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Forum Review

Clinical Perspective of Hypoxia-Mediated Pulmonary Hypertension

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ABSTRACT

Pulmonary hypertension is a condition associated with a variety of pulmonary disorders whose common denominator is alveolar hypoxia. Such disorders include chronic obstructive pulmonary disease, pulmonary fibrosis, sleep-disordered breathing, and exposure to high altitude. Acute hypoxia is characterized by vasoconstriction of small pulmonary arteries, a phenomenon called hypoxic pulmonary vasoconstriction. With prolonged hypoxia, thickening of the smooth vascular layer of the small pulmonary arteries occurs, a phenomenon described as pulmonary vascular remodeling. Although the core mechanisms of both vasoconstriction and remodeling are thought to reside in the smooth muscle cell layer, the endothelium modulates these two processes. The purpose of this review is briefly to (a) discuss the mechanisms of hypoxic pulmonary hypertension as it pertains to certain disease states, and (b) examine the pathways that have potential therapeutic applications for this condition. *Antioxid. Redox Signal*. 8, 711–721.

Pulmonary hypertension is defined as a mean pulmonary arterial (PA) pressure exceeding 25 mm Hg at rest or 30 mm Hg with exercise. Elevations in mean PA pressure to 26–35 mm Hg are considered mild, those to 36–45 mm Hg, moderate, and those >45 mm Hg, severe (1, 2). Hypoxic pulmonary hypertension has been a long-recognized entity that negatively affects morbidity and mortality, irrespective of associated conditions. The hallmark of acute hypoxia is vasoconstriction of the muscular pulmonary arteries that results in an acute elevation in PA pressure and pulmonary vascular resistance (94). Chronic hypoxia, persistent or intermittent, produces remodeling of the pulmonary circulation and leads to development of chronic pulmonary hypertension (Fig. 1) (55). When hypoxic conditions resolve, pulmonary hypertension tends to regress. Conversely, when hypoxia is due to permanent destruction of lung parenchyma and pulmonary vasculature (as in chronic lung disease), pulmonary hypertension is far less likely to resolve, even with oxygen supplementation (Fig. 1) (48, 91). In the face of long-standing pulmonary hypertension and increased pulmonary vascular resistance, the right ventricle adapts by becoming chronically hypertrophied, and later, dilated (28). Cardiac output, which initially is preserved, declines, and death is usually due to right heart failure.

PHYSIOLOGIC RESPONSES TO HYPOXIA

Acute hypoxia

Alveolar hypoxia is a potent stimulus that affects the lungs in a unique way. Pulmonary arteries that are adjacent to the hypoxic alveoli undergo vasoconstriction (Fig. 2). The mechanism is known as hypoxic pulmonary vasoconstriction (HPV). As a result, blood is redistributed to optimally ventilated lung segments, in an attempt to improve ventilation/perfusion (V/Q) mismatch and subsequently arterial hypoxia. Sites of HPV are small muscular (resistance) pulmonary arterioles <200 μm in diameter (46) and veins of <900 μm (97), the veins accounting for 20% of the total pulmonary vascular resistance. Large-conduit pulmonary arteries do not constrict to hypoxia. HPV has its onset within seconds of

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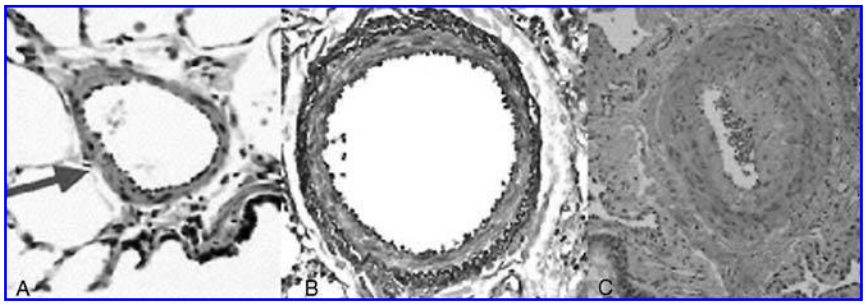

FIG. 1. Pathologic changes with hypoxia. (**A**) Normal alveolus. (**B**) Remodeling of pulmonary artery after 2 weeks of hypoxia. Note the thickening of the smooth muscle cell layer. (**C**) Remodeling of pulmonary artery in chronic lung disorders associated with hypoxia. Note the endothelial layer and adventitial thickening in addition to changes in the smooth muscle cell layer.

alveolar hypoxia and reverses promptly when normoxia is restored. The vasoconstrictor response to hypoxia is particular to the lung, because in both in humans and animals, hypoxia dilates most systemic arteries (56).

HPV in animal models

Since 1946, when the first model of hypoxia-induced pulmonary hypertension was described in cats (96), a plethora of studies has been performed by using various animals such as rats, mice, dogs, cattle, and humans. HPV has been demonstrated in intact animals, perfused lungs, and pulmonary arterial rings. The vasoconstrictor response is prompt (within seconds) and maximal. Repeated hypoxic exposures do not increase nor decrease the magnitude of vasoconstriction. On restoration of normoxia, pulmonary vascular resistance rapidly returns to normal.

The first conclusion one can draw from animal studies is that interspecies variability exists in the magnitude of HPV. Cattle are the most susceptible to hypoxia, whereas the rabbit has almost no reaction to hypoxia. Similarly, human response to hypoxia is heterogeneous. Although in most races, HPV develops in response to acute hypoxia, and pulmonary hypertension, to chronic hypoxia, Tibetans have little or no response to either acute or chronic hypoxia. The variation in HPV intensity between and within species has important effects on adaptation to high altitude. These differences have long been known, based on the work of high-altitude physiologists on species adapted to high altitude (69). Prolonged hypoxia ultimately results not only in occurrence of pulmonary hypertension, but also in selective blunting of HPV (93).

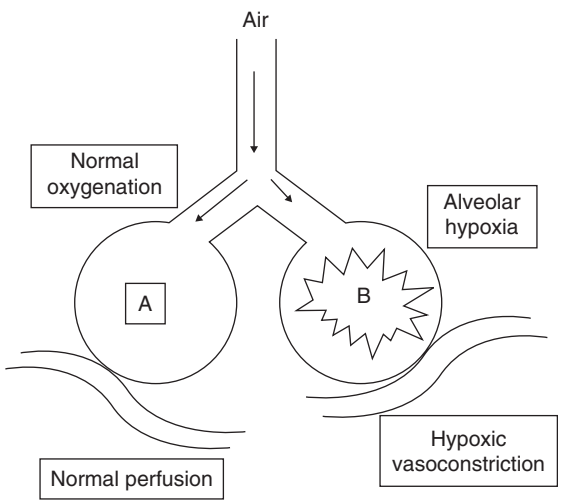

FIG. 2. Schematic of the mechanism of hypoxic pulmonary vasoconstriction. (**A**) Normal alveolus. (**B**) Alveolar hypoxia; the pulmonary artery adjacent to the hypoxic alveolus is constricted, in an attempt to divert the blood to better-ventilated areas (**A**) and to improve V/Q matching.

Chronic hypoxia

With prolonged exposure to hypoxia, pulmonary muscular arteries and arterioles undergo a process of vascular remodeling, characterized by hypertrophy of the muscular layer. This in turn leads to a persistently elevated pulmonary vascular resistance and an increase in right ventricular workload with subsequent right ventricular hypertrophy. Interestingly, unlike other forms of pulmonary arterial hypertension (*i.e.*, idiopathic), endothelial cell hypertrophy is absent, suggesting that the primary mechanism in hypoxic pulmonary hypertension is in the smooth muscle cells of the small pulmonary arteries.

MOLECULAR BASIS OF HYPOXIC PULMONARY HYPERTENSION

Although the physiologic responses of the pulmonary vasculature to acute and chronic hypoxia have been extensively studied, the cellular mechanisms of vasoconstriction of the muscular pulmonary arteries during acute hypoxia and the vascular remodeling after chronic hypoxia are far from being elucidated.

Role of Ca^{2+}, mitochondria, and oxygen-sensing mechanisms

Ca^{2+} influx in the pulmonary vascular smooth muscle cells is probably the most important step in HPV and plays a significant role in pulmonary vascular remodeling of chronic hypoxia. The initial mechanism is a redox-based oxygen sensor that, under hypoxic conditions, inhibits voltage-gated K^+ channels (38), allowing influx of Ca^{2+} in the cytoplasm and resulting in vasoconstriction. Mitochondria play a key role in sensing the lack of intracellular oxygen and promoting Ca^{2+} influx. How exactly mitochondria react to hypoxia is not clear, but the proposed mechanism involves modulation in reactive oxygen species production [increases (98) or decreases (6)]. The resulting increase in intracellular Ca^{2+} triggers calmodulin-mediated activation of myosin light-chain kinase, actin–myosin interaction, and contraction.

Signaling pathways involved in hypoxia

Intracellular signaling via the small guanosine triphosphate (GTP)-binding protein RhoA and its downstream effector Rho-kinase plays a role in regulating diverse cellular functions, including cell contraction, migration, gene expression, proliferation, and differentiation. In both isolated pulmonary artery rings (71) and intact animal models of hypoxia (26), the Rho kinase inhibitor Y27632 inhibited hypoxia-induced pulmonary hypertension. Rho kinase activation is thought to block myosin light-chain phosphatase (89), resulting in enhanced contractility. In a rat model of hypoxia-induced pulmonary hypertension, Y27632 attenuated the degree of pulmonary hypertension, but the result was a nonselective vasodilation of both pulmonary and systemic vasculature (64). This may be explained by the similar effects of Rho kinase inhibition on pulmonary and systemic vasculature (95).

Another Rho kinase inhibitor compound is fasudil, clinically available in Japan for cerebral vasospasm (85) and vasospastic angina (54). Inhaled fasudil decreased pulmonary hypertension in chronically hypoxic rats (63), whereas intravenous fasudil decreased pulmonary vascular resistance in a small group of patients with pulmonary hypertension, without producing systemic hypotension (30). A signaling pathway that seems to be downstream of Rho kinase is p38MAPK and ERK1/2MAPK (31). p38MAPK blockade with SB-202190 abolished HPV in isolated pulmonary artery rings (45), suggesting an active role of p38MAPK in HPV. Therefore, therapeutic approaches aiming at blocking Rho kinase and/or p38MAPK signaling pathways hold promise in the treatment of hypoxia-induced pulmonary hypertension. In addition to the Rho kinase pathway, the platelet-derived growth factor (PDGF) is a potent mitogen of pulmonary vascular smooth muscle cells. A recent study showed that the PDGF-receptor inhibitor STI571 (Gleevec) reversed hypoxia and monocrotaline-induced pulmonary hypertension in mice and rats, respectively (79). This is of clinical significance, because Gleevec is a compound already approved by the Food and Drug Administration for the treatment of leukemia.

Role of endothelium

The main mechanism of HPV involves the smooth muscle layer. Nevertheless, the endothelium plays an important role in modulating this effect. The importance of the endothelium can be emphasized by the fact that diseases that distort and destroy the parenchyma (chronic obstructive pulmonary disease, COPD; interstitial lung disease, ILD) result not only in thickening of the vascular smooth muscle, but also in endothelial cell proliferation. In these conditions, pulmonary hypertension is minimally reversible, even with oxygen supplementation and correction of hypoxia. In contrast, pulmonary hypertension from high altitude has an intact endothelium and is reversible on descent. Endothelium releases local mediators of vasodilation (prostacyclin and nitric oxide, NO) as well as vasoconstrictors (endothelin, ET-1). An imbalance in these mediators that act locally on the smooth muscle layer is thought to modulate both HPV and chronic hypoxia-induced pulmonary hypertension. The three pathways discussed later are of major importance in various forms pulmonary hypertension, and therapeutic agents affecting these pathways are either approved or being investigated in clinical trials. Therefore, it is of clinical interest to assess their involvement in hypoxia-induced pulmonary hypertension.

The endothelin pathway (Fig. 3). ET-1 is a potent vasoconstrictor, cell mitogen, and proinflammatory peptide, produced by endothelial cells. ET-1 acts via two receptors: ET-A receptors on the smooth muscle cells are responsible for the known actions of ET-1; ET-B receptors are abundant on the endothelial cells of the small pulmonary vasculature and are thought to produce vasodilation and have antiproliferative effects by stimulating the release of NO and prostacyclin (21). ET-B receptors are also clearance receptors for circulating ET-1 (21, 23). Increased concentrations of ET-1 in the lung and pulmonary arteries of hypoxic animals have been documented (43). Experimental data suggest that blockade of the ET-1 pathway via either ET-A selective (103) or ET-A/B nonselective (17) receptor blockers attenuates hypoxia-induced pulmonary hypertension. In distal pulmonary arteries, vigorous HPV was abolished by endothelial denudation or BQ123 (an ET-1 receptor antagonist) and restored after denudation by exposure to a threshold ET-1 concentration (50). In a newborn mouse model, chronic hypoxia-induced pulmonary vascular remodeling was completely prevented and partially reversed by blockade of the ET-A receptor (5). In contrast, ET-B receptor–deficient rats have worse hypoxia-induced pulmonary hypertension compared with their hypoxic controls (42).

Although animal data suggest that selective ET-A receptor blockade may be advantageous over the nonselective receptor blockade, clinical data have not confirmed this hypothesis.

The NO pathway (Fig. 3). NO increases intracellular cyclic guanosine monophosphate (cGMP) by directly activating soluble guanylate cyclase. cGMP then activates cGMP kinases, opens potassium channels, and dilates blood vessels. Inhaled NO has been shown in both animal and human studies to be a potent, selective pulmonary vasodilator, and it is approved for the treatment of pulmonary hypertension of the newborn. The effects of intracellular cGMP are short-lived, however, because of rapid degradation by phosphodiesterase 5 (PDE 5) (82). Thus, inhibition of the enzymatic degradation of cGMP, using PDE 5 inhibitors, offers another way to increase intracellular cGMP and achieve pulmonary vasodilatory and antiproliferative effects (52). Sildenafil, which is a selective PDE 5 inhibitor, has similar actions with NO (67, 84). Sildenafil is now approved by the Food and Drug Administration for the treatment of group I WHO pulmonary arterial hypertension (idiopathic, familial, related to connective tissue disease, *etc.*). Both NO and sildenafil were shown to be beneficial in humans with different forms of hypoxia-induced pulmonary hypertension, as discussed later.

The prostacyclin pathway (Fig. 3). Prostacyclin is released by endothelial cells, stimulates cyclic adenosine monophosphate (cAMP) production, produces relaxation of the underlying vascular smooth muscle, and prevents platelet aggregation. Overexpression of the enzyme responsible for prostacyclin production, prostacyclin synthase, in lungs of

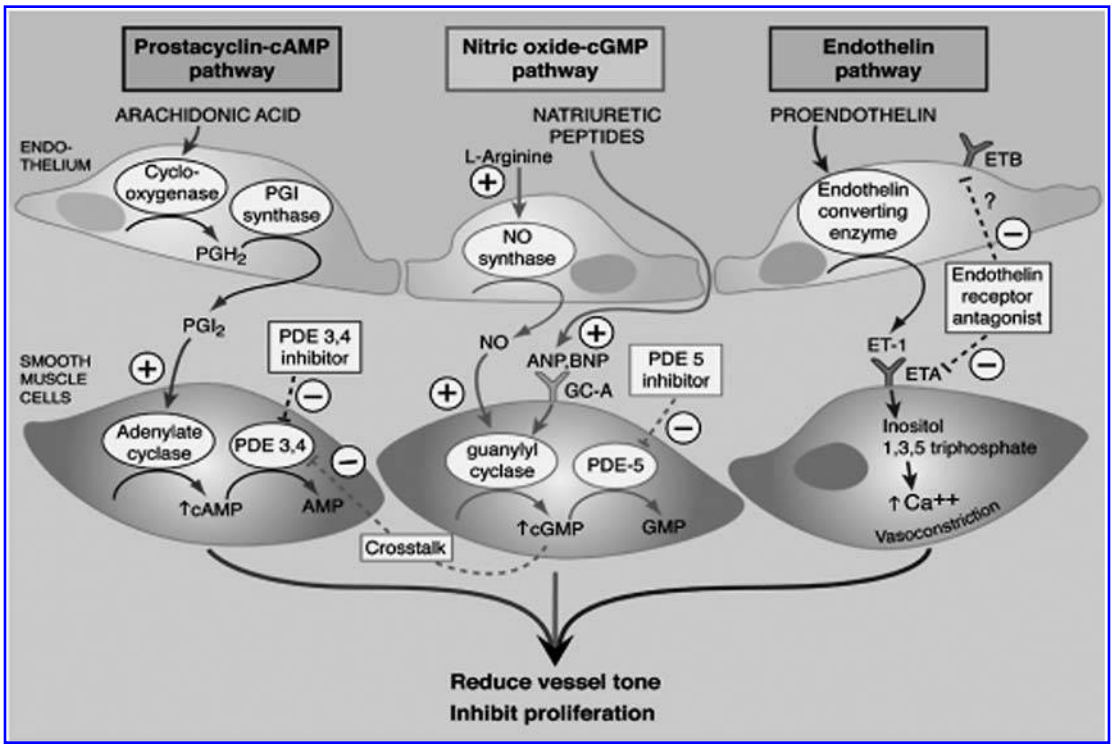

FIG. 3. The endothelin, nitric oxide and prostacyclin pathways, and their effect on the pulmonary vasculature. With permission from Dr. Nicholas Hill, Pulmonary Hypertension Therapy. Armonk, NY: Summit Communications, 2006. cAMP, Cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET-A, ET-B, ET-A and -B receptors; ET-1, endothelin-1; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; PGI, prostacyclin; PDE, phosphodiesterase.

mice exposed to hypoxia, protected them from the development of pulmonary hypertension (32). Prostacyclin has also a major role in idiopathic pulmonary hypertension. Patients with idiopathic pulmonary hypertension have improved survival with long-term therapy with the prostacyclin analogue, epoprostenol (10). Therefore, mediators of endothelial cell origin that participate in the balance of maintaining an open pulmonary vascular bed are possible therapeutic targets in hypoxia-induced pulmonary hypertension.

Role of serotonin (5-hydroxytryptamine, 5-HT). In the lung, serotonin is secreted by the neuroendocrine cells. Serotonin has opposite effects on the circulation, mimicking the effects of hypoxia: it is a potent pulmonary vasoconstrictor, a bronchoconstrictor (18), a mitogen for pulmonary smooth muscle cells (27), and is a vasodilator in the systemic circulation (39). Administration of serotonin to rats exposed to prolonged hypoxia magnifies the degree of pulmonary hypertension (25). Serotonin acts via a transporter (SERT), or a class of receptors, the most important in the lung vasculature being 5-HT_{A1}, 5-HT_{A2}, 5-HT_{B1}, and 5-HT_{B2}. Polymorphism in the SERT gene includes the short (S) allele and the long (L) allele, the latter being associated with increased gene transcription. In a recent European study, patients with COPD who had the LL genotype had more severe pulmonary hypertension than the SS or the heterozygotes (24). Both animal data and human studies suggest that serotonin is an important modulator of different forms of pulmonary hypertension.

Role of nonresident cells. In addition to hypertrophy of resident smooth muscle cells, new evidence suggests that cells of other origin, such as monocytes and fibroblasts, migrate into the smooth muscle cell layer and may contribute to the vascular remodeling (29). Circulating mononuclear cells isolated from neonatal calves exposed to hypoxia were found to differentiate into endothelial and smooth muscle cell phenotypes, depending on culture conditions (20). Therefore, circulating cells could become residents of the injured small pulmonary arterial wall and participate in vessel wall thickening in the setting of hypoxia-induced pulmonary hypertension.

Role of inflammatory mediators. Generalized hypoxia produces an accumulation of leukocytes in the perivascular space of many vascular beds (102). Acute hypoxia is associated with a transient increase in lung neutrophils, and later, with an influx of alveolar macrophages. The increased numbers of macrophages and neutrophils is coupled with marked induction of proinflammatory cytokines and chemokines [monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-2, interleukin (IL)-1β, IL-6]. Both endothelin and vascular endothelial growth factor (VEGF) are known to attract monocytes from circulation in hypoxic tissue. VEGF-A expression is increased in the pulmonary artery adventitia of chronically hypoxic animals in association with increased neovascularization and monocyte accumulation. Thus, VEGF, produced locally by a number of different cell types in response to

hypoxia, can attract monocytes into the local environment. In addition, metabolites of arachidonic acid, such as 5- and 12-lipoxygenases, may participate in either endothelial cell dysfunction (44) or smooth muscle cell proliferation (68). In conclusion, increasing evidence suggests that inflammation plays an important role in the occurrence and progression of pulmonary vascular changes associated with hypoxia. Therapeutic agents with anti-inflammatory properties may be of benefit.

PHYSIOLOGIC ASPECTS OF HYPOXEMIC STATES: PULMONARY CIRCULATION OF THE FETUS

Oxygenation of fetal blood is achieved via the placental circulation. The vascular resistance of the pulmonary circulation is very high *in utero* (Fig. 4) (74). Consequently, oxygenated blood returning from the placenta into the right heart bypasses the lung vasculature and is diverted into the systemic circulation through the foramen ovale and ductus arteriosus. Some evidence suggests that the high pulmonary vascular resistance of the fetal circulation is due to a continuous vasoconstrictive state through an HPV mechanism. At birth, when the alveoli are exposed to oxygen for the first time, pulmonary arteries rapidly dilate, with subsequent decrease in pulmonary vascular resistance, and the neonatal pulmonary circulation adjusts to a high-flow, low-vascular-resistance state. The predominant oxygen-sensitive channel that maintains the HPV of the fetal circulation is the Ca^{2+}-sensitive K channel (19). After birth, other channels become more important, such as voltage-gated K channels Kv1.5 and Kv2.1 (7, 58). Treatment with potassium chloride produces marked depolarization of the pulmonary arteries, supporting the important role of K channels in HPV (72). Nevertheless, even after marked depolarization by potassium chloride, hypoxia induces further contraction, indicating that other mechanisms independent of the K-channel function are involved in the HPV. At the same time, after transition from fetal to extrauterine life, the ductus arteriosus has an opposite reaction to oxygen exposure, by constricting and, in the end, closing. This results in diversion of the venous blood through the pulmonary circulation, to achieve adequate oxygenation through the alveolocapillary membrane. The same Kv channels that are involved in HPV of the pulmonary arteries seem to be implicated in the vasoconstriction of the ductus arteriosus when exposed to normoxia (92). Rings from the ductus arteriosus maintained in normoxia undergo a downregulation of the Kv1.5 and Kv2.1 channels, as evidenced by a decreased mRNA expression for these proteins (57). The presence of oxygen in initiating the adaptive mechanism of vasoconstriction of the ductus arteriosus is highlighted by the increased incidence of patent ductus arteriosus in babies born at high altitudes (4).

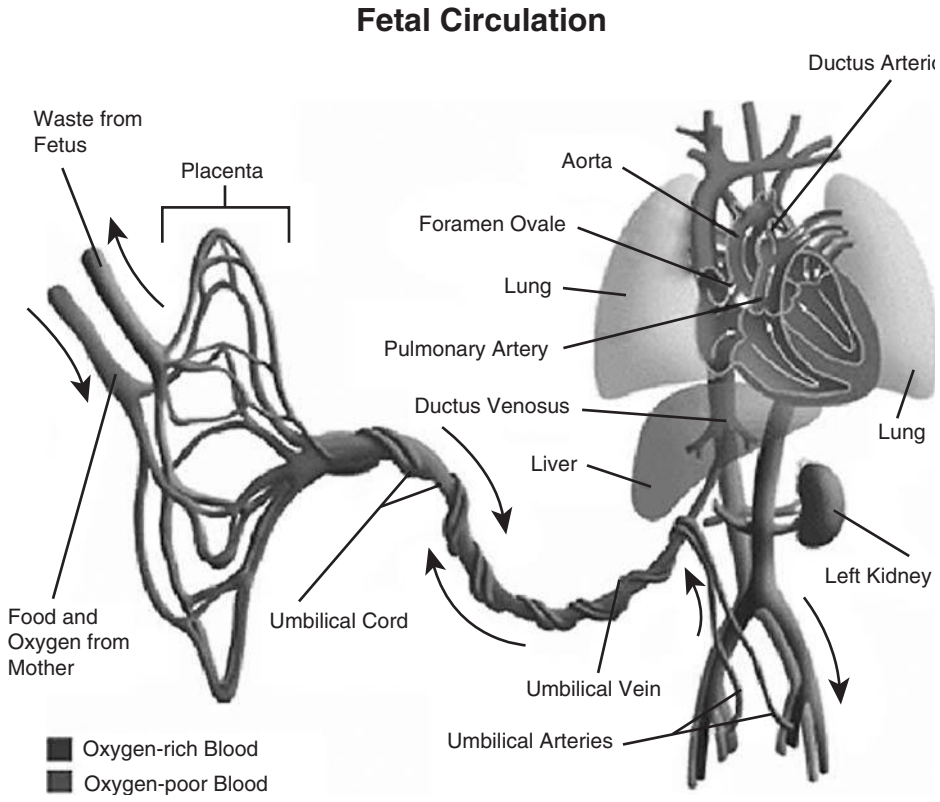

FIG. 4. Schematic of the fetal circulation.

HYPOXIC PULMONARY HYPERTENSION IN DISEASE STATES

HPV can occur focally, such as in areas of the lung affected by pneumonia or atelectasis, or it can involve the entire pulmonary vasculature, as in ascending to high altitude. Depending on the magnitude of the alveolar hypoxia (focal *versus* global), pulmonary vascular resistance can increase by up to 300% (12).

Pulmonary hypertension associated with chronic hypoxic lung diseases is regarded as a separate entity according to the latest WHO classification. This includes COPD, ILD, sleep disordered breathing, and prolonged exposure to high altitude (2). Regardless of the underlying pulmonary disease, the occurrence of pulmonary hypertension is associated with increased morbidity and mortality (49, 61). Although the main therapeutic treatment is oxygen supplementation, new reports suggest that selective pulmonary vasodilators may be beneficial in both the acute setting and when given over the long term (16). Conversely, nonselective vasodilators should be used with caution, as they may worsen the V/Q mismatch and worsen hypoxemia (see later).

Pulmonary hypertension associated with interstitial lung diseases

ILD such as idiopathic pulmonary fibrosis or pulmonary fibrosis secondary to connective tissue diseases is characterized by pathologic changes of the interstitium, with deposition of collagen, destruction of the normal architecture of the alveolocapillary membrane, distortion of the interstitial space, and damage of the pulmonary vasculature. V/Q mismatch is thought to be the main mechanism of hypoxemia. Patients become hypoxemic initially with ambulation and in late stages, even at rest. The degree of pulmonary hypertension in ILD usually correlates with the severity of restrictive lung disease (86). A number of vasodilators have been tested in this form of pulmonary hypertension. For example, in a randomized controlled, open-label trial in 16 individuals admitted with pulmonary hypertension secondary to lung fibrosis, the pulmonary vascular resistance index was reduced in the short term by NO [–21.9%; 95% confidence interval (CI), –14.1 to –36.2], epoprostenol (–36.9%; –24.4 to –59.6), and sildenafil (–32.5%; –10.2 to –54.1). Both NO and sildenafil maintained V/Q matching, whereas epoprostenol worsened V/Q mismatch and oxygenation (35). Because NO is delivered via the inhalation route, it reaches preferentially the pulmonary arteries adjacent to the well-ventilated alveoli, thus improving V/Q matching and subsequently the degree of hypoxemia and pulmonary hypertension. Sildenafil is a preferential pulmonary vasodilator because of increased expression of PDE5 in the hypoxic lung (51). Intravenous prostacyclin has nonselective vasodilatory effects, dilating arteries from both ventilated and nonventilated areas, worsening the V/Q mismatch and hypoxemia. Conversely, when delivered via the inhaled route, prostacyclin analogues have beneficial effects similar to those with inhaled NO. For example, in eight patients with lung fibrosis and pulmonary hypertension, aerosolized iloprost (a prostacyclin analogue) caused preferential pulmonary vasodilatation with a significant decrease in mean PA pressure and pulmonary vascular resistance, whereas intravenous prostacyclin worsened oxygenation (65). Although these preliminary studies are encouraging, both inhaled NO and prostacyclin analogues and sildenafil are still used in experimental setting in this form of pulmonary hypertension (16).

Pulmonary hypertension associated with COPD

Pulmonary hypertension is present in a wide range in patients with COPD. The exact incidence of clinically significant pulmonary hypertension is difficult to estimate in COPD patients. Up to 90% of COPD patients have exercise-induced pulmonary hypertension. In contrast, clinically significant pulmonary hypertension is reported less frequently (5–30%) (62, 78). The progression of pulmonary hypertension is slow in COPD patients, and PA pressures may remain stable over periods of 3–10 years (99). Initially, COPD patients become hypoxemic during sleep because of decreased intercostal muscle activity, decreased motor neuron input, increased airway resistance, and worsening V/Q mismatch, all leading to nocturnal hypoventilation. Nocturnal desaturations during sleep coincide with an increase in PA pressures. Diurnal hypoxemia develops later in the disease progression and is mainly due to V/Q mismatch, which is caused by blood-flow inequalities, tissue loss, and loss of distal vessels as a consequence of severe parenchymal destruction. Pathologic changes in pulmonary vessels of COPD patients with pulmonary hypertension involve all vessel layers, including intimal proliferation of the endothelium. This pathologic feature is unlike the predominant medial hypertrophy that develops with chronic hypoxia at high altitudes, and it may explain the irreversibility of the pulmonary hypertension associated with COPD. Whereas high altitude–induced pulmonary hypertension is reversible after a return to normoxic conditions, pulmonary hypertension and vascular remodeling of COPD patients is only partially reversible with oxygen treatment. To date, the only specific treatment proven to have an impact on survival in hypoxemic COPD patients is long-term oxygen therapy, which ameliorates the degree of PH and improves survival (104). A distinct subgroup of patients with moderate COPD in whom severe PH develops has been described (90, 99). Their PH correlates with the severity of underlying hypoxemia, but not with the severity of airway obstruction. It is therefore possible that these patients may respond to selective pulmonary vasodilators. Although most studies showed a beneficial effect on PA pressures and oxygenation with short-term inhaled NO (33, 60, 73), others showed a worsening of V/Q mismatching and oxygenation (9).

Pulmonary hypertension associated with sleep-disordered breathing

Obstructive sleep apnea (OSA) is defined as intermittent repeatable cessation of airflow to the lung (apnea) due to closure of upper airways. It is a common disease that, in its severe form, leads to intermittent alveolar hypoxia and HPV. Patients with severe OSA demonstrate an increase in PA pressure during apneic episodes. The prevalence of PH in OSA patients has been reported to be ~20%. The degree of PH, though, is mild to moderate unless patients have other cardiopulmonary comorbidities. Therefore, it is believed that

intermittent nocturnal hypoxemia results in mild to moderate PH. Nevertheless, PH can be severe in patients who have concomitant COPD and OSA, or in patients with obesity hypoventilation syndrome, who also have chronic daytime hypoxemia. Treatment of PH in OSA is geared toward maintaining an open airway during sleep. This is usually achieved with continuous positive airway pressure devices (76).

Pulmonary hypertension associated with high altitude: acute exposure

When exposed to high altitudes, a prompt increase in PA pressure develops in most lowlanders, usually moderate in severity, via an HPV mechanism. Among healthy newcomers at high altitudes (>3,000 m), some have an excessive response to hypoxia, with elevations of systolic PA pressures of >40 mm Hg. These individuals are thought to be susceptible to high-altitude sickness (81). Acute exposure to high altitude can lead to two distinct conditions: acute mountain sickness and high-altitude pulmonary edema (HAPE).

Acute mountain sickness is common in individuals who ascend quickly from sea level to ~3,000 m. It is characterized by headache, lightheadedness, shortness of breath, fatigue, and insomnia. Symptoms occur few hours after ascent, last for 2–3 days, and are usually self-limited. Changes in the blood–brain barrier with altered capillary permeability due to hypoxemia (13) and low carbon dioxide (due to hyperventilation) (37), resulting in mild cerebral edema, are thought to occur. New evidence suggests that circulating unbound VEGF, which promotes vascular leakage, is involved in the pathogenesis of acute mountain sickness (22). Prompt descent to a low altitude rapidly resolves symptoms of acute mountain sickness.

HAPE is a more serious condition that is potentially fatal. HAPE occurs in 1–10% of people who ascend above 3,000 m (100). The mechanism is thought to be an acute and robust HPV with subsequent severe elevations in PA pressure. Invasive studies showed that HAPE-susceptible individuals have increased PA pressures up to 144 mm Hg, with an average of 60–80 mm Hg (11, 41, 81). The high PA pressure is transmitted to some of the capillaries, in an uneven distribution, with disruption of the endothelial layer and extravasation into the interstitium and alveoli of fluid with high protein content and erythrocytes, causing high-permeability pulmonary edema (83). In addition, impaired clearance of fluid from alveolar space may play a role (80). Invasive hemodynamic monitoring consistently showed that the capillary wedge pressure is normal; hence the left ventricular end-diastolic pressure is not affected, and the pulmonary edema is not due to left-heart dysfunction (66). In addition, on immediate descent, HAPE resolves quickly, suggesting that the endothelial leakage is completely reversible. A reversible disruption of the basement membrane with distortion of type IV collagen fibers is thought to occur (101). Subjects who are susceptible to developing HAPE have abnormally elevated PA pressures during short- and long-term hypoxic exposures and a greater increase in PA pressures with exercise in normoxic conditions (40, 47), suggesting an abnormally reactive pulmonary vascular bed. Although no clear marker distinguishes susceptible individuals, recent studies have highlighted the role of an impaired endothelial function with an imbalance in vasoactive endothelial mediators. HAPE-susceptible individuals have lower exhaled NO (14) and higher plasma levels of ET-1, which correlate with systolic pulmonary artery pressures (77). Additionally, inhaled NO improved pulmonary hypertension and oxygenation in susceptible individuals exposed to short-term high altitude and treated for the pulmonary edema (81). In addition, in 14 healthy mountaineers at the Mount Everest base camp, the PDE 5 inhibitor sildenafil significantly reduced systolic PA pressure at rest and during exercise and increased maximal workload and cardiac output (34), making this class of agents an attractive therapeutic option for HAPE. Another PDE 5 inhibitor, tadalafil, prevented HAPE as much as dexamethasone did (53) (whose vascular effects are probably through an increase in NO production). Conversely, bosentan, a nonselective ET-A and ET-B receptor blocker, reduced systolic PA pressure elevations in healthy subjects who ascended to high altitude (4,559 m) (59). However, both urinary volume and free water clearance also were significantly reduced by bosentan, which may increase the risk of pulmonary edema. In none of the climbers did HAPE develop, so it is unclear whether bosentan reduces the incidence or severity of HAPE. Addition of a diuretic may prevent the volume overload caused by bosentan. Alternatively, because ET-B receptor–deficient animals display an exaggerated lung vascular protein leak in normoxia and hypoxia exacerbates that leak (15), a selective ET-A blocker with preservation of the ET-B function may be safer in the treatment/prevention of HAPE. HAPE usually develops within 4–5 days of ascent, or not at all. After few days at high altitude, vascular remodeling occurs and probably prevents fluid leakage into the interstitium. People in whom HAPE develops are at risk of redeveloping the syndrome with repeated ascent (11), suggesting that genetic factors may predispose to the development of HAPE. Although possible genetic factors involved in high-altitude pulmonary hypertension are a topic of interest, so far they remain exploratory (75).

Prolonged exposure to high altitude

Neonates born at high altitude have a slower transition from fetal to adult pulmonary circulation. Some neonates have persistent elevation of pulmonary pressures throughout infancy (87). Adult residents of high altitudes are at risk of developing chronic mountain sickness (CMS, or Mongue disease, as it was described in the natives of the Andes). This entity is characterized by headache, insomnia, impaired memory in incipient forms, and by severe erythrocytosis, cyanosis, and pulmonary hypertension in its more severe forms. Erythrocytosis is thought to be an adaptive mechanism to low-hemoglobin oxygen content geared toward increasing oxygen-carrying capacity of the blood. Typically, the symptoms of chronic mountain sickness and pulmonary hypertension resolve if subjects are moved to lower altitudes, but they recur after return to high altitudes. In late stages of this disease, right heart failure develops. Interestingly, among people of different nations residing at similarly high altitudes, Tibetans have the least pulmonary hypertension and have a blunted HPV (36), whereas Han Chinese and natives of the Andes are more prone to develop severe pulmonary hypertension and

right-heart failure. In high-altitude natives, the administration of oxygen reduced PA pressures by only 15–20%, and the lung circulation failed to dilate with exercise, supporting the vascular remodeling as an anatomic basis for the increased vascular resistance.

The most important treatment for highlanders in whom high-altitude pulmonary hypertension develops is descending to lower altitudes, if possible. Pulmonary hypertension disappeared when high-altitude Peruvian natives were taken for 2 years to Lima near sea level (8, 88). A few reports suggest that PDE 5 inhibitors may also alleviate the pulmonary hypertension. For example, sildenafil protected against the development of altitude-induced pulmonary hypertension in a small group of healthy volunteers exposed for 6 days at 4,350 m (70). In addition, in a group of natives living above 2,500 m who had high-altitude pulmonary hypertension demonstrated by a right-heart catheterization, 3 months of treatment with sildenafil improved significantly the mean pulmonary artery pressures and functional capacity, as measured by the 6-minute walk test (3). To date, PDE 5 inhibitors are still investigational in high-altitude pulmonary hypertension.

In summary, for the past four decades, important advances have been made in understanding the physiologic response of the lung vasculature to acute and chronic hypoxia. Recently, cellular mechanisms responsible for HPV and vascular remodeling have implicated various second messengers and signaling pathways. Current therapies besides oxygen supplementation and descent to low altitude are largely investigational, but modulation of pathways such as NO, prostacyclin, and/or ET-1 holds promise. Future research geared at unraveling the genetic factors that predispose to the developing of pulmonary hypertension associated with different conditions will help establish better therapies.

ABBREVIATIONS

AMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; ET-1, endothelin-1; HAPE, high-altitude pulmonary edema; HPV, hypoxic pulmonary vasoconstriction; ILD, interstitial lung disease; NO, nitric oxide; OSA, obstructive sleep apnea; PA, pulmonary artery; PDE 5, phosphodiesterase 5; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; V/Q, ventilation/perfusion; WHO, World Health Organization.

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