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REVIEW

Pathophysiology of persistent pulmonary hypertension of the newborn: Impact of the perinatal environment

Physiopathologie de l'hypertension artérielle pulmonaire persistante du nouveau-né : rôle de l'environnement périnatal

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Summary The main cause of pulmonary hypertension in newborn babies results from the failure of the pulmonary circulation to dilate at birth, termed 'persistent pulmonary hypertension of the newborn' (PPHN). This syndrome is characterized by sustained elevation of pulmonary vascular resistance, causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and foramen ovale and severe hypoxaemia. It can also lead to life-threatening circulatory failure. There are many controversial and unresolved issues regarding the pathophysiology of PPHN, and these are discussed. PPHN is generally associated with factors

Abbreviations: CDH, congenital diaphragmatic hernia; cGMP, cyclic guanosine monophosphate; ECMO, extracorporeal oxygenation; eNOS, endothelial nitric oxide synthase; iNO, inhaled nitric oxide; NO, nitric oxide; NOS, nitric oxide synthase; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PO_2, oxygen pressure; PPHN, persistent pulmonary hypertension of the newborn; PUFA, polyunsaturated fatty acid; PVR, pulmonary vascular resistance; SpO_2, saturation of peripheral oxygen; SSRI, selective serotonin reuptake inhibitor; VEGF, vascular endothelial growth factor.

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such as congenital diaphragmatic hernia, birth asphyxia, sepsis, meconium aspiration and respiratory distress syndrome. However, the perinatal environment—exposure to nicotine and certain medications, maternal obesity and diabetes, epigenetics, painful stimuli and birth by Caesarean section—may also affect the maladaptation of the lung circulation at birth. In infants with PPHN, it is important to optimize circulatory function. Suggested management strategies for PPHN include: avoidance of environmental factors that worsen PPHN (e.g. noxious stimuli, lung overdistension); adequate lung recruitment and alveolar ventilation; inhaled nitric oxide (or sildenafil, if inhaled nitric oxide is not available); haemodynamic assessment; appropriate fluid and cardiovascular resuscitation and inotropic and vasoactive agents.

MOTS CLÉS
Hypertension pulmonaire ;
Nouveau-né ;
NO inhalé ;
Hypoxémie

Résumé La principale cause d'hypertension pulmonaire du nouveau-né résulte d'une vasodilatation pulmonaire insuffisante à la naissance, appelée « hypertension artérielle pulmonaire persistante du nouveau-né » (HTAPP). Ce syndrome est caractérisé par une élévation des résistances vasculaires pulmonaires, responsable d'un shunt droit-gauche par le foramen ovale et le canal artériel et d'une profonde hypoxémie. L'HTAPP est à risque vital lorsque qu'elle s'accompagne d'une défaillance circulatoire. La prise en charge nécessite un recrutement pulmonaire adéquat, l'inhalation de monoxyde d'azote et un support cardiovasculaire adapté. Néanmoins, la physiopathologie et la prise en charge sont toujours l'objet de recherches innovantes. Ainsi, de plus en plus d'arguments existent pour penser que l'environnement périnatal joue un rôle déterminant dans la genèse et l'aggravation de ce syndrome.

Background

Pulmonary hypertension in newborns results from the failure of the pulmonary circulation to dilate at birth. Termed 'persistent pulmonary hypertension of the newborn' (PPHN), it occurs in an estimated 1—2 infants per 1000 live births [1]. This syndrome is characterized by sustained elevation of pulmonary vascular resistance (PVR), causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and foramen ovale and severe hypoxaemia [2,3] (Fig. 1). PPHN is frequently associated with low systemic pressure and low cardiac output because of increased right ventricular afterload and myocardial dysfunction [2,4]. PPHN-induced circulatory failure is a life-threatening condition. Cardiac failure further impairs oxygen delivery to the tissues and contributes to significant mortality and morbidity in newborn infants with PPHN [2—4].

Management requires adequate lung recruitment and alveolar ventilation, inhaled nitric oxide (iNO), and appropriate fluid and cardiovascular resuscitation [5]. Early initiation of inotropic and vasoactive agents is commonly used to increase cardiac output, maintain adequate blood pressure and enhance oxygen delivery to the tissue [4,6]. Nevertheless, there are many controversial and unresolved issues regarding the pathophysiology and the most effective management of PPHN. Growing evidence is emerging that indicates that the perinatal environment plays a key role in this syndrome.

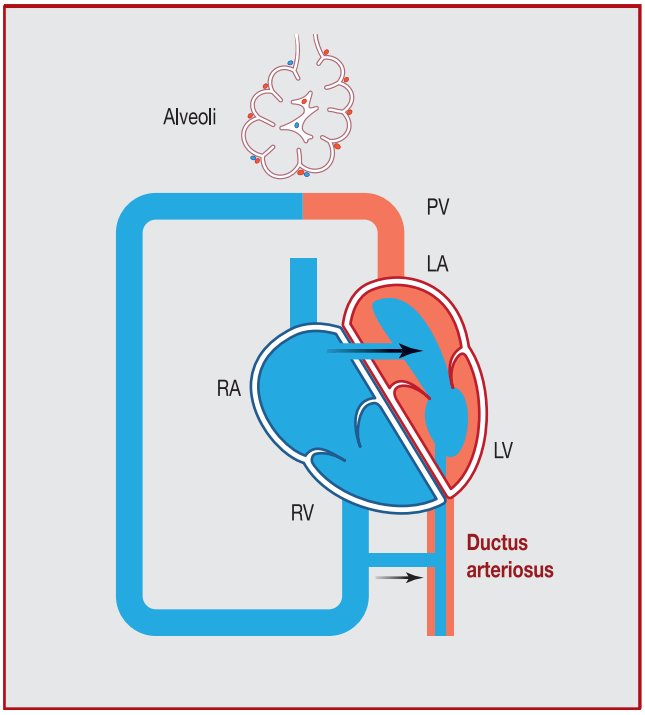

Figure 1. Schematic representation of the circulation in PPHN. Sustained elevation of PVR contributes to low pulmonary blood flow and high pulmonary pressure, causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and foramen ovale and severe hypoxaemia. LA: left atrium; LV: left ventricle; PPHN: persistent pulmonary hypertension of the newborn; PV: pulmonary vein; PVR: pulmonary vascular resistance; RA: right atrium; RV: right ventricle.

Pathophysiology

Foetal circulation

The foetal pulmonary circulation is characterized by high PVR and low blood flow. Despite high pulmonary artery