Hypoxic pulmonary vasoconstriction: clinical implications

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HPV is an adaptation for fetal development and affords some advantage in optimising gas exchange in adults http://ow.ly/Uh54o

Hypoxic pulmonary vasoconstriction (HPV) and its mechanism of action continue to be of great interest to clinicians and physiologists. Sommer *et al.* [1] have reviewed HPV in this issue of the *European Respiratory Journal*. The literature is so extensive that another recent comprehensive review contained 2229 references [2].

Fetal origin of HPV

HPV originates in the fetus [3]. Vasomotor tone can be detected in the human fetal pulmonary circulation in the last trimester of pregnancy [4]. HPV contributes significantly to the high pulmonary vascular resistance (PVR) in the fetus (only 10–15% of right ventricular outflow goes to the lungs) [5], mainly because pulmonary artery and alveolar fluid oxygen tension (P_{O_2}) levels are considerably lower (18 mmHg) than they are after birth; also, the fetal pulmonary arteries are more muscularised (this regresses in the neonatal period). The low P_{O_2} in the fetal pulmonary artery, *versus* that in the fetal aorta, is due to "streaming" in the right ventricle, whereby oxygen-poor blood from the tissues enters *via* the superior vena cava and is directed to the pulmonary circulation; oxygen-enriched blood (*via* the placental vein) enters from the inferior vena cava and passes into the left ventricle *via* the foramen ovale.

At birth, the lungs expand with air from the first breath, alveolar liquid is reabsorbed, the alveolar P_{O_2} (P_{AO_2}) increases dramatically, which reduces HPV, and vasodilators such as nitric oxide and prostacyclin (also called prostaglandin I_2 (PGI_2)) are synthesised and released [5]. All these factors combine to reduce PVR five-fold (for a review, see Gao and Raj [3]). Pulmonary artery pressure falls from about 50 to 20 mmHg and pulmonary blood flow increases three-fold. This remarkable transition at birth is, in large part, due to the inhibition of HPV. HPV clearly has a role to play in the latter third of fetal development in helping to adjust the distribution of the combined ventricular outputs in the most favourable manner for organ growth and development. HPV occurs in almost all vertebrates [1]. How useful or otherwise is its persistence into post-natal life?

HPV in the normal post-natal lung

In adult mammals, the pulmonary arteriolar (pre-acinar) vessels constrict when local P_{AO_2} is reduced, and dilate when it increases. This occurs over a wide P_{AO_2} range, from 40 to 150 mmHg [6, 7]. The response is attenuated by local hypocapnia [8] or a rise in pulmonary artery pressure [9], and is augmented by a rise in local carbon dioxide tension (P_{CO_2}) [8]. In experimental models (dog [10] or sheep [8]), inspired P_{O_2} was lowered in one or more lobes and blood flow diversion measured. With a calculated reduction in alveolar ventilation (V'_A) of 70%, affecting 10–20% of total lung units, HPV reduced local blood flow by 45–50% [8, 10]. If 50% of the lung was "hypoxic", the reduction was 30% [8], presumably because of the attenuating

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effect of a rise in pulmonary artery pressure [9]. Studies at a sublobar level were not possible because of intralobar collateral ventilation. The coatimundi (*Nasua nasua*) lung lacks collateral ventilation and GRANT *et al.* [7] were able to catheterise lobules of <1% overall lung volume. They showed, for example, that a reduction in local P_{AO_2} from 13 to 10.7 kPa (from 98 to 80 mmHg), caused by a reduction in V'_A of ~70%, was accompanied by a 60% reduction in lobule blood flow. Had there been no HPV, local P_{AO_2} would have fallen to 8.7 kPa (65 mmHg). Thus, half the expected fall in P_{AO_2} (98 to 80 mmHg *versus* 98 to 65 mmHg) and arterial oxygen saturation (S_{aO_2}) (97% to 94% *versus* 97% to 91%) was prevented by HPV.

The effectiveness of HPV is greatest at moderately reduced ventilation/perfusion (V'_A/Q') ratios of approximately 0.5 (P_{AO_2} ~10 kPa (75 mmHg)), being dependent on the reactivity of the pulmonary resistance vessels and the instantaneous slope of the oxygen dissociation curve (the tangent to the curve at a specific P_{O_2}) [11]. The vasoconstrictor effect is not uniform, peaking at an effective "tissue" P_{O_2} of 9.33 kPa (70 mmHg) (about halfway between the mixed venous P_{O_2} and arterial P_{O_2} (P_{aO_2})), and becoming less strong at lower "tissue" P_{O_2} levels [12]. This relative "hypoxic vasodilatation" is the reason why, in model experiments simulating widespread V'_A/Q' dispersion and hypoxaemia, the presence of local HPV can lead to a deterioration in P_{aO_2}, with blood flow being diverted from the maximally constricted but comparatively well-oxygenated units (V'_A/Q' ~0.5) to less constricted but more poorly oxygenated units (V'_A/Q' <0.2) [11, 12]; this supposition has not been investigated clinically.

Studies of HPV in normal subjects and patients with respiratory disease

MORRELL *et al.* [13] occluded a lobar bronchus during fibreoptic bronchoscopy in normal subjects. Distal to the occlusion, P_{AO_2} and alveolar P_{CO_2} rapidly approached mixed venous levels during the 80–300 s of occlusion; lobar blood flow fell by 50%, which is consistent with animal studies [7, 8, 14]. Clinical studies in, for example, asthma and chronic obstructive pulmonary disease (COPD) patients cannot be as invasive or as controlled as in the HPV assessments already described. The interventions, at the level of the whole lung, have been either 100% oxygen breathing (to reverse HPV) *versus* air breathing, or the administration of other HPV inhibitors such as the vasodilators prostacyclin, nifedipine or sildenafil, or inhaled nitric oxide. The before and after output parameters are either a 50-compartment distribution of ventilation and blood flow *versus* V'_A/Q' ratios (the multiple inert gas elimination technique (MIGET)) in the case of 100% oxygen studies or P_{aO_2} for vasodilator interventions. A comprehensive account of HPV-related clinical studies in asthma, COPD, acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and other respiratory diseases is given in the review by SYLVESTER *et al.* [2]. Inhibition of HPV by 100% oxygen breathing or by the administration of vasodilators usually causes some deterioration in V'_A/Q' distribution and in P_{aO_2}; nevertheless, not all the changes may be specific or due to inhibition of HPV, especially if mixed venous P_{O_2} changes, and there has been no clinical quantification of the benefits gained from the presence of HPV. The diffuse nature of respiratory disease makes an accurate assessment of gain from HPV more difficult. An example of the complexity of interpretation is given in the study of BALLESTER *et al.* [15]. In patients hospitalised after an acute asthmatic attack, gas exchange measurements were made before and after 100% oxygen breathing or intravenous infusion of the β_2-agonist salbutamol (a vasodilator that inhibits HPV, as well as bronchodilator). Both interventions caused a deterioration in MIGET-measured V'_A/Q' matching, consistent with HPV inhibition. However, there was no deterioration in P_{aO_2} following *i.v.* salbutamol because other effects (increased cardiac output and oxygen consumption) acted against HPV.

Advantage or disadvantage?

The downside of HPV is its role in high-altitude pulmonary hypertension (HAPH) and high-altitude pulmonary oedema (HAPE), and its contribution to the pulmonary hypertension in COPD and other chronic lung diseases, including obstructive sleep apnoea [2].

HAPE occurs in susceptible subjects within 2–4 days of arrival at high altitude. HPV is the causal factor since the oedema and pulmonary hypertension usually resolve with treatments that inhibit HPV, such as descent to lower altitude, supplemental oxygen to breathe, and vasodilators (inhaled nitric oxide, nifedipine and sildenafil). The pathogenesis of the oedema in HAPE is incompletely understood. Although HPV-induced arteriolar constriction should protect the capillary bed from the high pressures associated with HAPH and from filtration into the interstitial and alveolar spaces, it is thought that HPV must be uneven in its effect [16]. The argument is that the more constricted vessels divert flow to the less constricted ones, where over-perfusion leads to capillary pressures greater than the filtration threshold. There is also evidence that the over-perfused capillaries are "leaky" [17], possibly because of stress failure at high transmural pressures [18]. Just as HAPE resolves rapidly when P_{AO_2} is increased, so endothelial and epithelial disruptions "close" soon after the high pressure stress ceases [18].

In more prolonged residence at high altitude, in susceptible populations living at altitudes >2000 m, HPV may be the initiator leading to the chronic pulmonary hypertensive state (HAPH) [2]. HPV is not the only

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factor, since HAPH only partially resolves when supplemental oxygen or vasodilators are given. The pulmonary arteries and arterioles remodel in response to increased pulmonary artery pressure with muscle hypertrophy and hyperplasia, which may narrow the vascular lumen.

Biological significance of HPV

The widespread occurrence of HPV throughout the animal kingdom [1] suggests an evolutionary advantage, occurring in the later stages of fetal development *in utero*. HPV is switched off at birth, but responds in adult life to external (high-altitude) or internal (local hypoventilation) hypoxia. The disadvantage of HPV in those who live, work and perform athletic training at altitude is the extra load incurred by the right ventricle [19] from the pulmonary hypertension induced by exercise in hypoxia [20]. There is considerable interest currently in how populations that have lived at altitudes >4300 m, either in the Tibetan or the Andean (Quechua and Aymara residents) plateaus have adapted with success to chronic hypoxia. There are many physiological adaptations (erythropoiesis, ventilatory drive and angiogenesis, and notably an increased transfer factor for carbon monoxide and nitric oxide [21]) all linked to the hypoxia-inducible factor (HIF) family of genes and to cellular hypoxia (see [22] for an overview).

In the context of HPV, those of Tibetan ancestry have a diminished pulmonary hypertensive response to hypoxia compared with a group of Han Chinese, their closest ethnic group [23]. A blunted pulmonary vascular response in Tibetans (and Sherpas) has also been found in exercise studies at altitude [24] and in comparison with acclimatised lowlanders and Quechuas from the Andes [21]. In peripheral blood lymphocytes in Tibetans, the expression and hypoxic induction of HIF-regulated genes was lower than in the Han Chinese [23]. Thus, Tibetans who have lived at altitude for >25 000 years (>1000 generations) may express genes in adult life, but presumably not in fetal life, which suppress HPV and contribute a survival advantage.

In diffuse lung disease (asthma, COPD, ALI/ARDS), there is suggestive evidence, even if indirect, of a benefit to gas exchange efficiency from the presence of HPV, but measurements of how much benefit are lacking, except in modelling simulations [12]. Studies using control theory [11, 12] predict that HPV is most effective at the relatively moderately reduced V'_A/Q' ratio of 0.5 rather than at V'_A/Q' ratios of <0.1, which contribute most to arterial hypoxaemia; therefore, a large effect of HPV on P_{aO_2} is unlikely.

Summary

HPV is an adaptation for fetal development that persists into adult life, where it affords some advantage in optimising gas exchange to those living at sea level and up to moderate altitude (~2000 m), but HPV must be a disadvantage to those living at or going to altitudes of ⩾3000 m, unless they have acquired genetic mutations to suppress it.

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