Hypoxic Pulmonary Vasoconstriction

Physiology and Anesthetic Implications

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ABSTRACT

Hypoxic pulmonary vasoconstriction (HPV) represents a fundamental difference between the pulmonary and systemic circulations. HPV is active in utero, reducing pulmonary blood flow, and in adults helps to match regional ventilation and perfusion although it has little effect in healthy lungs. Many factors affect HPV including pH or Pco2, cardiac output, and several drugs, including antihypertensives. In patients with lung pathology and any patient having one-lung ventilation, HPV contributes to maintaining oxygenation, so anesthesiologists should be aware of the effects of anesthesia on this protective reflex. Intravenous anesthetic drugs have little effect on HPV, but it is attenuated by inhaled anesthetics, although less so with newer agents. The reflex is biphasic, and once the second phase becomes active after about an hour of hypoxia, this pulmonary vasoconstriction takes hours to reverse when normoxia returns. This has significant clinical implications for repeated periods of one-lung ventilation. (Anesthesiology 2015; 122:932-46)

Features of the HPV Reflex

Studying HPV is challenging due to the multitude of biological mechanisms involved, which results in variation between studies involving intact animals, isolated lungs, blood vessels, or cells. In animal experiments, there is considerable variation between species, and HPV varies with the duration of hypoxia making comparisons between studies, even within the same species, problematic. Finally, studying HPV in humans is further complicated by the difficulties of measuring PAP and the effects of pathology or drugs.

Stimulus and Time Course of HPV

For HPV to achieve its primary aim of matching regional ventilation and perfusion, the stimulus would ideally be solely alveolar PO2 (Pao2). However, in an intact animal, Pao2 is influenced not only by alveolar ventilation but also by the PO2 of the pulmonary capillaries, that is, mixed venous PO2 (PvO2). The overall tissue PO2 in the region of the pulmonary arterioles will therefore be determined by both alveolar and mixed venous values. In a ventilated lung, Pao2 is always the higher of the two, so this is the predominant stimulus. In animal studies in which both Pao2 and PvO2 were altered independently, the stimulus PO2 was quantified as:


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There is no reason to believe this equation to be invalid in humans. Therefore, in clinical practice, the numerous factors that alter $P_{\text{a}}O_2$ will also influence HPV including changes in cardiac output, oxygen consumption, and systemic vasodilation or vasoconstriction. In clinical situations where areas of lung are not ventilated such as one-lung ventilation (OLV) or pulmonary collapse, the stimulus $P_{\text{a}}O_2$ will equal $P_{\text{a}}O_2$.

The precise anatomical site of HPV is uncertain. In animals, hypoxia reduces blood flow in small pulmonary arteries, arterioles, capillaries, and venules although the response is greatest in distal pulmonary arteries. As pulmonary capillaries have no smooth muscle in their walls, reduced capillary blood flow in response to hypoxia is surprising. One possible mechanism is the presence of contractile cells within the alveolar septa which contract in response to hypoxia and directly constrict the capillaries or kink them by distorting the alveolar wall.\(^6\) The possibility of matching perfusion to ventilation at the alveolar level is intriguing and if confirmed would be an impressive affirmation of Haldane hypothesis.

Hypoxic pulmonary vasoconstriction has two distinct phases. Phase 1 begins within a few seconds and is maximal at 15 min. With moderate hypoxia ($P_{\text{a}}O_2$ 30 to 50 mmHg), the response is sustained, but in animal studies of severe hypoxia ($P_{\text{a}}O_2 < 30$ mmHg), phase 1 quickly declines again to almost normoxic values. When moderate hypoxia is sustained for more than 30 to 60 min, phase 2 of HPV begins and a further increase in pulmonary vascular resistance (PVR) is seen, reaching a peak at 2 h.\(^7\) This pattern is seen in healthy human volunteers (fig. 1).

It can also be seen from figure 1 that when normoxia returns after a sustained period of hypoxia, PVR does not immediately return to baseline, indicating a mechanism that takes hours to reverse.\(^7\) Furthermore, after a period of several hours of hypoxia, the response to acute hypoxia is enhanced, and the increase in PVR being almost double that seen before the prolonged hypoxia occurred (fig. 2).\(^8\)

### Physiological Factors Affecting HPV

#### Age

Compared with adults, HPV is more intense in the fetal and neonatal circulations, and this is described in the Fetal and Neonatal Circulation section. Some animal studies show diminution of HPV with ageing, but this has not been demonstrated in humans.

#### Carbon Dioxide and pH

Both respiratory and metabolic acidosis cause pulmonary vasoconstriction, the response resulting from alteration of extracellular $H^+$ concentration, this response being independent of HPV. Even a modest degree of hypercapnia in humans ($P_{\text{a}}CO_2$ 52 mmHg) leads to significantly increased PVR,\(^9\) although the response is slow, having not reached a plateau after 4 h.\(^10\) It is unknown whether this response occurs globally or only regionally; if the latter were true, this would be another mechanism for regional matching of pulmonary perfusion to ventilation.

Hypercapnia and acidosis have inconsistent effects on HPV; most probably as a result of species differences, variable hypoxic stimuli, and the degree of pulmonary vasoconstriction present. For example, recent animal studies indicate that in conditions of high pulmonary vascular tone, induced by either hypoxia or infusion of endothelin, hypercapnia vasodilates the pulmonary circulation.\(^11\) Human data are lacking, so hypercapnic augmentation of HPV cannot yet be cited as an explanation for the clinical benefits of permissive hypercapnia when ventilating lung-injured patients.

Both respiratory and metabolic alkalosis lead to pulmonary vasodilation,\(^4\) and the response to normoxic hypercapnia in humans is also slow to develop.\(^10\) Attenuation of HPV by alkalosis is a more consistent finding than the effect of acidosis,\(^4\) and it occurs in humans rendered hypoxic by simulated altitude.\(^12\) Furthermore, the reduction of PAP induced by hypocapnia in hypoxic conditions has been shown to improve gas exchange by facilitating better ventilation/perfusion (V/Q) matching.\(^12\)

#### Temperature

A single animal study has shown that HPV is attenuated by hypothermia and enhanced by hyperthermia.\(^13\) The relation between decrease in blood flow to a hypoxic lobe and temperature was approximately linear between 31° and 40°C, the response being halved at 31°C compared with normothermia. Hyperthermia per se increased PVR and this increased pulmonary vascular tone under normoxic conditions probably explains the observations. Although never studied in humans, if this effect is present in patients, then it has significant implications for the efficiency of HPV in the many clinical situations when body temperature is not 37°C.
Iron Availability

The iron status of a subject affects the HPV response. This has been elegantly demonstrated in humans by observing the effect on HPV of intravenous infusions of both iron and the iron chelator desferrioxamine. Iron attenuates HPV and also greatly reduces the enhanced response normally seen after prolonged hypoxic exposure (fig. 2). Reduction of iron availability with desferrioxamine increases PAP in normoxic subjects with a similar time course to that seen with hypoxia, implying a common mechanism. Desferrioxamine also increases the acute HPV response.

Outside of the laboratory, similar findings have been demonstrated by using high altitude as the hypoxic stimulus. In these studies, some volunteers were rendered iron deficient by prior venesection and then iron supplementation given when at altitude. In keeping with the laboratory studies, iron status was correlated with the altitude-induced increase in PAP which was exacerbated in iron-depleted subjects and attenuated by iron supplementation.

The influence of iron status on HPV in pathological situations is currently unknown. Iron deficiency is common in patients with idiopathic or inheritable pulmonary hypertension, opening up a new potential therapy for diseases that are notoriously difficult to treat. Similarly, avoidance of iron deficiency may have a place in the prevention of altitude-induced pulmonary illness. Finally, iron supplementation has been suggested as a possible therapy for patients in intensive care who have a life-threatening combination of hypoxemia and pulmonary hypertension.

Heterogeneous Nature of HPV

Animal studies of pulmonary edema formation and research into high-altitude pulmonary edema (HAPE) both indicated pulmonary capillary stress failure as an underlying cause. However, in hypoxic situations with increased pulmonary vascular tone, pulmonary arterioles are constricted so the capillary bed should be protected from the high PAP. A possible explanation for this anomaly was first proposed in 1962 by Visscher who suggested that the pulmonary vasoconstriction was patchy and so may result in flow heterogeneity, that is, only some areas of lung vasoconstrict and so the remaining regions receive excessive blood flow leading to mechanical capillary damage. This hypothesis fits well with the patchy nature of the pulmonary edema seen in HAPE (see Altitude Illness) and its association with high cardiac output. Studies using microspheres have confirmed that HPV is nonuniform in pigs. Human studies only became possible with the development of functional magnetic resonance imaging. This technique has demonstrated that HPV is heterogeneous in humans (fig. 3) and allowed the degree of heterogeneity to be quantified for investigation of diseases such as HAPE (see “Altitude illness” paragraph in V/Q Matching in Respiratory Disease section).

Mechanisms of HPV

All pulmonary blood vessels constrict in response to hypoxia, and the effect is more intense in the presence of other circulating vasopressors. Studies using pulmonary arterial smooth muscle cells (PASMCs) confirm that HPV occurs in these cells even when isolated, that is, removed from their contact with endothelial cells (ECs) or local or blood-borne mediators. Much of the research on the molecular mechanism of HPV has therefore focussed on the PASMC.

Oxygen Sensing in the PASMC

Oxygen can influence the biological systems either by binding reversibly to molecules and so inducing conformational change (e.g., hemoglobin) or by taking part in biochemical reactions (e.g., cellular energy production). Potential oxygen-sensing systems in a PASMC include the following:

1. Modulation of K+ channels, in which oxygen binds reversibly to sulfur-containing residues of the protein, altering its function. The same areas of the protein are however also sensitive to the overall redox state of the cell,
so evidence for a direct effect of oxygen on K⁺ channels is lacking.

2. Redox state in the cytoplasm is dependent on oxygen availability and includes ratios of the redox couples of glutathione and nicotinamide adenine dinucleotide. It is possible that in normoxic conditions, the cell's redox state maintains voltage-gated K⁺ channels (Kᵥ) in the open position to establish the normal resting membrane potential, and that when hypoxic, the Kᵥ channels close, changing membrane potential and activating voltage-gated calcium channels. Redox state may also cause PASMC contraction via an effect on Ca²⁺ release from sarcoplasmic reticulum.

3. Mitochondrial reactive oxygen species (ROS) production. In normoxic mitochondria, approximately 3% of electron flux results in ROS formation, and these are removed by ubiquitous antioxidant systems. In hypoxic mitochondria, ROS production may increase or decrease depending on the relative availability of oxygen and electron donors from elsewhere in the cell. However, hypoxia most commonly leads to an increase in ROS which are believed to be important signaling molecules in HPV.

4. Cellular energy state. Even when hypoxic, cellular levels of high-energy molecules such as adenosine triphosphate and phosphocreatine are well maintained by glycolysis, provided glucose remains freely available. In PASMCs hypoxia causes increased glucose uptake into the cell and enhances glycolysis. Adenylate kinase activity converts any available adenosine diphosphate molecules into adenosine triphosphate, increasing adenosine monophosphate levels. Excessive adenosine monophosphate activates an oxygen-sensitive enzyme adenosine monophosphate–activated kinase which initiates a range of intracellular changes to reduce adenosine triphosphate consumption and may also lead to release of Ca²⁺ from sarcoplasmic reticulum.

5. Membrane-bound protein function. Hemeoxygenase is a membrane-bound enzyme, normally responsible for heme degradation, which is also sensitive to PO₂. A normal product of hemeoxygenase activity is carbon monoxide, which suppresses pulmonary vascular reactivity, so although not directly an oxygen sensor in HPV hemeoxygenase does influence the response.

6. Hypoxia-inducible factor (HIF) is a ubiquitous cellular enzyme responsible for initiating transcription of many hypoxia-induced genes. HIF contains two subunits, an oxygen-sensitive α subunit and a constitutive β subunit. In normoxic cells, the most common α subunit, HIF-1α, has a half-life of just 5 min due to its rapid breakdown by the von Hippel-Lindau protein and multiple prolyl hydroxylase domain enzymes which are required for von Hippel-Lindau to bind to HIF-1α. The activity of prolyl hydroxylase domains is dependent on oxygen across a wide range of PO₂ levels, and the action of HIF itself on DNA is also oxygen dependent, so both its stabilization and activity are oxygen sensitive. Prolyl hydroxylase domain activity is also dependent on iron concentration within the cytoplasm, potentially explaining the dependence of HPV on iron status.

7. Cyclooxygenase and lipoxygenase use molecular oxygen as a substrate so are inherently oxygen sensitive. Activity of both leads to the generation of many vasoactive prostanoids and leukotrienes, so alteration of their activity by hypoxia can have variable effects on the pulmonary vasculature. Evidence suggests that cyclooxygenase and lipoxygenase...
activity are not primarily responsible for oxygen sensing in HPV but may be involved in modulating the response.

With so many contenders for the role of HPV oxygen sensor, it is unsurprising that no consensus exists on how this happens in vivo. Many of the mechanisms described are interlinked, and multiple mechanisms almost certainly involved depending on the phase of HPV, degree of hypoxia, etc.

Transduction of the Response in PASMCs
Depolarization of the PASMC membrane occurs due to inhibition of ion efflux across K’ channels, which then gives rise to sodium influx and chloride efflux across nonspecific ion channels. The exact channels involved vary with species, anatomical location, and age with, for example, different K’ channels being involved in fetal and adult HPV. Ultimately, for PASMC contraction to occur, there must be an increase in cytosolic Ca2+ concentration and this Ca2+ may enter from outside the cell or be released from sarcoplasmic reticulum. Both mechanisms are believed to occur in HPV. Increased intracellular calcium concentration ([Ca2+]i) causes smooth muscle contraction in PASMC in the same way as in any other tissues, that is, when calcium binds to calmodulin, myosin light-chain kinase is activated, the conformation of myosin alters, and contraction occurs. The situation is, however, more complex, with the sensitivity of the PASMC myofilament to calcium being variable. Intrinsic factors such as phosphorylation by protein kinase C or external factors such as nitric oxide release or stimulation by endothelin may all contribute to increased calcium sensitivity during hypoxia.

Modulation
Modulation describes systems that enhance or inhibit HPV but are not required for the response to occur. Although some factors such as intracellular pH may modulate HPV by a direct effect on the inherent activity of PASMCs, the more clinically important modulation arises from cells closely associated with the PASMC.

Modulation by Pulmonary Artery ECs. The oxygen-sensing mechanisms in ECs are similar to those in the PASMC, including involvement of K’ channels and ROS leading to an increased [Ca2+]i. Numerous mediators are released by ECs in response to hypoxia:

1. Nitric oxide is produced by both constitutive endothelial and inducible nitric oxide synthase (NOS). In the PASMC, nitric oxide generates cyclic guanosine monophosphate which reduces [Ca2+], and myofilament calcium sensitivity to relax the vascular smooth muscle. Basal nitric oxide production by endothelial NOS is believed to maintain the pulmonary circulation in a permanent state of active vasodilation. NOS uses molecular oxygen and L-arginine to synthesize nitric oxide, so in hypoxic conditions, the synthesis of nitric oxide is reduced. This may contribute to HPV by simply removing the normal basal nitric oxide–induced pulmonary vasodilation or by increasing PASMC calcium sensitivity. However, reversal of basal nitric oxide production would only account for a small proportion of the total HPV response seen and expired nitric oxide, a marker of basal nitric oxide production, is not significantly associated with the onset of HPV on ascent to altitude.24 Conversely, some studies have demonstrated that inhibition of NOS potentiates HPV and so concluded that nitric oxide possibly acts as a “braking mechanism” for HPV.25

2. Prostacyclin (PGI2) is a vasodilator released by both pulmonary and systemic ECs acting via stimulation of adenylate cyclase and increased cyclic adenosine monophosphate production. During hypoxia, prostacyclin release increases in pulmonary ECs, attenuating HPV.

3. Endothelin-1 is a small peptide (21 amino acids), which is a potent pulmonary vasoconstrictor.26 It is a paracrine mediator, the majority being released from ECs into the interstitial space. Acting via two G-protein–coupled receptors ET1 and ET2 on PASMCs, endothelin causes a variety of effects that enhance HPV, but the most important mechanism seems to be sensitization of several classes of calcium channels, enhancing the increase in [Ca2+]i, seen with hypoxia. Stimulation of the pulmonary vasculature by endothelin produces an intense and prolonged vasoconstriction. Endothelin has also been implicated in the vascular remodeling that occurs in the pulmonary vasculature with long-term hypoxia. As a result, endothelin antagonist drugs (see Endothelin Antagonists) are important in the treatment of chronic pulmonary hypertension.26,27

Humoral Modulation. Animal studies have demonstrated many humoral modulators of HPV such as adenosine, histamine, and 5-hydroxytryptamine, none of which are believed to play a significant role in humans.4 Angiotensin II is a pulmonary vasoconstrictor in normoxic human lungs and enhances HPV in several species including humans.28 Evidence that angiotensin II may play a role in humans derives from the observation that angiotensin-converting enzyme inhibitors may attenuate HPV (see Angiotensin-converting Enzyme Inhibitors).

Neural Modulation. Sympathetic nerves are known to innervate pulmonary arteries down to approximately 60 μm diameter but are not closely involved in the maintenance of normal vascular tone and not believed to be modulators of HPV. These nerves may be involved in the development of some types of pulmonary edema, including neurogenic pulmonary edema and HAPE. Parasympathetic and sensory nerves in the lung are not believed to modulate HPV.

Physiological Roles of HPV

Fetal and Neonatal Circulation
In Utero. As soon as the pulmonary circulation develops in the fetus, HPV is believed to be present and active. Less than 10% of cardiac output passes through the pulmonary
circulation in utero, a circulation deliberately designed to maximize flow through the placenta for exchange of respiratory gases and uptake of nutrients. The high PVR results from:

1. The underdeveloped structure of the pulmonary vasculature, with thick-walled vessels.
2. The presence of fluid in the alveoli. In late pregnancy, fetal breathing movements cause fluid to be sucked into the lung and maintain this at a slightly positive pressure. This is believed to not only prevent lung collapse and stimulate cell growth in the developing lung but also compresses the pulmonary vasculature.
3. HPV. A variety of vasodilator and vasoconstrictor systems exist in the fetal pulmonary circulation, but the balance of these strongly favors vasoconstriction. The mechanisms of HPV in utero differ from those in adults. Potassium channels are still a fundamental part of the response, but instead of the Kv subtype found in adults, a calcium-dependent K+ channel BK_{Ca} is involved. Endothelin plays a key role in maintaining a high PVR in the last trimester with high expression of messenger RNA for both endothelin and the ET_{A} receptor.

**Changes at Birth.** In the late stages of pregnancy, fetal physiology changes in preparation for birth, in particular, endothelin production declines. At birth, PVR must reduce quickly and permanently, which results from a combination of the following effects:

1. Lung expansion. Compression of the chest during parturition is followed by sudden expansion and increased lung volume at birth. As in adults, one of the physical determinants of PVR is lung volume, so this change reduces PVR immediately.
2. Increased PO_{2} in the lung at birth decreases PVR by reversing HPV, particularly that resulting from endothelin stimulation, and probably also by increasing nitric oxide production by ECs.
3. Increased systemic vascular resistance from loss of the placental circulation and closure of the ductus arteriosus raises left-sided pressures in the heart leading to foramen ovale closure. Pulmonary blood flow therefore increases, and recruitment and distension of pulmonary capillaries facilitate this. This distension of blood vessels may contribute to further pulmonary vasodilatation by causing ECs to release vasodilator modulators in response to increased shear stress on the cells.
4. Breathing. Mechanical deformation of the lungs may be responsible for the release of vasodilator modulators by pulmonary ECs and so reduced intensity of HPV. Possible mechanisms include increased production of prostacyclin and nitric oxide and increased BK_{Ca} sensitivity.

**Neonatal Pulmonary Circulation.** After the dramatic pulmonary vasodilatation at birth, PVR continues to decrease further in the first few days and weeks of neonatal life. Continuing recruitment of pulmonary vasculature, functional changes to K+ channels and modulator release (e.g., nitric oxide) and gradual loss of PASMCs toward a more adult morphology all contribute to reducing PVR. However, until this occurs, HPV is a dangerous reflex as the highly muscular pulmonary vessels can effectively shut down the pulmonary circulation and return the neonate to a fetal circulation and dangerously low arterial PO_{2}. Active attenuation of HPV therefore occurs at this stage, most likely as a result of greater prostacyclin synthesis by the ECs, possibly helped by increased nitric oxide secretion, and the different subgroups of K+ channels found in neonatal PASMC compared with adults.

**Matching of Regional Ventilation and Perfusion**

In adults, matching of alveolar ventilation (V) and perfusion (Q) is crucial to optimize gas exchange, particularly oxygenation. Although global V and Q are both approximately 5 liters/min and so the overall V/Q ratio equals 1, on a regional basis, this is not the case. In the extreme example of all ventilation going to one lung and perfusion to the other, overall V/Q ratio will still be 1, but no gas exchange will occur. HPV therefore serves to reduce blood flow through areas of lung where PO_{2} is low, as illustrated in figure 4.

As can be seen from figure 4, the concept of HPV simply diverting blood away from less well-ventilated regions is misleading. Reducing blood flow through a region with low V/Q is helpful to reduce its effect on arterial PO_{2}, but if ventilation to the region remains unchanged, then reduced blood flow also improves the V/Q ratio of that lung region and so the PO_{2} of blood leaving it.

These theoretical considerations do seem to be relevant in vivo. Animal studies in which a region of lung is ventilated separately with hypoxic gas mixtures consistently show reduced perfusion to the region. The maximal effect seems to occur at alveolar PO_{2} values from 25 to 50 mmHg; with severe hypoxia of less than 25 mmHg, HPV becomes less effective. Achieving this degree of hypoxia in a lung region of a patient is challenging, given that both alveolar and mixed venous blood PO_{2} must be low, but is still possible in patients with severe lung pathology. Carbon dioxide must also be taken into account when considering the in vivo efficacy of HPV: as described in the Carbon Dioxide and pH section, both Pco_{2} and pH influence PVR, in particular, hypopcapnia. Fortunately, regional hypopcapnia is unusual in clinical practice, and inadequate ventilation of a lung region normally results in increased rather than lowered Pco_{2}. Also, for oxygen, the Pco_{2} effect on HPV is determined by Pco_{2} of both alveolar gas and mixed venous blood, and the latter is unlikely to be reduced. Thus, hypopcapnia is unlikely to have a clinically significant effect on HPV, although avoidance of hypopcapnia is advisable in situations where HPV is useful, for example, OLV. Finally, the size of the region of low V/Q influences the ability of HPV to improve oxygenation, being maximal when between 30 and 70% of the lung is hypoxic.
Hypoxic Pulmonary Vasoconstriction

V˙ /Q˙ Matching in Normal Lungs. The contribution of HPV to V˙ /Q˙ matching in normal healthy subjects is controversial. Ways of studying this include physiological modeling, using the multiple inert gas elimination technique to quantify V˙ /Q˙ relations, or observing the effect on arterial oxygenation of administering agents that enhance or impair HPV such as breathing 100% oxygen to abolish HPV in areas of V˙ /Q˙ less than 1. A problem with the latter approach is that 100% oxygen may promote absorption atelectasis in regions with very low V˙ /Q˙ ratio. However, despite recent theoretical evidence that vascular responses to oxygen are important in healthy humans,31 numerous animal and some human studies using varied techniques have found little in vivo evidence of this.4

V˙ /Q˙ Matching in Respiratory Disease. Studies in humans have demonstrated that occlusion of an airway quickly leads to a reduction in blood flow to that lung region of approximately 50%,32 with a similar finding in animals if regions of lung are collapsed.33 Do these pathophysiological changes translate into beneficial effects in patient with lung disease? Using the same methods as described in the previous paragraph, the answer seems to be yes.4 A summary of the role of HPV in pulmonary disease includes the following:

- Asthma. In stable asthma or in patients with asthma receiving artificial ventilation,34 breathing 100% oxygen worsens V˙ /Q˙ matching and increases shunt fraction.
- Chronic obstructive pulmonary disease (COPD). Similar findings occur in patients with COPD, when both stable or during exacerbations, when breathing 100% oxygen causes a worsening of V˙ /Q˙ matching.4 Inhibition of HPV by either nifedipine (see Calcium Antagonists) or sildenafil (see Phosphodiesterase Inhibitors) causes a deterioration in oxygenation in patients with COPD.35,36 The role of HPV in patients with COPD having general anesthesia (GA) is discussed in the section Relevance of HPV in Lung Disease.
- Acute lung injury (ALI). Unlike asthma and COPD, the major physiological barrier to oxygenation in ALI is right-to-left shunt. There is some evidence that HPV

Fig. 4. Theoretical demonstration of hypoxic pulmonary vasoconstriction (HPV) correcting arterial oxygen saturation with ventilation/perfusion (V˙ /Q˙) mismatch in a patient breathing air. (A) Normal situation where V˙ /Q˙ ratio of all lung regions = 1. Blood flowing through all regions is fully saturated with oxygen and, therefore, is arterial blood. (B) V˙ /Q˙ mismatch without HPV. Alveolar PaO₂ in the poorly ventilated lung regions (V˙ /Q˙ = 0.2) is approximately 51 mmHg, so blood from these regions has a saturation of 86% and so reduces SaO₂ significantly. (C) V˙ /Q˙ mismatch with HPV. Blood flow to the poorly ventilated region is halved by HPV, increasing the V˙ /Q˙ ratio to 0.4. As a result, PaO₂ increases to approximately 70 mmHg, and the blood from these regions is now 94% saturated. The lower blood flow through, and improved saturation from, this region means the SaO₂ increases to almost normal. (D) Worsening V˙ /Q˙ mismatch with HPV. There is now an area of unventilated lung (V˙ /Q˙ = 0), and PaO₂ in this region now equals that of mixed venous blood. HPV intensifies and reduces blood flow further, but the oxygen saturation of blood leaving the region is now only 75%. Arterial saturation still remains acceptable at 95% due to the efficiency of HPV. Also, the PaO₂ of mixed venous blood will now have a significant effect on the intensity of HPV and so SaO₂. Assumptions made for the figure. \( P_{\text{O}_2} = 40 \text{mmHg}, \text{PaO}_2 \text{ when V˙ /Q˙ of 0.2 = 51 mmHg and V˙ /Q˙ of 0.4 = 70 mmHg, Hb = 14 g/dl, respiratory quotient = 0.8.} \) PaO₂ = partial pressure of alveolar oxygen; Po₂ = partial pressure of oxygen; Sao₂ = arterial oxygen saturation.
contributes to reducing the shunt fraction. For example, when diltiazem or intravenous nitrates are used to impair HPV, the shunt fraction increases, and when almitrine is used to enhance HPV, it reduces. Unfortunately, numerous animal studies have also found that endotoxaemia, which is commonly present in ALI, may inhibit HPV.

- Altitude illness. HPV has a crucial role in the development of HAPE. Subjects who are susceptible to HAPE have a more intense and patchy HPV response (fig. 3) making them more likely to develop capillary stress failure and edema as described in the Heterogenous Nature of HPV section. The mechanism of this different HPV response in HAPE-susceptible subjects is unknown, but some of the drugs that attenuate HPV (described in the Drugs That Attenuate HPV section), specifically nifedipine, sildenafil, and dexamethasone, are now widely used for preventing or treating HAPE. If induced acutely, only modest levels of hypoxic hypoxia are required to stimulate HPV, and the cabin altitude of commercial aircraft is sufficient to induce an increase in PAP even in healthy subjects.36

Drugs Affecting HPV

Drugs That Augment HPV

Catecholamines. Pulmonary vessels contain α1 and β1 adrenoceptors and DA1-dopaminergic receptors, and animal studies of adrenaline, dopamine, dobutamine, dopexamine, and isoprenaline show that these drugs attenuate HPV.39-42 However, some of these studies also found that at high doses, these drugs caused pulmonary vasoconstriction in normoxic lung regions. For these nonspecific catecholamines, this is in keeping with the presence of opposing receptors on pulmonary vessels. At lower doses, vasodilatory stimulation of β2 receptors, which might attenuate HPV, is balanced by the vasoconstrictor effect of α1 stimulation, until at higher doses, α1 stimulation predominates and vasoconstriction occurs.39 Inhaled β2-agonists at clinically relevant doses do not inhibit HPV and may potentiate it.45

The use of α1 agonists such as norepinephrine or phenylephrine, both of which cause pulmonary vasoconstriction, is a more effective way of enhancing HPV. It must be remembered that in vivo these drugs are not specific for pulmonary vessels, being potent systemic vasoconstrictors, and so their ability to improve oxygenation in clinical situations is limited. A study using norepinephrine in patients with severe ALI found no improvement in oxygenation, a finding which the authors ascribed to the possibility of nonspecific diffuse vasoconstriction by norepinephrine.44 Conversely, a similar study using the pure α1 agonist phenylephrine found that half of patients did show improved oxygenation.45 Finally, a single case report of a pediatric patient having OLV described an impressive improvement in oxygenation with phenylephrine when all other manoeuvres had failed to correct severe hypoxemia.46

Adrenergic blockers may affect HPV, although animal studies have demonstrated that both peripheral (phenoxybenzamine) and central (clonidine) α-blockers have no effects.47,48 The β-blocker propranolol may either augment47 or abolish49,50 the response depending on the study conditions.

These inconsistent reports illustrate the variability of the effects of catecholamines on HPV as a result of the multiple adrenoreceptors and the differing effects of catecholamines on pulmonary and systemic vessels.

Almitrine. Animals studies show that at low doses almitrine enhances HPV51 by a vasoconstrictor effect specific to pulmonary arteries. Its mechanism of action remains unknown although the effect is inhibited by nifedipine suggesting a calcium-mediated action.52 When administered systemically, it has been shown to improve PaO2 during OLV53 but it is not used clinically due to problems with correct dose selection—at higher doses, almitrine vasoconstricts normoxic lung which is problematic during OLV.54 With chronic use, almitrine has been associated with peripheral neuropathy, and it has been removed from the market in many countries.55

Drugs That Attenuate HPV

Acetazolamide. Animal studies have demonstrated that at high doses, acetazolamide impairs HPV by a direct effect on PASMCs acting via an uncertain mechanism unrelated to its effects on carbonic anhydrase.56 At clinically used doses in humans, acetazolamide does not reduce PAP at altitude,57 but this does not rule out a useful role in HAPE-susceptible subjects.

Inhaled Nitric Oxide. Nitric oxide attenuates HPV by causing localized pulmonary vasodilatation, and by administering nitric oxide via inhalation, V/Q relations may be improved. By this route, nitric oxide is only delivered to lung regions with some ventilation, and perfusion of these regions will therefore be enhanced. This is in effect providing a complementary strategy to that of HPV, that is, normoxic pulmonary vasodilatation. In some patients with severe ALI, nitric oxide inhalation alone, or in combination with systemic vasoconstriction using phenylephrine, may improve oxygenation by either improving V/Q matching or by increasing cardiac output. The lack of predictability in this context may be due to the heterogeneity of the lung pathological lesion in patients with ALI.45 During OLV, administration of nitric oxide to the ventilated lung has generally been shown to be of no benefit in improving PaO2.58 This is probably because the ventilated lung is almost maximally vasodilated when using an inspired oxygen fraction (FIO2) of 1.0. However, some patients, particularly those with pulmonary hypertension, may show an increase in PaO2 with inhaled nitric oxide during OLV.59

Steroids. Acute administration of intravenous methylprednisolone has no effect on HPV in dogs.60 Conversely, HAPE-susceptible subjects have a significantly reduced HPV response at altitude after taking 8 mg dexamethasone twice daily before ascent.61 Corticosteroids may affect HPV via multiple mechanisms, including inducing endothelial
NOS production and so improving nitric oxide production or by attenuation of the sympathetic response to altitude and so reducing PAP.

**Phosphodiesterase Inhibitors.** Selective inhibitors of phosphodiesterase type 5 are now an established treatment option for pulmonary hypertension and HAPE. Phosphodiesterase 5 inhibitors such as sildenafil impair the breakdown of cyclic guanosine monophosphate, which is responsible for the action of nitric oxide and other vasodilators in the PASMC. Despite the uncertain contribution of nitric oxide to physiological HPV, oral sildenafil almost abolishes the HPV response in healthy volunteers breathing 11% oxygen, and animal studies by the same group showed that this effect is only partially due to enhancement of the nitric oxide pathway. In patients with pulmonary hypertension secondary to COPD, sildenafil improved pulmonary hemodynamics, but as may be predicted from the physiological role of HPV, V/Q relations and oxygenation worsened.

**Nitric Oxide Donors.** As may be expected from drugs targeting the nitric oxide system, HPV is attenuated by both sodium nitroprusside and nitroglycerine. However, this has only been directly demonstrated in animal studies more than 3 decades ago although there is no reason to believe humans would have a different response. Hydralazine is an inhibitor of HPV in humans at altitude, and there is evidence from a human study that sublingual nitroglycerine causes a small degree of hypoxemia which the authors ascribed to attenuated HPV.

**Prostacyclin.** Prostacyclin has potent pulmonary vasodilator properties and may be administered either intravenously or by inhalation. Intravenous prostacyclin is useful for treating pulmonary hypertension in critically ill patients, but its effects on the systemic circulation cause significant adverse effects. When delivered by inhalation, very little prostacyclin is metabolized by the lung, so systemic absorption still occurs, but the dose by inhalation is small, so systemic side effects are reduced. This route of administration also has the same benefits as inhaled nitric oxide, that is, the drug is only delivered to lung regions where alveolar ventilation is present. Inhibition of the cyclooxygenase pathway by nonsteroidal antiinflammatory medications may decrease the production of prostacyclin and potentiate HPV. This has been demonstrated with indomethacin in animal studies but has not been demonstrated in humans. There has been one case report of the use of inhaled prostacyclin, in combination with systemic phenylephrine, to improve oxygenation during OLV.

**Calcium Antagonists.** In animals, there is a dose-dependent reduction in HPV by verapamil and nifedipine, and similar findings have been reported with nifedipine in humans with COPD.

**Angiotensin-converting Enzyme Inhibitors.** Healthy subjects taking either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers have been shown to reduce mortality in patients with COPD in the long term and after exacerbations, probably as a result of their immunomodulatory effects.

**Endothelin Antagonists.** These drugs competitively antagonize either ET_A and ET_B receptors (e.g., sitaxsentan) or are specific for ET_A (e.g., bosentan). Which of the drugs is most effective for treating pulmonary hypertension remains uncertain. Apart from being a pulmonary vasodilator, endothelin is also involved in the vascular remodeling of pulmonary vessels with long-term hypoxia, and ET antagonists may also slow this process.

### Effects of Anesthetic Drugs on HPV

Many drugs used during anesthesia have an effect on HPV. No commonly used drugs augment HPV, but many drugs inhibit HPV. Essentially any drug that is a vasodilator may inhibit HPV. All modern volatile anesthetic agents inhibit HPV in a dose-dependent manner. Halothane has been well studied and is a reasonably potent inhibitor of HPV. Inhalation of 0.5 minimal alveolar concentration (MAC) halothane inhibited HPV by 50% in a rat study. Isoflurane is a less potent inhibitor of HPV than halothane and in animals requires a dose of approximately 1.3 MAC isoflurane to equal the HPV inhibition of 1 MAC halothane. A human study during OLV showed a similar pattern for the effects of these two volatile anesthetics on HPV. Conversion from 1 MAC halothane inhalational anesthesia to intravenous anesthesia (sodium thiopental, diazepam, and fentanyl) caused a statistically significant increase in mean PaO_2 (116 to 155 mmHg) and a decrease in shunt (44 to 37%). In a separate group of patients, conversion from 1 MAC isoflurane to intravenous anesthesia caused a nonsignificant increase in PaO_2 (232 to 245 mmHg) and decrease in shunt (38 to 36%).

There does not seem to be any difference between the modern volatile anesthetics isoflurane, sevoflurane, and desflurane in their inhibition of HPV for equivalent MAC doses.

The common intravenous anesthetic agents show no inhibition of HPV. Even though propofol causes some systemic vasodilation, it does not inhibit HPV. One randomized cross-over study comparing propofol–alfentanil anesthesia versus 1 MAC isoflurane showed no statistically significant difference in mean PaO_2 values (228 vs. 214 mmHg respectively); however, this study was only powered to detect a difference of 40 mmHg between groups.

Human clinical studies comparing arterial oxygenation during OLV with the newer volatile anesthetics versus intravenous anesthetics have generally not shown any significant difference. However, these studies have only measured blood gases, and direct indicators of HPV such as changes in PVR or V/Q distribution have not been documented.
Unlike other current volatile anesthetics, nitrous oxide is not a vasodilator and seems to have pulmonary vasoconstrictive properties. The effects of nitrous oxide on HPV are not clear. Animal studies have suggested some inhibition of HPV by nitrous oxide, but this has not been reported in humans.

**HPV during Anesthesia and OLV**

**HPV during GA**

Changes in chest wall and diaphragm shape, regional lung compliance, and artificial ventilation all contribute to abnormal V/Q matching during GA. Multiple inert gas elimination technique studies show that during GA, there are more areas of high and low V/Q (fig. 5) contributing to impairment of oxygenation and increased alveolar dead space. These changes suggest that HPV should be important for maintaining oxygenation, but clinical studies to demonstrate this are lacking except during OLV. The variable effects of anesthetic agents on HPV described in the Effects of Anesthetic Drugs on HPV section indicate that there may be some impairment of the response but only at higher doses or with older agents. Furthermore, the numerous other factors that affect HPV will impact on its contribution during GA including changes in cardiac output, mixed venous oxygen, drugs taken for comorbidities or administered by the anesthesiologist, duration of the hypoxia, PCO2 levels, body temperature, and the patient’s iron status.

**Role in OLV**

**Hypoxemia during OLV.** One of the primary stimuli for research into HPV during anesthesia is the use of OLV for thoracic surgery. OLV is commonly performed to facilitate surgical access in the chest during lung, mediastinal, and intrathoracic esophageal surgery. The incidence of hypoxemia during OLV is currently reported to be in neighborhood of 5% of cases. There is no agreed standard for the definition of hypoxemia during OLV; however, an arterial oxygen saturation of less than 90% with an FIO2 of 1.0 is commonly accepted as a level at which some intervention by the attending anesthesiologist is required. It is generally thought that the incidence of hypoxemia during OLV is decreasing. Studies from the 1970s and before suggest that the incidence of hypoxemia during OLV was in the range of 25%. There is no clear single reason for this recent clinical improvement; however, several advances may combine to produce this improved outcome. First, improved methods of lung isolation with the routine use of fiber-optic bronchoscopes to position double-lumen endotracheal tubes and bronchial blockers may lead to better ventilation during OLV and decreased risk of lobar obstruction; second, a better understanding of the physiology of OLV; and finally, improved anesthetic agents and techniques that cause less inhibition of HPV during OLV. The high incidence of desaturation seen in studies of OLV from the 1970s may be due in part to the use of halothane as the sole drug for maintenance of anesthesia.

Theoretically, a patient with a 20% shunt through the nonventilated lung during stable OLV with an intravenous anesthetic could be expected to have a maximal increase of 4% in total shunt with the introduction of 1 MAC isoflurane. In practice, the increase in shunt may be less than this because during stable OLV, the volatile anesthetic agent is delivered to the pulmonary vascular site of HPV action in the lung by the mixed venous blood, not by the alveolus. Similar to the pattern of HPV triggering by low PO2, the effects of the volatile agent on HPV are much more potent when delivered by the alveolus than by the mixed venous blood.

As with other studies of HPV, extrapolating the results of research investigations to clinical anesthetic practice requires many assumptions. Research models have used a wide variety of species and anesthetic preparations such as hypoxic ventilation or lobar isolation that are dissimilar to standard clinical OLV, and this may explain the occasional contradictory findings in some studies. During OLV, the relative contributions of HPV and lung collapse to pulmonary blood flow diversion away from the nonventilated lung are unknown and may vary depending on the clinical context. One study of the infusion of the vasodilator nitroprusside during OLV to inhibit HPV showed no significant increase in shunt during nitroprusside infusion.

![Fig. 5.](https://pubs.asahq.org/anesthesiology/article-pdf/122/4/932/455287/20150400_0-00036.pdf)
This has led to some uncertainty of the importance of HPV during OLV. However, this study was performed in closed-chest patients and there was some decrease in mean \( \text{PaO}_2 \) levels (285 to 225 mmHg) and increase in shunt (29.0 to 32.8%) with nitroprusside although these changes did not achieve statistical significance in this small study (n = 7).

On the basis of the animal studies, the maximal HPV response during OLV is to decrease the lung blood flow by 50%. If the lung is then allowed to become atelectatic, the blood flow will decrease further to 12.5% of cardiac output.\(^9\) During clinical OLV, the venous admixture is usually in the region of 20 to 25% of total cardiac output. This means that a group of patients who will usually have a mean \( \text{PaO}_2 \) of approximately 400 mmHg during two-lung ventilation with an \( \text{FiO}_2 \) of 1.0 will have a mean \( \text{PaO}_2 \) in the 150 to 200 mmHg range during OLV.

Either atelectasis or HPV alone could explain a 50% decrease in blood flow to the nonventilated lung and it is impossible, in a realistic clinical model of OLV, to separate the mechanical effects of atelectasis on diversion of pulmonary blood flow from those of HPV. Lung volume has a large effect on PVR. PVR is lowest when the lung is at functional residual capacity and it increases in a parabolic manner as lung volume increases or decreases above or below functional residual capacity. However, it is likely that both HPV and atelectasis are important because of the airway pressure differential, which develops between the ventilated lung and the nonventilated lung during OLV. At the initiation of OLV, the sudden decrease in mean airway pressure in the nonventilated lung, compared with the ventilated lung, tends to preferentially redistribute pulmonary blood flow to the nonventilated lung, causing a transient decrease in the end-tidal carbon dioxide from the ventilated lung.\(^9\) This increased pulmonary blood flow in the nonventilated lung is then opposed by both HPV and lung collapse. After equilibration, the blood flow of the nonventilated lung decreases from a transiently increased level of somewhere greater than 50% of cardiac output but not to the level (12.5%) expected in a totally atelectatic lung. Because PVR is lowest when the lung is at functional residual capacity, it is important during OLV to manage the ventilated lung in a manner that keeps it as close to its functional residual capacity as possible. This will optimize the redistribution of pulmonary blood flow from the nonventilated to the ventilated lung and thus improve arterial oxygenation.\(^9\)

**Time Course of HPV during OLV.** Hypoxic pulmonary vasoconstriction was previously assumed to be a rapid-onset and rapid-offset reflex, but as described in the section Stimulus and Time Course of HPV, HPV is now accepted as being a biphasic response (fig. 1), with the initial response occurring within seconds. In clinical practice, if the ventilated lung does not develop atelectasis and cardiac output is maintained, the \( \text{PaO}_2 \) will usually reach its lowest level 20 to 30 min after the start of OLV and then gradually increase during the next 1 to 2 h. Of note, it has also been shown that once the slow phase of HPV has begun, the offset of HPV will also be delayed (fig. 1).\(^9\) In one animal study,\(^9\) it was demonstrated that after 90 min of OLV, blood flow to the previously collapsed lung had only returned to 92% of its initial baseline value 90 min after the resumption of two-lung ventilation, while ventilation had returned to 100% of its baseline value (fig. 6). This delayed offset of HPV explains, in part, the clinical observation that during repeated episodes of unilateral lung collapse and reexpansion, the HPV reflex appears to be augmented during the subsequent periods of OLV. Patients may desaturate less during a second or third period of OLV than during the initial trial of OLV because the blood flow in the temporarily reinflated lung has probably not returned to baseline before the subsequent hypoxic challenge. However, part of this resistance to desaturation during repeated periods of lung collapse may also be due to a preconditioning effect on the HPV reflex\(^8\) (fig. 2). Clinically, this is a useful aspect of the HPV reflex because patients who desaturate during an initial trial of OLV may tolerate a second or third trial of OLV after a recovery period of two-lung ventilation.

This delayed offset of HPV also has important implications for bilateral thoracic surgery procedures (e.g., bilateral wedge resections for pulmonary metastases or lung volume reduction procedures) involving sequential periods of alternating OLV. It is common during bilateral procedures to have more desaturation during OLV of the second lung. This may in part be due to surgical trauma of the first lung. However, it may also be that HPV of the lung which was collapsed first has not completely relaxed and is opposing pulmonary blood flow redistribution during the collapse of the second lung.

**Other Factors Affecting HPV during OLV.** Acid–base status is important during OLV because the pulmonary vasculature vasoconstrictrons in response to acidosis and dilates during alkalosis.\(^12\) It is unclear whether HPV is enhanced by acidosis (see Carbon Dioxide and pH) but allowing acidosis to develop...
during stable OLV is usually of no clinical benefit because both the pulmonary vascular beds of the ventilated and non-ventilated lung are constricted and there is no net redistribution of blood flow between the lungs. However, alkalosis during OLV should be avoided because the vasodilation in the nonventilated lung opposes HPV while the ventilated lung is usually already almost maximally vasodilated and there can be a net redistribution of blood flow to the nonventilated lung.

Hypoxic pulmonary vasoconstriction will tend to decrease if cardiac output increases and PAPs increase. Also, as cardiac output increases mixed venous oxygen saturation will usually increase and this will also diminish HPV. Although the shunt of mixed venous blood with a higher oxygen content will mitigate the decrease in arterial \( P_{O_2} \) from increasing cardiac output, the net effect of artificially increasing cardiac output above baseline with inotropes during OLV is usually to cause a decrease in \( P_{O_2} \) (fig. 7).\(^{100}\) Similarly, a decrease in cardiac output and a passive decrease in PAP will usually make HPV more efficient, decreasing shunt during HPV. However, the potential benefits are overshadowed by the concomitant decrease in the oxygen content of the mixed venous blood, and the net effect again is a decrease in \( P_{O_2} \) if cardiac output is decreased during OLV.\(^{101}\)

There are other factors that affect the redistribution of blood flow between the ventilated and nonventilated lung during OLV. One clinically important factor is patient position. Most lung surgery and OLV are performed in the lateral position, and gravity tends to increase the proportion of blood flow (approximately 10%) to the dependent (ventilated) lung.\(^{102}\) Patients tend to desaturate more when OLV is performed in the supine position (e.g., some bilateral procedures such as lung transplantation).\(^{103}\) However, HPV and lung collapse seem to be the two main determinants of pulmonary blood flow distribution during OLV.

### Effects of Epidural Analgesia on HPV

There has been some suggestion that neuraxial blockade with local anesthetics, specifically thoracic epidural analgesia, may decrease HPV and impair oxygenation during OLV.\(^{104}\) However, there is no good evidence that HPV is subject to any central neurogenic control. Other studies have failed to find a decrease in \( P_{O_2} \) during OLV with thoracic epidural anesthesia.\(^{105}\) Occasional reports of a decrease in \( P_{O_2} \) related to epidural analgesia during OLV are more likely due to a decrease in cardiac output and a decrease in mixed venous oxygen saturation from the vasodilation with epidural neuraxial blockade and not due to an effect on HPV.

### Relevance of HPV in Lung Disease

Patients with severe COPD have extreme heterogeneity of regional lung function. Although patients with severe COPD tend to have less of an HPV response than normal patients,\(^ {106}\) they are very dependent on HPV to maintain an adequate \( V/Q \) matching.\(^ {107}\) Whenever a high \( F_{I_{O_2}} \) is administered to these patients, HPV in poorly ventilated lung units will be decreased leading to an increase in venous admixture and a reciprocal increase in alveolar dead space in well-ventilated lung units.\(^ {108}\) The increase in shunt may not be clinically obvious because the increased \( F_{I_{O_2}} \) will prevent any desaturation. However, the increase in dead space may lead to an increase in arterial \( P_{C_{O_2}} \) if the awake patient is not able to compensate by increasing alveolar ventilation or the anesthesiologist cannot adequately increase ventilation during GA. This can particularly be a problem in the postanesthesia recovery room after GA in patients with severe COPD. Supplemental oxygen must be titrated carefully in these patients to avoid hypoxemia, at a time when hypoxemic ventilatory drive may be decreased by residual anesthetics. At the same time, it is necessary to avoid hypercapnia due to the effect of excess \( F_{I_{O_2}} \) on \( V/Q \) matching.

Patients with liver failure often have a relative hypoxemia, which has been called the hepatopulmonary syndrome. This is characterized by preserved pulmonary blood flow to atelectatic lung regions and a diminished HPV response. The exact etiology of this blunted HPV response is unclear but seems to involve, in part, an increase in pulmonary endothelial production of nitric oxide.\(^ {109}\)

### Conclusions

In clinical situations where HPV is an ally for the anesthesiologist such as during OLV, GA in patients with respiratory disease, and when treating ALI, clinicians should be aware of its physiology and the effects of drugs on the reflex. Further human studies are needed to clarify the role of HPV in many of the areas of clinical practice described in this review, but it is likely that maintaining body temperature, \( pH \), \( P_{C_{O_2}} \), and \( P_{O_2} \) close to normal values will enhance any contribution of HPV to oxygenation. In situations where effective HPV may be crucial, for example, OLV in patients with respiratory...
disease, avoidance of drugs that attenuate the response and the use of drugs that may enhance it, for example α agonists, can help to avoid dangerous hypoxia.

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Competing Interests
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