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# Hypoxic Pulmonary Vasoconstriction in Cardiothoracic Surgery: Basic Mechanisms to Potential Therapies

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Hypoxic pulmonary vasoconstriction is postulated to be an adaptive mechanism to match lung perfusion with ventilation; however, the consequences of the maladaptive effects of pulmonary vasoconstriction represent formidable therapeutic challenges. Understanding the basic mechanisms of hypoxic pulmonary vasoconstriction will enhance the assimilation of translational research into clinical practice. The purposes of this review are to (1)

define basic mechanisms of pulmonary vasoconstriction and vasorelaxation; (2) delineate the biphasic contractile response to hypoxia; (3) critically examine data that support the mediator hypothesis versus the ion channel hypothesis; and (4) explore potential mechanistic-based therapies for hypoxic pulmonary vasoconstriction.

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**P**ulmonary vasoreactivity is regulated by neural and humoral mechanisms, and systemic processes such as endotoxemia or hypoxemia affect pulmonary vascular resistance [1–4]. Pulmonary arteries contract when oxygen tension is acutely decreased (Fig 1). This response distinguishes pulmonary vessels from systemic vessels, which dilate under hypoxic conditions. Acute hypoxic pulmonary vasoconstriction (HPV) may be an adaptive mechanism to match lung perfusion with ventilation. Sustained vasoconstriction, on the other hand, may lead to vascular remodeling, pulmonary hypertension, and cor pulmonale.

Hypoxic pulmonary vasoconstriction may play a role in acute lung injury and the adult respiratory distress syndrome (ARDS) because hypoxemia is inherent to ARDS. Increased pulmonary vascular resistance is frequently observed with ARDS, and pulmonary hypertension associated with ARDS has an extremely poor prognosis [5]. Pulmonary vasoconstriction presents a formidable challenge in pediatric patients with congenital heart disease. These patients are particularly susceptible to developing pulmonary hypertensive crises after cardiac surgery [6]. Moreover, hypoxia is a potent vasoconstrictive stimulus in this population of patients [7]. Pulmonary vascular resistance is often increased after lung transplantation [8], and the pulmonary vasoconstrictive response to hypoxia is preserved after lung transplantation [9]. Thus, a mechanistic understanding of HPV may lead to development of adjunct therapies for pulmonary vasoconstriction in ARDS, primary pulmonary hypertension, pediatric patients with congenital heart disease, and lung transplantation.

Since first being described by von Euler and Liljestrand in 1946 [10], pulmonary vasoconstriction secondary to acute hypoxia has been studied extensively in numerous animal models. However, the exact mechanism of HPV remains unknown. The mechanisms described thus far can be broadly divided into two groups: (1) inhibition or secretion of an endogenous mediator that results in vasoconstriction; and (2) opening or closing of calcium or potassium channels in the pulmonary vascular smooth muscle cell that leads to contraction. Understanding the pathways leading to HPV requires a basic comprehension of the normal control of pulmonary vascular tone. This background knowledge can then be applied to examine the two HPV hypotheses, which serve as models for evaluating potential therapies aimed at attenuating the pulmonary vascular response to hypoxia. The purposes of this review are to (1) define basic mechanisms of pulmonary vasoconstriction and vasorelaxation; (2) delineate the biphasic contractile response to hypoxia; (3) critically examine data that support the mediator hypothesis versus the ion channel hypothesis; and (4) explore potential mechanistic-based therapies for HPV.

## Normal Regulation of Pulmonary Vascular Tone

The pulmonary circulation in the normal adult is a low-pressure, low-resistance circuit. Small pulmonary arteries are the main site of pulmonary vascular resistance, and changes in pulmonary arterial tone are influenced by neural and humoral mechanisms [11]. The normal regulation of pulmonary vascular tone represents a finely tuned balance between the forces of vasoconstriction and vasorelaxation. Moreover, this balance is

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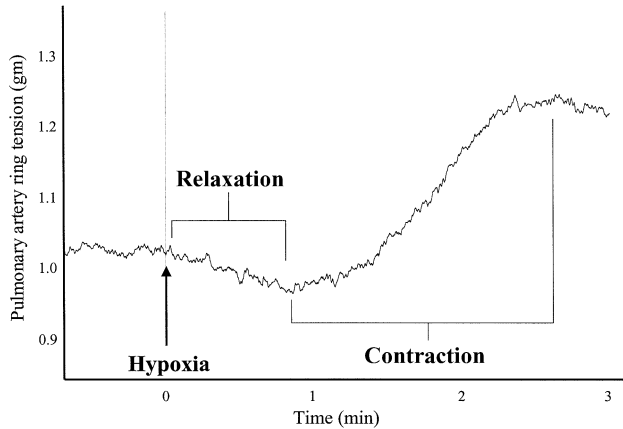


Fig 1. Actual tracing of isolated pulmonary artery ring tension in response to hypoxia. Isolated rat pulmonary artery, suspended on steel wires in a 37°C organ bath containing modified Krebs-Henseleit solution and connected to a force transducer, was precontracted with phenylephrine ( $10^{-7}$  M) and gassed with 95%  $N_2$ -5%  $CO_2$  (hypoxia). The resulting tension tracing exhibits an immediate relaxation preceding a transient vascular contraction.

regulated by endothelium-dependent and endothelium-independent factors.

#### Endothelium-Dependent Mediators

There are several vasoactive factors produced by the endothelium that mediate both vasoconstriction and vasorelaxation (Fig 2). Endothelium-derived relaxing factor was first described by Furchgott and Zawadzki in 1980 [12]. They found that acetylcholine-mediated vasodilation was caused by a substance released from the endothelium. At least part, if not all, of the vasodilatory effect of endothelium-derived relaxing factor has been attributed to nitric oxide (NO). Nitric oxide is synthesized in endothelial cells by NO synthase from the substrate l-arginine [13, 14]. Once formed, NO stimulates guanylate cyclase in vascular smooth muscle cells to produce guanosine 3', 5'-cyclic monophosphate (cGMP). The mechanism of cGMP-mediated vasodilation is thought to involve activation of a protein kinase, inhibition of inositol triphosphate, inhibition of calcium influx, and myosin light chain dephosphorylation. Prostacyclin is also produced by the endothelium and stimulates adenylate cyclase in vascular smooth muscle to produce adenosine 3', 5'-cyclic monophosphate. The mechanism of adenosine 3', 5'-cyclic monophosphate-mediated vasodilation appears to be similar to that of cGMP.

The endothelium also produces vasoconstricting factors called endothelins, of which endothelin-1 is the most studied. Endothelin-1 has both contracting and dilating properties, which are mediated by at least two subtypes of receptors,  $ET_A$  and  $ET_B$ . The  $ET_A$  receptor is located on vascular smooth muscle and mediates vasoconstriction, whereas  $ET_B$  receptors are located on endothelium and mediate vasodilation (Fig 2). The signal transduction mechanism after endothelin receptor activation involves phospholipase C and protein kinase C activation, result-

ing in mobilization of intracellular calcium for contraction, whereas vasodilation may be modulated through release of NO and prostacyclin [15].

#### Endothelium-Independent Mediators

Pulmonary vascular tone is also affected by neural and humoral mechanisms that occur independent of the endothelium. Pulmonary vascular smooth muscle receives adrenergic innervation, predominantly  $\alpha_1$ -adrenergic receptors and  $\beta_2$ -adrenergic receptors, which mediate vasoconstriction and vasorelaxation, respectively (Fig 2). Phenylephrine and norepinephrine bind to  $\alpha_1$ -adrenergic receptors and cause vasoconstriction by stimulating phospholipase C, which results in release of inositol triphosphate and diacylglycerol and subsequent activation of protein kinases.  $\beta_2$ -Adrenergic receptor activation results in adenylate cyclase activation, production of adenosine 3', 5'-cyclic monophosphate, and subsequent vasodilation. Sodium nitroprusside is an endothelium-independent vasodilator that acts directly on guanylate cyclase to increase production of cGMP.

There are numerous other circulating mediators and hormones that exhibit vasoactive effects. Angiotensin II, produced by angiotensin-converting enzyme primarily in

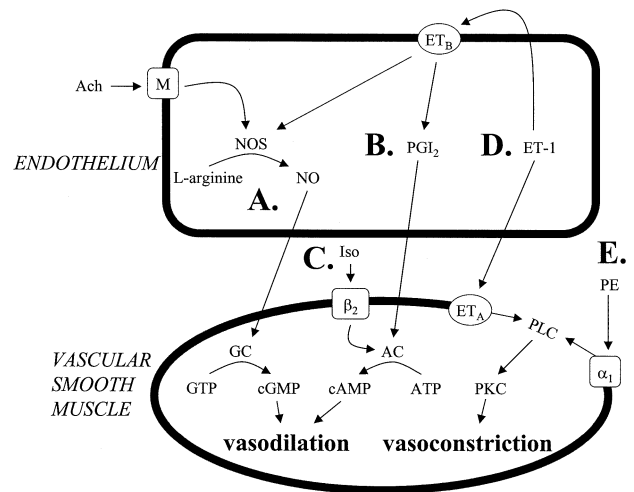


Fig 2. Role of endothelium in vascular tone. (A) Nitric oxide (NO), produced by nitric oxide synthase (NOS), stimulates guanylate cyclase (GC) in vascular smooth muscle to produce guanosine 3', 5'-cyclic monophosphate (cGMP). Acetylcholine (ACh) acts through muscarinic receptor (M) binding by stimulating nitric oxide synthase. (B) Prostacyclin ( $PGI_2$ ) produced by the endothelium stimulates adenylate cyclase (AC) in smooth muscle to produce adenosine 3', 5'-cyclic monophosphate (cAMP). (C)  $\beta_2$ -Adrenergic receptor ( $\beta_2$ ) activation also induces adenosine 3', 5'-cyclic monophosphate production. Both adenosine 3', 5'-cyclic monophosphate and guanosine 3', 5'-cyclic monophosphate cause vasodilation. (D) Endothelin-1 ( $ET_1$ ) binds to  $ET_A$  receptors on smooth muscle cells and activates phospholipase C (PLC) and protein kinase C (PKC), which results in vasoconstriction. Endothelin-1 mediates vasodilation through  $ET_B$  receptor activation and subsequent nitric oxide and prostacyclin production. (E)  $\alpha_1$ -Adrenergic receptor ( $\alpha_1$ ) activation results in vasoconstriction by activating phospholipase C. ( $ET_A$ ,  $ET_B$  = endothelin receptors; GTP = guanosine triphosphate; PE = phenylephrine.)

the lung, is a potent vasoconstrictor. Bradykinin causes pulmonary vasodilation by stimulating NO release. Histamine, produced by mast cells in the lung, and serotonin, which is a product of activated platelets, can cause both constriction and relaxation. These are a few examples of the many circulating factors that affect pulmonary vasoreactivity, and there are undoubtedly other factors that have not yet been identified.

The regulation of pulmonary vascular tone encompasses complex interactions between various mediators. The pulmonary circulation is dependent on the endothelium for maintaining baseline low tone, but pathologic processes result in an alteration of the normal milieu of vasoactive mediators. With this basic understanding of pulmonary vascular tone, the response to acute hypoxia can be analyzed.

### Hypoxic Pulmonary Vasoconstriction

Pulmonary arteries contract when oxygen tension is acutely decreased (Fig 1). This response distinguishes pulmonary vessels from systemic vessels, which dilate under hypoxic conditions. Early work on HPV was performed in intact animals and isolated whole lung preparations. Although they provide reproducible responses, the potential interactions of numerous mediators make it difficult to establish a true causal relationship. It is generally accepted that precapillary pulmonary arteries are the principal site of resistance during HPV [16]. Accordingly, isolated pulmonary artery rings and vascular smooth muscle cell cultures have been increasingly used in the study of HPV because they limit extraneous factors that may interfere or influence the hypoxic response.

#### *Biphasic Contractile Response to Hypoxia*

Isolated pulmonary arteries demonstrate a biphasic response to hypoxia. Segments of isolated pulmonary artery are suspended on a pair of steel wires and placed in an organ bath containing a nutrient-containing physiologic salt solution at 37°C. The steel wires are connected to a force transducer, which can measure the change in tension across the vessel. Various conditions (eg, agonists, inhibitors, hypoxia) can be introduced into the bath, and the change in vascular tone is recorded. Inasmuch as resting artery has no tone, agonist-induced contraction is required before introducing hypoxia. In isolated pulmonary artery rings submaximally precontracted with phenylephrine, exposure to 95% N<sub>2</sub>-5% CO<sub>2</sub> results in an immediate vasorelaxation followed by a rapid contraction (Fig 1). The contraction diminishes rapidly and is followed by relaxation. With continued hypoxia, there is a second, sustained contraction [17-23]. The initial transient contraction may be the compensatory perfusion-ventilation mechanism, whereas the sustained contraction may be responsible for the maladaptive effects of pulmonary vasoconstriction. Studies examining the separate phases of contraction suggest that different mechanisms may be responsible for each phase [20, 24-26].

The mechanisms responsible for the biphasic contraction are not completely understood and existing evidence is conflicting. The early contraction may be dependent on calcium influx as calcium-channel blockers abolished this phase of HPV [20, 21], whereas the delayed contraction may be dependent on the presence of a functional endothelium [23, 24]. On the other hand, Jin and colleagues [18] and our unpublished results suggest that the endothelium is necessary for early but not delayed HPV. Jin and colleagues [18] propose that delayed contraction is mediated by calcium influx and protein kinase C activation. It is possible that the two phases of contraction may share components of the mechanistic pathways, and an ultimate end-effector has yet to be identified. Teleologically, HPV as an adaptive response to match ventilation and perfusion is a practical concept. Sustained vasoconstriction, however, leads to vascular remodeling and smooth muscle hypertrophy [27].

#### *Endothelium-Derived Factors*

Because the endothelium plays a vital role in the modulation of pulmonary vascular tone, initial studies on HPV focused on the endothelium and the vasoactive factors it produces. Basal release of NO is believed to account for the relatively low vascular tone in the pulmonary arteries. Therefore, inhibition of NO synthesis may potentially initiate HPV. Studies supporting the role of NO inhibition in the cause of HPV have shown potentiated vasoconstriction with NO synthase inhibitors [25, 26, 28], attenuated contraction with guanylate cyclase stimulation [29], and decreased cGMP production in hypoxic conditions [29-31]. There is, however, contradictory evidence regarding the role of NO in HPV. Hampl and associates [32] measured increased NO levels during hypoxia, and Jones and colleagues [33] found no effect of NO synthase inhibition on HPV. These findings suggest that NO may not be involved in hypoxic contraction. It is possible that, analogous to myocardial exposure to NO, the source and quantity of NO may explain apparently disparate effects [34].

Another hypothesis is that hypoxia stimulates the release of a contracting factor such as endothelin-1. Increased secretion of endothelin-1 under hypoxic conditions has been demonstrated [35, 36]. Furthermore, a selective ET<sub>A</sub> receptor antagonist, BQ123, has been shown to inhibit HPV [37-39], implicating endothelin-1 as a mediator of the contractile response to hypoxia. In addition, several studies show that the potassium-channel blockers glibenclamide and 4-aminopyridine reverse the inhibitory effect of endothelin receptor antagonists, suggesting that endothelins act by suppressing potassium-channel activity [38, 39]. There are contradictory reports of endothelin involvement in HPV as other investigators demonstrate that the endothelin receptor antagonists BQ-123 [24, 40] and bosentan [23] do not inhibit HPV. A recent study by Robertson and coworkers [24] suggested that HPV was mediated by a yet-to-be-identified vasoconstrictor substance released from the endothelium that exerted its effect by increasing the calcium sensitivity of the contractile apparatus. It ap-

pears as though prostanoids, which are also produced by the pulmonary endothelium, do not play a role in HPV. Hypoxia has been shown to both increase [41] and decrease [42] prostacyclin release, and cyclooxygenase inhibitors applied to isolated pulmonary artery rings had no effect on HPV [43].

The clinical process that causes hypoxia is often associated with an inflammatory stimulus, such as in ARDS. Hypoxia alone, in the absence of blood loss or tissue injury, has been shown to induce release of proinflammatory cytokines [44]. Thus, it is practical to examine the influence of inflammatory mediators on HPV. Primed and activated neutrophils disrupt endothelium and cause dysfunction of endothelium-dependent and endothelium-independent cGMP-mediated vasorelaxation, and they have been shown to mediate endotoxin-induced acute lung injury [1, 45-49]. Hypoxemia in the clinical setting enhances cytotoxic function of neutrophils [50]. Furthermore, activated resident macrophages release inflammatory mediators, which likely disrupt endothelium-dependent vasorelaxation [51]. Proinflammatory cytokines, specifically tumor necrosis factor- $\alpha$ , interleukin-1, and interleukin-6, contribute to pulmonary vasoconstriction and pulmonary hypertension [52, 53], and pretreatment with either endotoxin or tumor necrosis factor- $\alpha$  potentiates HPV [54, 55].

Inflammatory mediators themselves are not vasoactive, but are thought to augment hypoxic contraction by inhibition of constitutive NO synthase activity or by endothelial "stunning." Moreover, it has been demonstrated that tumor necrosis factor- $\alpha$ , interleukin-1, or lipopolysaccharide augmented the downregulation of constitutive NO synthase expression associated with hypoxia [56]. Nuclear factor-kappa B, a transcription factor involved in the transcription of proinflammatory molecules, may also be involved in the signaling pathway of HPV. This was suggested by a study showing that nuclear factor-kappa B inhibitors blocked HPV [57]. Mitogen-activated protein kinases, which may act upstream from nuclear factor-kappa B, have also been associated with HPV. Karamsetty and associates [19] demonstrated that p38 mitogen-activated protein kinase plays a role in mediating the sustained phase of HPV in isolated rat pulmonary arteries.

### Ion Channels

The role of endothelium-derived mediators such as NO and endothelin on HPV led some to believe that HPV is dependent on the presence of a functional endothelium. Others have shown that HPV occurs in isolated pulmonary artery rings denuded of endothelium [43, 58] as well as in isolated smooth muscle cells [42]. Therefore, pulmonary vascular smooth muscle cells have the capacity to serve as both sensors and effectors of hypoxic contraction.

There is accumulating evidence that the regulation or initiation of HPV occurs by means of potassium and calcium ion channels [58-61]. An increase in cytosolic calcium concentration appears to be a key event in HPV (Fig 3). Calcium accumulation occurs by release from

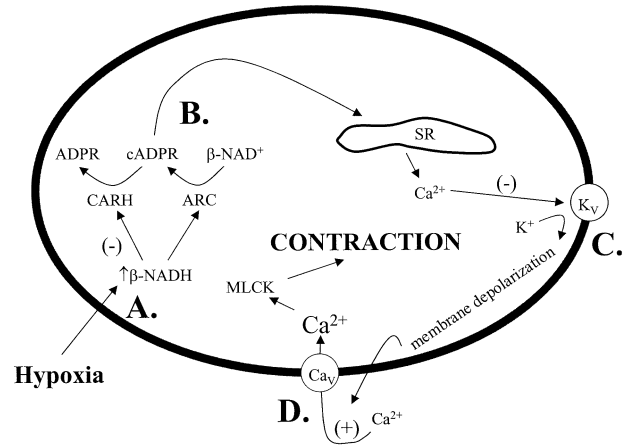


Fig 3. Redox sensor and ion channel response to hypoxia in vascular smooth muscle cell. (A) Hypoxia increases reduced  $\beta$ -nicotinamide-adenine dinucleotide ( $\beta$ -NADH) levels, which stimulate adenine dinucleotide phosphate (ADP)-ribosyl cyclase to produce cyclic ADP-ribose (cADPR). Reduced  $\beta$ -nicotinamide-adenine dinucleotide simultaneously inhibits cyclic ADP-ribose hydrolase from metabolizing cyclic ADP-ribose. (B) Accumulation of cyclic ADP-ribose stimulates the sarcoplasmic reticulum (SR) to release calcium ( $Ca^{2+}$ ). (C) The rise in intracellular calcium closes voltage-gated potassium ( $K_v$ ) channels in the cell membrane. Blockage of outward potassium ( $K^+$ ) current results in membrane depolarization. (D) Voltage-gated calcium ( $Ca_v$ ) channels are then activated, and the subsequent influx of calcium causes contraction by means of myosin light chain kinase activation (MLCK). (ADPR = ADP-ribose; ARC = ADP-ribosyl cyclase; CARH = cyclic ADP-ribose hydrolase;  $\beta$ -NAD $^+$  =  $\beta$ -nicotinamide-adenine dinucleotide.)

intracellular stores such as the sarcoplasmic reticulum or influx through voltage-dependent channels. Investigators have shown that blocking calcium channels [18, 20, 59], depletion of intracellular calcium stores [20, 32, 58, 62], and removing extracellular calcium [18, 63] inhibit hypoxic contraction, whereas calcium agonists potentiate HPV [43]. Moreover, inhibition of protein kinase C, which potentiates vascular contraction through influx of calcium, attenuates HPV [64, 65]. Increases in intracellular calcium are also known to activate mitogen-activated protein kinases, which are involved in smooth muscle contraction by increasing the sensitivity of the contractile apparatus to calcium and, thus, may play a role in HPV. Indeed, it has been demonstrated that inhibition of p38 mitogen-activated protein kinases attenuated sustained hypoxic contraction [19].

Hypoxia has also been shown to block an outward potassium current, which results in membrane depolarization [61, 66]. When potassium-channel inhibitors are incubated with isolated pulmonary artery rings, HPV is potentiated [59]. Conversely, potassium-channel openers attenuate HPV [26, 59]. Potassium channels involved in HPV have been identified as part of the voltage-gated potassium ( $K_v$ ) channel family, specifically  $K_v1.5$  and  $K_v2.1$  [67], and mice deficient in  $K_v1.5$  channels have an impairment in HPV [68].

Clearly, these two channels, potassium and calcium,

play an important role in mediating the hypoxic response (Fig 3). Calcium release from intracellular stores (eg, sarcoplasmic reticulum) appears to be an initial event in HPV [32, 62, 69]. It has been suggested that this initial rise in intracellular calcium inhibits Kv channels [62], which results in membrane depolarization and subsequent activation of voltage-gated calcium channels [59, 61]. Calcium influx then leads to myosin light chain phosphorylation and smooth muscle contraction. There is evidence that potassium channels are gated by changes in redox status, which may be affected by reduced nicotinamide-adenine dinucleotide phosphate oxidase activity [60, 70]. Recently, it has been suggested that redox sensing may occur by means of an adenosine diphosphate-ribosyl cyclase-cyclic adenosine diphosphate-ribose hydrolase pathway [71]. Hypoxia increases reduced  $\beta$ -nicotinamide adenine dinucleotide levels, which activates adenosine diphosphate-ribosyl cyclase and inhibits cyclic adenosine diphosphate-ribose hydrolase. This results in accumulation of cyclic adenosine diphosphate-ribose, which stimulates calcium release from the sarcoplasmic reticulum and subsequent events leading to vasoconstriction. Furthermore, these authors show that a cyclic adenosine diphosphate-ribose antagonist abolishes the sustained phase of HPV.

### Potential Therapies

In the setting of acute hypoxemia, it must be remembered that oxygen therapy is most effective at restoring the physiologic baseline. However, oxygen therapy alone is often insufficient to overcome the primary mechanism responsible for hypoxemia and the associated pulmonary vasoconstriction. This is particularly true when normal physiologic gas exchange is disrupted, such as in ARDS and cyanotic congenital heart disease. Therefore, additional therapies are required to ameliorate HPV and its sequelae. Vasodilators are currently the most common agents used to decrease pulmonary vascular resistance. However, they are often limited by their ability to selectively target the pulmonary vasculature without affecting systemic blood vessels or cardiac performance. Newer agents such as inhaled NO and prostaglandins are currently used in the treatment of primary pulmonary hypertension. Children with congenital heart disease represent a subset of patients that may respond favorably to pharmacologic pulmonary vasodilation [72]. Other agents that may potentially be used in the treatment of HPV include endothelin receptor antagonists, protein kinase C inhibitors, and potassium-channel activators (Fig 4).

#### Inhaled Nitric Oxide

Nitric oxide, synthesized in vascular endothelial cells by NO synthase from the substrate L-arginine, mediates vasodilation through a cGMP-dependent mechanism. Exogenous administration of an inhaled preparation of NO has found broad clinical utility. Inhaled NO reduces pulmonary vascular resistance without affecting systemic vascular resistance or cardiac function [73, 74] and also

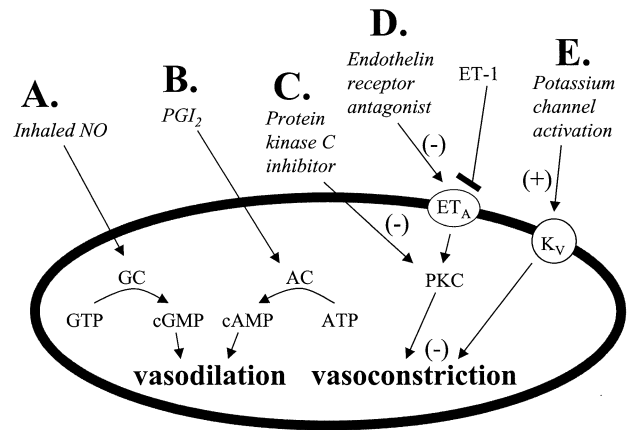


Fig 4. Therapeutic strategies for blocking hypoxic pulmonary vasoconstriction. (A) Inhaled nitric oxide (NO) and (B) prostacyclin (PGI<sub>2</sub>) activate guanylate cyclase (GC) and adenylate cyclase (AC), respectively, to cause vasodilation. (C) Protein kinase C (PKC) inhibitors prevent protein kinase C-mediated vasoconstriction. (D) Endothelin receptor (ET<sub>A</sub>, ET<sub>B</sub>) antagonists prevent endothelin-1 (ET-1) binding to ET<sub>A</sub>, thus inhibiting vasoconstriction. (E) Potassium channel activation prevents calcium-dependent vasoconstriction. (ATP = adenosine triphosphate; cAMP = adenosine 3', 5'-cyclic monophosphate; cGMP = guanine 3', 5'-cyclic monophosphate; GTP = guanosine triphosphate; K<sub>v</sub> = voltage-gated potassium channel.)

decreases inflammatory cytokine production by lung macrophages [13, 14]. The selectivity of NO for the pulmonary circulation and its relatively short half-life are advantages over alternative therapies. Inhaled NO has been used in the treatment of transient pulmonary hypertension secondary to congenital or acquired heart disease, primary pulmonary hypertension, chronic obstructive pulmonary disease, ARDS, and perioperatively in cardiothoracic surgery [75-78]. Inhaled NO is also used as a testing agent to determine vascular reactivity in patients with primary pulmonary hypertension [79, 80]. Furthermore, determination of "operability" in children with congenital heart disease often depends on the severity of concomitant pulmonary vascular disease [81]. Pharmacologic vasodilation with inhaled NO is a useful test to assess pulmonary vasoreactivity before surgical repair [82].

The efficacy of inhaled NO depends on the concentration applied. Frostell and colleagues [83] administered inhaled NO at 40 ppm to healthy human volunteers with induced hypoxia and found selective pulmonary vasodilation without systemic effects. The pulmonary selectivity of inhaled NO made it a promising candidate for the treatment of ARDS. Initial results with inhaled NO did demonstrate improvement in patients with ARDS [75, 84]. Gerlach and colleagues [85] reported that NO doses greater than 10 ppm worsen arterial oxygenation and suggest the use of low doses (1 to 10 ppm) in the treatment of ARDS. In the phase II trial by Dellinger and associates [86] examining the use of inhaled NO in ARDS, dose concentrations ranged from 1.25 to 80 ppm,

and the authors reported no adverse effects except for increased methemoglobin concentration in the groups receiving 40 and 80 ppm. Despite this initial enthusiasm, recent studies question whether inhaled NO improves overall mortality in ARDS [86-88].

A limiting factor in the widespread use of inhaled NO is the potential toxicity of the substance, especially in high concentrations. Chemical reactions with oxygen and reactive oxygen species yield toxic nitrogen oxides and hydroxyl radicals. Nitric oxide reacts with superoxide to form peroxynitrite, which results in pulmonary cellular injury and death [89]. Methemoglobinemia is another potential adverse effect of inhaled NO, but this is a rare complication at the concentrations used in clinical practice [77].

Although highly effective in a select group of patients, the potential toxicity of inhaled NO prompted the search for safer agents that could reproduce the effects of inhaled NO. L-Arginine supplementation may have therapeutic benefit in pulmonary hypertension [90, 91], and NO donors (NONOates), which release NO spontaneously after aerosolized administration, reduce pulmonary hypertension without systemic effects [92-94]. Moya and colleagues [95] reported on the use of an inhaled gas, O-nitrosoethanol, that increased the concentration of S-nitrosothiols, a bioactive form of NO, in airway lining fluid. In a porcine model, inhaled O-nitrosoethanol ameliorated HPV without affecting systemic hemodynamics. Advantages of L-arginine, NO donors, and O-nitrosoethanol over inhaled NO include reduced development of tolerance and reduced formation of toxic metabolites.

#### *Prostaglandins*

Prostaglandins, produced by vascular endothelial cells, have vasodilatory and antiplatelet effects. Exogenous prostaglandin supplementation is supported by studies demonstrating reduced synthesis of prostaglandins in children with pulmonary outflow tract obstruction [96]. Intravenous prostacyclin (epoprostenol) was the first drug approved by the US Food and Drug Administration for the treatment of primary pulmonary hypertension. In a randomized controlled trial, Barst and colleagues [97] found improved exercise capacity, hemodynamics, and survival with intravenous epoprostenol in patients with primary pulmonary hypertension. Although highly effective, intravenous preparations require an indwelling central venous catheter, and the medication needs refrigeration and daily preparation. Chronic subcutaneous infusion of a prostacyclin analog may be an acceptable alternative in the treatment of pulmonary arterial hypertension [98]. Aerosolized prostacyclin (iloprost) has shown selective vasodilatory properties in patients with ARDS [84], and long-term treatment with inhaled iloprost is efficacious in the treatment of primary pulmonary hypertension [99].

#### *Endothelin Receptor Antagonists*

Endothelin-1 is a potent endogenous vasoconstrictor produced by vascular endothelium. Increased plasma levels

of endothelin-1 have been measured in patients with acute lung injury and ARDS [100]. In animal models using isolated lung, endothelin receptor antagonists abrogate HPV [37-39]. There have been several reports [101, 102] of orally administered bosentan, a nonselective ET<sub>A</sub> and ET<sub>B</sub> receptor antagonist, attenuating HPV in rats. Channick and colleagues [103] administered oral bosentan to patients with chronic pulmonary hypertension and observed an improvement in exercise capacity after a 12-week treatment period compared with placebo. Thus, endothelin receptor blockade offers a potential therapeutic target for pulmonary vasoconstriction. However, the efficacy of dual endothelin receptor blockade versus selective ET<sub>A</sub> receptor blockade requires further investigation.

#### *Potassium Channels*

The involvement of potassium channels in regulating HPV provides another potential target for therapeutic intervention. When potassium-channel openers are incubated with isolated pulmonary artery rings, HPV is attenuated [26, 59]. Clinical use of potassium-channel openers is not currently feasible because of the nonspecific actions of these agents. However, targeted activation of specific Kv channels may be beneficial. A recent study [104] used in vivo gene transfer of the Kv1.5 channel in chronically hypoxic rats with pulmonary hypertension and found restoration of potassium current and decreased pulmonary vascular resistance. These results suggest that Kv channels are downregulated with chronic hypoxia and gene transfer of Kv channels may be a novel therapeutic strategy in the management of pulmonary hypertension.

Finally, there are likely other hypoxia-inducible factors that may influence pulmonary vascular tone. For example, endothelial-monocyte-activating polypeptide II, a tumor-derived cytokine that provokes the host inflammatory response, is upregulated by hypoxia [105]. The effects of this and other unknown factors on HPV are subject to future research. Therapies designed to specifically block the synthesis of hypoxia-inducible vasoconstrictive agents may prove to be of therapeutic value for patients with chronic HPV.

#### **Conclusion**

Five decades of research into HPV have provided a wealth of new information. Unfortunately, the results are often contradictory, and the exact mechanism of HPV is still largely unknown. Endothelium-derived factors appear to play a modulatory role, but they are likely not the primary mediators of HPV. Instead, membrane ion channels and their gating mechanisms appear capable of initiating HPV independent of any vasoactive factors. More research is needed to elucidate the oxygen-sensing mechanism and its relation to smooth muscle contraction. This information may eventually translate into adjunctive intervention for processes such as pulmonary hypertension, ARDS, pulmonary vasoconstriction after

pediatric cardiac surgical procedures, and heart and lung transplantation.

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## **Hypoxic pulmonary vasoconstriction in cardiothoracic surgery: basic mechanisms to potential therapies**

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