Review

Physiology in medicine: importance of hypoxic pulmonary vasoconstriction in maintaining arterial oxygenation during acute respiratory failure

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Abstract

Hypoxic pulmonary vasoconstriction continues to attract interest more than half a century after its original report because of persistent mystery about its biochemical mechanism and its exact physiological function. Recent work suggests an important role for pulmonary arteriolar smooth muscle cell oxygen-sensitive voltage-dependent potassium channels. Inhibition of these channels by decreased PO_2 inhibits outward potassium current, causing membrane depolarization, and calcium entry through voltage-dependent calcium channels. Endothelium-derived vasoconstricting and vasodilating mediators modulate this intrinsic smooth muscle cell reactivity to hypoxia. However, refined modeling of hypoxic pulmonary vasoconstriction operating as a feedback mechanism in inhomogeneous lungs, using more realistic stimulus–response curves and confronted with direct measurements of regional blood flow distribution, shows a more effective than previously assessed ability of this remarkable intrapulmonary reflex to improve gas exchange and arterial oxygenation. Further studies could show clinical benefit of pharmacological manipulation of hypoxic pulmonary vasoconstriction, in circumstances of life-threatening hypoxemia.

Keywords: acute respiratory failure, feedback, hypoxia, hypoxic pulmonary vasoconstriction, vascular smooth muscle cells

What is hypoxic pulmonary vasoconstriction?

Pulmonary hypertension as a result of asphyxia has been observed since the beginning of this century, but the first convincing evidence of hypoxic pulmonary vasoconstriction (HPV) together with a still valid functional interpretation was reported by von Euler and Liljestrand in 1946 [1]. These authors ventilated anesthetized cats with either hypoxic (fraction of inspired O_2 [FIO_2], 0.1) or hypercapnic (fraction of inspired CO_2, up to 19.6%) gas mixtures, and found that both interventions increased pulmonary artery pressure (Ppa) without change in left atrial pressure. Hypoxia increased Ppa proportionally more than hypercapnia in these experiments. Pulmonary blood flow ($\dot{Q}$) was not measured, and the possible explanation that at least part of the changes in Ppa could have been caused by hypoxia-induced or hypercapnia-induced increases in cardiac output was not taken into consideration. In the discussion of their results, the authors noted that "… oxygen

ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; FIO_2 = fraction of inspired O_2; Gfb = gain due to feedback; HPV = hypoxic pulmonary vasoconstriction; NO = nitric oxide; PAO_2 = alveolar PO_2; Ppa = pulmonary artery pressure; PVR = pulmonary vascular resistance; VA = alveolar ventilation.

want and carbon dioxide accumulation have exactly the reverse effects on the systemic and pulmonary circulations respectively; in both cases, however, they seem to be adapted for their special purposes. They cause a dilatation of the vessels in the working organs which need a greater blood supply than during rest, but they call for a contraction of the lung vessels, thereby increasing the blood flow to better aerated lung areas, which leads to improved conditions for the utilization of alveolar air" [1].

According to this view, in lung parenchyma, local PO_2 is determined by a ratio between oxygen delivery to the lungs, or alveolar ventilation (VA), and oxygen delivery from the lungs to the systemic tissues, or perfusion (Q):

$$PO_2 = VA/Q$$

In systemic tissues, however, local PO_2 is determined by a ratio between oxygen delivery to the tissues, or perfusion (Q), and local oxygen consumption (VO_2):

$$PO_2 = Q/VO_2$$

It has now been better appreciated that alveolar hypoxia indeed increases the gradient between Ppa and left atrial pressure independently of associated changes in cardiac output, thus increasing pulmonary vascular resistance (PVR), but that CO_2 has two opposing actions on pulmonary vascular tone. These actions are a direct relaxing effect and a constricting effect mediated by a decrease in pH [2].

Fifty years after the initial report of von Euler and Liljestrand, the basic attributes of HPV can be summarized as follows [3–5]. HPV occurs within seconds of the onset of alveolar hypoxia. HPV can be observed in isolated perfused lungs, pulmonary artery rings denuded of endothelium, and in single pulmonary artery smooth muscle cells. HPV seems to decrease with age, and exhibits marked interspecies and interindividual differences. The magnitude of HPV *in vivo* is inversely proportional to lung segment size. The main determinant of HPV is alveolar PO_2 (PAO_2), but mixed venous PO_2 contributes to approximately one fifth of the response. HPV is inhibited by a variety of mediators present in the blood or released from lung parenchyma, such as substance P, calcitonine gene-related peptide, and atrial natriuretic peptides, by endothelium-derived vasodilators such as prostacyclin and nitric oxide (NO), by α-adrenergic blockade, by β-adrenergic stimulation, by increased left atrial pressure, by increased alveolar pressure, by alkalosis, and by peripheral chemoreceptor stimulation. HPV is enhanced by acidosis, by $\alpha\beta$-adrenergic blockade, by epidural blockade, by low-dose serotonin, and by the inhibition of cyclooxygenase (aspirin, indomethacin) or NO synthase (L-arginine analogs). These latter two effects indicate that HPV is attenuated acutely by endogenous NO and prostacyclin. HPV can be inhibited by a series of vasodilating drugs including calcium channel blockers and halogenated anesthetics, and can be enhanced by the peripheral chemoreceptor stimulant almitrine and the appetite suppressant fenfluramines.

Hypoxic vasoconstriction mainly occurs in small precapillary arterioles [3–5] but small pulmonary veins also constrict in response to hypoxia, although not to more than 20% of the total change in PVR [6]. An exaggerated hypoxic pulmonary venoconstriction could explain certain forms of pulmonary edema, such as high altitude pulmonary edema, which is initially caused by an increase in pulmonary capillary pressure [7].

The cellular mechanism of HPV

Numerous studies have been devoted to the mechanism responsible for relating pulmonary vascular tone to changes in PO_2. A series of vasoconstrictors including histamine, serotonin, angiotensin, prostaglandins, and leukotrienes have been excluded as potential mediators. The hypothesis that hypoxia initiates pulmonary vasoconstriction by a reduction of high-energy phosphates has not been confirmed. Other hypotheses, including cytochrome P450 as a sensor of the decrease in PO_2 triggering pulmonary vasoconstriction, or HPV as a result of the inhibition of endogenous vasodilator mediators such as NO, have also not been confirmed [5].

It has recently been shown that pulmonary vascular smooth muscle cells and type I cells of the carotid body share the ability to sense changes in PO_2. Hypoxia has been demonstrated in both cells to inhibit outward potassium current, causing membrane depolarization and calcium entry through the voltage-dependent calcium channels [5]. There is evidence in both cells to suggest that changes in the redox status of the oxygen-sensitive potassium channels may control the current flow, so that the channel is open when oxidized and closed when reduced [5]. Two such oxygen-sensitive potassium channels, $Kv_{2.1}$ and $Kv_{1.5}$, have been identified in rat pulmonary arteries [8]. In systemic arteries, hypoxia causes an inward current through ATP-dependent potassium channels and vasodilatation. Profound hypoxia also dilates pulmonary arteries by the same mechanism.

Stimulus–response curves for HPV

The relationship between FIO_2 or PAO_2 and HPV, expressed as a change in Ppa at a given flow or as an amount of flow diversion at a given Ppa, has been generally found in experimental animal preparations to be either sigmoid [9] or linear [10] in shape, with a continued constriction as long as FiO_2 or PAO_2 was decreased. However, in isolated *in vivo* pig lungs at constant flow, in which particular attention was paid to reaching a steady state before each measurement, the Ppa–PAO_2 curve

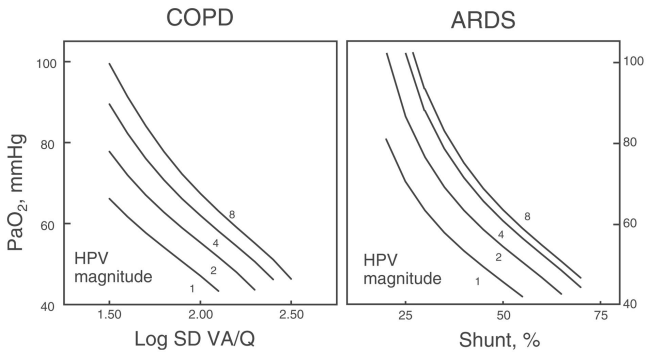
was shown to be biphasic, with a maximum at PAO_2 between 30 and 60 Torr, and a down sloping portion, or hypoxic pulmonary vasodilation, at lower PAO_2 [11]. In dogs, a species with a pulmonary vasoreactivity to hypoxia comparable with that of man [4], the relationship between FIO_2 progressively decreased from 1 to 0.06, and Ppa measured at a constant *Q* has also been shown to be biphasic, with a down sloping portion at a FIO_2 lower than 0.1, corresponding to a PaO_2 of 36–38 Torr [12]. Evidence of hypoxic pulmonary vasodilation in man was obtained during Operation Everest II [13], in which normal subjects were decompressed in a hypobaric chamber for 40 days to an atmospheric pressure (Pb) equivalent to the summit of Mount Everest. The subjects presented an average Ppa of 34 mmHg at rest and of 54 mmHg at exercise at a Pb of 282 Torr (7620 m; resting PaO_2, 37 Torr), that decreased to 33 and 48 mmHg, respectively, at a Pb of 240 Torr (8840 m; resting PaO_2, 30 Torr) [13].

The efficiency of HPV

Grant *et al* [10] used the equations of control theory and the linear relationships between lobar blood flow and PAO_2 found in the Coatimundi, an animal with a strong hypoxic pressor response, to calculate the efficiency of HPV as a mechanism to stabilize PAO_2. They found a gain due to feedback (Gfb) of a maximum of 0.9 at a PAO_2 between 60 and 80 Torr, rapidly falling off outside these values. A Gfb of 0.9 represents an active correction of 47% of the decrease in PAO_2 that would occur in a passive system without HPV. Mélot *et al* [14] used the same equations and linear relationships between compartmental blood flow and PAO_2 derived from inert gas elimination data obtained in healthy volunteers, and found a maximum Gfb of 0.63 at a PAO_2 of 60 Torr, also rapidly falling off at lower and at higher PAO_2. A Gfb of 0.63 represents an active correction by 39% of a decrease in PAO_2 that would occur in a passive system without HPV. These studies suggested that the hypoxic pressor response is only a moderately efficient feedback mechanism, acting essentially at PAO_2 values higher than known to occur in severe lung diseases. The studies even supported the speculation that HPV would be merely some fetal remnant and not useful in extra-uterine life. However, more recent evaluations of the efficiency of hypoxic pressor response using a multicompartment lung model [15] fed by real data biphasic stimulus–response curves [16] have led to the conclusions that HPV is really effective in improving gas exchange in severe respiratory insufficiency.

A quantification of the efficiency of HPV in terms of correction of arterial hypoxemia in either decompensated chronic obstructive pulmonary disease (COPD) or acute respiratory distress syndrome (ARDS) is presented in Figure 1. Patients with COPD are hypoxemic because of increased dispersion of the distributions of perfusion and ventilation, with increased perfusion to lung units with a lower than normal VA/*Q* value [17,18]. Altered pulmonary gas exchange in these patients can thus be quantified by the logarithm of the standard deviation of VA/*Q* dispersion, whereas the strength of HPV can be expressed as Ppa in hypoxia divided by Ppa in hyperoxia at constant flow [16]. The magnitude of HPV ranges normally from 1 to 4 in the canine and in the human species. It can be seen that, in COPD, PaO_2 may increase by up to 20 mmHg through the effects of vigorous HPV. This is indeed the range of PaO_2 observed in these patients from enhanced HPV by almitrine [17] to inhibited HPV by nifedipine [18].

Figure 1



Effects of HPV in COPD, a lung disease characterized by VA/*Q* mismatching, and in ARDS, a disease characterized by an increased shunt. LogSD VA/*Q*, logarithmic standard deviation of lognormal VA/*Q* distribution. FIO_2 was set at 0.3 in COPD and 0.4 in ARDS. (Reproduced with permission from [16].)

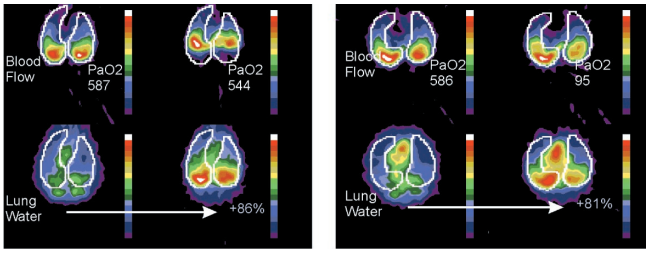
Patients with ARDS are hypoxemic mainly because of an increased shunt [19,20]. Altered gas exchange in these patients can thus be quantified by intrapulmonary shunt, expressed in percent of cardiac output. Figure 1 shows that, in ARDS, PaO_2 may increase by as much as 20 mmHg owing to vigorous HPV. This is in keeping with the magnitude of decreases in arterial oxygenation observed in patients with ARDS due to inhibition of HPV by diltiazem [19] or prostaglandin E_1 [20].

Recent positron emission tomography can studies in experimental oleic acid lung injury clearly show an increased perfusion in the most dependent lung regions, together with an important decrease in PaO_2 when HPV is ablated by a minute amount of endotoxin [21]. The results of a typical experiment are shown in Figure 2. The deterioration in PaO_2 by the inhibition of HPV in this experimental ARDS model conforms to multicompartment lung HPV model predictions [22].

HPV in acute lung injury

HPV has been reported inhibited in some models of acute lung injury. As already mentioned, HPV is preserved in

Figure 2



Positron emission tomography measurements of regional blood flow and lung water in a supine dog ventilated with pure oxygen, before and after induction of oleic acid lung injury, with intact (left) or ablated (right) hypoxic pulmonary vasoconstriction. Lung injury is associated with a significant increase in lung water. Pulmonary blood flow is redistributed upwards by hypoxic pulmonary vasoconstriction, and this is associated with preserved arterial PO_2. (Reproduced with permission from [21].)

oleic acid lung injury but can be ablated by minute amounts of endotoxin. That HPV is still operative in most patients with ARDS is indicated by the clinical observation of acute pulmonary hypertension at accidental interruption of artificial ventilation, and by the hypoxemic effects of intravenously administered vasodilator drugs that inhibit HPV [19,20]. The persistence of active pulmonary vascular tone is also shown by the effects of inhaled vasodilators such as NO [23] or prostacyclin [24], which increase PaO_2 because of an improved VA/Q matching by a redistribution of perfusion to the lung regions with the highest VA/Q value. These observations have led to attempts of correction of hypoxemia in patients with ARDS by a combination of inhaled vasodilators to vasodilate the most healthy lung regions, and by intravenous constrictors to vasoconstrict the most diseased lung regions [25,26]. However, until now there has been no demonstration of clinical benefit of improved gas exchange by pharmacological manipulation of HPV. This is probably due to the fact that an increase in arterial oxygenation by pharmacological enhancement of HPV would be of clinical relevance only in situations of life-threatening hypoxemia. Most patients with ARDS do not die from asphyxia, but from multiple organ failure.

Effects of anesthesia

Spinal anesthesia has been shown to enhance HPV [27], but the clinical relevance of this observation is uncertain. Intravenous anesthetics have generally been found to be without any effect on HPV [28]. Inhaled anesthetics have been reported to inhibit HPV in a variety of *in vitro* experimental preparations [28]. For example, in isolated rat lungs *in vitro*, halothane, enflurane, and isoflurane inhibit the hypoxic pressor response to the same extent at identical concentrations expressed as minimal alveolar concentrations units, with a 50% effective dose of approximately 0.6 [29]. In more intact animal preparations and in patients, however, higher concentrations than minimal alveolar concentration 1 are needed to inhibit HPV [30].

Conclusions

Pharmacological manipulations of HPV are feasible, and are associated with important changes in pulmonary gas exchange and in arterial oxygenation. The clinical relevance of this fascinating physiological phenomenon remains to be properly assessed.

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