Controlling pulmonary vascular resistance

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***Abstract*: The dynamic nature of pulmonary vascular resistance (PVR) in the neonate makes it difficult to maintain a Qp/Qs approximating 1. The reactive pulmonary vasculature is unpredictable and may result in poor systemic perfusion with pulmonary edema or inadequate oxygenation and elimination of carbon dioxide. The increase of pulmonary blood flow is at the expense of perfusion of the body and perfusion of the body at the expense of oxygenation and removal of carbon dioxide. The mortality is high if PVR is not managed properly and, therefore, an understanding of the physiology and treatment options is important to lowering the morbidity and mortality of unequal Qp/Qs. This article reviews the normal changes in PVR at birth, discusses various dynamic parameters of PVR, outlines accepted treatment options to maintain a Qp/Qs close to 1 in patients with reactive pulmonary vasculature, and discusses a new therapy for pulmonary hypertension that is being evaluated in the basic science laboratory.**

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***Key words*: pulmonary vascular resistance; nitric oxide; prostacyclin; milrinone; prostaglandin E1; eiconasoids; PVR**

Normal fetal circulation

Fetal pulmonary circulation is characterized by high arterial pressure and high vascular resistance that cause blood ejection by the right ventricle to bypass the lungs and ensure adequate blood flow to the fetal body. Blood returning from the placenta via the umbilical vein mixes with that in the inferior vena cava and traverses the foramen ovale to the left atrium and, a smaller portion, through the tricuspid valve to the right ventricle. Blood flow from the superior vena cava enters the right ventricle. Blood in the right ventricle is ejected into the main pulmonary trunk and then more than 90% passes to the descending aorta through the ductus arteriosus while the rest is ejected into the pulmonary system. Blood in the left ventricle is ejected into the ascending aorta and 90% supplies the upper body/head. The other 10% passes to the descending aorta to supply the lower body. The fetal cardiac circuits act in parallel rather than in series as in the newborn (Fig. 1).[1,2]

Blood pressures in the fetus are shown in Fig. 2. The pressures of the right ventricle, left ventricle, main pulmonary trunk, ascending aorta, and descending aorta are nearly equal. Pulmonary blood flow is as low as 100 ml/100 g lung weight. Fetal gas exchange occurs in the placenta, and pulmonary blood flow mainly meets the metabolic requirements of the lungs. Pulmonary vascular resistance (PVR) early in gestation is higher than in infants and adults because few arteries are present. In the fetal lamb model, the number of small blood vessels in the lungs increases forty-fold between 85 and 145 days of gestation. Blood flow per unit of fetal lung does not change. The decrease of PVR during the last half of gestation is associated with growth of new arteries and an increase of cross-sectional area of the pulmonary vasculature. The baseline PVR in the fetus, however, is still much higher than after birth. The high PVR and low pulmonary blood flow in the fetus are caused primarily by vasoconstriction.[3]

Vasoconstrictors of the pulmonary circulation of the fetus and newborn include arachidonic acid, prostaglandin F2α, thromboxane A2, leukotriene D4, and low oxygen tension. Decreasing oxygen tension in fetuses (103- to 104-day gestation) does not increase PVR, but PVR doubles if oxygen tension is low at 132- to 138-day gestation. Increasing oxygen tension before 100 days gestation does not change PVR, but decreases PVR markedly and increases blood flow to normal newborn levels at 135 days of gestation.[4,5] These findings suggest that the reactivity of the pulmonary vasculature changes during development.

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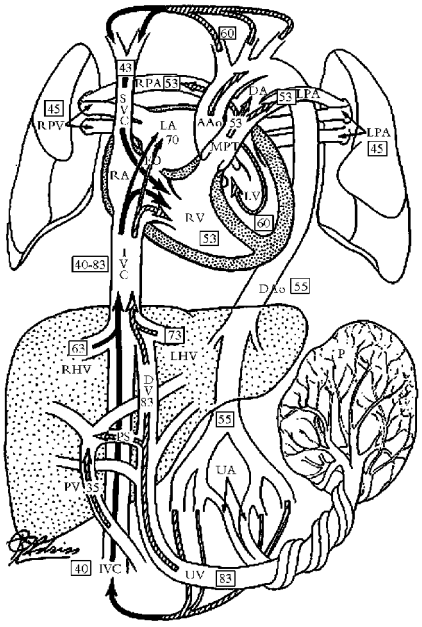


Fig. 1. Circulation of the fetus.

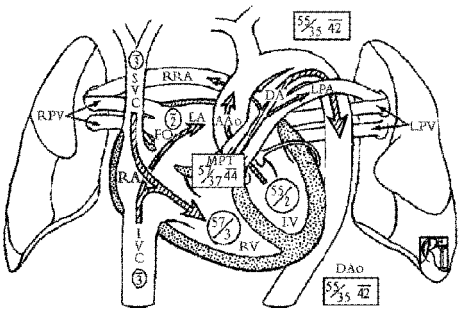


Fig. 2. Pressures of fetal circulation.

Changes at birth

At birth, the decrease of PVR is initiated by ventilation of the lungs with a gas, lowering of carbon dioxide tension, and raising oxygen tension in the lungs. Increasing oxygen levels alone decreases PVR and increases blood flow in the fetal lungs. Inflation of the lungs with a gas may decrease PVR by mechanical effects. Oxygen may dilate by direct effects on the vascular smooth muscle. These stimuli may also dilate by releasing endogenous mediators. At birth, small pulmonary vessels are highly muscular, pulmonary vascular resistance is high, and vascular reactivity is great. Normal pulmonary vessels become thin-walled and vascular resistance falls. Regulators of PVR include physical factors, vasoactive factors, and vascular remodeling.[6-9]

Regulators of pulmonary vascular resistance

Physical factors affecting PVR are expressed by two equations: the hydraulic equivalent of Ohm's law and the Poiseuille-hagen relation. These are shown below:

Hydrolic equivalent of Ohm's law

$R = (P_{PA} - P_{PulmV})/Q$

R: pulmonary vascular resistance; P: pressure (pulmonary artery and pulmonary veins); Q: pulmonary blood flow.

Poiseuille-hagen relation

$R = (P_{PA} - P_{PulmV})/Q = (8/\pi)(l/r^4)(\eta)$

R: pulmonary vascular resistance; P: pressure (pulmonary artery and pulmonary veins); Q: pulmonary blood flow; l: length of tubular system; r: overall internal radius of the tube; η: coefficient of viscosity.

PVR increases as functional residual capacity increases to total lung capacity. Inflation of the lungs, therefore, is a determinant of PVR.

Oxygen, carbon dioxide, and pH also influence PVR. Reduction of PO_2 to less than approximately 30 mm Hg in newborn animals increases PVR. Low PO_2 in the fetus accounts for some pulmonary vasoconstriction and increase of PVR. Effects of the change in oxygen tension is mainly due to local factors (direct or mediated by secondary release and activity of vasoactive substance). The response of PVR to changing oxygen tension is affected by pH (acidemia accentuates the vasoconstriction asociated with hypoxemia, but not by carbon dioxide).

Eicosanoids is a collective name for molecules derived from 20-carbon fatty acids and include prostaglandins, prostacyclins, thromboxanes, leukotrienes, lipoxins, and peroxy- or hydroxyl-fatty acid derivatives. Arachidonic acid is derived from linoleic acid (9,12-octadecadienoic acid) and is metabolized through 3 major pathways (Fig. 3). Exogenous PGE_2 and PGI_2 (prostacyclin) are vasodilators in the perinatal period. Mechanical stimulation of the lung (stretch) induces prostacyclin production. Ventilation of fetal lungs, without changing oxygen pressure, increases the venous blood concentration of prostacyclin, indicating production by the lungs, and the decrease of PVR with ventilation is attenuated by cyclooxygenase inhibition with indomethacin. Pulmonary vascular endothelium in culture also produces prostacyclin and is stimulated by histamine, angiotensin Ⅱ, bradykinin, catecholamines, thyroid hormone, estradiol, platelet-activating factor, leukotrienes, ATP, and shear stress.

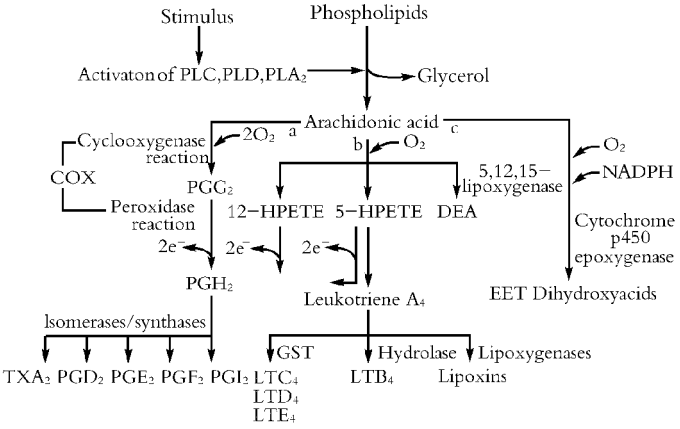
Vasodilation by prostacyclin is mediated by cyclic adenosine monophosphate. Prostacyclin and its metabolites are fetal pulmonary vasodilators more potent than PGE_2. Meclofenamate (another prostaglandin synthesis inhibitor) blocks almost all of the response to rhythmic distension of the lungs with a gas that does not change oxygen and carbon dioxide tension. The role of endoge-

nous prostacyclin at birth is questioned: production declines within hours after birth, and indomethacin only moderately disrupts the decrease of PVR, which occurs at birth and does not disrupt the transition to gas exchange by the lungs. However, inhaled prostacylin has the same effect and may be useful in treating high PVR.[10-12]

Purines, adenosine triphosphate and adenosine are also potent vasodilators in the fetal lamb. Specific membrane receptors for these purines are present on endothelial cells and smooth muscle cells. Adenosine receptors (P_1) are divided into two types: A_1 receptors, which are located predominantly in the heart where they mediate negative chronotropic and inotropic effects and A_2 receptors, which are located on endothelial cells and mediate vasodilation. ATP receptors (P_2) are, likewise, divided into two types: P_{2x} receptors are found on smooth muscle cells and mediate vasoconstriction and P_{2y} receptors are found on endothelial cells and mediate vascular relaxation. Vasodilation caused by adenosine and ATP may occur indirectly through effects on vascular endothelium or through direct effects on smooth muscle cells. ATP-induced vascular relaxation via P_{2y} receptors is associated with formation of endothelium-derived relaxing factor (nitric oxide) resulting in an increased concentration of cGMP in smooth muscle cells. Adenosine stimulates P_1-A_2 receptors on pulmonary arteries and veins and elicits vaso-dilation via the endothelial synthesis of nitric oxide. ATP also induces the release of prostacyclin via the P_{2y} receptor. This may contribute to vasodilation. Adenosine and ATP play a significant role in the mediation of oxygen-induced pulmonary vasodilation in fetal lambs (Fig. 4).

Nitric oxide (endothelium-derived relaxing factor) is a potent dilator of the fetal pulmonary circulation. There is strong evidence that nitric oxide is an important mediator of the decrease of PVR at birth.[13] The fetal pulmonary circulation dilated by an increase in oxygen tension is mediated by the endogenous synthesis of nitric oxide.[14,15] Acetylcholine, bradykinin, and histamine stimulate the production of nitric oxide by vascular endothelium.[16] Nitric oxide, in turn, activates soluble guanylate cyclase to produce cGMP.[17] cGMP induces relaxation of vascular smooth muscle through the activation of cGMP-dependent protein kinase that lowers intracellular calcium (in part through the activation of potassium channels). Inhaled nitric oxide has the same effects as that produced by the body and is used in the management of high PVR.[18-22]

Leukotrienes may partially mediate hypoxic pulmonary vasoconstriction in adults and newborns. In fetal lambs, leukotriene receptor antagonism and inhibition of leukotriene synthesis increase pulmonary blood



The three major pathways involved in arachidonic acid metabolism
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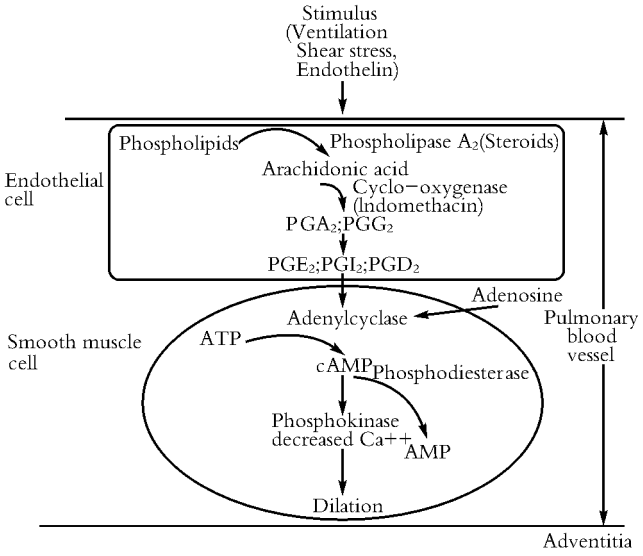
Fig. 3. Three major pathways in arachidonic acid metabolism.



The cAMP pathway of vasodilation

Fig. 4. Roles of ATP and adenosine in vasodilation of pulmonary blood vessels.

flow to levels associated with ventilation after birth.

Vascular remodeling during the first 3 days of life is also an important factor in the change of PVR. The decrease of PVR is accompanied by structural remodeling of the pulmonary vascular bed (from the main arteries to the capillaries) and changes in smooth muscle shape and geometric orientation cause the lumens to enlarge. There is maturation of smooth muscle function, thinning of endothelial cells, and changes in elastic and connective tissue over the first several weeks of life.

Principles of managing pulmonary hypertension

In the neonate, infant, and child, etiologies of elevated

pulmonary vascular resistance include parenchymal lung disease, release of vasoconstriction, an abnormal vascular bed (i. e. acute asphyxia, chronic hypoxemia, constriction of the ductus arteriosus, and hypoplasia of the lungs), and blockade of the nitric oxide pathway. The principles of managing the resultant pulmonary hypertension are the same regardless of the etiology.[23-26] First, it is necessary to minimize lability by using sedation and minimal stimulation. Paralysis may be needed. Patient-triggered ventilators are better in these patients. Second, it is imperative to support the systemic circulation and maintain the systolic blood pressure at the upper limits of normality (decreases right-to-left shunting at the ductal or foramen level). Volume and/or inotropes may be needed. Third, correction of alveolar hypoxia/hypercarbia is required. Fourth, recruitment of lung units is necessary using surfactant, liquid perfluorocarbon, and/or high frequency oscillation. Fifth, vasodilation of the pulmonary vasculature is required using nonselective vasodilators (tolazoline, nitriprusside, prostacyclin, fentanyl, isoproterenol, chlorpromaze) and/or selective vasodilators (respiratory alkalosis, nitric oxide, blockade of cGMP), if needed. Extracorporeal membrane oxygenation (ECMO) may be used as a last resort.[27]

Role of prostacyclin and milrinone in treatment of pulmonary hypertension

Prostacyclin induces a dose related decrease of pulmonary artery pressure, pulmonary artery resistance, and right atrial pressure. Cardiac output and systemic oxygen delivery are increased. Both endogenous and inhaled prostacyclin induce relaxation of vascular smooth muscle and decreased platelet adhesion, aggregation, and activation (Fig. 5). $T_{1/2}$ is 2 to 3 minutes and metabolites may be measured in urine and plasma. It has been used in the acute and chronic therapy of primary pulmonary hypertension in adults;[28] however, some of the first reports of its use were in infants and children. Lack of selectivity of infused prostacyclin leads to generalized vasodilation and perfusion of ventilated and non-ventilated lung. Systemic vasodilatation is problematic in pulmonary hypertension. Advantages of inhaled prostacyclin include no systemic side effects like hypotension, and its short half-life makes it easy to titrate its effects on PVR. Lack of toxicity of prostacyclin or its metabolites make accurate measurement of the drug in inspiratory and expiratory gases not critical (unlike nitric oxide), and the delivery system for inhaled prostacyclin is inexpensive and readily available at any medical center. Inhaled prostacyclin has been rarely reported in infants and children.[29-32] Doses of inhaled prostacyclin delivered to adults and children in clinical trials vary from 10 to 100 ng · kg^{-1} · min^{-1}. In studies by Haraldsson et al,[33,34] inhaled prostacylin resulted in a reduction of PVR greater than 20% with a decrease of SVR less than 5%. This was additive with inhaled milrinone.[35-37]

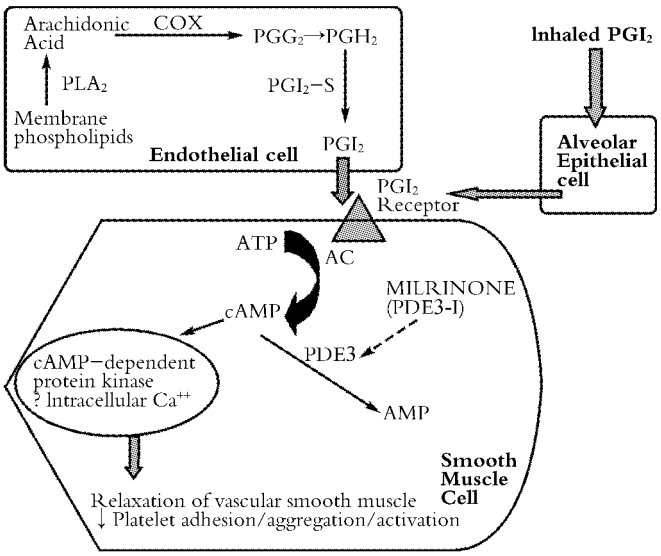


Fig. 5. Roles of ATP and adenosine in vasodilation of pulmonary blood Vessels. PLA_2: phospholipase A_2; COX: cyclo-oxygenase; PGI_2-S: prostacyclin synthase; AC: adenylate cyclase; PGI_2: prostacyclin; PDE_3: phosphodiesterase III; PDE_3-I: inhibitor of PDE_3.

Intracellular levels of second messenger molecules like cAMP and cGMP are controlled by a group of cyclic nucleotide hydrolyzing enzymes called phosphodiesterases.[38-43] Amrinone and its analog milrinone are inhibitors of the low-K_m cGMP-inhibited cAMP phosphodiesterase (Type III PDE). Their positive inotropic and chronotropic effects are ascribed to an increase in cAMP levels.[44] Unlike catecholamines, milrinone produces positive inotropic effects with concurrent vasodilation and no chronotropic effect. It has been a valuable drug in the management of congestive heart failure, shock, and post-operative management following cardiac surgery.

At the University of Buffalo, intratracheal prostacyclin and intravenous milrinone are being evaluated in the management of primary pulmonary hypertension of the newborn (PPHN).[45-49] Increasing doses of intratracheal prostacyclin decreases PVR in a ductal ligation model of pulmonary hypertension in a dose dependent manner. Pulmonary arterial pressures also decrease with increasing does of intratracheal prostacyclin with no significant drop in mean systemic blood pressures. Pulmonary blood flow increases—more apparent at higher doses. The same changes are seen in the L-NAME model of PPHN.

Intravenous milrinone by itself decreases PVR by greater than 20%. The addition of intratracheal prostacyclin further decreases PVR. Intravenous milrinone produces a marked decrease in PVR at lower does of intratracheal prostacyclin compared to intratracheal prostacyclin alone. This synergistic effect is being further evaluated in the ductal ligation lamb model of PPHN.

Summary

PVR is highest during early gestation and decreases during pregnancy. At birth, PVR normally decreases and is dependent on regulators of pulmonary vascular resistance. The latter include physical factors, vasoactive factors, and vascular remodeling. Elevated pulmonary vascular resistance may be a result of parenchymal lung disease, release of vasoconstriction, an abnormal vascular bed, and blockade of the nitric oxide pathway. Current principles of managing pulmonary hypertension include minimizing lability, supporting the circulation, correction of alveolar hypoxia and/or hypercarbia, recruitment of lung units, vasodilating, and the use of extracorporeal membrane oxygenation when indicated. New management strategies that are being evaluated in the laboratory are inhaled prostacyclin with or without intravenous milrinone.

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