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Congenital diaphragmatic hernia-associated pulmonary hypertension

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ABSTRACT

Congenital diaphragmatic hernia (CDH) is a complex entity wherein a diaphragmatic defect allows intrathoracic herniation of intra-abdominal contents and both pulmonary parenchymal and vascular development are stifled. Pulmonary pathology and pathophysiology, including pulmonary hypoplasia and pulmonary hypertension, are hallmarks of CDH and are associated with disease severity. Pulmonary hypertension (PH) is sustained, supranormal pulmonary arterial pressure, and among patients with CDH (CDH-PH), is driven by hypoplastic pulmonary vasculature, including alterations at the molecular, cellular, and tissue levels, along with pathophysiologic pulmonary vasoreactivity. This review addresses the basic mechanisms, altered anatomy, definition, diagnosis, and management of CDH-PH. Further, emerging therapies targeting CDH-PH and PH are explored.

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Introduction

Congenital diaphragmatic hernia (CDH) continues to challenge pediatricians, neonatologists, and surgeons. Advances in prenatal diagnosis and treatment, critical care, surgical approaches, and extracorporeal life support have led to incremental improvements in overall morbidity and mortality over the last quarter century. Despite this, at least 25–30% of live-born infants with CDH will succumb to their disease and most of these infants will have pulmonary hypertension (CDH-PH). Clearly, novel discoveries will be necessary in CDH and, in particular PH, to improve mortality and reduce morbidity. Understanding the underlying process of CDH-PH is paramount in clinical and research endeavors focused on CDH.

What is pulmonary hypertension?

Pulmonary hypertension (PH) is a pathologic state of the pulmonary vasculature, which results in pathophysiologic pulmonary circulation, usually affecting oxygenation, ventilation, and/or cardiac function.[1,2] It is generically classified as primary (idiopathic) or secondary (resulting from one of a variety of distinct disease entities).[2] The World Health Organization (WHO) classifies PH into the following 5 main categories/groups: (1) pulmonary arterial hypertension, (2) pulmonary venous hypertension due to left heart disease, (3) pulmonary hypertension due to lung disease and/or hypoxia, (4) chronic thromboembolic pulmonary hypertension, and (5) pulmonary hypertension with unclear multifactorial mechanisms (Table 1).[2,3] Hemodynamically, PH is defined by a pulmonary artery pressure (Ppa) $\geq$ 25 mm Hg (mean), measured by right heart catheterization at rest, and subdivided into precapillary or postcapillary based on pulmonary artery wedge pressure.[2] In pediatric patients beyond 3 months of age, the definition remains essentially the same; however, neonates in the first few months of life pose a particular definitional challenge due to transitional circulation and small size.[3] A unique classification system (the "Panama" classification) specific for early childhood PH balances the angiogenic/vasculogenic mechanisms with vascular diminution secondary to intrinsic or extrinsic pressures (Table 2).[3,4]

Congenital diaphragmatic hernia-associated PH (CDH-PH) can be defined as pathologic pulmonary vasculature, in the setting of a congenital diaphragmatic hernia (CDH), which results in pathophysiologic pulmonary circulation, leading to supraphysiologic right-sided cardiac pressures with subsequent circulatory shunting, hypoxia, hypercarbia, and/or cardiac dysfunction. The hallmarks of the pulmonary vasculature in CDH-PH include vessel thickening at the medial and adventitial layers, a hypoplastic vascular bed with decreased arborization, and unconventional pulmonary artery/arteriole response to physiologic and pharmacologic signals.[5,6] Clinically and hemodynamically, CDH-PH lacks a standard, accepted definition, though most define it using echocardiographic findings of supranormal right-sided cardiac

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Table 1
World Health Organization classification of pulmonary hypertension.[2,3]

Group 1: pulmonary arterial hypertension (PAH)
1.1 Idiopathic (IPAH)
1.2 Heritable (HPAH)—*BMPR2, ALK1, ENG, SMAD9, CAV1,* and *KCNK3*
1.3 Drug and toxin induced
1.4 Associated with (APAH)—connective tissue diseases, human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease (CHD), schistosomiasis
Group 1': pulmonary venoocclusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH)
Group 1'': persistent pulmonary hypertension of the newborn (PPHN)
Group 2: pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular cardiac disease
2.4 Congenital/acquired left heart inflow/outflow obstruction and congenital cardiomyopathies
Group 3: pulmonary hypertension due to lung disease and/or hypoxemia
3.1 Chronic obstructive pulmonary disease (COPD)
3.2 Interstitial lung disease (ILD)
3.3 Other pulmonary disease with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 *Developmental abnormalities/lung disease**
Group 4: chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5: pulmonary hypertension (PH) with unclear multifactorial mechanisms
5.1 Hematological disorders—myeloproliferative disorders, splenectomy
5.2 Systemic disorders—sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders—glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others—tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

* Group/category for CDH.

pressures relative to systemic blood pressures. CDH-PH is secondary PH, probably best classified as WHO group 3 and as a *multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes* in the Panama classification.

The underlying mechanisms leading to the clinical challenges universal among patients with congenital diaphragmatic hernia are currently postulated to be the result of both an early embryogenic alteration of the pulmonary vasculature/parenchymal (and diaphragmatic) development, as well as external compression from herniated intra-abdominal contents, stifling pulmonary vasculature/parenchymal development; these 2 processes are amalgamated into the *dual-hit hypothesis*.[7] Although no consistent or definitive link exists, data have shown that the underlying etiology could be teratogenic, genetic, nutritional, sporadic, multifactorial, or yet undiscovered. Specific evidence of the origins, consequences, definitions, and therapeutic approaches, both current and emerging, for the pathologic pulmonary vasculature, and the overarching entity of CDH-PH, are discussed herein.

Molecular origins of CDH-PH

The molecular pathogenesis of CDH-PH is likely multifactorial, involving several known pathways, and is complicated by limited knowledge of causative versus associated changes. The retinoic acid pathway, nitric oxide pathway, endothelin pathway, and vascular endothelial growth factor are likely to contribute to the pathophysiologic genesis and/or progression of CDH-PH, though most of the findings presented below remain as *associations* undergoing active investigation.

Retinoid acid signaling

The retinoic acid signaling pathway (retinol metabolism) is critical in foregut embryogenesis and, specifically, lung development.[8] Incomplete diaphragmatic development and altered pulmonary development in CDH may be the result of defective retinoid signaling. Nitrofen, a teratogen associated with CDH when administered to pregnant rodents, is a retinal dehydrogenase inhibitor. Administration of nitrofen to pregnant dams at a specific time/dose yields offspring with a high rate of CDH, including pulmonary arterial thickening and decreased pulmonary vascular density (hypoplastic pulmonary vasculature) with pathophysiologic responses to pulmonary vasodilators.[9,10]

Data in humans to support retinol disturbances are lacking, though several small studies exist. One group investigated serum levels of retinol and retinol binding protein (RBP) in 11 newborn infants with CDH and 11 controls, as well as the mothers of 7 with CDH and 7 controls.[11] Serum levels of both retinol and RBP were 50% lower among CDH infants and, interestingly, retinol levels in

Table 2
Classification of pediatric pulmonary hypertensive vascular disease (Panama)—general categories.

Prenatal or developmental PH vascular disease
Perinatal pulmonary vascular maladaptation
Pediatric cardiovascular disease
Bronchopulmonary dysplasia
Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
*Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes**
Pediatric lung disease
Pediatric thromboembolic disease
Pediatric hypobaric hypoxic exposure
Pediatric pulmonary vascular diseases associated with other system disorders

* Group/category for CDH.