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SERIES "ADVANCES IN PATHOBIOLOGY, DIAGNOSIS, AND TREATMENT OF PULMONARY HYPERTENSION"
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Pulmonary arterial hypertension in children

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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.
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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].

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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.

Table 1. – Diagnostic classification of pulmonary hypertension

Pulmonary arterial hypertension
Primary pulmonary hypertension
Sporadic
Familial
Related to:
Collagen vascular disease
Congenital systemic-to-pulmonary shunts
Portal hypertension
HIV infection
Drugs/toxins
Anorexigens
Other
Persistent pulmonary hypertension of the newborn
Other
Pulmonary venous hypertension
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Extrinsic compression of central pulmonary vein
Fibrosing mediastinitis
Adenopathy/tumours
Pulmonary veno-occlusive disease
Other
Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitudes
Neonatal lung disease
Alveolar-capillary dysplasia
Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Obstruction of distal pulmonary arteries
Pulmonary embolism (thrombus, ova and/or parasites, foreign material)
In situ *thrombosis*
Sickle cell disease
Pulmonary hypertension due to disorders affecting the pulmonary vasculature
Inflammatory
Schistosomiasis
Sarcoidosis
Other
Pulmonary capillary haemangiomatosis

HIV: human immunodeficiency virus.

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

Table 2. – Classification of pulmonary hypertension

Type	Classification
Hyperkinetic	$P=F\times r$
Pulmonary vascular obstruction or pulmonary venous hypertension	$P=f\times R$

P: increased pulmonary artery pressure; *F*: high pulmonary blood flow; *r*: normal total pulmonary resistance; *f*: normal pulmonary blood flow; *R*: high total pulmonary resistance.

Table 3. – Causes of pulmonary hypertension

Reversible	
Hyperkinetic	Congenital systemic-to-pulmonary shunt, *e.g.* VSD, PDA
Pulmonary venous hypertension	Pulmonary venous obstruction, cor triatriatum, mitral stenosis, left ventricular failure
Irreversible	
Pulmonary vascular obstruction	Primary pulmonary hypertension, Eisenmenger's syndrome

VSD: ventricular septal defect; PDA: patent ductus arteriousus.

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

Primary pulmonary hypertension historically exhibited a course of relentless deterioration and early death. Unfortunately, the data available for children is much less than for adult patients (due to the decreased occurrence of primary pulmonary hypertension in children compared with adults). Several large survival studies of primarily adult patients with primary pulmonary hypertension conducted in the 1980s have provided a basis of comparison for subsequent evolving therapeutic modalities. These retrospective and prospective studies have yielded quite uniform results: adult patients with primary pulmonary hypertension who have not undergone lung or heart/lung transplantation have had actuarial survival rates at 1, 3 and 5 yrs of 68–77, 40–56 and 22–38%, respectively [1, 26–28]. However, there is significant biological variability in the natural history of the disease in both adults and children, with some patients having a rapidly progressive downhill course resulting in death within several weeks after diagnosis as well as instances of survival for at least several decades.

Pathobiology

By definition, the aetiology(ies) of primary pulmonary hypertension are unknown, *e.g.* primary pulmonary hypertension is also referred to as "unexplained" or "idiopathic" pulmonary hypertension. In young children, the pathobiology suggests failure of the neonatal vasculature to open and a striking reduction in arterial number. In older children, intimal hyperplasia and occlusive changes are found in the pulmonary arterioles as well as plexiform lesions. Despite significant advances (during the past several decades) in the understanding of the pathobiology of primary pulmonary hypertension, the mechanism(s) which initiate and perpetuate the disease process remain(s) speculative. Adults with primary pulmonary hypertension often have severe plexiform lesions and what appears to be "fixed" pulmonary vascular changes. In contrast, children with primary pulmonary hypertension have more pulmonary vascular medial hypertrophy and less intimal fibrosis and fewer plexiform lesions. In the classic studies by

WAGENVOORT and WAGENVOORT [29] in 1970, medial hypertrophy was severe in patients <15 yrs of age and it was usually the only change seen in infants. Among the 11 children <1 yr of age, all had severe medial hypertrophy, yet only three had intimal fibrosis, two with minimal intimal fibrosis and one with moderate intimal fibrosis and none had plexiform lesions. With increasing age, intimal fibrosis and plexiform lesions were seen more frequently. These *post-mortem* studies suggested that pulmonary vasoconstriction, leading to medial hypertrophy, may occur early in the course of the disease and may precede the development of plexiform lesions and other fixed pulmonary vascular changes (at least in some children). Furthermore, these observations may offer clues to the observed differences in the natural history and factors influencing survival in children with primary pulmonary hypertension compared with adult patients. Younger children in general appear to have a more reactive pulmonary vascular bed relative to both active pulmonary vasodilatation as well as pulmonary vasoconstriction, with severe acute pulmonary hypertensive crises occurring in response to pulmonary vasoconstrictor "triggers" more often than in older children or adults. Thus, based on these early pathological studies, the most widely proposed mechanism for primary pulmonary hypertension until the late 1980s and early 1990s was pulmonary vasoconstriction [5, 30–32]. Subsequent studies have identified potentially important structural and functional abnormalities; whether these perturbations are a cause or consequence of the disease process remains to be elucidated. These abnormalities include imbalances between vasodilator/antiproliferative and vasoconstrictive/mitogenic mediators, defects in the potassium channels of pulmonary artery smooth muscle cells and increased synthesis of inflammatory mediators which cause vasoconstriction as well as enhanced cell growth (fig. 1) [33–40].

The molecular process(es) behind the complex vascular changes associated with primary pulmonary hypertension include the following: the description of phenotypical changes in endothelial and smooth muscle cells in hypertensive pulmonary arteries, the recognition that cell proliferation contributes to the structural changes associated with the initiation and progression of primary pulmonary hypertension (as well as apoptosis contributing to hypertensive pulmonary vascular disease) and the role of matrix proteins and matrix turnover in vascular remodelling and the importance of haemodynamic influences on the disease process. It is now clear that gene expression in pulmonary vascular cells responds to environmental factors, growth factors, receptors, signalling pathways and genetic influences, which can interact with each other. Examples of effector systems controlled by gene expression include the following: transmembrane transporters, ion channels, transcription factors, modulators of apoptosis, kinases, cell-to-cell interactive factors, *e.g.* intergrins and membrane receptors, mechanotransducers, extracellular matrix turnover and growth factors/cytokines and chemokine networks. By identifying causes of molecular process(es) that are linked to epidemiological risk factors, as well as developing molecular, biochemical and physiological tests to monitor and diagnose primary pulmonary

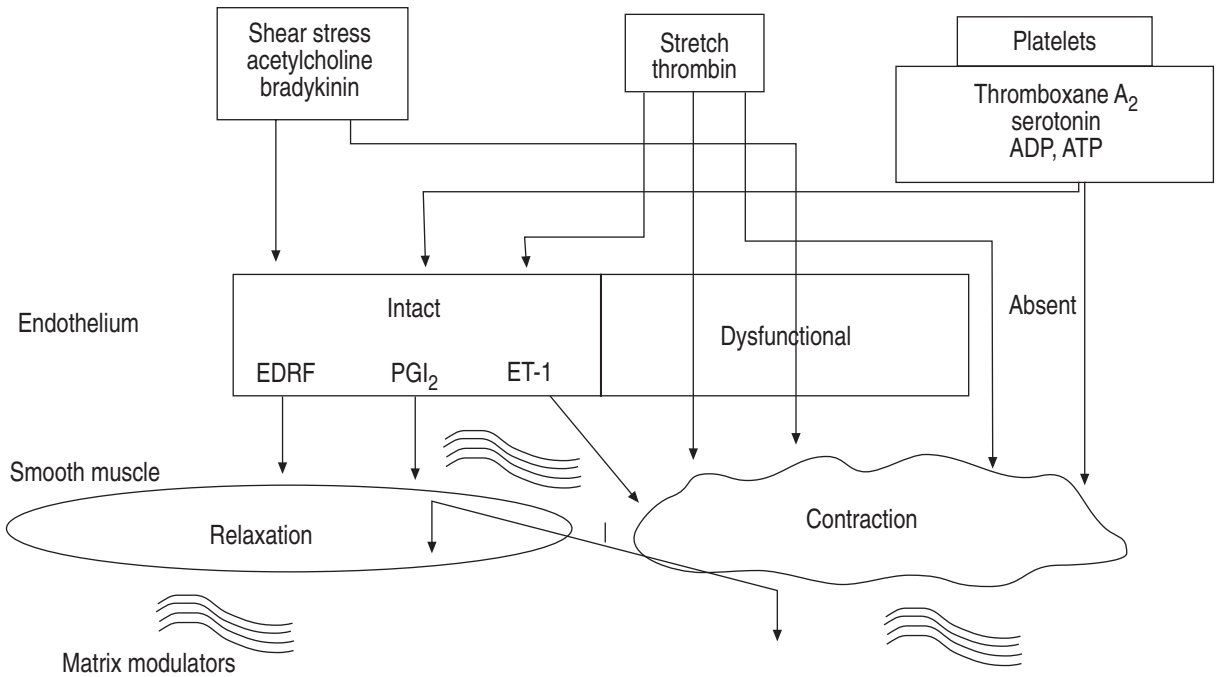

Fig. 1. – Schematic representation of the factors influencing the imbalance between relaxation and contraction in primary pulmonary hypertension. ATP: adenosine triphosphate; ADP: adenosine diphosphate; EDRF: endothelium-derived relaxing factor; PGI_2: prostacyclin; ET-1: endothelin-1. Reprinted from [42] with permission from Elsevier Science.

hypertension, novel treatment strategies based on established pathobiological mechanisms will increase the overall efficacy of therapeutic interventions for primary pulmonary hypertension. Although many important physiological processes have been identified from descriptive studies from patients (suggesting possible pathobiological mechanisms in the development of primary pulmonary hypertension, fig. 2), whether these observations are a cause or a consequence of the disease remains unclear.

The vascular endothelium, an important source of locally active mediators that contribute to the control of vasomotor tone and structural remodelling, appears to play a crucial role in the pathogenesis of primary pulmonary hypertension [42]. A number of studies have suggested that imbalances in the production or metabolism of several vasoactive mediators produced in the lungs may be important in the pathogenesis of primary pulmonary hypertension. An imbalance may exist in the vasoconstricting and vasodilator mediators as well as substances involving control of pulmonary vascular tone. These include increased thromboxane and decreased prostacyclin [33, 34], increased endothelin and decreased nitric oxide [35–37, 40], as well as other vasoactive substances yet to be described. Thromboxane and endothelin are vasoconstrictors as well as mitogens; in contrast, prostacyclin and nitric oxide are vasodilators with antiproliferative effects. Other factors may also be involved such as serotonin, platelet derived growth factor, angiotensin or the loss of pulmonary vascular prostacyclin or nitric oxide synthase gene expression. Vasoconstrictors may also serve as factors or cofactors that stimulate smooth muscle growth or matrix elaboration. It appears likely that endothelial injury results in the release of chemotactic agents leading to migration of smooth muscle cells into the vascular wall. In addition, this endothelial injury, coupled with excessive release of vasoactive mediators locally, promotes a procoagulant state, leading to further vascular obstruction. The process is characterised, therefore, by an inexorable cycle of endothelial dysfunction leading to the release of vasoconstrictive and vasoproliferative substances, ultimately progressing to vascular remodelling and progressive vascular obstruction and obliteration. In addition, defects in the potassium channels of pulmonary resistance smooth muscles may also be involved in the initiation and/or progression of primary pulmonary hypertension; inhibition of the voltage regulated (Kv) potassium channel has been reported in pulmonary artery smooth muscle cells from patients with primary pulmonary hypertension [43]. Whether a genetic defect related to potassium channels in the lung vessels

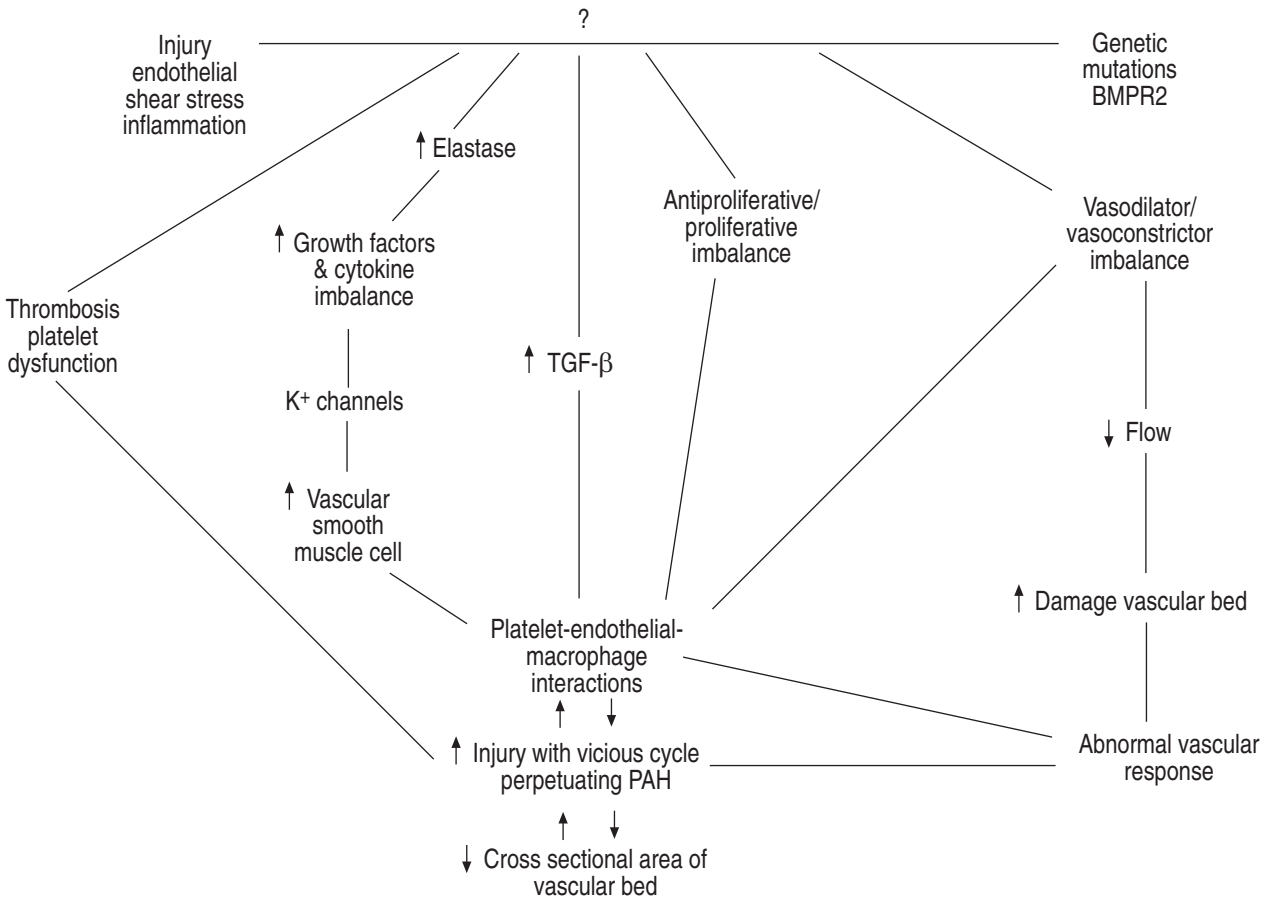

Fig. 2. – Possible pathogenesis of primary pulmonary hypertension. BMPR2: bone morphogentic protein receptor-2; TGF: transforming growth factor; PAH: pulmonary artery hypertension. Reprinted from [41] with permission from Elsevier Science.

in primary pulmonary hypertension patients leading to vasoconstriction is relevant to the development of primary pulmonary hypertension in some patients remains unknown. However, these studies suggest that primary pulmonary hypertension is a disease of "predisposed" individuals, in whom various "stimuli" may initiate the pulmonary vascular disease process. Whether or not vasoconstriction is the initiating event in the pathobiology of primary pulmonary hypertension, it is an important component in the pathophysiology of the disease (in at least a subset of patients). There may also be subsets of patients in whom endothelial dysfunction is the initiating "injury" as opposed to vasoconstriction. Regardless, pulmonary vasoconstriction is an exacerbating factor in the disease progression. Exaggerated episodes of pulmonary vasoconstriction in susceptible individuals can damage the pulmonary vascular endothelium, resulting in further alterations in the balance between vasoactive mediators. Coagulation abnormalities may also occur, initiating or further exacerbating the pulmonary vascular disease [44, 45]. The interactions between the humoral and cellular elements of the blood on an injured endothelial cell surface result in remodelling of the pulmonary vascular bed and contribute to the process of pulmonary vascular injury [46, 47].

Migration of smooth muscle cells in the pulmonary arterioles occurs as a release of chemotactic agents from injured pulmonary endothelial cells [48]. Endothelial cell damage can also result in thrombosis *in situ*, transforming the pulmonary vascular bed from its usual anticoagulant state (owing to the release of prostacyclin and plasminogen activator inhibitors) to a procoagulant state [49]. Elevated fibrinopeptide-A levels in primary pulmonary hypertension patients also suggests that *in situ* thrombosis is occurring [50]. Further support for the role of coagulation abnormalities at the endothelial cell surface comes from the reports of improved survival in patients treated with chronic anticoagulation [2, 26, 51].

Pathophysiology

Although the histopathology in children with primary pulmonary hypertension is often qualitatively the same as that seen with adult patients, the clinical presentation, natural history and factors influencing survival may differ. These differences appear to be most apparent in the youngest children. Children also appear to have differences in their hemodynamics parameters at the time of diagnosis compared with adult patients [52]. The increased cardiac index in children (as opposed to adults) may reflect an earlier diagnosis and why children tend to have a greater acute vasodilator response rate with acute vasodilator testing than adults. The findings of higher heart rates and lower systemic arterial pressures in children is not unexpected. In order to understand the signs and symptoms of pulmonary arterial hypertension, one must first briefly review normal physiology of the pulmonary circulation. The pulmonary vascular bed normally has a remarkable capacity to dilate and recruit unused vasculature to accommodate increases in blood flow. In pulmonary arterial hypertension, however, this capacity is lost, leading to increases in pulmonary artery pressure at rest and further elevations in pulmonary artery pressure with exercise. In response to this increased afterload, the right ventricle hypertrophies. Initially, the right ventricle is capable of sustaining normal cardiac output at rest, but the ability to increase cardiac output with exercise is impaired. As pulmonary vascular disease progresses, the right ventricle fails and resting cardiac output decreases. As right ventricular dysfunction progresses, right ventricular diastolic pressure increases and evidence of right ventricular failure, the most ominous sign of pulmonary vascular disease, manifests. Although the left ventricle is not directly affected by the pulmonary vascular disease, progressive right ventricular dilatation can impair left ventricular filling, leading to moderately increased left ventricular end diastolic and pulmonary capillary wedge pressures. Dyspnoea, the most frequent presenting complaint in adults with primary pulmonary hypertension as well as in some children with primary pulmonary hypertension, is due to impaired oxygen delivery during physical activity as a result of an inability to increase cardiac output in the presence of increased oxygen demands. Syncopal episodes, which occur more frequently with children than with adults, are often exertional or postexertional, and imply a severely limited cardiac output, leading to diminished cerebral blood flow. Peripheral vasodilatation during physical exertion can exacerbate this condition.

From the pathobiology and pathophysiology of primary pulmonary hypertension, the two most frequent mechanisms of death are progressive right ventricular failure and sudden death, with the former occurring far more often [1]. With progressive right ventricular failure, the scenario, described above, leads to dyspnoea, hypoxaemia and a progressive decrease in cardiac output. Pneumonia may be fatal as a result of alveolar hypoxia causing further pulmonary vasoconstriction and an inability to maintain adequate cardiac output, resulting in cardiogenic shock and death. When arterial hypoxaemia and acidosis occur, life-threatening arrhythmias may develop. Postulated mechanisms for sudden death include brady- and tachyarrhythmias, acute pulmonary emboli, massive pulmonary haemorrhage and sudden right ventricular ischaemia. Haemoptysis appears to be due to pulmonary infarcts with secondary arterial thromboses.

Diagnosis and assessment

Although the diagnosis of primary pulmonary hypertension is one of exclusion, it can be made with a high degree of accuracy if care is taken to exclude all likely related or associated conditions. A thorough and detailed history and physical examination, as well as appropriate tests, must be performed to uncover potential causative or contributing factors, many of which may not be readily apparent. Questions should be asked about family history:

pulmonary hypertension, connective tissue disorders, congenital heart disease, other congenital anomalies, and early unexplained deaths. If the family history suggests familial primary pulmonary hypertension, careful screening of all family members is recommended. It is reasonable to consider a transthoracic echocardiogram in all first degree relatives of the patient diagnosed with primary pulmonary hypertension (at the time of his/her diagnosis), as well as at any time symptoms consistent with pulmonary arterial hypertension occur, and subsequently every 3–5 yrs in asymptomatic family members (per the World Health Organization (WHO) World Symposium on Primary Pulmonary Hypertension recommendations 1998) [53]. Although it is reasonable to believe that initiating therapy in "asymptomatic" siblings with familial primary pulmonary hypertension may improve outcome, this remains to be proven. Additional issues to address include a carefully detailed birth and neonatal history, a detailed drug history, prolonged medication history including psychotropic drugs and appetite suppressants, exposure to high altitude or to toxic cooking oil [54, 55], travel history and any history of frequent respiratory tract infections. Problems with coagulation should also be queried. The answers to these questions may offer clues to a possible "trigger" or the "injury" initiating the development of the pulmonary arterial hypertension.

The diagnostic evaluation in children suspected of having primary pulmonary hypertension is similar to that of adult patients (fig. 3), although certain conditions, *e.g.* chronic thromboembolic disease or obstructive sleep apnoea, seen not uncommonly in adult patients, rarely occur in children. A functional assessment is also helpful using the modified New York Heart Association functional classification, *i.e.* WHO functional classification, for patients with pulmonary hypertension (as shown in table 4) [53].

Cardiac catheterisation acute vasodilator testing

Although noninvasive tests are useful in the evaluation of suspected pulmonary arterial hypertension, cardiac catheterisation confirms the diagnosis. In adults, haemodynamic values obtained at cardiac catheterisation can also be used to predict survival, although this has not been validated in children. Cardiac output can accurately be measured by the thermodilution technique in patients without significant shunting through a patent foramen ovale, however it remains controversial whether using the

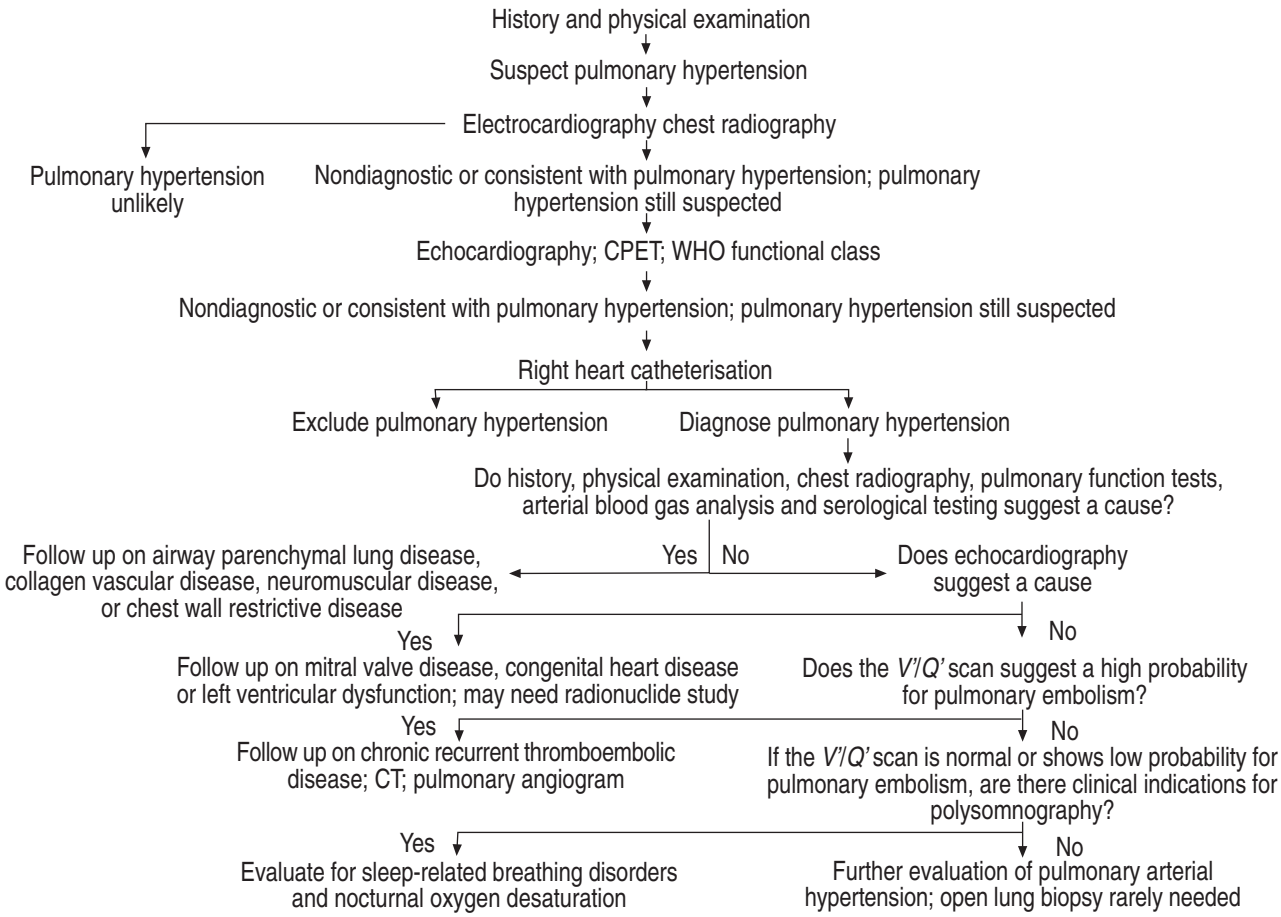

Fig. 3. – Diagnostic evaluation in children suspected of having primary pulmonary hypertension. CPET: cardiopulmonary exercise testing; WHO: World Health Organization; *V'/Q'*: ventilation perfusion ratio; CT: computed tomography.

Table 4. – World Health Organization class

Class I	Patients with pulmonary hypertension but without resulting limitations of physical activity Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity They are comfortable at rest Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity They are comfortable at rest Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms These patients manifest signs of right heart failure Dyspnoea and/or fatigue may even be present at rest Discomfort is increased by any physical activity

thermodilution technique is accurate in the face of significant pulmonary or tricuspid regurgitation. The Fick method is used with measured oxygen consumption if there is any concern regarding pulmonary or tricuspid regurgitation as well as if there is a patent foramen ovale. Because of the increased risk of cardiac catheterisation in patients with severe pulmonary vascular disease, special precautions should be taken during cardiac catheterisation, particularly with children who may have a more reactive pulmonary vascular bed than adult patients, *i.e.* prone to acute pulmonary hypertensive crises: adequate sedation to minimise anxiety without depressing respiration and prevention of hypovolaemia and hypoxaemia are important issues that need to be addressed. As shown in the treatment algorithm guideline (fig. 4), it was recommended that all children undergo acute testing at the time of the initial right heart catheterisation with a short-acting vasodilator to determine vasodilator responsiveness. Unfortunately, there are

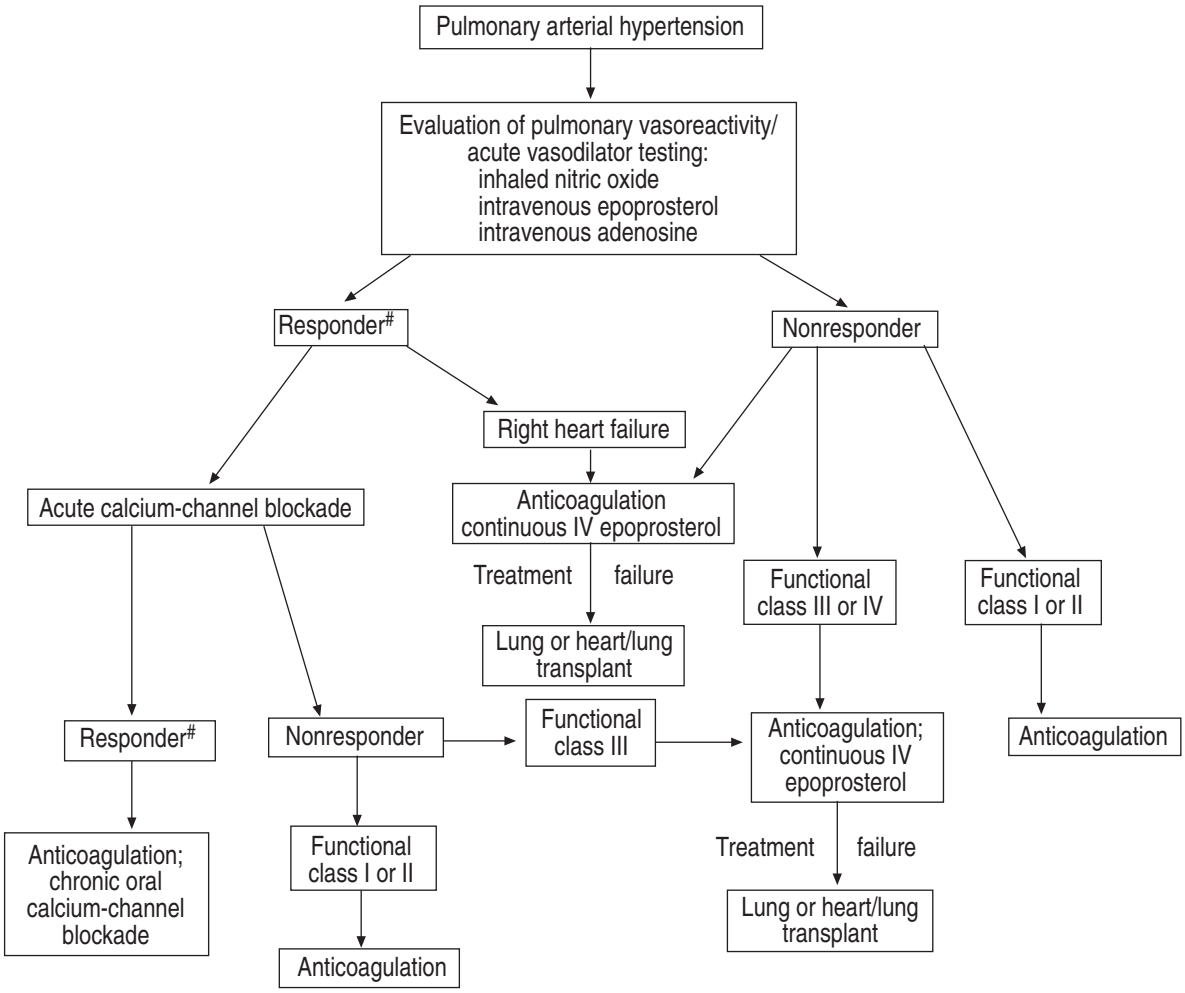

Fig. 4. – Treatment algorithm for primary pulmonary hypertension prior to novel therapeutics. IV: intravenous. #: responder to acute vasodilator testing defined as a significant fall in mean pulmonary arterial pressure, *e.g.* $\geqslant$20%, without a fall in the cardiac output.

no haemodynamic or demographic variables that accurately predict whether or not a child will respond to acute vasodilator testing. Although the younger the child is at the time of diagnosis, the more likely it is that the child will respond to acute testing, there is a wide spectrum of variability (fig. 5) [56]. Children with symptoms for several years suggestive of severe pulmonary vascular compromise may manifest near complete reversibility with chronic oral calcium channel blockade therapy (as discussed below), while others with a brief duration of symptoms may have what appears to be irreversible disease. These observations underscore the marked biological variability in the time course of primary pulmonary hypertension and serve to emphasise the need to individualise the therapeutic approach for each child. The following vasodilators are recommended for acute vasodilator drug testing: intravenous epoprostenol sodium, dose range 2–12 $ng \cdot kg^{-1} \cdot min^{-1}$ (although higher doses may be needed with children for acute vasodilator drug testing compared with adult patients), half-life 2–3 min; inhaled nitric oxide, dose range 10–80 parts per million, half-life 15–30 s; and/or intravenous adenosine 50–200 $ng \cdot kg^{-1} \cdot min^{-1}$, half-life 5–10 s; inhaled iloprost, dose range 14–17 μg, half-life of 20–30 min. Patients who are responsive to acute vasodilator testing are likely (although not always) to have a favourable response with acute calcium channel blocker testing and subsequently chronic oral calcium channel blockade therapy [2, 56]. Although there is no consensus regarding the definition of an acute vasodilator response, an acceptable response would be a significant reduction in mean pulmonary artery pressure, *e.g.* at least 20%, with no change or an increase in cardiac output. Patients who do not manifest a response to acute vasodilator challenge are unlikely to have clinical benefit from chronic oral calcium channel blockade therapy. Furthermore, acute deterioration and decompensation may occur with empiric calcium channel blockade therapy [57, 58].

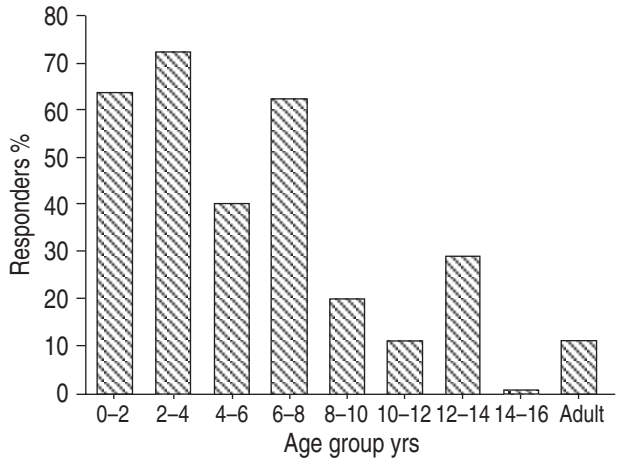

Fig. 5. – Primary pulmonary hypertension: response to acute vasodilator drug testing by age. The younger the child at the time of testing, the greater the likelihood of eliciting acute pulmonary vasodilatation ($p<0.005$). Reproduced with permission from Lippincott Williams and Wilkins [56].

Clinical presentation

The presenting symptoms in children with primary pulmonary hypertension may differ when compared with adult patients. Infants with primary pulmonary hypertension often present with signs of low cardiac output, *e.g.* poor appetite, failure to thrive, lethargy, diaphoresis, tachypnea, tachycardia and irritability. In addition, infants and older children may be cyanotic with exertion, owing to right-to-left shunting through a patent foramen ovale. Children without adequate shunting through a patent foramen ovale can also present with syncope, which is more often effort-related in children than in adult patients. After early childhood, children present with similar symptoms as adults. In the older children, the most common symptoms are exertional dyspnoea and, occasionally, chest pain. Clinical right ventricular failure is rare in young children, occurring most often in children >10 yrs of age with severe long-standing primary pulmonary hypertension. The interval between onset of symptoms and time of diagnosis is usually shorter in children than in adults, particularly in those children who present with syncope. Some infants have crying spells, presumably as a result of chest pain that cannot be otherwise verbalised. In addition to exertional or postexertional syncope, children also not uncommonly present with seizures resulting from exertional syncope as well as exaggerated pulmonary vasoconstriction with mild systemic arterial oxygen desaturation during sleep (particularly in the early morning hours). Children of all ages also commonly complain of nausea and vomiting (reflecting low cardiac output). Chest pain or angina results from right ventricular ischaemia and is often underappreciated. Peripheral oedema is generally a reflection of right ventricular failure and is more likely to be associated with advanced pulmonary vascular disease.

Physical examination

Many of the physical findings in children are typical of any patient, child or adult with pulmonary arterial hypertension, whether or not the pulmonary arterial hypertension is primary or related to other conditions. An increased pulmonic component of the second heart sound is usually audible; however, a right-sided fourth heart sound is not heard as often in children as it is in adults. Children may have distortion of their chest wall, secondary to severe right ventricular hypertrophy. Tricuspid regurgitation is very common, whereas pulmonary insufficiency is heard less often. Clinical signs of right-sided heart failure, *e.g.* hepatomegaly, peripheral oedema and acrocyanosis are rare in young children, particularly in those who present with syncope. Clubbing is not a typical feature of primary pulmonary hypertension, although on rare occasions it has been observed in patients with long-standing

disease who develop chronic hypoxaemia secondary to right-to-left shunting *via* a patent foramen ovale.

Treatment

Although there is no cure for primary pulmonary hypertension, nor is there a single therapeutic approach that is uniformly successful, therapy has improved dramatically over the past several decades, resulting in sustained clinical and haemodynamic improvement, as well as increased survival in children with primary pulmonary hypertension [56]. An overview of the current approach (in 2001) to treatment is shown in figure 4. Noninvasive studies obtained prior to initiating therapy, as well as periodically thereafter, may be useful in guiding changes in therapeutic regimens, particularly in light of recent advances with various novel therapeutic agents. Serial follow-up is necessary to maintain an "optimal" therapeutic regimen for children based on overall risk/benefit considerations.

General measures

The paediatrician plays an invaluable role in the care of children with pulmonary arterial hypertension. Since children often have a more reactive pulmonary vascular bed than adult patients, any respiratory tract infection that results in ventilation/perfusion mismatching from alveolar hypoxia can result in a catastrophic event if not treated aggressively. Annual influenza vaccination as well as pneumococcal pneumonia vaccination are recommended unless there are contraindications. The current authors recommend that children with pneumonia be hospitalised for the initiation of antibiotic therapy, with antipyretics administered for temperature elevations >38°C (101°F) to minimise the consequences of increased metabolic demands. Children may also require aggressive therapy for acute pulmonary hypertensive crises occurring with episodes of pneumonia or other infectious diseases. The present authors have seen the adult respiratory distress syndrome occur not uncommonly in children with pulmonary hypertension following viral infections, requiring aggressive cardiopulmonary support including inhaled nitric oxide, intravenous epoprostenol and, on rare occasion, extracorporeal membrane oxygenation, in addition to conventional maximal cardiopulmonary support to recover. Diet and/or medical therapy should be used to prevent constipation, since Valsalva manoeuvres transiently decrease venous return to the right side of the heart and may precipitate syncopal episodes.

Anticoagulation

Consideration for chronic anticoagulation in children with primary pulmonary hypertension is based on studies in adult primary pulmonary hypertension patients [2, 26, 51]: histopathology demonstrating thrombotic lesions in small pulmonary arteries in the majority of adult patients with primary pulmonary hypertension and biochemical data consistent with a hypercoagulable state in some patients. The rationale for anticoagulation, to prevent secondary thrombosis *in situ* from occurring which can exacerbate the underlying pulmonary vascular disease, is certainly logical in states with low pulmonary blood flow, *e.g.* right heart failure. Whether or not secondary thrombosis *in situ* is a significant exacerbating factor in patients with a normal resting cardiac output is unknown. Clinical data supporting the chronic use of anticoagulation is limited but supportive. Warfarin has been shown to be associated with improved survival in two retrospective studies and one prospective study; all three were with adult patients only [2, 26, 51]. The optimal dose of warfarin in these studies was not determined, although the range of anticoagulation that is usually recommended is to achieve an international normalised ratio (INR) of 1.5–2; however, certain clinical circumstances, *e.g.* positive lupus anticoagulant, positive anticardiolipin antibodies, Factor V Leiden and/or Factor II 20210A variant [59–62], as well as documented chronic thromboembolic disease, may require dose adjustment to maintain a higher INR, as well as dose adjustment to maintain a lower INR for patients at a higher risk of bleeding, *e.g.* patients with significant thrombocytopenia. Whether or not chronic anticoagulation is efficacious as well as safe with a low risk/benefit profile for children with pulmonary hypertension remains to be determined. The current authors′ approach has been to anticoagulate children with right heart failure, as with adult patients. In children who are extremely active, particularly toddlers, unless there is severe pulmonary vascular disease, the authors recommend maintaining an INR <1.5 and in some situations minidose oral anticoagulation with warfarin that may not significantly increase the INR from baseline at all. Antiplatelet therapy with aspirin or dipyridamole does not appear to be effective in areas of low flow where thrombosis *in situ* is known to occur. Parents should be advised to avoid administering other medications that could interact with the warfarin unless the drug/drug interactions are known and the dose of the warfarin is adjusted as needed. Frequent adjustments in warfarin dosage may be necessary when right-sided heart failure is present; heparin may be preferred in these children. As in the authors′ approach with adult pulmonary hypertension patients, if anticoagulation with warfarin is contraindicated or dose adjustments are difficult, either intravenous heparin to achieve an activated partial thromboplastin time of 1.3–1.5 times control or low molecular weight heparin at a dose of 0.75–1 $mg \cdot kg^{-1}$ by subcutaneous administration once or twice daily may be reasonable alternatives, although the long-term side effects of heparin, such as osteopenia and thrombocytopenia, may be troublesome. To date there are no studies comparing the safety and efficacy of anticoagulation with warfarin and heparin; however experimental studies by Thompson *et al.* [63] *in vivo* and Benitz *et al.* [64] *in vitro* suggest that vascular smooth muscle growth inhibitors, such as heparin, may be useful in preventing pulmonary vascular disease.

Calcium channel blockade

Calcium channel blockers are a chemically heterogeneous group of compounds that inhibit calcium influx through the slow channel into cardiac and smooth muscle cells. Their usefulness in pulmonary hypertension is believed to be based on the ability to cause vasodilatation of pulmonary vascular smooth muscle. The rationale for this is based on histopathological studies that demonstrated an apparent progression in vascular remodelling from medial hypertrophy to plexiform arteriopathy [29], although this is now controversial with current speculation that there may be subsets of patients with a vasoconstrictive component initiating the process in some patients and a proliferative initiation in other patients. The recent discovery of the primary pulmonary hypertension-1 (bone morphogenic protein receptor-2) (fig. 6) [65, 66] gene also suggests that primary pulmonary hypertension is a proliferative disorder

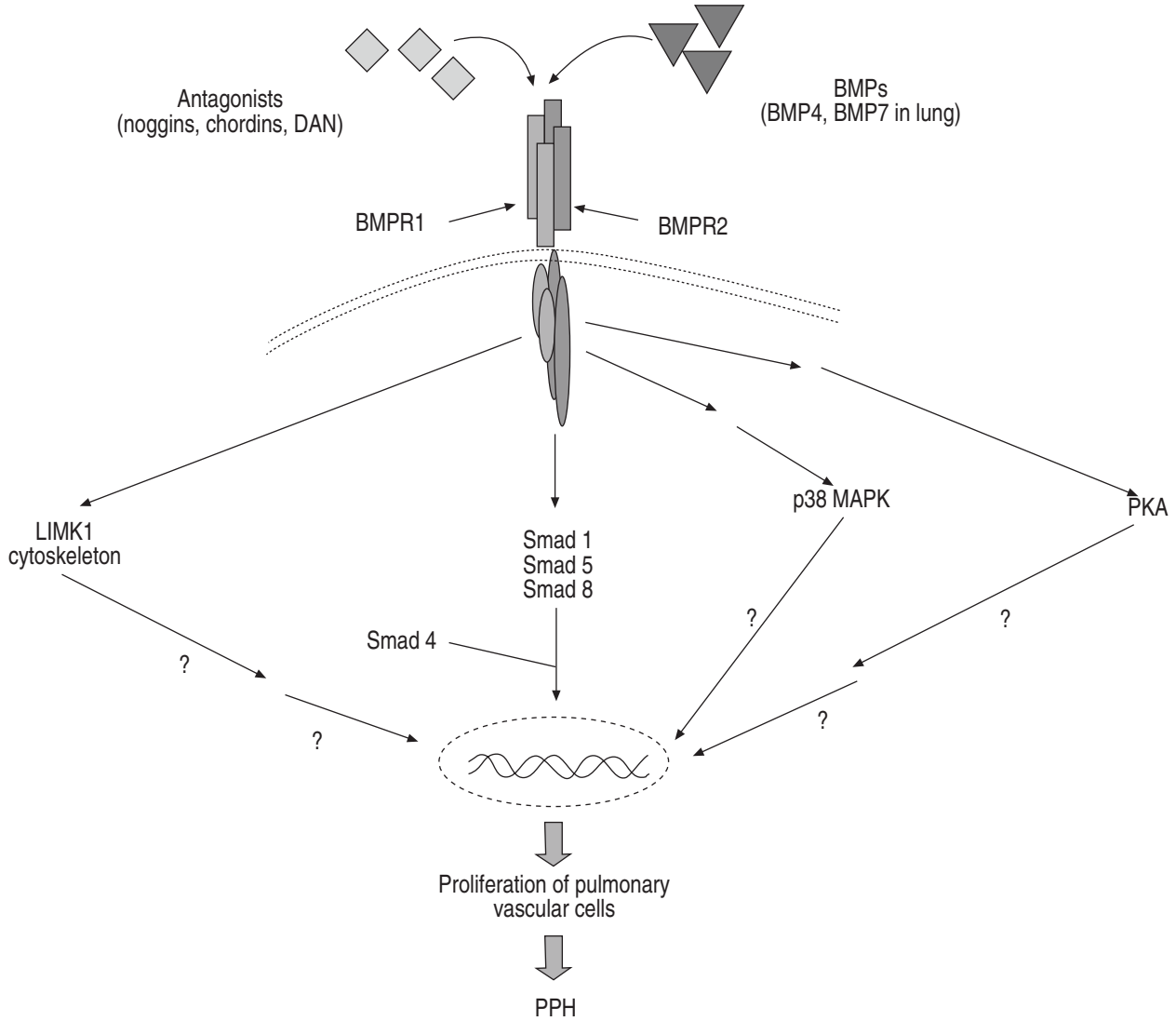

Fig. 6. – Signalling pathways of the bone morphogenetic protein receptor (BMPR)2. In the extracellular space, bone morphogentic proteins (BMPs) bind directly to the BMPR2 on the cell membrane. The bioavailability of BMPs is regulated by the presence of BMPR2 receptor antagonists such as noggins, chordins and differential screening-selected gene (DAN). The binding of ligands to BMPR2 leads to the recruitment of BMPR1 to form a heteromeric receptor complex at the cell surface. This results in the phosphorylation and activation of the kinase domain of BMPR1. The activated BMPR1 subsequently phosphorylates and activates cytoplasmic signalling proteins Smads. Phosphorylated Smads bind to the common mediator Smad 4 and the resulting Smad complex moves from the cytoplasm into the nucleus and regulates gene transcription. Other downstream signalling pathways that can be activated following the engagement of BMPR1 and BMPR2 by BMPs include cell-type dependent activation of p38 mitogen activated protein kinase (p38 MAPK) and protein kinase A (PKA). In addition, the cytoplasmic tail of BMPR2 has been shown to interact with the LIM motif-containing protein kinase 1 (LIMK1) that is localised in the cytoskeleton. Germline mutations of the gene encoding BMPR2 underlie primary pulmonary hypertension (PPH) that is characterised by the abnormal proliferation of pulmonary vascular cells. However, the specific cytoplasmic proteins and nuclear transcription factors that are involved in the development of PPH have not been identified. The molecular mechanism of how defects of BMPR2 lead to primary pulmonary hypertension remains to be elucidated.

and that there may be a role for both pulmonary vasodilators and antiproliferative agents in the treatment of primary pulmonary hypertension. Regardless, since medial hypertrophy is presumably associated with vasoconstriction and plexiform lesions are associated with fixed pulmonary vascular disease if a significant portion of the pulmonary vascular bed has a reactive component, whether or not this is early in the course of the disease (when fewer vessels are affected with "fixed" obstruction), chronic vasodilator therapy with an oral agent such as calcium channel blockers should be efficacious. In the 1970s, the advent of vasodilator drugs to treat systemic hypertension led to vasodilator therapy for primary pulmonary hypertension.

Although only a minority (~20%) of adult patients with primary pulmonary hypertension will respond with chronic oral calcium channel blockade [2], *e.g.* documented by improvement in symptoms, exercise tolerance, haemodynamics (*via* reduction in pulmonary artery pressure and an increase in cardiac output) and survival, a significantly greater percentage of children are acute responders (40%) and can be effectively treated with chronic oral calcium channel blockade [56]. In addition, although most studies have used calcium channel blockers at relatively high doses, *e.g.* long-acting nifedipine 120–240 mg daily or amlodipine 20–40 mg daily (for children as well as adults, *i.e.* children tolerating and appearing to need a higher $mg \cdot kg^{-1}$ dose than adults), the optimal dosing for patients, both children and adults with primary pulmonary hypertension, is uncertain. Children with no evidence of an acute haemodynamic response (during acute vasodilator testing including testing with calcium channel blockers) are unlikely to benefit from chronic therapy. Because of the frequent reporting of significant adverse effects with calcium channel blockade in these nonresponders, including systemic hypotension, pulmonary oedema, right ventricular failure and death, it is not recommended that calcium channel blockers be used in patients in whom acute effectiveness has not been demonstrated.

Serial re-evaluations

Serial re-evaluations, including repeat acute vasodilator testing, to maintain an optimal chronic therapeutic regimen is essential to the care of children with primary pulmonary hypertension. In the present authors' experience, acute responders who are treated with chronic oral calcium channel blockade therapy continue to do exceedingly well as long as they remain acutely reactive with vasodilator testing at repeat cardiac catheterisation. In contrast, children who have initially been acute responders and treated with chronic calcium channel blockade, who no longer demonstrate active vasoreactivity on repeat testing, more often than not subsequently deteriorate clinically and haemodynamically despite continuation of chronic calcium channel blockade therapy; they are then switched to chronic intravenous epoprostenol with improvement with chronic epoprostenol therapy similar to that seen with children who are initiated on epoprostenol because they are nonresponders at their initial evaluation.

Prostaglandins

The use of prostacyclin (epoprostenol) or a prostacyclin analogue for the treatment of primary pulmonary hypertension is supported by the demonstration of an imbalance in the thromboxane to prostacyclin metabolites in patients with primary pulmonary hypertension [34], as well as the demonstration of a reduction in prostacyclin synthase in the pulmonary arteries of primary pulmonary hypertension patients [39]. Although chronic intravenous epoprostenol does improve exercise tolerance, haemodynamics or survival in patients with primary pulmonary hypertension, its mechanism(s) of action remains unclear [3, 4, 67–69]. In addition to lowering pulmonary artery pressure, increasing cardiac output and increasing oxygen transport, based on studies demonstrating that the lack of an acute response to epoprostenol does not preclude a chronic beneficial response, an effect on reversing pulmonary vascular remodelling with chronic intravenous epoprostenol is raised [56]. The development of tolerance to the effects of intravenous epoprostenol remains unknown; some children appear to need periodic dose escalation, which may represent tolerance and/or disease progression. In addition, the optimal dose of intravenous epoprostenol is also unclear. The starting dose, similar to that in adult patients, is $2\ ng \cdot kg^{-1} \cdot min^{-1}$ with incremental increases most rapid during the first few months after epoprostenol is initiated. Although the mean dose in adult patients at 1 yr is ~20–40 $ng \cdot kg^{-1} \cdot min^{-1}$, the mean dose at 1 yr in children, particularly young children, is closer to 50–80 $ng \cdot kg^{-1} \cdot min^{-1}$, with a significant patient variability with regards to the optimal dose.

Prostacyclin analogues

Prostacyclin analogues (oral, inhaled, subcutaneous) were clinically developed to provided a less invasive treatment alternative for patients with pulmonary arterial hypertension, with continuous intravenous epoprostenol having significant adverse events, including serious adverse events due to the delivery system, *e.g.* sepsis, paradoxidal emboli as well as temporary interruption of the epoprostenol which can result in catastrophic pulmonary hypertensive crises.

Oral prostacyclin analogue

Beraprost sodium is an oral prostacyclin analogue. It is chemically stable and an orally active prostaglandin I_2 derivative with a substantially longer half-life than epoprostenol (half-life: 1.11±0.1 h; peak plasma level is obtained within 2 h; time to maximal concentration: 1.42±0.15 h). The drug has similar properties to epoprostenol (prostacyclin), *e.g.* increases

red blood cell flexibility, decreases blood viscosity, inhibits platelet aggregation, produces vasodilatation and decreases platelet adherence to the endothelium as well as disaggregating platelets that have already clumped. Its potency is ~50% of epoprostenol. Preliminary data from Japan suggests that beraprost is efficacious in improving haemodynamics and survival in primary pulmonary hypertension patients [70, 71]. Although these studies were open-label, uncontrolled clinical trials, they provided proof of concept for further clinical investigation. More recently, a 12-week double-blind, randomised, placebo-controlled trial in Europe demonstrated improved exercise capacity and quality of life in adults with pulmonary arterial hypertension, although a longer study (1 yr only) demonstrated transient improvement in exercise capacity at 3 and 6 months that disappeared by 9 and 12 months.

Inhaled prostacyclin analogue

Although inhaled iloprost, a stable synthetic analogue of prostacyclin, has been shown to be efficacious in improving haemodynamics and exercise capacity in pulmonary arterial hypertension patients [72–76], the clinical experience with children is extremely limited. It has a similar molecular structure to prostacyclin and works though prostacyclin receptors present on vascular endothelial cells. Iloprost is more stable than epoprostenol and can be stored at room temperature without needing protection from light [74]. It has a biological half-life of 20–30 min [77]. The acute effects of inhaled nitric oxide with aerosolised iloprost have been evaluated in children with pulmonary hypertension associated with congenital heart defects and it was demonstrated that both agents appear to be equally efficacious [78]. This opens the door for consideration of using aerosolised iloprost to treat children with various forms of pulmonary arterial hypertension including primary pulmonary hypertension.

Subcutaneous prostacyclin analogue

Treprostinil sodium is a chemically stable prostacyclin analogue which also shares the same pharmacological actions as epoprostenol. Previous studies have demonstrated similar acute haemodynamic effects to intravenous epoprostenol in patients with primary pulmonary hypertension, however, treprostinil is stable at room temperature and neutral pH and has a longer half-life of ~3 h when delivered subcutaneously [79]. Similar to epoprostenol, treprostinil is infused continuously, through a portable pump, however, it is administered subcutaneously. Double-blind, randomised, controlled trials demonstrated improved exercise capacity, clinical signs and symptoms as well as haemodynamics in patients with pulmonary arterial hypertension including children with pulmonary arterial hypertension [80]. With regard to adverse effects, the risk of central venous line infection is eliminated when treprostinil is used subcutaneously. Although no serious adverse events related to treprostinil or its delivery system have been reported, there are side-effects with this therapeutic modality; the most common side-effect attributed to chronic subcutaneous treprostinil therapy is discomfort at the infusion site [81].

Endothelin receptor antagonists

Endothelin-1, one of the most potent vasoconstrictors identified to date [82], has been implicated in the pathobiology of pulmonary arterial hypertension, thus providing the rationale for endothelin receptor antagonists as promising drugs for the treatment of pulmonary arterial hypertension. Plasma endothelin-1 levels are known to be increased in patients with primary pulmonary hypertension and correlate inversely with prognosis [83]. There are at least two different receptor subtypes: endothelin (ET)A receptors are localised on smooth muscle cells and mediate vasoconstriction and proliferation while ETB receptors are found predominantly on the endothelin cells and are associated with endothelium dependent vasorelaxation through the release of vasodilators, *e.g.* prostacyclin and nitric oxide, but are also responsible for the clearance of endothelin, as well as initiating vasoconstriction (on smooth muscle cells) and bronchoconstriction (fig. 7). The oral dual endothelin receptor antagonist bosentan has been shown to improve exercise capacity, quality of life, as well as cardiopulmonary haemodynamics in patients with pulmonary arterial hypertension [85, 86]. Although these studies were primarily carried out in adult patients, the present authors anticipate that bosentan will also be efficacious in children. Clinical investigation is also underway, evaluating whether a selective ETA receptor antagonist such as sitaxsentan will be more or less efficacious than a dual endothelin receptor antagonist. In an open-label, uncontrolled study of 20 patients including children, the selective ETA receptor antagonist sitaxsentan improved exercise capacity and haemodynamics [87]. A 12-week, double-blind, placebo-controlled trial has recently been completed (results pending).

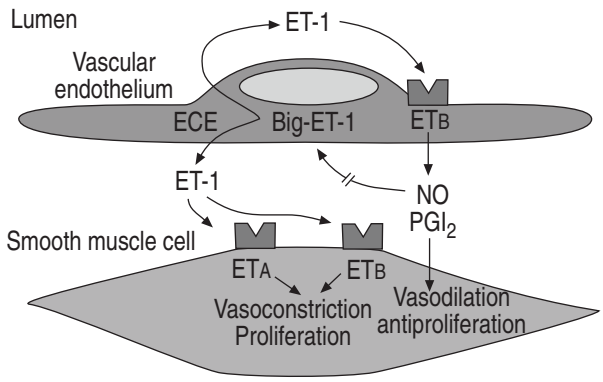

Fig. 7. – Endothelin system in vascular disease. ET: endothelin; Big-ET-1: proendothelin-1; ECE: endothelin-converting enzyme; NO: nitric oxide; PGI_2: prostacycin. Reproduced with permission from Elsevier Science [84].

Both ETA and ETB receptors play a fundamental role in pulmonary vasoconstriction, inflammation, proliferation of smooth muscle cells, fibrosis and bronchoconstriction. In addition, because ETB receptors may be upregulated on smooth muscle cells in certain pathological conditions, as well as crosstalk occurring between ETA and ETB receptors, whether dual endothelin receptor blockade or selective ETA receptor blockade will prove more efficacious remains to be elucidated. Adverse events associated with endothelin receptor antagonists include an increase in liver function, which may require a decrease in dose or discontinuation of therapy, teratogenicity as well as possibly irreversible male infertility. Furthermore, whether the addition of endothelin receptor antagonists to chronic oral calcium channel blockade therapy, continuous intravenous epoprostenol or a prostacyclin analogue, will increase the overall efficacy and risk/benefit profile for treating children with pulmonary arterial hypertension remains to be elucidated.

Nitric oxide

Nitric oxide is an inhaled vasodilator that exerts selective effects on the pulmonary circulation (fig. 8) [89]. Nitric oxide activates guanylate cyclase in pulmonary vascular smooth muscle cells, which increases cyclic guanosine monophosphate (GMP) and decreases intracellular calcium concentration,

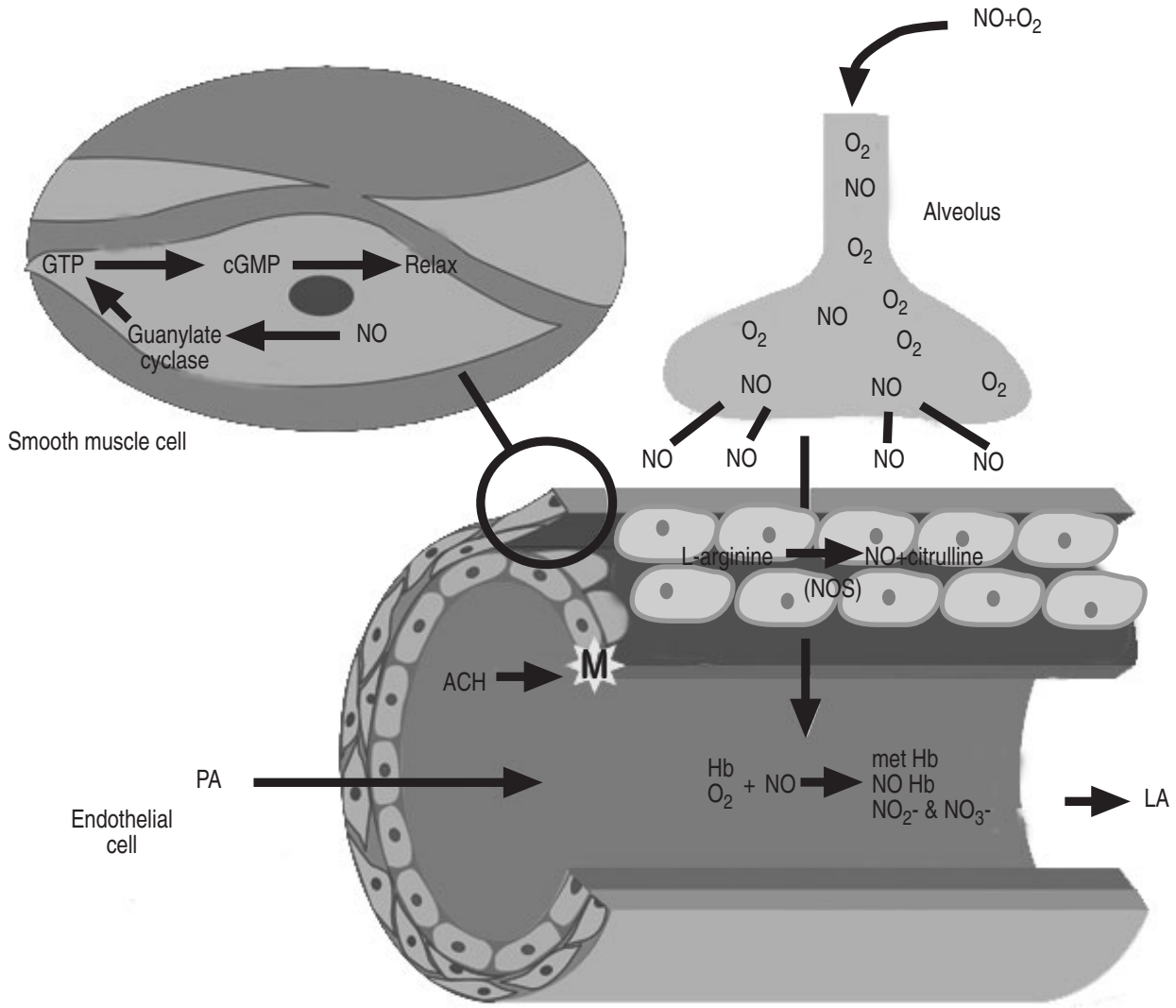

Fig. 8. – Nitric oxide (NO) is endogenously formed from L-arginine after acetylcholine (ACh) binds to muscarinic receptors (M) on the intact endothelium and stimulates endothelial nitric oxide synthase (NOS). NO exists as a gas and can be delivered to alveoli. It diffuses across alveolar membrane to closely adjacent vessels. Constricted pulmonary vessels dilate as the result of increased intracellular cyclic guanosine monophosphate (cGMP) production in smooth muscle cells. NO is immediately inactivated by haemoglobin with the formation of methaemoglobin (met Hb), nitrosylhaemoglobin (NO Hb), nitrates (NO_3^-) and nitrites (NO_2^-) limiting its activity to the pulmonary circulation. GTP: guanosine triphosphate; O_2: oxygen; PA: pulmonary artery; LA: left atrium. Reprinted from [88] with permission from Elsevier Science.

thereby leading to smooth muscle relaxation. When inhaled, the rapid combination of nitric oxide and haemoglobin inactivates any nitric oxide diffusing into the blood, preventing systemic vasodilatation. Nitric oxide is therefore a potent and selective pulmonary vasodilator when administered by inhalation. Inhaled nitric oxide has been demonstrated to be safe and efficacious in the treatment of persistent pulmonary hypertension of the newborn [90, 91]. Despite the differences between primary pulmonary hypertension and persistent pulmonary hypertension in the newborn, these studies suggest that inhaled nitric oxide may be useful in the treatment of primary pulmonary hypertension as well as other forms of pulmonary arterial hypertension. Although there is considerable experience with the use of inhaled nitric oxide as a short-term treatment for pulmonary arterial hypertension in a variety of clinical situations, the role of inhaled nitric oxide as a chronic therapy for pulmonary arterial hypertension remains under clinical investigation [92]. Analogous to the suggestion that the improved survival in some children on long-term epoprostenol therapy is unrelated to its acute effects and may be related to antiproliferative effects on smooth muscle and/or anti-aggregatory effects on platelets, nitric oxide may also have antiproliferative effects on smooth muscle and inhibit platelet adhesion. It is possible that in suitable children, a low-dose inhalation of nitric oxide may become a useful agent in the treatment of pulmonary arterial hypertension, both by reversing the vasoconstrictor component when present as well as encouraging the regression of remodelling which obliterates the pulmonary vascular bed. Employing such therapeutic strategies for nitric oxide as well as epoprostenol challenges the presumed irreversibility and lethality of pulmonary arterial hypertension. This seems particularly true for infants with pulmonary arterial hypertension who have substantial capacity for smooth muscle regression, alveolar growth and angiogenesis. Despite this rationale, clinical trials are needed to evaluate the safety and potential toxicity, as well as efficacy of chronic inhaled nitric oxide.

Phosphodiesterase inhibitors

Additional investigations evaluating nitric oxide potentiating compounds, such as type-5 phosphodiesterase inhibitors, *e.g.* sildenafil, are also being performed [93, 94]. These strategies are aimed at raising cyclic GMP to potentiate pulmonary vasodilatation in response to nitric oxide, as well as to facilitate withdrawal of nitric oxide. Phosphodiesterase type-5 inhibitors may be particularly beneficial in conjunction with chronic inhaled nitric oxide, where inadvertent withdrawal of nitric oxide may otherwise lead to a precipitous rise in pulmonary arterial pressure. Intravenous, long acting oral or aerosolised forms of phosphodiesterase type-5 inhibitors all have therapeutic appeal. Carefully designed studies of its possible therapeutic use alone, and in combination with inhaled nitric oxide, appear warranted. Preliminary safety and efficacy trials are underway with due concern for potential toxicity in the paediatric population.

Elastase inhibitors

Cowan and co-workers [95, 96] have suggested that increased activity of an elastolytic enzyme may be important in the pathophysiology of pulmonary vascular disease. A cause and effect relationship between elastase and pulmonary vascular disease is supported by studies reporting the reversal of advanced pulmonary vascular disease induced by monocrotaline in rats. Part of the novelty of these observations is the complete regression of pathophysiological findings in the treatment group, even though treatment began after the disease was far advanced. The presumed mechanism of an apoptotic cascade with regression of smooth muscle hypertrophy and neointimal proliferation has exciting therapeutic implications and human trials are being considered. However, one must bear in mind that the monocrotaline model does not exhibit identical vascular pathology to the human condition and rodent models of successful treatment of vascular disease have not always borne similar success in analogous human diseases. Moreover, there was no apparent growth of new blood vessels despite the vascular recovery, possibly limiting angiogenesis potential. However, what seems clear from these studies is that the presumed irreversibility and fatality of progressive pulmonary arterial hypertension now needs further assessment.

Gene therapy

With the identification of a primary pulmonary hypertension gene in selected families, attention has focused on gene replacement therapy linked to the mutated 2q33 chromosome. An alternative therapeutic approach has been to induce the overexpression of vasodilator genes, notably endothelial nitric oxide synthase and prostacyclin synthase. Patients with primary pulmonary hypertension have been shown to have deficiencies in prostacyclin synthase, nitric oxide production as well as other endothelial functions. Given the preliminary clinical observations that exogenous administration of chronic nitric oxide or epoprostenol may have salutary effects on even advanced forms of the disease, it seems meritorious to pursue these alternative modes of drug delivery. Coupled with advances in the understanding of the genetic predisposition associated with at least some, if not all, patients with pulmonary arterial hypertension, it seems likely that an important gene delivery treatment for this disease may be close at hand.

Oxygen

Some children, who remain fully saturated while awake, demonstrate modest systemic arterial oxygen desaturation with sleep, which appears to be due to

mild hypoventilation [97]. During these episodes, children may experience severe dyspnoea, as well as syncope with or without hypoxic seizures. Desaturation during sleep usually occurs during the early morning hours and can be eliminated by using supplemental oxygen. The current authors also recommend that children have supplemental oxygen available at home for emergency use, even if they do not use it on a routine basis. Children should also be treated with supplemental oxygen during any significant upper respiratory tract infections if systemic arterial oxygen desaturation occurs, even if the child is treated at home with oral antibiotics. If more than mild oxygen desaturation occurs, the child should be treated in a hospital setting. Children with desaturation due to right-to-left shunting through a patent foramen ovale usually do not improve their oxygen saturation with supplemental oxygen. Although a small study of children with Eisenmenger's syndrome demonstrated improved long-term survival with supplemental oxygen [98], a more recent study with 23 adult patients with Eisenmenger's syndrome did not observe any significant improvement in survival with nocturnal oxygen [99]. Whether children with Eisenmenger's syndrome benefit from treatment with nocturnal oxygen remains unclear. Supplemental oxygen may also reduce the degree of polycythaemia in children with significant right-to-left shunting *via* a patent foramen ovale. Similar to the experience with adult patients, some children experience arterial blood oxygen desaturation with exercise as a result of increased oxygen extraction in the face of fixed oxygen delivery. These children may benefit from ambulatory supplemental oxygen. In addition, children with severe right ventricular failure and resting hypoxaemia, resulting from a markedly increased oxygen extraction, should also be treated with continuous oxygen therapy.

Additional pharmacotherapy: cardiac glycosides, diuretics, antiarrhythmic therapy, inotropic agents and nitrates

Although controversy persists regarding the value of digitalis in primary pulmonary hypertension [100], the present authors believe that children with right-sided heart failure may benefit from digitalis, in addition to diuretic therapy. Diuretic therapy must be initiated cautiously, since these patients appear to be extremely dependent on preload to maintain optimal cardiac output. Despite this, relatively high doses of diuretic therapy are commonly needed.

Although malignant arrhythmias are rare in pulmonary hypertension, they require treatment if documented. Atrial flutter or fibrillation often precipitates an abrupt decrease in cardiac output and clinical deterioration once atrial systole is lost. As opposed to healthy children, in whom atrial systole is responsible for ~25% of the cardiac output, atrial systole in children with primary pulmonary hypertension often contributes as much as 70% of the cardiac output. Therefore, aggressive treatment of atrial flutter of fibrillation is advised. The treatment of children with clinically significant supraventricular tachycardias as well as frequent episodes of nonsustained ventricular tachycardia and complex ventricular arrhythmias is recommended, but it should probably be avoided for the treatment of lesser grades of arrhythmia.

There are no studies on the usefulness of intermittent or continuous treatment with inotropic agents. The present authors occasionally add dobutamine for additional inotropic support to continuous intravenous epoprostenol for a child with severe right ventricular dysfunction who is awaiting transplantation. Children have occasionally also benefited from short-term inotropic support during acute pulmonary hypertensive crises to augment cardiac output during a period of increased metabolic demands.

Oral and sublingual nitrates have been used to treat some children with primary pulmonary hypertension, although the experience with these agents remains somewhat limited. Children who complain of chest tightness, or pressure, or vague discomfort that is responsive to sublingual nitroglycerin should be treated with chronic oral nitrates as well as sublingual nitroglycerin.

Atrial septostomy

Children with recurrent syncope or severe right heart failure have a very poor prognosis [1, 101]. Exercise-induced syncope is due to systemic vasodilatation, with an inability to augment cardiac output to maintain cerebral perfusion pressure. Children with pulmonary arterial hypertension and recurrent syncope are unable to adequately shunt through a patent foramen ovale [102]. If right-to-left shunting through an interatrial communication is present, cardiac output can be maintained or increased if necessary. In addition, right-to-left shunting at the atrial level alleviates signs and symptoms of right heart failure by decompression of the right atrium and right ventricle. Increased survival has been reported in primary pulmonary hypertension patients with a patent foramen ovale, although there has been some controversy regarding this [103]. Patency of the foramen ovale may improve survival if it allows sufficient right-to-left shunting to occur to maintain cardiac output, as is evidenced by systemic arterial oxygen desaturation at rest and/or during exercise. Although there is a worldwide experience in >100 patients, the procedure should still be considered investigational. Successful palliation of symptoms with atrial septostomy has been reported in several series [104–108]. In the current authors' experience, patients with pulmonary arterial hypertension with recurrent syncope and/or right heart failure significantly improve clinically as well as haemodynamically following atrial septostomy; *e.g.* patients experience no further syncope after the procedure and signs and symptoms of right-sided heart failure improve. Although systemic arterial oxygen desaturation decreases, cardiac output and oxygen delivery improve through right-to-left shunting at the atrial level. The authors have also observed an improvement in survival at 1 and 2 yrs;

e.g. survival rates of 87 and 76%, respectively, following atrial septostomy compared with standard therapy (64 and 42% at 1 and 2 yrs, respectively) [107]. Thus, although atrial septostomy does not alter the underlying disease process, it may improve quality of life and represent an alternative for selected patients with severe primary pulmonary hypertension. Although this invasive procedure is not without risk, the indications for the procedure include: recurrent syncope and/or right ventricular failure despite maximal medical therapy as well as a bridge to transplantation if deterioration occurs despite maximal medical therapy. Closure of the atrial septal defect can be performed at the time of transplantation.

Transplantation

Heart/lung, single lung and bilateral lung transplantation have been performed successfully for children and adults with pulmonary arterial hypertension. Since 1981, over 1,500 patients have undergone transplantation for pulmonary arterial hypertension worldwide. The operative mortality ranges between 16 and 29% and is affected by the primary diagnosis. The 1-yr survival is between 70 and 75%, 3 yr survival 55–60% and 5 yr survival 40–45% [109, 110]. For paediatric lung and heart/lung recipients, the data from the registry of the International Society for Heart and Lung Transplantation demonstrates that current survival is ~65% at 2 yrs and ~40% at 5 yrs [111].

Transplantation should be reserved for patients with pulmonary arterial hypertension who have progressed in spite of optimal medical therapy. As progress is made in the medical management of pulmonary arterial hypertension, the indications for transplantation will evolve. The appropriate time for evaluation and listing for transplantation remains problematic. The course of the disease and the waiting time must be taken into account. Timing a referral for transplantation depends upon the patient's prognosis with optimal medical therapy, the anticipated waiting time for transplantation in the region and the expected survival after transplantation. Ideally, children should be listed when their probability of 2-yr survival without transplantation is $\leqslant 50\%$. There are several transplantation options. Acceptable results have been achieved with heart/lung transplantation, bilateral lung transplantation and single lung transplantation. While there are advantages and disadvantages to each operation, there is currently no consensus regarding the optimal procedure. The availability of donor organs also influences the choice of procedure. It is possible that the data on long-term survival of transplantation recipients may demonstrate a survival advantage of one procedure over another. Although lung and heart/lung transplantation are imperfect therapies for pulmonary arterial hypertension, when offered to an appropriately selected population transplantation may offer prolongation of an improved quality of life. Early referral to a centre with expertise in paediatric lung and heart/lung transplantation may decrease pretransplantation mortality and allow families to have adequate time to make an informed and thoughtful choice about this therapy. Living related donor transplantation remains controversial; although living related donor transplantation has been successful, there is limited experience [112, 113].

Conclusions

Although recent therapeutic advances appear to have significantly improved its natural history, pulmonary arterial hypertension in children remains a devastating disease. The current authors' experience demonstrates that chronic vasodilator therapy with calcium channel blockade in acute responders to vasodilator testing and continuous intravenous epoprostenol in nonresponders (as well as in responders who fail to improve on calcium channel blockade) is at least as effective in children as in adults with respect to increasing survival, improving haemodynamics and relieving symptoms [2–4, 6, 66, 114, 115]. This is a pivotal time for the treatment of pulmonary arterial hypertension, as there are a number of very promising new drugs, *e.g.* prostacyclin analogues, endothelin receptor antagonists and inhaled nitric oxide. Based on distinct mechanisms of action of these various agents, a role for combination therapy may further improve the efficacy of a child's medical regimen, *e.g.* combining endothelin receptor antagonists with either intravenous epoprostenol or with a prostacyclin analogue. Furthermore, future investigations with other agents, such as inhaled nitric oxide, phosphodiesterase inhibitors, *e.g.* type-5 to increase or maintain cyclic GMP activity (sildenafil) or type-3/4 to increase or maintain cyclic adenosine monophosphate activity, substrate loading agents, *e.g.* arginine to increase nitric oxide production, as well as consideration of elastase inhibitors, should further improve treatment options for children with pulmonary arterial hypertension. Whether these new agents will, in fact, replace intravenous epoprostenol in selected children remains unknown.

The therapeutic algorithm that the current authors have followed to date, with regard to chronic medical treatment for children with pulmonary arterial hypertension as shown in fig. 4, will hopefully change as more experience is gained with the novel therapeutic agents discussed previously. Thus, in the future, a therapeutic algorithm for children with pulmonary arterial hypertension may look something like that which is presented in fig. 9.

Future developments in vascular biology will help improve the understanding of the aetiology(ies) and pathobiology of pulmonary arterial hypertension, as well as providing rationale for more specific medical therapies. The authors hope that by increasing the understanding of the pathobiology of pulmonary arterial hypertension, one day this disease can be prevented or cured, as opposed to only providing palliative therapy.

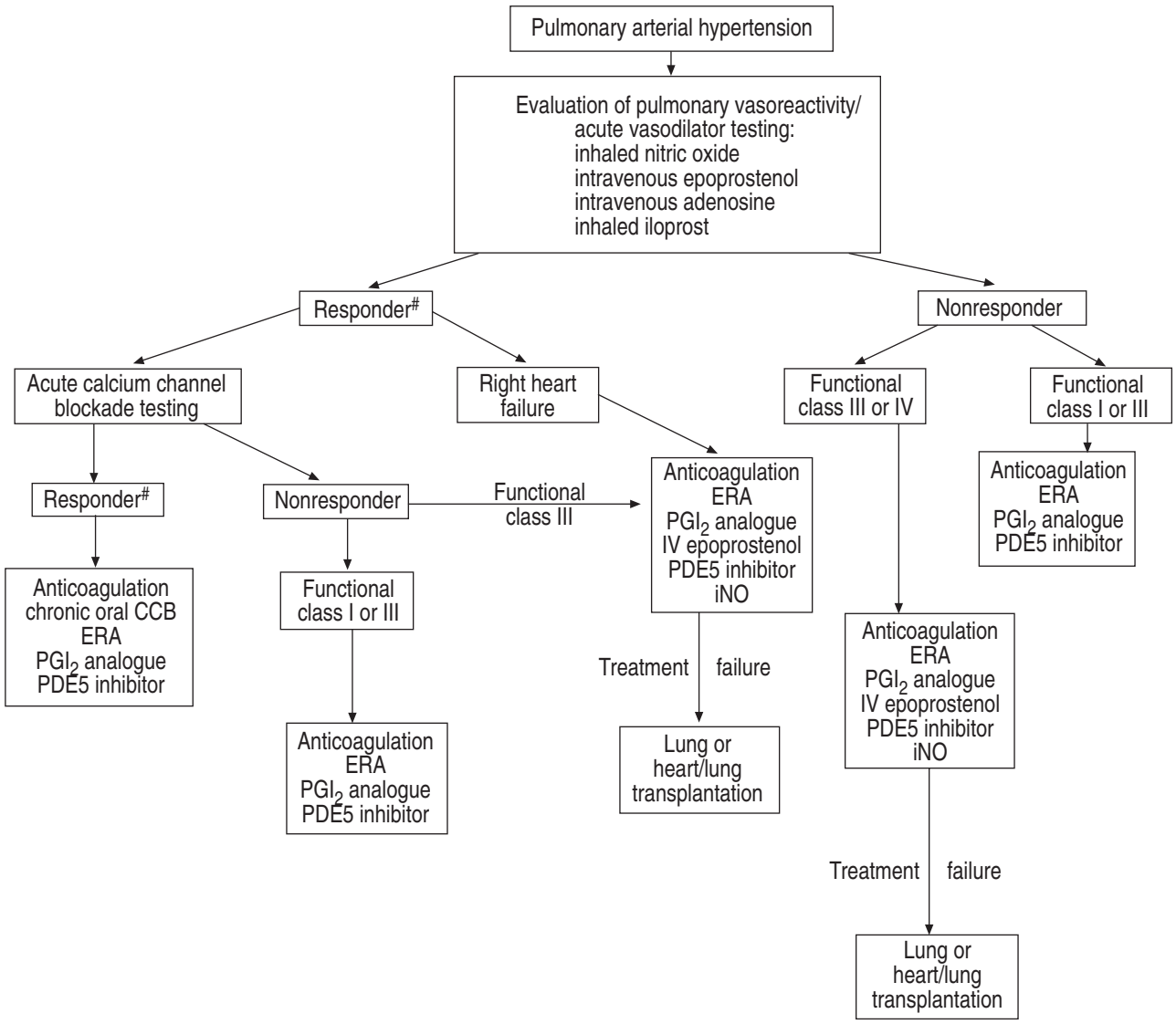

Fig. 9. – The role of novel therapeutic agents on the treatment algorithm for primary pulmonary hypertension. #: responder to acute vasodilator testing defined as a significant fall in mean pulmonary arterial pressure, *e.g.* $\geqslant$20%, without a fall in the cardiac output. ERA: endothelin receptor antagonist; PGI_2: prostacyclin; IV: intravenous; PDE: phosphodiesterase; iNO: inhaled nitric oxide; CCB: calcium channel blockade.

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