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Pulmonary hypertension management in neonates

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ABSTRACT

The management of pulmonary hypertension is multi-faceted, with therapies directed at supporting cardiovascular and pulmonary function, treating the underlying cause (if feasible), and preventing irreversible remodeling of the pulmonary vasculature. Recently, manipulation of signaling pathways and mediators contained within the pulmonary vascular endothelial cell has become a new target. This article will review the pathophysiology of pulmonary hypertension and the broad principles involved in its management, with specific emphasis on pharmacological therapies directed at the pulmonary vascular endothelium.

Pulmonary hypertension affects almost 10% of infants with respiratory failure, with one-third of these infants being near-term or term neonates. It is defined as an elevation of pulmonary arterial pressures >25 mmHg when there is equal distribution of pulmonary blood flow to all lobes of the lung bilaterally.[1] From a practical point of view, pulmonary hypertension can also be defined as pulmonary arterial pressure that is $>50\%$ of systemic blood pressure.

The classification of pulmonary hypertension (PHTN) has undergone significant revision since its initial description in 1998 (WHO Classification), which focused predominantly on adult diseases.[2] However, two subsequent modifications, the Dana Pont in 2009, and most recently the Nice modification in 2013, have highlighted specific aspects of pediatric disorders, including pulmonary hypertension of the newborn and developmental lung diseases, which include congenital diaphragmatic hernia.[3,4] The basic pathophysiology of PHTN is related to increased pulmonary vascular resistance (PVR) with right to left shunting through the ductus arteriosus (DA) and/or foramen ovale (FO). This leads to a reduction in pulmonary blood flow and systemic desaturation. Associated with PHTN is cardiac dysfunction, primarily of the right ventricle (RV), secondary to increased afterload provided by the pulmonary circulation. There is also concomitantly reduced coronary perfusion to the RV due to a reduced pressure gradient between the aorta and the RV.

The management of neonatal PHTN is complex and requires a firm understanding of the transitional circulation and factors affecting pulmonary vascular resistance in order to provide initial cardiovascular and respiratory support. When these initial strategies fail, novel therapies that target the pulmonary vascular endothelium are utilized.

Transitional circulation and the pulmonary vasculature

At birth, the fetus must make an abrupt and rapid transition from a liquid-filled environment to an air-filled one. *In utero,* low oxygen tension levels lead to high pulmonary vascular resistance (PVR). Thus, 85–90% of the cardiac output is shunted away from the lungs, through the FO and DA, to the systemic circulation. There is also increased production of vasoconstrictors, such as endothelin-1 (ET-1), and decreased production of vasodilators such as nitric oxide (NO) and prostacyclin (PGI_2), all of which keep the basal pulmonary vascular tone high.[5] As the fetus approaches term, the levels of NO and PGI_2 increase in preparation for increased pulmonary blood flow once the fetus is born. After delivery, there is rapid clearance of alveolar fluid and a dramatic increase in alveolar oxygen tension that causes pulmonary vasodilation and eventual closure of the patent FO and DA.

The normal pulmonary vasculature is a low-pressure system that is able to deliver the entire cardiac output (CO) at a fraction of systemic pressures. It also is a high compliance and low resistance system due to its organization as a continuous sheet that behaves as parallel instead of series circulation. Normal pulmonary vessels are quite elastic and have less smooth muscle, which allows for an almost 2.5-fold increase in blood flow without increasing pulmonary arterial pressures. Indeed, there is very minimal distal smooth muscle extending into the intra-acinar pulmonary arteries and a single cell lining of endothelium. Pulmonary vascular resistance

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reduces and its reactivity stabilizes over the first 4–6 post-natal weeks of life.

Factors affecting pulmonary vascular resistance

Several factors affect PVR. These include the following: (a) abnormal transitional changes to the pulmonary vasculature, (b) altered hemodynamics and pulmonary blood flow, (c) lung volume and recruitment, (d) pulmonary vascular smooth muscle tone, (e) the endothelium, and (f) alveolar/arteriolar development.

Abnormal transitional changes

Abnormal transitional changes within the pulmonary vasculature can occur as a result of several mechanisms. These include fetal hypoxia, maternal toxic exposures, and lung developmental problems.[6,7] This abnormal transitioning leads to remodeling of the pulmonary vasculature, where smooth muscle extends well into the intra-acinar pulmonary arterioles. This leads to pulmonary vascular hyper-reactivity and decreases the lumenal diameter of the pulmonary vessels, which both contribute to increases in PVR.

Hemodynamics and pulmonary blood flow

The RV is extremely sensitive to increases in afterload, leading to significant reductions in RV output and subsequently, pulmonary blood flow. In the context of severe PHTN and a failing RV, prostaglandin has been used to maintain DA patency, sacrificing oxygenation to maintain systemic blood flow. Concomitant left ventricular (LV) dysfunction can make the clinical picture even worse. LV dysfunction from hypoxia can lead to left atrial distension, *pulmonary venous hypertension,* and subsequent pulmonary edema and surfactant dysfunction. The addition of pulmonary arterial vasodilators such as inhaled nitric oxide (iNO) in this context may actually worsen the hypoxia and ventilation-perfusion (V/Q) mismatching that has already occurred as more blood enters the pulmonary vasculature.

The use of inotropic support aids in improving cardiac output and emptying. Thus, efforts should be made to maintain blood pressure norms for age and preductal saturations above 85%. Furthermore, the use of inotropic support to increase pulmonary blood flow actually has beneficial effects, as this will recruit otherwise open yet poorly perfused pulmonary arterioles. This recruitment ultimately leads to lower PVR.

Lung volumes and recruitment

Another important factor affecting PVR is optimal lung recruitment. Alveolar overdistension leads to compression of intra-alveolar blood vessels and distension of the extra-alveolar ones, thereby increasing PVR. If inadequate lung recruitment occurs (i.e., insufficient lung volumes), the extra-alveolar vessels are collapsed and contorted, again leading to increased PVR. Thus, ventilation around the functional residual capacity (FRC) of the lung ideally leads to the lowest PVR.[8]

Pulmonary vascular tone

Unlike systemic blood vessels, pulmonary arteries vasoconstrict with alveolar hypoxia and this is a necessary mechanism to improve V/Q mismatching. However, in severe cases of parenchymal disease

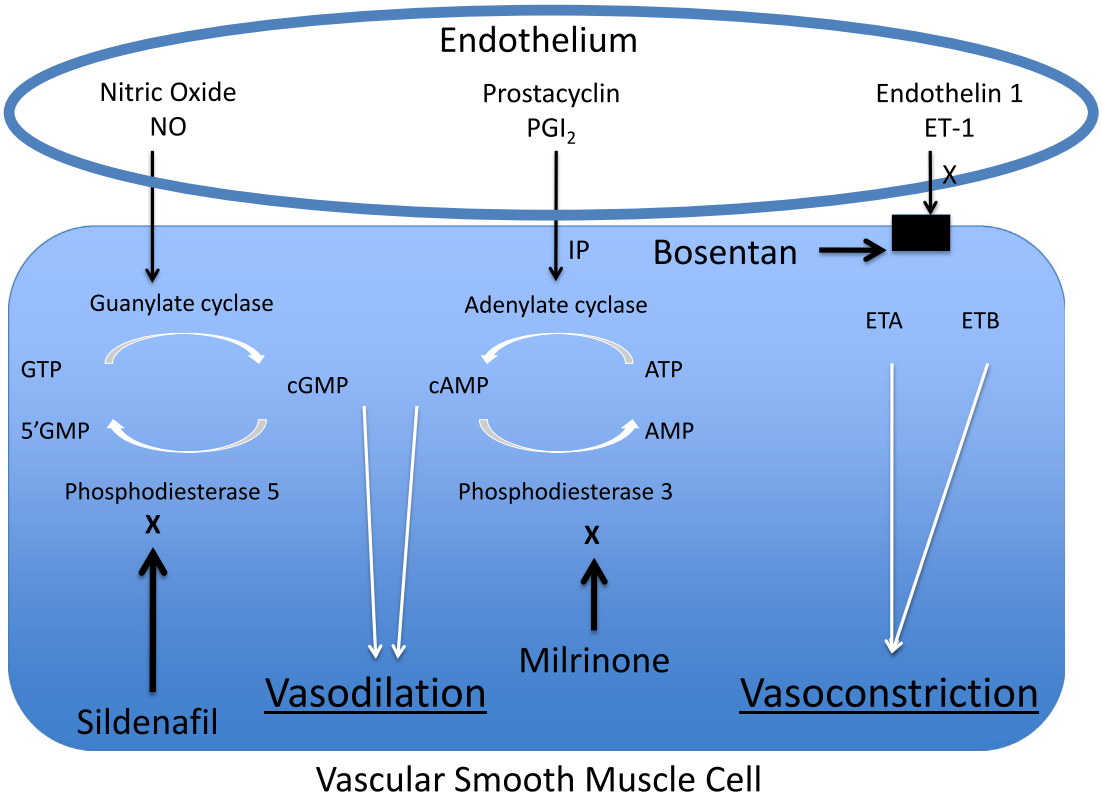

Fig. cGMP and cAMP are second messengers within the pulmonary vascular endothelium that lead to pulmonary vasodilation. Increased levels of cGMP are produced through the use of inhaled nitric oxide (iNO), which induces soluble guanylate cyclase, or through the administration of sildenafil, which prevents its degradation by phosphodiesterase-5. Prostanoids such as prostacyclin ($PG1_2$) act on adenylate cyclase to increase conversion of cAMP from adenosine triphosphate (ATP). The degradation of cAMP to adenosine monophosphate can be inhibited through the use of milrinone, which inhibits phosphdiesterase-3. Bosentan, an endothelin-1 receptor (ET-1) antagonist, acts on cell-surface receptors on the pulmonary vascular endothelium to prevent the production of endothelin-A (ET-A) and endothelin-B (ET-B), both of which mediate vasoconstriction.