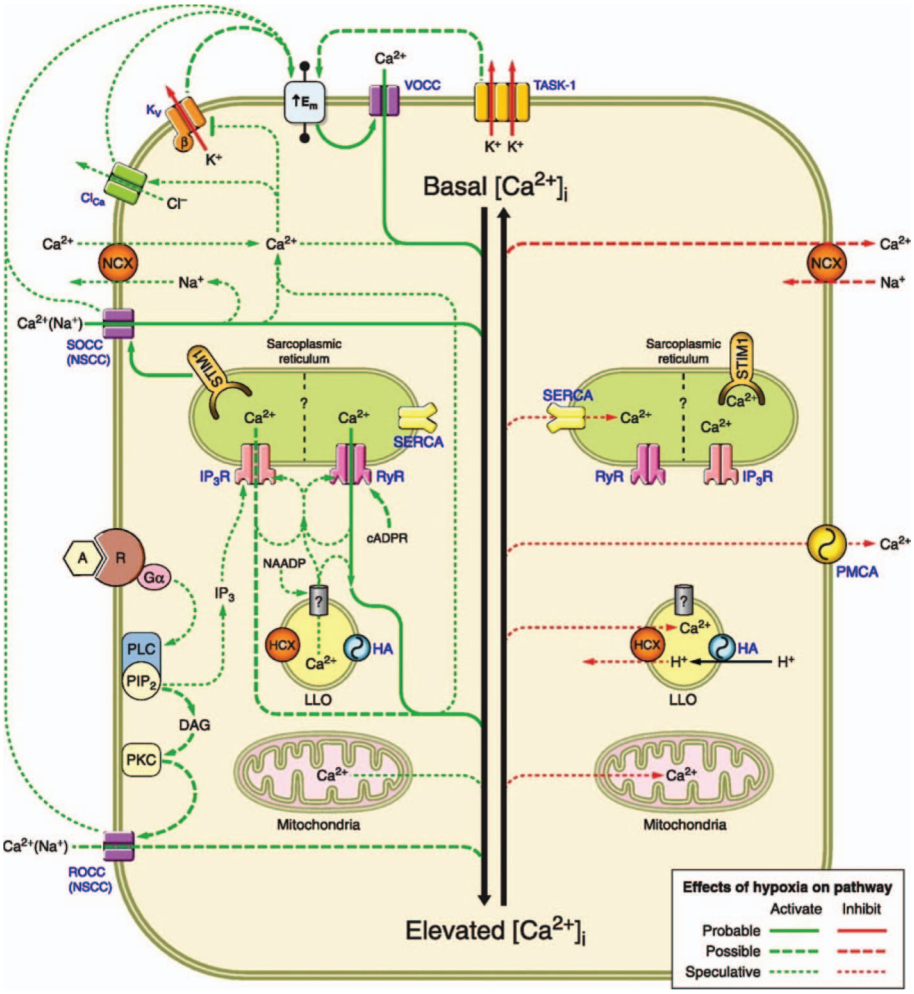


Figure 5. Diagram of pulmonary arterial smooth muscle cell intracellular calcium ([$Ca^{2+}$]i) pathways with acute hypoxia. Pathways that increase ([$Ca^{2+}$]i are shown on the *left*, while those that decrease ([$Ca^{2+}$]i are on the *right*. Hypoxia can activate (green) or inhibit (red) these pathways. Whether these effects are probable, possible, or speculative is indicated by solid, dashed, and dotted lines, respectively, as shown in the key at the bottom. With respect to plasma membrane and associated cytosolic signals, TASK-1 is TWIK-related acid-sensitive channel-1;VOCC, $K_V$, $Cl_{Ca}$, SOCC, NSCC, and ROCC indicate voltage-operated $Ca^{2+}$, voltage-dependent $K^+$, calcium-dependent Cl, store-operated $Ca2^+$, nonselective cation, and receptor-operated $Ca^{2+}$ channels, respectively. NCX, Na-Ca exchanger; A, agonist; R, receptor; PLC, phospholipase C; $PIP_2$, phosphatidylinositol 4,5-bisphosphate; $IP_3$, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PKC, protein kinase C; PMCA, plasma membrane Ca2_-ATPase. With respect to sarcoplasmic reticulum (SR) and associated cytosolic signals, SERCA is sarcoplasmic-endoplasmic reticulum ATPase, IP3R is IP3 receptor, RyR is ryanodine receptor, STIM1 is stromal interaction molecule 1, and cADPR is cyclic ADP ribose. With respect to lysosome-like organelles (LLO) and associated cytosolic signals, NAADP is nicotinic acid adenine dinucleotide phosphate, HCX is H-Ca exchanger, and HA is $H^+$-ATPase. Mito, mitochondria. (Sylvester et al. *Physiol Rev,* 2012.)

responses, HIF-1 activity and HIF-mediated protein expression were higher in the strain with greater PH.[92] In contrast, mice with heterozygous HIF-1 alpha deficiency have weaker acute and chronic hypoxic responses in isolated pulmonary vascular smooth myocytes and pulmonary vessels than wild-type mice.[93,94] Further supporting pharmacological evidence for HIF-1 alpha mediation of HPV was demonstrated in mice by reduction in hypoxic PH[95] with digoxin, a known inhibitor of HIF-1 alpha transcriptional activity.[96] At present it is not fully clear how HIF-dependent gene transcription affects HPV, but it likely involves upregulation of TRPC on the vascular smooth muscle cell membrane[97] and alterations in pulmonary vascular smooth muscle calcium signaling.[95] Iron is emerging as a critical element in HPV and pulmonary vascular changes with hypoxia. Iron supplementation and iron chelation reduce and increase HPV respectively,[98,99] possibly via altered HIF metabolism[100] involving prolyl hydroxylases, the $O_2$-sensitive enzymes that degrade HIF and require iron. HIF-mediated gene transcription also drives much of the longer-term remodeling of the vasculature.[14]

## RELEVANCE OF HPV IN HEALTH

At low altitudes where humans evolved, it would appear that the sensitivity to oxygen of the lung vasculature evolved along with HCPV as mechanisms[101] to shift blood flow from poorly or nonventilated lung regions with localized airway or airspace pathology in post-fetal life to better ventilated and healthy areas as elegantly advanced by von Euler and Liljestrand[1] in their landmark paper. Based on whole lung pulmonary vascular responses to changes in alveolar $PO_2$ and $PCO_2$, Dorrington et al[101] modelled that improvements in $V_A/Q$ matching and gas exchange by HPV are most important in the lower range of $V_A/Q$ (0.01 to 1.0), and that HCPV has its greatest impact in the $V_A/Q$ ratio of 1 to 100. The ability of both HPV and HCPV to divert blood flow and minimally raise PA pressure are more effective when the area of $V_A/Q$ mismatching is smaller.[3] From an evolutionary perspective, HPV may have conferred a survival (and ultimately a reproductive) advantage for individuals with severe pneumonia or thoracic trauma with acute pneumothorax by limiting the degree of severe life threatening shunt-induced hypoxemia. This may still be the case even in the modern clinical era of effective antibiotics and surgery before patients can be treated.[102]

Alternatively, others have argued it may be simply a vestige of fetal existence. In this regard, HPV maintains a high vascular resistance to limit blood flow in the nonventilated lung (in combination with a patent ductus arteriosis and foramen ovale) to allow an 80% to 90% right to left shunt to provide more blood flow to the placenta and better oxygenated blood to the developing brain.[103] However, many other aspects of the fetal lung also contribute to higher PVR, including its liquid-filled nonventilated high volume

state, lack of surfactant, relative hypercapnia and acidosis, a limited slower growing vascular bed relative to the faster growing airway and parenchymal structure, lesser endothelial vasodilator generation, greater endothelial vasoconstrictor production, and lack of bronchial epithelial NO generation.[103,104] In fact, HPV in the fetal lung does not appear until the middle of the third trimester of gestation. Thus, it would appear to reduce PVR and prepare the pulmonary circulation to accommodating the entire cardiac output at birth as the ductus arteriosis closes and the lungs are ventilated and assume gas exchange duties from the placenta.[104] In this sense, HPV should perhaps more correctly be renamed "oxygen-dependent vasodilation." If strong HPV is an evolutionary advantage in utero, then one might predict a fetal survival disadvantage in Tibetans, who have much lower HPV as adults than other populations.[105] Yet, birth rates and neonatal survival in this population exceed those of newcomers to high altitude.[106]

## RELEVANCE OF HPV IN CHRONIC LUNG DISEASE

In the setting of chronic lung diseases, several questions regarding HPV are relevant. The first is whether it is present and what is its magnitude. The second is how useful is HPV in maintaining as optimal state of gas exchange as possible. The third is what benefit or harm is realized with therapies that either directly alter HPV or alter it as a consequence of targeting some other aspect of the disease.

In answering the first and second questions, if the model of chronic global hypoxia[107,108] such as that occurring with long-term high-altitude exposure is any answer, then the finding that after several weeks at high altitude there is little pulmonary vasodilation with breathing oxygen would suggest HPV should not be present to any great extent in chronic hypoxic lung diseases.[8,105] Some patients with chronic obstructive pulmonary disease (COPD) and chronic bronchitis given high levels of inspired oxygen acutely show deterioration in $V_A/Q$ matching suggestive of inhibition of HPV,[109] but this has not been shown in every case.[110] Although these data and data from other studies have been used to support the idea that HPV is contributing to the high vascular tone, in studies with right heart catheterization there is minimal reduction in PH with supplemental oxygen therapy either acutely or chronically in most patients.[112] This apparent paradox might be explained either by there being only small regions of lung having any HPV, such that gas exchange deterioration still takes place, but reduction in overall PA pressure is minimal. A second possibility is that simultaneous increase in local carbon dioxide brought about by an increase in blood flow with release of HPV[113] in these areas leads to counteracting HCPV and limits the fall of pulmonary artery pressure. Despite the equivocal salutary effects of short-term oxygen, it is clearly established that chronic supplemental oxygen extends life in hypoxemic COPD patients and that this is associated with a mild improvement in pulmonary hemodynamics in those using continuous oxygen.[114] In patients exhibiting a significant drop in mean PA pressure of >5 mm Hg the benefits were greatest.[115] The benefits of oxygen therapy are multiple and stem largely from improvements in systemic oxygenation. However, the pulmonary vascular effects of oxygen in the long run may be related to HPV in much the same way that all models of chronic hypoxic PH in animals and in humans relocating from high altitude to sea level ultimately show regression of PH after return to normoxia.[107,108]

In interstitial lung disease the story is different. Two studies have shown no significant vasodilator response or change in $V_A/Q$ matching with 100% oxygen,[116,117] and chronic home oxygen administration does not alter mortality in fibrotic lung diseases.[118] Therefore, from these data it appears that HPV does not contribute greatly to PH in interstitial lung disease.[119]

HPV can be decreased for treatment purposes by a variety of pharmacological agents that act on many of the endothelial cell-derived modulators of PVR, signal transduction pathways, and gene transcription discussed above, including NO, nitrates, calcium channel blockers, phosphodiesterase 5 inhibitors, endothelin receptor blockers, prostacyclin analogs, soluble guanylate cyclase (sGC) activators, angiotensin converting enzyme inhibitors, and some carbonic anhydrase inhibitors, such as acetazolamide.[22] While these drugs certainly inhibit HPV at high altitude and some are quite useful to prevent and treat HAPE and high-altitude PH,[66] it must be appreciated that none of these agents are truly specific HPV inhibitors, except perhaps for acetazolamide.[120] Their pressure-lowering effects act on intracellular calcium signaling, mediator release, or receptor engagement, some of which may be common to HPV.

Several of these drugs that have been tested in patients with COPD and idiopathic pulmonary fibrosis (IPF) (as will be discussed in the 2 accompanying articles in this issue) may impair gas exchange efficiency by inhibiting HPV and/or by general vasodilation more in areas of shunt or low $V_A/Q$. For instance, with oral sildenafil in COPD, PA pressure is lowered at equivalent exercise intensity,[121] but in some arterial $PO_2$ falls. In those that derive an exercise and pressure-lowering effect, the drop in oxygenation could be likely prevented by small increases in their supplemental oxygen flow rate. Whether this is a tenable approach and might increase exercise capacity requires formal testing. (Note added in proof: A recent study by Blanco et al. (Eur Respir J. 2013;42:982-99) showed no benefit of sildenafil to a comprehensive pulmonary rehabilitation program in exercise endurance or quality of life.)

Lastly, the adverse effect of giving these agents orally might be mitigated by giving them by inhalation in order to vasodilate preferentially in the better ventilated regions and not worsen $V_A/Q$ mismatch such as with iloprost.[122,123]

## CONCLUSION

The search for more potent and selective vasodilators for the treatment of nonhypoxic forms of PH grows apace, and it is likely that most will have the ability to inhibit HPV. It may be useful in selected patients without an obvious ventilatory limitation at maximal exercise to

measure how much both oxygen and medications lower PA pressure and restrict their use to those with reductions in PVR associated with increased functional capacity or decreased dyspnea while adding or increasing supplemental oxygen as needed to maintain acceptable arterial oxygenation levels.

There is considerable diversity among WHO Group 3 PH patients and within the individual diagnostic subsets comprising this group. While HPV may play a variable role in the pathogenesis of PH in Group 3 patients, and treatment of hypoxia remains an important therapeutic consideration, the heterogeneity of this population poses significant challenges for development of effective treatment.

Multiple pathways associated with HPV, HCPV, other $V_A/Q$ matching mechanisms, hyperinflation, inflammation, vascular remodeling, and parenchymal loss contribute to the development of PH and pose significant challenges for identification and evaluation of potential therapeutic agents. Understanding these mechanisms and identifying patient groups where similar pathways predominate is a critical component in the evolution of treatment for WHO Group 3 PH.

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