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Hypoxic pulmonary vasoconstriction

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Key points

- Hypoxic pulmonary vasoconstriction (HPV) helps to match regional perfusion to ventilation in the lungs.
- Physiological factors that influence HPV include pH, P_{CO_2}, temperature, age, and iron status.
- HPV increases pulmonary vascular resistance and pulmonary artery pressure, which can precipitate right heart failure.
- Inhaled anaesthetic agents inhibit HPV in a dose-dependent fashion, but at clinically relevant doses the currently used agents have a negligible effect.
- Managing acute severe pulmonary hypertension needs careful consideration to ventilation, fluid management, inotropes, and vasopressors.

Hypoxic pulmonary vasoconstriction (HPV) is a reflex contraction of vascular smooth muscle in the pulmonary circulation in response to a low regional partial pressure of oxygen. It is an important mechanism for matching of regional perfusion and ventilation in the lung. This article will summarize the physiology of HPV and discuss the relevance of the reflex to the clinical practice of anaesthesia and intensive care in adults.

Physiology

The systemic circulation dilates in the presence of hypoxia, in contrast to the pulmonary circulation, which vasoconstricts. This response of the pulmonary circulation is known as hypoxic pulmonary vasoconstriction and is a protective physiological reflex that aims to divert blood flow away from hypoxic areas of the lungs to areas with better ventilation and oxygenation. It is a mechanism to match regional ventilation and perfusion and thus acts as an important physiological process for maintaining oxygenation. The nature of the pulmonary circulation's low-resistance, low-pressure system means that HPV, by causing localized high resistance to blood flow, promotes diversion of flow to areas of lower resistance where the mechanisms of passive distension and recruitment of pulmonary capillaries lead to increased perfusion.

Ventilation–perfusion matching

Matching of alveolar ventilation and perfusion is a crucial determinant of gas exchange. In an ideal lung model, ventilation and perfusion would be distributed identically, with perfect matching. This is not the case *in vivo* as both ventilation and perfusion increase from non-dependent to dependent areas, with perfusion increasing to a greater extent. The ventilation to perfusion ratios ($\dot{V}/\dot{Q}$) therefore tend to differ slightly throughout different regions of lung (e.g. in the upright posture there is more perfusion and less ventilation at the bases, i.e. low $\dot{V}/\dot{Q}$ ratios; and more ventilation with less perfusion at the apices, i.e. high $\dot{V}/\dot{Q}$ ratios). The HPV reflex aims to improve matching of ventilation and perfusion, although its role is believed to be minimal in normal healthy lungs with already well-matched ventilation and perfusion.

In contrast, the role of HPV is much more significant in chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease. In these chronic respiratory conditions maintaining normal gas exchange is dependent on optimizing $\dot{V}/\dot{Q}$ matching, which is influenced by HPV. The heterogeneous nature of the lungs in

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these diseases means that a local regional response, such as with HPV, aids long-term adequate oxygenation. Inappropriate delivery of supplemental oxygen in these scenarios, in addition to some drugs, can attenuate HPV, worsen $\dot{V}/\dot{Q}$ matching, and lead to a deterioration in oxygenation. Unfortunately, chronic exposure of the pulmonary circulation to areas of high resistance also contributes to the development of irreversible pulmonary hypertension, right ventricular hypertrophy, and cor pulmonale.

HPV plays a role in acute respiratory pathology. Acute $\dot{V}/\dot{Q}$ mismatch is commonly the cause of hypoxia in acute respiratory diseases, such as acute asthma, pneumonia, pulmonary embolus, and pulmonary oedema. HPV is likely to offer a beneficial effect in these clinical settings by the redirection of pulmonary blood flow to areas of better ventilated lung, so improving the $\dot{V}/\dot{Q}$ matching.[1]

HPV mechanism

The stimulus for HPV is the tissue partial pressure of oxygen in the region of the pulmonary arteriole. This is determined by two factors, the partial pressures of oxygen in the alveolus (P_{AO_2}) and the mixed venous blood (P_{VO_2}),[2] and quantitatively is represented by the following equation, which was obtained from animal studies:

$$P_{\text{stimulus}}O_2 = PAO_2^{0.62} + P\bar{V}O_2^{0.38}$$

In most circumstances, even in areas of lung with low $\dot{V}/\dot{Q}$ ratios, P_{AO_2} will be higher than P_{VO_2} so this is the primary stimulus. However, in areas of non-ventilated lung the predominant stimulus will be P_{VO_2}. Thus the degree of HPV is also influenced by the determinants of mixed venous oxygen, which are cardiac output, oxygen delivery, and uptake, and therefore affected by conditions such as sepsis, cardiac failure, and anaemia.

The site of action for HPV is in pulmonary arterial smooth muscle cells (PASMCs). The mechanism involves three components: biological oxygen sensing, PASMC contraction, and modulation of these responses. Details of the biological oxygen sensing system in the pulmonary vasculature have not been fully elucidated. Several theories regarding potential oxygen sensing mechanisms are listed in Table 1. In practice these mechanisms are closely interlinked and it is likely that all are involved under various circumstances *in vivo*.

The mechanism by which PASMCs contract is membrane depolarization after sodium ion influx, leading to an increase in cytosolic calcium ion concentration. This causes an increase in calcium ions binding to calmodulin, activating myosin light chain kinase. The subsequent alteration in the shape of the myosin results in contraction of the smooth muscle.

This HPV mechanism is susceptible to modulation, a process by which HPV can be inhibited or enhanced. It can occur by direct physiological means, via local mediators, or by humoral mechanisms. Direct modulation can occur through changes in intracellular pH or temperature, and humoral modulation via angiotensin II in humans. While neural sympathetic innervation can precipitate some types of pulmonary oedema (e.g. neurogenic pulmonary oedema), neuronal modulation is not thought to be a major determinant of HPV. The predominant modulation is via localized mediators produced by pulmonary endothelial cells in the presence of hypoxia. Table 2 shows the three principal mediators, all of which have been used as therapeutic targets for drug treatment of pulmonary hypertension.

HPV in humans has two distinct temporal phases. Phase 1 begins within a few seconds and is maximal at 15 min, and most probably mediated by potassium channels. When moderate hypoxia is sustained for more than 30–60 min phase 2 begins, and a further increase in pulmonary vascular resistance is seen, reaching a peak at 2 h. This phase is most probably a result of increased release of endothelin. When normoxia returns it can take several hours for pulmonary vascular resistance to return to baseline.[3]

Table 1 Different theories for how oxygen sensing occurs in PASMCs to initiate HPV

Direct modulation of potassium channels
Changes to cytoplasmic redox state
Mitochondrial reactive oxygen species production
Cellular energy state (e.g. concentrations of high-energy compounds)
Alteration of membrane-bound protein function
Activation of transcription enzymes via hypoxia-inducible factor
Alteration of cyclo-oxygenase or lipoxygenase systems

Physiological factors influencing HPV

A series of physiological factors can influence the HPV mechanism, including extracellular pH and P_{CO_2}, temperature, age, and iron status. Hypercapnia increases pulmonary vascular resistance (PVR) and so increases pulmonary arterial pressure. HPV is potentiated by acidaemia independently of P_{CO_2}.[4] In contrast, alkalosis, both respiratory and metabolic, leads to attenuated HPV and decreased pulmonary vascular resistance. HPV is inhibited by hypothermia and potentiated by hyperthermia. Age has influence upon the HPV response. At birth the HPV mechanism is more pronounced and it is a key physiological process for the transition from a fetal to an adult circulation. The HPV response is intense in infants but this declines in the first few years of life.[5] The HPV response becomes highly significant in anaesthesia for paediatric congenital cardiac surgery when the balancing of pulmonary and systemic vascular resistances can be crucial.

An individual's iron status also affects HPV, with an iron deficiency causing an enhanced HPV response. This has been demonstrated with trials of supplemental i.v. infusions of iron and trials of inducing iron deficiency with venesection or iron chelators.[6] An appropriate iron status is therefore important in individuals with pulmonary hypertension and those exposed to prolonged hypoxia environments (e.g. at altitude). It is an area of ongoing research to develop the evidence base for the role for iron supplementation as a therapy for pulmonary hypertension.

Clinical implications of HPV

General anaesthesia

General anaesthesia is known to lead to atelectasis and altered ventilation and perfusion matching, with studies using the multiple inert gas elimination technique during general anaesthesia demonstrating an increase in areas of both high and low $\dot{V}/\dot{Q}$ ratios.[7] The supine position, changes in chest wall and diaphragm shape, altered regional lung compliance, and the distribution of positive pressure ventilation all contribute to this. Logically, this would suggest that HPV would be important for maintaining oxygenation during general anaesthesia but clinical studies to demonstrate this are lacking. Thus HPV seems

Table 2 Mediators produced by pulmonary endothelial cells and their mechanism for modulating HPV

Mediator	Mechanism
Nitric oxide	Although not fully understood, nitric oxide is continuously produced by pulmonary endothelial cells and maintains a constant state of pulmonary dilatation by reducing intracellular calcium, relaxing smooth muscle. Hypoxia reduces basal nitric oxide production and thus HPV is enhanced
Prostacyclin	Prostacyclin is a vasodilator that stimulates cyclic adenylate cyclase and increases cyclic adenine monophosphate production
Endothelin-1	Endothelin-1 is a small peptide paracrine mediator with potent vasoconstrictor properties. It acts via G-protein receptors on PASMCs

unlikely to be clinically significant for routine two-lung general anaesthesia, perhaps because routine use of increased $F_{I_{O_2}}$ prevents alveolar hypoxia in areas of low $\dot{V}/\dot{Q}$ ratio.

It is important to understand the impact of the drugs used in anaesthesia and how they may impact on HPV. All volatile anaesthetic agents inhibit HPV in a dose-dependent manner, with older agents such as halothane having a greater effect. Animal studies have failed show a detectable effect of one minimal alveolar concentration (MAC) of sevoflurane on HPV.[8] There does not seem to be significant difference between the modern volatile anaesthetics isoflurane, sevoflurane, and desflurane in their inhibition of HPV at equi-MAC doses.[9] The effect of nitrous oxide on HPV is not clear, but it has been demonstrated to increase PVR and should be used cautiously in patients with pulmonary hypertension.[10] Propofol does not inhibit HPV.[11] In human studies comparing propofol with sevoflurane- or isoflurane-based anaesthesia during one-lung ventilation (OLV), there is a paucity of evidence to show superiority of one approach over the other.

Considering the effects of pH, P_{CO_2}, and temperature on HPV, close control of these variables is important during general anaesthesia to maintain HPV. Using an unnecessarily high fractional inspired oxygen concentration during general anaesthesia may not only contribute to absorption atelectasis but in ventilated areas this will inhibit HPV and so potentially affect $\dot{V}/\dot{Q}$ matching.

One-lung ventilation

One-lung ventilation is indicated for thoracic surgical procedures, for prevention of cross-contamination of the lungs and to control the distribution of ventilation (e.g. in bronchopleural fistula). Patients who require OLV for thoracic surgery are placed in the lateral position. The lower, dependent lung is ventilated and the upper, non-dependent lung is allowed to collapse. As the lung collapses PVR will increase because of the low lung volume, and the alveoli will become hypoxic, activating HPV and so redirecting pulmonary blood flow away from the non-ventilated lung. This redistribution of blood flow improves $\dot{V}/\dot{Q}$ matching and so the patient's oxygenation. A failure of the lung to collapse or an ineffective HPV response can affect the $\dot{V}/\dot{Q}$ matching and oxygenation, and hypoxia remains a common occurrence during OLV. Insufflating oxygen to the non-ventilated lung is a rescue technique for this situation, and is usually effective even though it will abolish HPV in the ventilated lung regions. This presumably is because abolishing HPV in the ventilated regions is irrelevant as the blood flowing through these areas is being oxygenated. As described above, there is no clinical difference on HPV between modern inhaled anaesthesic agents and propofol target-controlled infusion during OLV. Thoracic epidurals have no effect on the HPV mechanism. Vasopressor drugs used during anaesthesia to treat systemic hypotension during OLV are unlikely to have a major influence on HPV, although α_1 agonists may enhance the response. Augmentation of cardiac output or pulmonary vascular pressure tends to improve pulmonary blood flow, which often improves oxygenation.[12]

Pulmonary hypertension

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (PAP) at rest >25 mm Hg. It is considered mild when mean PAP is between 25 and 40 mm Hg, moderate when mean PAP is between 41 and 55 mm Hg and severe if >55 mm Hg. Pulmonary hypertension can manifest acutely or chronically. Table 3 shows a classification and the major causes of PH.

Severe PH can occur acutely or be an acute on chronic manifestation in patients with established chronic PH. Acute PH can be present in critically ill patients and those who need major emergency surgery. The endotoxins released in sepsis are known to play a significant role in the development of acute PH. There is excessive release of inflammatory mediators that disturbs the balance between nitric oxide, endothelin, and prostanoids in the pulmonary vascular capillaries. Severe acute PH can lead to the life-threatening situation of refractory systemic arterial hypotension, severe hypoxaemia, right ventricular failure, and cardiogenic shock. Many instances of acute PH remain under-diagnosed and the management can be challenging. The choice of inotropes and vasopressors in patients with shock and severe PH should take into consideration their effect on HPV and PVR. A balance has to be struck to inhibit HPV, dilating the pulmonary artery, with the need to maintain systemic blood pressure to maintain coronary artery perfusion pressure. Some have advocated using vasopressin and norepinephrine with milrinone to achieve this.[14] Pulmonary vasodilators, such as nitric oxide, prostaglandins, and other phosphodiesterase (PDE) inhibitors, are other treatment options to consider for severe PH.

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is an acute diffuse, inflammatory lung injury leading to increased pulmonary vascular permeability, loss of aerated lung tissue, with hypoxaemia and bilateral radiographic opacities. It is associated with increased physiological dead space and decreased lung compliance. In ARDS, both HPV and pulmonary vascular damage can lead to pulmonary hypertension and right ventricular dysfunction. The impact of hypoxia, hypercapnia, lung volumes, PEEP, and atelectasis can all have physiological effects on activity of HPV. Extremes of lung volume and high plateau pressures should be avoided. PEEP can be used to recruit and ventilate areas of lung atelectasis to promote ventilation and perfusion matching. The cornerstone of ARDS management is the

Table 3 Classification and causes of pulmonary hypertension[13]

Classification	Examples
Pulmonary arterial hypertension (PAH)	• Idiopathic • Heritable • Drugs/toxins • Others: connective tissue disease, portal hypertension, congenital heart disease
Pulmonary hypertension attributable to left heart disease	• Left ventricular systolic/diastolic dysfunction • Valvular disease • Congenital heart disease
Pulmonary hypertension attributable to lung disease and/or hypoxia	• COPD • Interstitial lung disease • Sleep-disordered breathing • Chronic high altitude
Chronic thromboembolic pulmonary hypertension	• Chronic thromboembolism • Other pulmonary artery obstructions (e.g. angiosarcoma)
Pulmonary hypertension with unclear or multifactorial mechanisms	• Haematological (e.g. myeloproliferative disorders) • Systemic (e.g. sarcoidosis) • Metabolic disorders

optimization of ventilation along ARDS network protocols. Nitric oxide has consistently failed to show an improvement in mortality in ARDS patients and is now infrequently used. Attempts to manipulate HPV are challenging as pulmonary artery pressures are infrequently directly measured and echo measurements can be difficult and unreliable with high ventilatory pressures. Even so, it is important to remain aware of the strain on the right heart from the disease pathology, HPV, and the ventilation strategies normally applied.

Altitude sickness

Altitude sickness is a commonly used term for syndromes encountered at an altitude >2500 m, comprising acute mountain sickness (AMS), high-altitude cerebral oedema (HACE), and high-altitude pulmonary oedema (HAPE). The high-altitude environment causes hypobaric hypoxia. In this environment HPV is triggered in all lung regions, and the response can become exaggerated and pathological. In HAPE there is increased sympathetic tone and very active HPV, resulting in uneven pulmonary vasoconstriction, leading to over-perfusion of some regions of the pulmonary vascular bed. Increased pulmonary capillary pressure then leads to stress failure of pulmonary capillaries. The end result is a patchy accumulation of extravascular fluid in the alveolar spaces that impairs lung function and can, in severe instances, prove fatal. In people at altitude who are susceptible to HAPE, dexamethasone can reduce the HPV response and be used to prevent and treat HAPE. The calcium channel blocker nifedipine is another drug used to prevent and treat HAPE. However, the most effective and reliable treatment of established HAPE is immediate descent and adequate flow of supplemental oxygen accompanied by rest from strenuous physical activity.[15]

Drug effects on HPV

PDE inhibitors

The PDE 5 inhibitor group (e.g. sildenafil) is an established oral therapy for pulmonary hypertension. It inhibits HPV via impairing cGMP breakdown, potentiating nitric oxide and dilatation of PASMCs. The PDE 3 group of inhibitors (e.g. milrinone) increase cAMP and lead to augmented myocardial contractility with dilatation of the pulmonary vasculature. Nebulized milrinone has also been used for pulmonary hypertensive crisis.[16]

Inhaled nitric oxide

Inhaled nitric oxide is a potent pulmonary vasodilator with a short half-life owing to rapid inactivation by haemoglobin. This minimizes systemic vasodilatation, but necessitates continuous delivery into the inspired gases. Nitric oxide selectively reduces PVR and improves cardiac output in pulmonary arterial hypertension. The reduction in right ventricular afterload has not been clearly correlated with clinical outcome benefits. Similarly, no studies have conclusively demonstrated survival benefit in adults with ARDS.[17] It is used in paediatric intensive care units as a therapeutic option for treatment of respiratory failure with severe pulmonary hypertension in young children.

Prostacyclin

Prostacyclin analogues are potent systemic and pulmonary vasodilators that also have antiplatelet and antiproliferative effects. Examples of pharmacological agents include epopostenol, treprostinil, and iloprost. Delivery options include i.v. infusions and inhalation nebulizers. They reduce PVR and can be used in the treatment of patients with pulmonary hypertension with New York Heart Association (NYHA) functional class III or IV symptoms.

Catecholamines

The catecholamines with β-receptor effects (e.g. epinephrine, dopamine, and dobutamine), inhibit the HPV response at standard doses. Dobutamine can be used to augment right ventricular function and reduce PVR. It does also reduce systemic vascular resistance, leading to systemic hypotension, which is important to anticipate. Vasopressors with predominant α_1 actions, e.g. norepinephrine and phenylephrine, enhance HPV.[18] The potential adverse effects of norepinephrine on PVR are likely to occur at higher doses. Most evidence supporting this

comes from animal studies in models of pulmonary vascular dysfunction when norepinephrine exceeds 0.5μg/kg/min.[19]

Vasopressin

Arginine vasopressin (AVP) causes systemic vasoconstriction via the vasopressin V1 receptor. Experimental animal studies have revealed pulmonary vasodilator properties at low doses through an NO-dependent mechanism. This property is thought to manifest clinically as a reduction in the PVR/SVR ratio. Vasopressin has been used in patients during PH crisis. It has been used safely in sepsis, in addition to patients with acute PH and right ventricular failure with hypotension after cardiac surgery, and hypotension associated with chronic PH in several settings.[20]

Endothelin receptor antagonists

This class of drugs represents a significant therapeutic option for patients with pulmonary hypertension. These oral drugs competitively antagonize endothelin (ET) receptors, and examples include bosentan, sitaxsentan, ambrisentan, and macitentan. Bosentan specifically antagonizes the ET_A receptor whereas sitaxsentan antagonizes both ET_A and ET_B receptors. These drugs prevent endothelin receptor–induced pulmonary vasoconstriction, thus reducing vascular resistance. As well as being a pulmonary vasodilator, endothelin is also involved in vascular remodelling of pulmonary vessels with long-term hypoxia, and endothelin antagonism may also slow this process. The anaesthetist should aim to continue these drugs perioperatively.

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor that is commonly used for altitude acclimatization. Although the exact mechanism is unclear it is also believed to attenuate the HPV response at high doses.

Angiotensin converting enzyme inhibitors

These commonly used drugs are known to reduce the HPV response. Anaesthetists should be aware of this action as they are commonly prescribed for a multitude of conditions.

Conclusion

HPV is a reflex contraction of vascular smooth muscle in the pulmonary circulation in response to low regional partial pressure of oxygen. It is a protective physiological mechanism that diverts blood flow away from hypoxic areas of the lungs to areas with better oxygenation. It is a mechanism to match regional ventilation and perfusion and is important for maintaining oxygenation. The HPV mechanism is affected by a multitude of physiological and pharmacological influences, which are important for the anaesthetist to understand.

Clinical case report

A 40-yr-old female with a background of severe idiopathic pulmonary arterial hypertension presented with an acute abdomen, a computed tomography-proven bowel perforation, and needed general anaesthesia for an emergency laparotomy. She was known to have normal left ventricular function but moderate to severely impaired right ventricular function. At presentation she had sepsis and was hypotensive. The patient was optimized for theatre with i.v. fluids, insertion of a central line, urinary catheterization, and administration of antibiotics. Anaesthesia was induced, with invasive monitoring *in situ*. A cardiostable modified rapid sequence induction was performed. Maintenance of anaesthesia was with sevoflurane. Once hypovolaemia had been corrected, systemic hypotension was treated with norepinephrine, and early introduction of vasopressin. The patient was ventilated with a pragmatic strategy of ARDS network ventilation with 6 ml kg^{-1} tidal volume, controlled peak inspiratory pressure, and PEEP. The patient was transferred to intensive care after surgery. A transthoracic echocardiogram was performed on intensive care. This showed right heart failure, and milrinone was added. The patient's cardiovascular status was optimized with fluid, vasopressors, and inotropes. The patient's acid–base status began to improve. The next morning a sedation hold was performed followed by successful extubation.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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