Review

Modulation of pulmonary vasomotor tone in the fetus and neonate

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Abstract

The high pulmonary vascular resistance (PVR) of atelectatic, hypoxic, fetal lungs limits intrauterine pulmonary blood flow (PBF) to less than 10% of combined right and left ventricular output. At birth, PVR decreases precipitously to accommodate the entire cardiac output. The present review focuses on the role of endothelium-derived nitric oxide (NO), prostacyclin, and vascular smooth muscle potassium channels in mediating the decrease in PVR that occurs at birth, and in maintaining reduced pulmonary vasomotor tone during the neonatal period. The contribution of vasodilator and vasoconstrictor modulator activity to the pathophysiology of neonatal pulmonary hypertension is also addressed.

Keywords: nitric oxide, perinatal, potassium channels, prostacyclin, pulmonary hypertension

Introduction

During late fetal development, PVR is high and PBF is limited to less than 10% of combined ventricular output. This provides adequate nutrition and stimulus for growth to the lung, while optimizing flow to other fetal tissues and the placenta. At birth, mechanical distention of the lungs, increased oxygen tension, and increased shear stress result in a precipitous decrease in PVR and increase in PBF to 100% of cardiac output. Failure of this normal transition leads to persistent right-to-left shunting across fetal cardiovascular channels, resulting in profound hypoxemia and ultimately death. Even when PVR decreases normally at birth (Fig. 1), subsequent pulmonary vasoconstriction in response to hypoxia or other pressor stimuli can lead to a resumption of right-to-left shunting across fetal cardiovascular channels, with potentially fatal consequences. The present review addresses the contributions of NO, prostacyclin, and potassium channel activation to the normal transition from fetal to neonatal pulmonary hemodynamics and to the defense against postnatal pulmonary vasoconstriction.

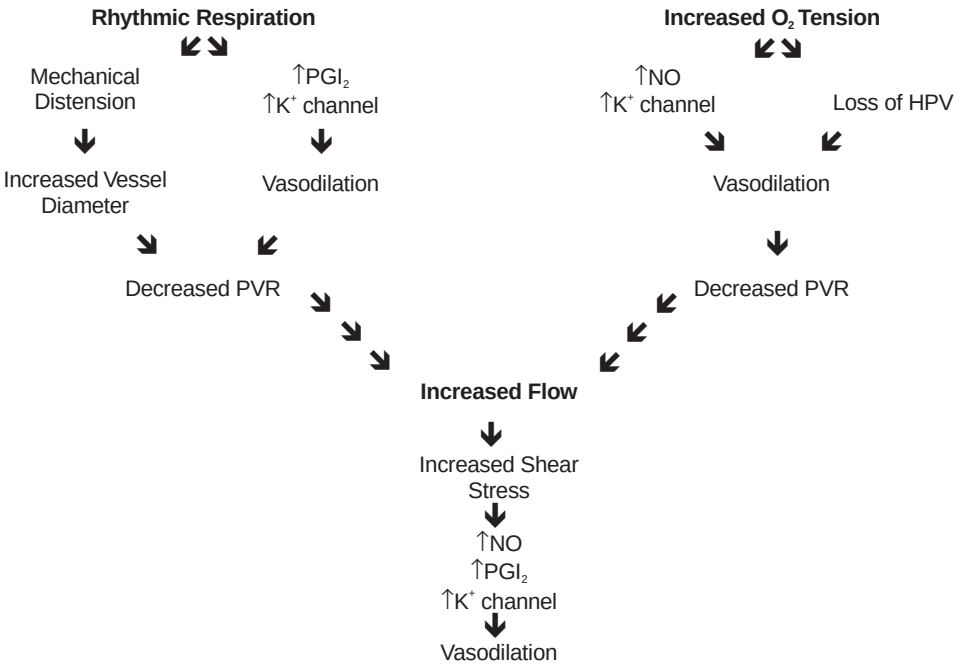
Pulmonary vascular resistance during fetal development

During early fetal development, PBF is limited by the paucity of pulmonary vessels. The number of fetal pulmonary vessels increases by an order of magnitude between mid-gestation and term. PVR remains high during the last trimester, however, and most of the right heart output is shunted across the ductus arteriosus and foramen ovale to the low-resistance systemic circuit. This is due in part to mechanical compression of pulmonary vessels by the fluid-filled, atelectatic lungs. In addition, fetal pulmonary vessels exhibit active tone.

In sheep, at 90–100 days of gestation (term 140 days) maternal hyperoxia increased fetal partial oxygen tension from approximately 20 to 175 mmHg, but had no effect on

$ET_{A/B}$ = endothelin receptor subtype A/B; HPV = hypoxic pulmonary vasoconstriction; K_{ATP} = ATP-dependent potassium channel; K_{Ca} = calcium-dependent potassium channel; K_V = voltage dependent potassium channel; NO = nitric oxide; NOS = nitric oxide synthase; PBF = pulmonary blood flow; PPHN = persistent pulmonary hypertension of the newborn; PVR = pulmonary vascular resistance.

Figure 1



Birth-related stimuli that lead to decreased pulmonary vascular resistance. See text for details. PGI_2, prostacyclin.

fetal PBF [1]. In contrast, after 115–120 days of gestation (ie at >75% term) an increase in fetal partial oxygen tension to 40–50 mmHg was associated with an almost 10-fold increase in PBF [1,2]. Thus, hypoxic pulmonary vasoconstriction (HPV) appears to develop during the third trimester when the number of pulmonary vessels increases.

Unlike the mature pulmonary circulation, the fetal pulmonary vasculature also appears to autoregulate flow through a myogenic response. This may explain why stimuli such as ductal compression, endothelium-dependent vasodilators, and increased oxygen tension cause only a transient increase in fetal PBF [3,4]. Finally, the balance between endogenous vasoconstrictor and vasodilator modulators contribute to the high PVR of the fetus.

Vasoconstrictor modulators in the fetus

Arachidonic acid is metabolized via the cyclo-oxygenase, lipoxygenase, or cytochrome P450-dependent epoxygenase pathways to both vasodilator and vasoconstrictor modulators. Whether the epoxygenase metabolites contribute to fetal vasomotor tone has not been established. The cyclo-oxygenase pathway is active in the fetus [5], however, and gives rise to both vasodilator prostaglandins and the vasoconstrictor thromboxane A_2. The observation that thromboxane A_2 inhibition caused fetal vasodilatation [6] provided evidence that thromboxane A_2 contributes to basal PVR in the fetus. Lipoxygenase metabolites of arachidonic acid, particularly leukotriene D_4, may also contribute to elevated fetal PVR [7], although the importance of this modulator in maintaining basal tone has been questioned [8]. More recently, several studies have suggested that the potent endothelium-derived contracting factor endothelin-1 plays a key role in maintaining high fetal pulmonary vasomotor tone. Endothelin-1 causes vasoconstriction by activating endothelin receptor subtype A (ET_A) receptors, and ET_A receptor blockade enhanced the increase in PBF seen during ductal compression *in utero* [9]. Furthermore, levels of endothelin-1 mRNA expression, endothelin-1 peptide, and ET_A receptor mRNA expression are all highest at 125–130 days of gestation in ovine fetuses, and then decline as term approaches and the need for vasodilatation becomes paramount [10].

Vasodilator modulators in the fetus

The vasoconstrictor effects of hypoxia, myogenic tone, and pressor modulators are counterbalanced by several endogenous vasodilator modulators of vasomotor tone. Of these, NO and prostacyclin play particularly important roles in maintaining adequate PBF during fetal development and in mediating the precipitous decrease in PVR at birth. Endothelial, inducible, and neuronal nitric oxide synthase (NOS) have all been identified in fetal lungs. However, the present review focuses on the role of endothelium-derived NO, which is synthesized from L-arginine by endothelial NOS in the presence of calcium and other cofactors. NO diffuses from endothelial cells into adjacent pulmonary vascular smooth muscle cells, where

it causes vasodilatation through several mechanisms. These include the classic NO-induced activation of guanylate cyclase, leading to increased levels of cGMP. The cGMP in turn stimulates production of a cGMP-dependent kinase that can cause vasodilatation through direct action on myosin phosphorylation. In addition, there is evidence that NO can directly or indirectly activate vascular smooth muscle potassium channels, leading to hyperpolarization and a decrease in cytosolic calcium in both the fetal [11] and mature pulmonary vasculature [12].

Immunohistochemical studies [13] have identified endothelial NOS as early as under one-third of term in lamb fetal lungs. Both expression of the endothelial NOS gene [14] and the NO-induced increase in cGMP concentration [15] appear to increase as term approaches. In addition, the endothelin receptor subtype B (ET_B) receptor, which mediates vasodilatation through a NO-dependent mechanism, is most abundant at term and may explain the apparently paradoxic vasodilatation seen in response to endothelin-1 infusion in the late gestation fetus [10,16]. Other endothelium-dependent pulmonary vasodilators that act by increasing endothelial NOS activity cause acute vasodilatation in fetal pulmonary vessels, and *in utero* administration of NOS inhibitors increases fetal PVR and blocks endothelium-dependent vasodilatation [17–19]. Furthermore, authentic NO, NO donors, and cGMP analogs all cause vasodilatation of fetal lungs and isolated fetal vessels [2,18].

Vasodilator responses to physiologic as well as pharmacologic stimuli appear to be mediated by NO in the fetus. For example, endothelial NO synthesis was greater at elevated oxygen tension in fetal pulmonary arteries [15], and the increase in fetal lamb PBF caused by maternal hyperoxia was blocked by NOS inhibition [4]. Shear stress-induced vasodilatation in the fetus also appeared to be dependent on NO [20], although this might have been due to increased inducible as well as endothelial NOS activity.

Like the NOS isoforms, both constitutive and inducible cyclo-oxygenase (cyclo-oxygenase 1 and 2) are present in the ovine fetal lung [5]. Infusion of several cyclo-oxygenase metabolites of arachidonic acid (eg prostacyclin, and prostaglandins E_1, E_2, D_2 and H_2) causes vasodilatation of the high-vascular-resistance fetal pulmonary circulation. However, prostacyclin is the most potent vasodilator prostaglandin [8]. Prostacyclin acts on the vascular smooth muscle by activating adenylate cyclase. The increased cAMP subsequently causes smooth muscle relaxation either through a direct effect on myosin phosphorylation or by activating a potassium channel via a cAMP-dependent kinase, leading to vascular smooth muscle hyperpolarization [21]. Prostacyclin synthesis increases during the last trimester [22], and several endothelium-dependent vasodilators, including acetylcholine and bradykinin, act at least in part by enhancing prostacyclin synthesis in the fetus [23]. Prostacyclin does not appear to contribute to the vasodilatory effects of maternal hyperoxia [24], however, and cyclo-oxygenase inhibitors have little effect on basal PVR in the fetus, probably because they block both vasoconstrictor and vasodilator prostanoids.

Over the past two decades, calcium-dependent (K_{Ca}), ATP-dependent (K_{ATP}), and several voltage-dependent (K_V) potassium channels have been identified on both pulmonary endothelial and vascular smooth muscle cells. Shear stress can activate endothelial potassium channels, leading to NO synthesis [25], which then causes vasodilatation as described above. Vascular smooth muscle cell potassium channel activation leads to hyperpolarization of the vascular smooth muscle and to a decrease in cytosolic calcium, which results in vasodilatation. These channels can be activated by NO, prostacyclin, and other endothelium-derived hyperpolarizing factors. Studies of isolated arteries and intact lambs [26] suggest that vascular smooth muscle K_{ATP} channels are present in fetal lambs, but inhibition of these channels appears to play little role in regulating basal pulmonary vasomotor tone. K_{Ca} channels are also present in vascular smooth muscle cells of the fetal pulmonary circulation, and there is evidence [11] that they mediate the NO-dependent vasodilatation that is seen in response to some endothelium-dependent vasodilators. K_V channels (particularly $K_{V2.1}$) have been implicated as sensors and mediators of HPV in mature lungs. There appears to be little $K_{V2.1}$ activity in the fetal pulmonary circulation, however. Instead, K_{Ca} channels may play an important role in sensing and mediating fetal and neonatal HPV [27].

Changes in pulmonary vascular resistance at birth

At birth, PVR must decrease abruptly to accommodate 100% of cardiac output, thus allowing the lungs to assume their normal extrauterine gas exchange and metabolic functions. Several inter-related stimuli, including expansion of the lungs, increased oxygen tension and increased systemic vascular resistance, contribute to the decrease in PVR. Collectively, these stimuli, as well as the increase in levels of several endogenous vasoactive substances, lead to a marked increase in the ratio of vasodilator to vasoconstrictor modulators.

It has long been known that the initiation of rhythmic breathing causes vasodilatation, even in the absence of an increase in oxygen tension [28]. This is partly due to mechanical distension of the lungs, which increases vessel radius – a key physical determinant of vascular resistance. In addition, mechanical deformation of the lungs may directly enhance vasodilator modulator synthesis. Studies of neonatal animals found that ventilation caused an increase in prostacyclin synthesis [29] and cyclo-oxygenase inhibition prevented that normal decrease

in PVR associated with rhythmic lung distension at birth [30,31]. NOS inhibition [32] and K_{Ca} channel inhibition [33] also blunt ventilation-induced pulmonary vasodilatation.

Increased oxygen tension at birth also reduces PVR, even in the absence of ventilation [28]. This is partly due to the loss of HPV. The mechanism of HPV remains uncertain, but several factors appear to contribute to the response. Recent studies of mature animal preparations [34,35] support the hypothesis that hypoxia causes ET_A-mediated inhibition of a K_V channel; this leads to vessel depolarization and calcium influx, resulting in vasoconstriction. The increase in oxygen at birth, together with the perinatal decrease in ET_A receptor message, probably contributes to decreased HPV at birth. However, it is noteworthy that K_{Ca} rather than K_V channels may play the depolarizing/hyperpolarizing role in response to changes in oxygen tension [27,36]. In addition to reducing HPV, the increased oxygen tension appears to enhance NO synthesis at birth [15]. A major role for NO in the transitional circulation is further supported by studies [19,32] that showed that NOS inhibition blunts the oxygen-induced decrease in PVR at birth.

Although the above paragraphs imply that oxygenation and ventilation have specific and direct effects on NO and prostacyclin synthesis, these stimuli, in conjunction with the recruitment and distension of the pulmonary vasculature by increased left atrial pressure, may act together through a flow-induced increase in shear stress. In the postnatal pulmonary circuit, increased shear stress in response to increased flow is a potent stimulus for endothelium-derived vasodilator modulator synthesis. This in turn establishes a positive feedback loop that enhances PBF until the increase in shear stress due to increased flow is offset by the decrease in shear stress due to increased vessel diameter. Distinguishing the role of shear stress, or indeed the effects of increased synthesis of other endogenous vasoactive substances (eg adenosine, bradykinin, etc), from the direct effects of oxygen and ventilatory movements remains an unfinished task.

Changes in pulmonary vascular resistance during neonatal development

Following the initial acute decrease in PVR at birth, there is a more gradual decline in resistance over the following days and weeks. Initially, this decrease in PVR reflects further recruitment and distension of the vascular bed, and spreading of the endothelial and vascular smooth muscle cells [37]. In addition, some studies [38] have identified a progressive decrease in arterial muscularization during the first few days of life. These developmental changes lead to a major decrease in PVR within days of birth [39]. Subsequently, lung growth and the increase in intra-alveolar vessel number lead to a more gradual reduction in PVR until adult levels are achieved.

During the early newborn period, however, an increase in PVR due to hypoxia or other pressor stimuli can lead to a resumption of right-to-left shunting across fetal cardiovascular channels. The resultant profound hypoxemia can lead to significant morbidity or death if pulmonary vasoconstriction is not reversed. Fortunately, despite evidence of increased pulmonary vascular muscularization in young newborn lungs, HPV appears to be more attenuated in younger than in older neonates [40–43]. Several factors may contribute to the neonatal defenses against pulmonary vasoconstriction. There is some evidence that hypoxia is not sensed as well by the younger newborn pulmonary vasculature [42], possibly because of the relative paucity of $K_{V2.1}$ channels [27]. Alternatively, the relative immaturity of neonatal pulmonary vascular smooth muscle may impair contractility [44]. Finally, there is considerable evidence that modulators of vasomotor tone attenuate vasoconstriction more in younger than in older newborns.

Prostacyclin synthesis is enhanced by hypoxia in arteries from 1- to 2-week-old newborns, but not in arteries from older newborns [22]. Furthermore, prostacyclin concentrations are higher in the perfusate of hypoxic 1-day-old than in 1-month-old lamb lungs [42]. In addition, prostaglandins E_1, E_2 and D_2 cause vasodilatation in hypoxic newborn lungs, but cause vasoconstriction in older animals [8]. Finally, cyclo-oxygenase inhibition enhances HPV more in lungs from lambs that are younger than 4 days old than in those from lambs older than 2 weeks [43]. Whether NO modulates pulmonary vasomotor tone more in younger than in older newborns is more controversial. In some studies of isolated vessels [18,45] endothelium-dependent vasodilatation was greater in arteries from younger than in those from older animals, whereas in others [46] it decreased with age. On the other hand, studies of isolated lungs suggest that both endothelium-dependent and -independent vasodilatation is greater in younger newborns [47], and NOS inhibition increased vasoconstriction more in lungs from younger than in those from older newborns [48].

Vasodilator modulators and the pathogenesis of neonatal pulmonary hypertension

Not only does acute inhibition of vasodilator modulators increase basal PVR and enhance vascular reactivity in normal newborn lungs, but also there is evidence that an imbalance between vasoconstrictor and vasodilator modulators may contribute to the pathogenesis of various forms of neonatal pulmonary hypertension. The syndrome of persistent pulmonary hypertension of the newborn (PPHN) is characterized by abnormally increased pulmonary vascular muscularization and severe neonatal pulmonary hypertension in the absence of other pulmonary or cardiac disease. Studies conducted during the 1970s and 1980s [49] found that chronic *in utero* cyclo-oxygenase inhibition could result in the anatomic and physiologic features of

PPHN. More recently, a study of newborn lambs [50] showed that *in utero* infusion of a NOS inhibitor for 10 days mimicked the physiologic, but not the anatomic features of PPHN. In addition, chronic fetal ET_B receptor inhibition, which results in unopposed ET_A-mediated constriction, led to pulmonary hypertension [51]. Conversely, both acute and chronic intrauterine pulmonary hypertension due to ductal compression led to impaired endothelium-dependent vasodilatation [52,53] and reduced K_{Ca} channel expression [54]. Chronic hypoxia during the newborn period also leads to pulmonary hypertension, associated with decreased NOS protein and message, and impaired endothelium-dependent vasodilatation [55,56].

The pathophysiology of PPHN is not only dependent on a deficiency in the vasodilator modulators, but may also result from an excess of vasoconstrictor modulators. In one study of infants with PPHN [57], leukotriene C_4 and leukotriene D_4 concentrations were higher than in neonates without PPHN. Lung thromboxane A_2 concentrations were also higher in an ovine model of PPHN than in control lambs [58]. Finally, serum endothelin-1 concentrations were higher in infants with PPHN [59].

Conclusion

Although modulators of pulmonary vasomotor tone appear to contribute to elevated fetal pulmonary vasomotor tone, the decrease in PVR at birth, and the defenses against pulmonary vasoconstriction during early life, many questions remain. Is there sufficient redundancy among modulator classes that the loss of one can be compensated for by an increase in another? Do the reported differences in modulator activity between arteries and veins mean that all modulators must be synthesized in order to achieve normal development [17,60]? What do apparent interspecies differences in modulator activity imply for the prevention and therapy of neonatal pulmonary hypertension in humans? Can the loss of modulator activity be identified and treated *in utero*? Future studies must address these and other questions in order to gain a better understanding of the physiology and pathophysiology of pulmonary vasomotor tone in the fetus and young neonate.

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