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Pulmonary arterial hypertension in children

A. Widlitz, R.J. Barst

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Abstract

For physicians to admit that a group of patients remains for whom no cure is available in modern medicine is intellectually unsatisfying. Pulmonary arterial hypertension is a rare condition. Because the symptoms are nonspecific and the physical finding can be subtle, the disease is often diagnosed in its later stages. The natural history of pulmonary arterial hypertension is usually progressive and fatal.

At the 1998 Primary Pulmonary Hypertension World Symposium, clinical scientists from around the world gathered to review and discuss the future of pulmonary arterial hypertension. Bringing together experts from a variety of disciplines provided the opportunity for a better understanding of the pathology, pathobiology, risk factors, genetics, diagnosis and treatment for pulmonary arterial hypertension.

Remarkable progress has been made in the field of pulmonary arterial hypertension over the past several decades. The pathology is now better defined and significant advances have occurred in understanding the pathobiological mechanisms. Risk factors have been identified and the genetics have been characterised. Advances in technology allow earlier diagnosis as well as better assessment of disease severity. Therapeutic modalities such as new drugs, *e.g.* epoprostenol, treprostinil and bosentan, and surgical interventions, *e.g.* transplantation and blade septostomy, which were unavailable several decades ago, have had a significant impact on prognosis and outcome. Thus, despite the inability to really cure pulmonary arterial hypertension, therapeutic advances over the past two decades have resulted in significant improvements in the outcome for children with various forms of pulmonary arterial hypertension.

This review of pulmonary arterial hypertension will highlight the key features of pulmonary hypertension in infants and children and the current understanding of pulmonary arterial hypertension with specific recommendations for current practice and future directions.

- paediatrics
- pulmonary arterial hypertension
- pulmonary heart disease

Until recently the diagnosis of primary pulmonary hypertension was virtually a death sentence. This was particularly true for children, in whom the mean survival was <1 yr. This bleaker outlook for children compared to adults was underscored by the data in the Primary Pulmonary Hypertension National Institutes of Health Registry [1]. In this Registry, the median survival for all of the 194 patients was 2.8 yrs, whereas it was only 10 months for children. Significant progress in the field of pulmonary hypertension has occurred over the past several decades. Advances in technology have also allowed a better diagnosis and assessment of the disease severity with treatment now available that improves quality of life and survival [2–4]. Nevertheless, extrapolation from adults to children is not straightforward for at least several reasons: 1) the anticipated lifespan of children is longer; 2) children may have a more reactive pulmonary circulation raising the prospect of greater vasodilator responsiveness and better therapeutic outcomes [5]; and 3) despite clinical and pathological studies suggesting increased vasoreactivity in children, before the advent of long-term vasodilator/antiproliferative therapy, the natural history remained significantly worse for children compared to adult patients [1], [6].

Definition and classification

The definition of primary pulmonary hypertension in children is the same as for adult patients. It is defined as a mean pulmonary artery pressure ≥25 mmHg at rest or ≥30 mmHg during exercise, with a normal pulmonary artery wedge pressure and the absence of related or associated conditions. The inclusion of exercise haemodynamic abnormalities in the definition of pulmonary arterial hypertension is important since children with pulmonary

arterial hypertension often have an exaggerated response of the pulmonary vascular bed to exercise as well as in response to hypoventilation compared with adults. Not uncommonly, children with a history of recurrent exertional or nocturnal syncope have a resting mean pulmonary artery pressure of only ~25 mmHg that markedly increases with modest systemic arterial oxygen desaturation during sleep, as well as with exercise.

In 1998, at the Primary Pulmonary Hypertension World Symposium, clinical scientists from around the world proposed a new diagnostic classification system (table 1⇓). This classification system categorises pulmonary vascular disease by common clinical features. This classification reflects the recent advances in the understanding of pulmonary hypertensive diseases as well as recognising the similarity between primary pulmonary hypertension and pulmonary hypertension of certain other causes. Thus, in addition to primary pulmonary hypertension (both sporadic and familial), pulmonary arterial hypertension related to the following: congenital systemic to pulmonary shunts; collagen vascular disease; portal hypertension; human immunodeficiency virus infection; drugs and toxins (including anorexigens); and persistent pulmonary hypertension of the newborn, is classified with primary pulmonary hypertension as pulmonary arterial hypertension. This classification separates these cases of pulmonary arterial hypertension from pulmonary venous hypertension, pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia, pulmonary hypertension due to chronic thrombotic and/or embolic disease, as well as pulmonary hypertension due to disorders directly affecting the pulmonary vasculature. This new diagnostic classification provides rationale for considering many of the therapeutic modalities that have been demonstrated to be efficacious for primary pulmonary hypertension for children who have pulmonary arterial hypertension related to these other conditions. Because the cause(s) of primary pulmonary hypertension, as well as pulmonary arterial hypertension related to other conditions, remains unknown or at least incompletely understood, the various treatment modalities used for pulmonary arterial hypertension have been based on the pathology and pathobiology of the pulmonary vascular bed. The pathology remains central to the understanding of the pathobiological mechanisms. As insight is advanced into the mechanisms responsible for the development of pulmonary arterial hypertension, the introduction of novel therapeutic modalities (alone and in combination) will hopefully increase the overall efficacy of therapeutic interventions for pulmonary arterial hypertension.

Persistent pulmonary hypertension of the newborn is a syndrome characterised by increased pulmonary vascular resistance, right-to-left shunting and severe hypoxaemia 7. Persistent pulmonary hypertension of the newborn is frequently associated with pulmonary parenchymal abnormalities including meconium aspiration, pneumonia or sepsis, as well as occurring when there is pulmonary hypoplasia, maladaptation of the pulmonary vascular bed postnatally as a result of perinatal stress or maladaptation of the pulmonary vascular bed *in utero* from unknown causes. In some instances there is no evidence of pulmonary parenchymal disease and the "injury" that is the "trigger" of the pulmonary hypertension is unknown. Persistent pulmonary hypertension of the newborn is almost always transient 8, with infants either recovering completely without requiring chronic medical therapy or dying during the neonatal period despite maximal cardiopulmonary therapeutic interventions. In contrast, patients with pulmonary arterial hypertension who respond to medical therapy appear to need treatment indefinitely. Some infants with persistent pulmonary hypertension of the newborn may have a genetic predisposition to hyperreact to pulmonary vasoconstrictive "triggers" such as alveolar hypoxia. It is possible that in some neonates the pulmonary vascular resistance may not fall normally after birth, although the diagnosis of

persistent pulmonary hypertension of the newborn is not made during the neonatal period and subsequently pulmonary hypertension is diagnosed as the pulmonary vascular disease progresses. Pathological studies examining the elastic pattern of the main pulmonary artery 9, 10 suggest that primary pulmonary hypertension is present from birth in some patients, although it is acquired later in life in others.

Whether pulmonary hypertension is due to increased flow or resistance (table 2⇓) depends on the cause of the pulmonary hypertension (table 3⇓). By definition, hyperkinetic pulmonary hypertension refers to pulmonary arterial hypertension from congenital systemic to pulmonary communications with increased pulmonary blood flow, *e.g.* ventricular septal defect or patent ductus arteriosus. Pulmonary venous hypertension is caused by disorders of left heart filling, *e.g.* mitral stenosis, pulmonary venous obstruction or left ventricular failure. Unless left heart obstruction or dysfunction is causing pulmonary venous hypertension, the pulmonary arterial wedge pressure is normal. Pulmonary vascular disease related to congenital heart disease (Eisenmenger's syndrome) is thought to develop after a hyperkinetic period of normal pulmonary vascular resistance and increased pulmonary blood flow. With pulmonary venous hypertension, as seen with mitral stenosis or left ventricular dysfunction, pulmonary artery pressure may vary from one child to another with the same elevations of pulmonary venous pressure accounted for by differences in pulmonary arterial vasoreactivity. Many different congenital heart defects are associated with an increased risk for the development of pulmonary vascular disease. Approximately one-third of patients with uncorrected congenital heart disease will die from pulmonary vascular disease 11. It is not known why some children with the same underlying congenital heart defect develop irreversible pulmonary vascular obstructive disease in the first year of life and others maintain "operable" levels of pulmonary hypertension into the second decade and beyond. In many children whose congenital heart disease is diagnosed late in life, an important and difficult decision is necessary to determine whether the patient is "operable" or has "irreversible" pulmonary vascular disease. In the past, this evaluation of operability has used anatomical criteria based on microscopic findings from lung biopsies to aid in the determination 12. More recently, new approaches to the evaluation of operability and perioperative management have allowed for surgical "corrections" in patients who present late in life with elevated pulmonary vascular resistance. The assessment of surgical operability requires an accurate determination of the degree of pulmonary vasoreactivity or reversibility. It is important to predict whether the elevated pulmonary vascular resistance will respond favourably to pharmacological vasodilatation. In the past several years, studies with inhaled nitric oxide and intravenous epoprostenol have proven useful in the preoperative evaluations, as well as in the treatment of postoperative patients with elevated pulmonary vascular resistance 13–19. If a patient with elevated pulmonary vascular resistance is being considered for surgery there is an increased risk of postoperative pulmonary hypertensive crises. Thus, knowing if the pulmonary circulation will respond favourably to inhaled nitric oxide or intravenous prostacyclin will help in guiding the management of this potentially life-threatening complication 14, 20.

Although misalignment of the pulmonary veins with alveolar capillary dysplasia is often diagnosed as persistent pulmonary hypertension of the newborn, it is a separate entity, *i.e.* a rare disorder of pulmonary vascular development that most often is diagnosed only after an infant has died from fulminant pulmonary hypertension 21. Features that will often alert clinicians to the possibility of alveolar capillary dysplasia include association with other nonlethal congenital malformations, the late onset of presentation (especially after 12 h) and severe hypoxaemia refractory to medical therapy. Infants most often present with severe

pulmonary arterial hypertension with transient responses to inhaled nitric oxide, which subsequently require increases in the dose of inhaled nitric oxide as well as transient responses after intravenous epoprostenol is added to the inhaled nitric oxide, with virtually all infants subsequently dying within the first several weeks of life. The only case with longer survival that the authors are aware of was an infant who presented at 6 months of age with what was initially thought to be overwhelming pneumonia requiring maximal cardiopulmonary support, including extracorporeal membrane oxygenation. The infant was initially diagnosed as having primary pulmonary hypertension, although upon further review of the open lung biopsy, alveolar capillary dysplasia was diagnosed with a very heterogeneous appearance on the biopsy. The infant significantly improved with inhaled nitric oxide and intravenous epoprostenol while awaiting heart-lung transplantation; she was subsequently weaned off extracorporeal membrane oxygenation as well as off mechanical ventilation and inhaled nitric oxide. She had marked clinical and haemodynamic improvement on chronic intravenous epoprostenol and continued chronic intravenous epoprostenol until she was nearly 4 yrs of age, at which time after acquiring a respiratory tract infection she rapidly deteriorated and died (unpublished data). *Post-mortem* examination confirmed the diagnosis of alveolar capillary dysplasia with a very heterogeneous involvement in the pulmonary parenchyma (consistent with the late presentation as well as significant palliative response with intravenous epoprostenol). This variability in clinical severity and histopathology is consistent with the marked biological variability that occurs in many forms of pulmonary arterial hypertension. When pulmonary hypertension results from neonatal lung disease such as meconium aspiration, the pulmonary vascular changes are most severe in the regions of the lung showing the greatest parenchymal damage.

Congenital heart disease is the most common cause of pulmonary venous hypertension in children due to total anomalous pulmonary venous return with obstruction, left heart obstruction or severe left ventricular failure. The lungs of those born with left inflow obstruction show pronounced thickening in the walls of both the arteries and the veins; and the outcome depends on the results of the surgical intervention. Pulmonary veno-occlusive disease has a distinct pathological feature of uniform fibrotic occlusion of peripheral small venules 22. Although rare, it does occur early in childhood and has been reported in familial cases 23. Progressive long-segment pulmonary vein hypoplasia leading to pulmonary venous atresia is another uniformly fatal condition presenting in infancy with severe pulmonary venous hypertension.

Epidemiology

The frequency of pulmonary arterial hypertension in children as well as in adults remains unknown. Estimates of the incidence of primary pulmonary hypertension ranges from one to two new cases per million people in the general population 24. Although the disease is rare, increasingly frequent reports of confirmed cases suggest that more patients (both children and adults) have pulmonary arterial hypertension than had been previously recognised. On occasion, infants who have died with the presumed diagnosis of sudden infant death syndrome have had primary pulmonary hypertension diagnosed at the time of *post-mortem* examination. The sex incidence in adult patients with primary pulmonary hypertension is ~1.7:1 females:males 25, similar to the current authors' experience with children, 1.8:1 with no significant difference in the younger children compared with the older children.

Natural history

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