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Review

Persistent pulmonary hypertension of the newborn: Advances in diagnosis and treatment

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SUMMARY

Persistent pulmonary hypertension of the newborn (PPHN) is a frequent cause for admission to the neonatal intensive care unit and is associated with mortality and variable morbidities. It is primarily a state of oxygenation failure representing a failure of the normal postnatal decline in pulmonary vascular resistance that may be associated with right ventricular dysfunction. Enhanced knowledge of the pathophysiologic contributors to this syndrome helps clinicians understand its phenotypic expression and facilitates more focused intensive care decision-making. The approach to treatment should be based on alleviation of the elevation in pulmonary vascular resistance and should include optimization of lung recruitment and judicious use of pulmonary vasodilators. When response to inhaled nitric oxide is suboptimal, the physiologic contributors to impaired oxygenation need further investigation. Targeted neonatal echocardiography provides novel physiologic insights; in particular, it may help assess the adequacy of right ventricular performance, the relative contribution of the fetal shunts and the magnitude of the overall impairment to cardiac output. This information may facilitate therapeutic next steps and whether adjunctive vasodilators or drugs to augment ventricular function are preferable. This article provides a comprehensive overview of the pathological contributors to PPHN, the physiologic constituents of its phenotypic expression, standard approach to therapeutic intervention, and the role of bedside echocardiography in enhancing the decision-making process.

1. Introduction

Pulmonary hypertension (PHT) is a serious cardiopulmonary disorder characterized by elevated mean pulmonary artery pressure (mPAP) and prolonged exposure of the right ventricle to high afterload. Physiologically, mPAP is directly related to pulmonary blood flow (PBF), pulmonary vascular resistance (PVR) and pulmonary capillary wedge pressure (PCWP) by the equation:

$$mPAP = (PBF \times PVR) + PCWP.$$

Although PHT may result from high PBF (e.g., large left-to-right shunts, severe chronic anemia) or rise in PCWP (e.g., left ventricular dysfunction), the vast majority of cases are secondary to high PVR. In neonates, PHT is almost always secondary to dysregulation of PVR. PHT is a frequent diagnosis in tertiary neonatal intensive care units and may arise secondary to a wide range of diseases. Broadly, PHT in neonates can be described as acute or chronic (Fig. 1), which are distinguished by intrinsic differences in their pathophysiology and clinical presentation [1]. While acute episodes of neonatal PHT may occur later in neonatal illnesses (e.g., secondary to sepsis), the most usual presentation is in the immediate postnatal period, secondary to abnormal transition of the pulmonary circulation from a high-resistance intrauterine to a low-resistance extrauterine circuit. This characteristic presentation of acute pulmonary hypertensive crises is widely referred to as persistent pulmonary hypertension of the newborn (PPHN). Chronic PHT, on the other hand, occurs due to secondary rise in PVR following initial successful postnatal transition, and is seen most frequently as a secondary complication of chronic neonatal lung disease in prematurely born neonates [2,3]. The majority of research in neonatal PHT has focused on PPHN, yet knowledge gaps remain and core physiologic

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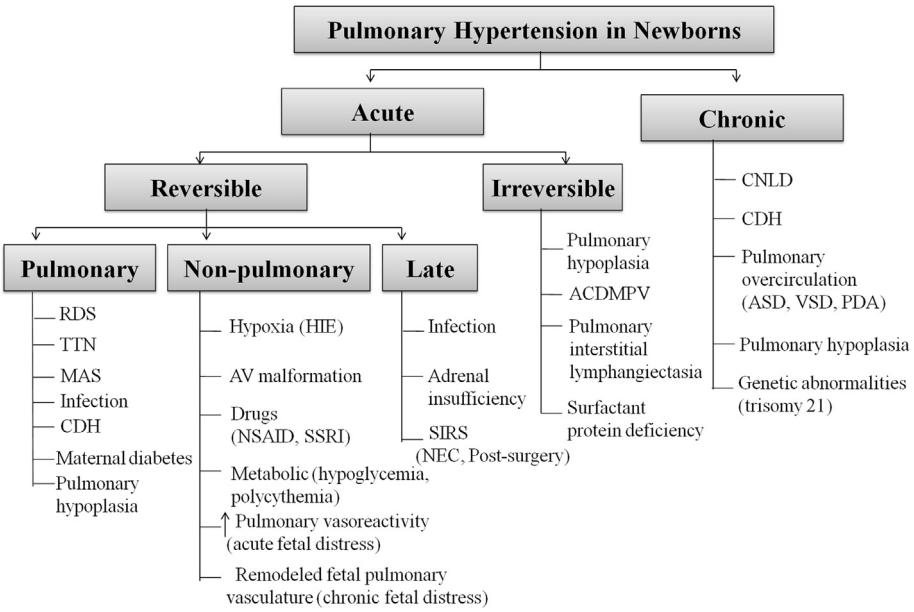

Fig. 1. Pulmonary hypertension in neonates can be classified as acute or chronic and may arise from a variety of underlying disorders. RDS, respiratory distress syndrome; TTN, transient tachypnea of newborn; MAS, meconium aspiration syndrome; CDH, congenital diaphragmatic hernia; HIE, hypoxic–ischemic encephalopathy; AV, arteriovenous; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitors; SIRS, systemic inflammatory response syndrome; NEC, necrotizing enterocolitis; ACDMPV, alveolar capillary dysplasia with misalignment of pulmonary veins; CNLD, chronic neonatal lung disease; CDH, congenital diaphragmatic hernia; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus. Reproduced with permission from Chapter 29, Avery's neonatology: pathophysiology and management of the newborn, 7th ed (in press).

concepts are oftentimes neglected; in addition, the relative contribution of chronic PHT to adverse clinical outcomes is just beginning to be realized.

Persistent pulmonary hypertension of the newborn is one of the most challenging acute disorders of postnatal transition with substantial morbidity and mortality. Perinatal asphyxia, meconium aspiration syndrome and sepsis account for the majority of cases; irreversible causes are fortunately rare. Occasionally, PPHN may be the primary diagnosis when no other underlying pathology can be identified. Although improved obstetric care has considerably reduced the incidence of these perinatal pathologies, PPHN continues to be an important clinical problem accounting for up to 4% of all admissions to some tertiary neonatal units. The incidence in developed countries ranges from one to two per 1000 live births with a mortality rate of ~10% [4,5]. Surviving neonates often require prolonged cardiorespiratory support, have a long hospital stay, and are at high risk of long-term adverse neurodevelopmental outcomes [6]. The incidence and burden of disease is likely to be much higher in the developing world. Although treatment with exogenous inhaled nitric oxide (iNO), the only approved pulmonary vasodilator in neonates, has reduced the need for extracorporeal membrane oxygenation (ECMO), these benefits have not translated into a survival advantage or minimization of long-term neurodisability [5,7]. Given the relatively high prevalence of these disorders in tertiary NICUs, it is imperative that clinicians caring for these babies familiarize themselves with the disease-specific physiology and associated hemodynamic alterations. Prompt recognition and early effective management is important for optimizing patient outcomes. In this article we suggest the need to reconsider PPHN as a physiologic continuum, with cardiopulmonary consequences that vary between patients and according to precipitating causes; in addition we attempt to justify the need to perform a thoughtful and comprehensive appraisal of actual physiology as an essential prerequisite of the clinical decision-making process.

2. Pathophysiology

2.1. Cellular pathways

Several cellular pathways involved in regulation of pulmonary vascular tone have been identified over the last two decades (Fig. 2) [1,8]. It is important for clinicians to be aware of these pathways, which modulate pathophysiological progression and clinical impact. Although inter-pathway interactions exist and relationships may be complex in nature, for the sake of simplicity, the relevant pathways could be described under following headings: (A) nitric oxide (NO)-soluble guanylate cyclase–cyclic guanyl monophosphate (cGMP); (B) prostaglandin–prostacyclin–cyclic adenosine monophosphate (cAMP); (C) rho-A/rho-kinase; (D) endothelin; (E) free radicals. Among these pathways, pathways (A), (B) and (D) have been the subjects of most interest. Oxygen and NO represent mediators of pulmonary vasodilatation translated into standard clinical practice. Subsequently, a number of other mediators have been identified, prompting the development of adjunctive/alternate therapeutic agents. Whereas successful use of many alternate therapeutic agents have been described in PPHN, the relative contributory role of each mediator in enabling successful physiological transition after birth and under pathological conditions has not been completely elicited. Pulmonary vasodilatation has been shown to occur in response to stimulation by nitric oxide (NO) [7], prostacyclin (PGI_2) [9,10] and soluble guanyl cyclase (sGC) [11] and inhibition of phosphodiesterase 3 and/or 5 (PDE 3/5) [12–14], endothelin 1 (ET 1) [15,16], reactive oxygen species (ROS) [17], and rho-kinase [18,19]. A basic knowledge of these regulatory pathways and target mediators is necessary for clinicians involved