Vascular Health and Risk Management

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REVIEW

Treatment of pediatric pulmonary hypertension

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This article was published in the following Dove Press journal:
Vascular Health and Risk Management
3 June 2009
Number of times this article has been viewed

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Abstract: Pulmonary hypertension was once thought to be a rare condition and only managed in specialized centers. Now however, with the advent of echocardiography, it is found in many clinical scenarios, in the neonate with chronic lung disease, in the acute setting in the intensive care unit, in connective tissue disease and in cardiology pre- and postoperatively. We have a better understanding of the pathological process and have a range of medication which is starting to be able to palliate this previously fatal condition. This review describes the areas that are known in this condition and those that are less familiar. The basic physiology behind pulmonary hypertension and pulmonary vascular disease is explained. The histopathologic process and the various diagnostic tools are described and are followed by the current and future therapy at our disposal.

Keywords: pulmonary hypertension, congenital heart disease, pulmonary vascular resistance, pulmonary vasodilators

Introduction

Pulmonary arterial hypertension (PAH) can be implicated in the morbidity and mortality of many areas of cardiac and noncardiac pathology, and is an important complication in many patients with congenital heart disease.[1–3] Traditionally, a diagnosis of PAH was accompanied by a bleak prognosis, with the survival with "primary" pulmonary hypertension being only 2.8 years. However, in recent years, increased awareness of this condition combined with more effective intervention at an early stage has reduced the number of patients with advanced pulmonary vascular disease (PVD), and improved survival rates.[1]

Definition

Pulmonary arterial hypertension can be defined as an increase in pulmonary arterial pressure (PA pressure) in the pulmonary vascular bed,[1] and is defined as a mean PA pressure of more than 25 mmHg at rest or 30 mmHg with exercise.[2] However, in clinical practice, echocardiography is often used instead of cardiac catheterization, and thus pulmonary hypertension (PH) is more commonly considered to occur when systolic PA pressure > half systolic systemic pressure.[3] This allows for age-related changes since a pressure of 30 mmHg in a 300 g baby has different implications to that in a 70 kg adult. PA pressure is formed by a combination of pulmonary blood flow and pulmonary vascular resistance, known as a modification of Ohm's law ($V = I \times R$) or Darcy's law.[4] In the fetus, the pulmonary vascular resistance (PVR) is high, which maintains a high mean PA pressure and so blood is preferentially shunted from the

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pulmonary artery to the systemic circulation via the arterial duct. Within a few days of birth, the PVR falls rapidly, leading to a consequent fall in PA pressure.[5] However, if there is a disease process which falls to allow the PVR to fall or if there is a pathological increase in either pulmonary blood flow or pulmonary vascular resistance, pulmonary hypertension will be maintained or will recur at a later age.

Causes of pulmonary hypertension

As the Venice classification states,[6] pulmonary hypertension can be divided into a number of causes, including pulmonary arterial hypertension, pulmonary venous hypertension, and pulmonary hypertension due to respiratory causes. This can be simplified for clinical practice in pediatrics (Table 1).[3] One of the main distinctions is between primary or idiopathic pulmonary arterial hypertension (IPAH), which is extremely rare in pediatric patients, and secondary pulmonary hypertension, which constitutes the remainder of the causes. Of these secondary causes, congenital heart disease with a large left to right shunt secondary to a VSD or AVSD and chronic lung disease are the most common after the first few days of life.[3]

Pathogenesis

The histopathologic changes seen in PH are characterized by a process of vascular remodeling, which varies somewhat depending on the etiology. This involves proliferation of smooth muscle cells into peripheral (usually nonmuscular) arteries,[7] together with medial hypertrophy in normally muscular arteries. Impaired growth and loss of arterioles leads to a reduction in arterial density, and this is eventually accompanied by dilatation complexes, plexogenic lesions and fibroid necrosis.[8] In turn, this leads to a process of luminal obliteration.[9,10] It is generally accepted that the early stages of this are reversible and the later stages are not.

Clinical features

Many of the symptoms of pediatric PH are nonspecific, and clinical features may be subtle even in advanced disease.[11] At birth, children commonly have cyanosis with hepatomegaly, an active right ventricle on palpation and a loud pulmonary second sound on auscultation.[3] This persistent pulmonary hypertension of the newborn (PPHN) may be difficult to treat but is well recognized in neonatal units and may improve with therapy to allow discharge home. If IPAH is left untreated, the most common presenting symptom is breathlessness, and children frequently present with poor appetite, faltering growth, lethargy, tachypnea, tachycardia, and irritability.[11,12] Symptomatic severity has been connected to prognosis, reinforcing the need for early diagnosis and management.[13] The child with congenital heart disease and a post-tricuspid shunt is however completely different. They may present late (especially if they have upper airway obstruction as in Down's syndrome) or may have inoperable or only partly palliated disease (such as pulmonary atresia with ventricular septal defect and aorto-pulmonary collateral arteries). Hence a systematic approach to investigation is required in order to identify those patients with PH.

Clinically, the severity of PH is assessed according to a modification of the New York Heart Association (NYHA)/World Health Organization (WHO) classification of functional capacity (Table 2).[14]

Table 1 Causes of pulmonary hypertension in pediatrics

Neonatal	Persistent pulmonary hypertension (PPHN – idiopathic)
	Bronchopulmonary dysplasia
	Infection, eg, *Streptococcus*
	Structural disease, eg, congenital diaphragmatic hernia
Cardiac	Left to right shunt, eg, VSD, AVSD, PDA, AP window
	Transposition of the great arteries (even without VSD)
	Obstructive lesions, eg, TAPVC, MS, HLHS, HOCM, DCM
Acquired	Chronic hypoxia, eg, cystic fibrosis, high altitude
	Scoliosis
	Airway obstruction, eg, tonsillar hypertrophy, tracheal stenosis/malacia
	Vasculitic, eg, Connective tissue disease, sickle cell.
Idiopathic	Sporadic 20% genetic in origin
	Familial 60% genetic in origin

Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; PDA, persistent ductus arteriosus; AP, aorto-pulmonary; TAPVC, total anomalous pulmonary venous connection; MS, mitral stenosis; HLHS, hypoplastic left heart syndrome; HOCM, hypertrophic obstructive cardiomyopathy; DCM, dilated cardiomyopathy.

Table 2 Functional classification of pulmonary hypertension

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea 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 dyspnea 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 dyspnea 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. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Diagnosis and investigation

A summary of the investigations recommended in the current British Cardiac Society (BCS) Guidelines[15] is shown in Table 3.

A chest radiograph may show pulmonary oligemia, with pruning of peripheral vessels[16] there may be right ventricular hypertrophy (RVH) on electrocardiogram (ECG), and a low partial pressure of oxygen (PaO_2) on arterial blood gas measurement. Echocardiography is a useful and sensitive investigation to identify possible secondary causes of PAH (such as ASD [rarely], VSD or cardiomyopathy), to provide a numerical assessment of the tricuspid regurgitation (TR) jet, and to assess left ventricular (LV) function. However, the results of derived formulae from echocardiography are to some extent operator-dependent. For older children, a six-minute walk test (6MWT) is a standardized method for assessing exercise tolerance in children,[17] and it correlates well with the WHO functional class system.

Cardiac catheterization remains the diagnostic gold standard for PH. Current UK guidelines state that right heart catheterization is essential in the investigation of new patients with suspected PH, and should be undertaken to

Table 3 Imaging investigations recommended for the assessment of PH

Investigation	Comments
Chest radiography	May show increase in cardiac chamber or PA size, hypoperfused areas of lung, and parenchymal lung disease.
ECG	May demonstrate RVH.
Echocardiography	Screening tool of choice for PAH. Detects cardiac disease (congenital, myocardial, valvular, intra-cavity clot or tumor, pericardial effusion). Use of contrast may be helpful to identify shunts.
Cardiac catheterization	Gold standard to define the extent of disease. PA pressures, PVR, cardiac output and oxygen saturations can be calculated accurately. Acute pulmonary vasoreactivity studies may also be carried out.
6 minute walk test (6 MWT)	Provides a functional assessment of exercise capacity and degree of limitation of activity.
Arterial blood gases, lung function tests	May be useful, although in patients with IPAH the results of lung function tests may be normal. A decline in PaO_2 is typically seen.
Blood investigations	Essential to exclude connective tissue diseases or pulmonary hypertension secondary to systemic disease: routine biochemistry and hematology, thyroid function, autoimmune screen (including anti-centromere antibody, anti-SCL70 and U1 RNP, phospholipid antibodies).
CT pulmonary angiography (CTPA)	Used to look for enlargement of pulmonary arteries, filling defects and webs in the arteries.
Ventilation perfusion scanning	More sensitive for chronic pulmonary thromboembolism than CTPA but not helpful when there is underlying parenchymal lung disease.
High resolution lung CT	May show parenchymal lung disease, mosaic perfusion (a sign of pulmonary vascular embolism or thrombosis but for which there are other causes such as air trapping), and features of pulmonary venous hypertension.
Cardiac MRI	Good investigation for imaging the right ventricle. Helpful in delineating congenital heart defects, and the pulmonary circulation by angiography.
Abdominal ultrasound	Used for investigation of liver disease and suspected portal hypertension.

Abbreviations: PA, pulmonary artery; RVH, right ventricular hypertrophy; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; IPAH, idiopathic pulmonary arterial hypertension.

assess specific and accurate measurements of PA pressure and PVR.[15] Vasodilator testing with inhaled nitric oxide[16] or prostacyclin[17] can also be carried out at the time of catheterization to assess the degree of reversibility of PH. In recent years, magnetic resonance imaging (MRI) has enabled detailed visualization of cardiac anatomy and pulmonary blood flow,[20] and may even be used to assess degree of vessel compliance.[21]

Control of pulmonary vascular resistance

There are a number of different pathways involved in the control of PVR, many of which are therapeutic targets in the management of PAH, and are therefore essential to an understanding of the management of this condition (Table 4).

Patients with PAH have increased levels of circulating endothelin-1.[22,23] As well as causing vasoconstriction, endothelin-1 leads to smooth muscle and fibroblast proliferation via endothelin A (ET_A), and/or endothelin B (ET_B) receptors.[24] Serotonin levels are also raised in PAH, which stimulates mitogenesis of vascular cells, and increased expression of the serotonin transporter is found in hypertensive arteries.[25] Patients with severe PAH have a relative deficiency of vasodilator pathways; they produce less endogenous prostacyclin, have reduced nitrogen oxide synthase (NOS) expression, and reduced vasoactive intestinal peptide (VIP) in the lungs.[26,27]

Prevention of pediatric pulmonary hypertension

Despite the advent of more efficacious therapeutics, prevention of pediatric pulmonary hypertension remains a priority. Patients with congenital heart defects secondary to a left to right shunt lesion should undergo early surgery to prevent development of PVD. This is particularly crucial in those patients with an AVSD or VSD.[28] Surgical and post-operative care is also crucial, and improvements in this area are likely to be a contributing factor in the declining incidence of post-operative pulmonary hypertension in children following cardiac surgery.[29] This involves adequate ventilation, chest physiotherapy, and, if necessary, antibiotics.

It is also essential to maintain good oxygenation, relatively low CO_2 and pH towards the upper limit of normal, in order to reduce the PA pressure as much as possible. Consequently, the effectiveness of pulmonary vasodilatation will also be maximized. Use of sedation with fentanyl and clonidine should also be used as prophylaxis against pulmonary hypertensive crises.[30]

Treatment of pediatric pulmonary hypertension

Current guidelines recommend that patients with PH should be managed by an experienced multiprofessional team at a specialist centre, with appropriate expertise and support for children and their families. Long-term community care involving clinical nurse specialists is also beneficial.[15]

Response to treatment is less predictable in children, and therefore, close monitoring and rapid alteration of treatment as necessary is required in pediatric patients.[15] Research has suggested that prompt medical treatment of PAH, even in patients with established disease and Eisenmenger's syndrome, may reduce the need for lung transplantation.[31] There are fewer therapeutic options currently available for patients with PH in comparison to those with PAH.

Initially, treatment of PH involves thorough investigation of potential underlying causes; treatment will thus be directed accordingly. For example, patients whose PAH is caused by upper airway obstruction might undergo adenotonsillectomy, and those with cystic fibrosis, asthma or bronchopulmonary dysplasia should be managed with the relevant therapeutics. Drugs with a propensity to cause vasoconstriction such

Table 4 Summary of mechanisms in PHT

Agent	Mechanism	Outcome
Hypoventilation	Not fully understood, due to hypoxia and hypercarbia	Vasoconstriction
Nitric oxide Nitrates	Increases guanylyl cyclase	Vasodilation
Phosphodiesterase type V inhibitors	Prevent cyclic GMP breakdown	Vasodilation
Endothelin	A – receptor B – receptor	Vasoconstriction Vasodilation and anti-mitogenic
Prostanoids	Increase cyclic AMP	Vasodilation and anti-mitogenic
Rho-Kinase inhibitors	Increase GMP effect	Vasodilation
Serotonin antagonists	5HT transporter	Vasodilation and anti-mitogenic

Abbreviations: GMP, guanosine monophosphate; AMP, adenosine monophosphate.

as sympathomimmetic decongestants with α-adrenergic properties should be avoided in children with pulmonary hypertension.

It is important to note that UK guidelines differ from those in other parts of the world; the American College of Chest Physicians (ACCP) and the European Society of Cardiologists (ESC) suggest that those in NYHA class III or IV should be treated with a specific oral therapy.[32,33]

Recent guidelines have suggested a treatment algorithm for the management of pediatric PAH[15] (Figure 1).

Treatment of acute disease

Children presenting with syncope, right heart failure or post-operative PAH must be diagnosed and treated promptly and safely.[34] This may be in an inhaled form (see Nitric oxide, below), orally with sildenafil, intravenously (see Epoprostenol, below), or with hemodynamic support (see Extracorporeal membranous oxygenation, below).[3]

Oxygen

Good ventilation in the intensive care unit is essential (see Treatment of pediatric pulmonary hypertension, above), and oxygen therapy has been shown to be of benefit acutely for both hypoxic and nonhypoxic patients with PAH.[15] Additionally, some patients may benefit from the use of domiciliary nocturnal oxygen therapy, both acutely, and alongside maintenance therapy.[35]

Nitric oxide

Nitric oxide (NO) inhalation is currently among the first line treatments for post-operative pediatric pulmonary hypertension or in the child with acute severe new presentation of PAH being managed on the intensive care unit,[36,37] as it reduces PA pressure rapidly.[38] Inhaled NO therapy is also used acutely in persistent pulmonary hypertension of the newborn.[39] The mode of action of NO is via the stimulation of guanylyl cyclase and hence increased production of cyclic guanylate monophosphate (cGMP) in pulmonary smooth muscle cells; this causes uptake of calcium into the sarcoplasmic reticulum, which then leads to muscle relaxation, reduced PA pressure and PVR, and hence increased oxygenation. Any NO absorbed from the lungs into the systemic circulation is quickly deactivated by combination with hemoglobin, minimising any effect on the systemic circulation. Therefore, NO acts solely on the pulmonary vasculature, leaving systemic arterial pressure unaffected.[40,41]

Oxygenation index (OI) is a calculation combining fraction of inspired oxygen (FiO_2), mean airway pressure and PaO_2 as an indicator of degree of respiratory compromise;[42] OI of more than 25 is the usual indication for initiation of treatment with NO.[43] Acutely, doses start at 20 parts per million (ppm),[44] although post-operative PAH may be treated with doses as low as 3–10 ppm.[45] Sustained high doses of NO may lead to methemoglobinemia,[45,46] and acute withdrawal of treatment may precipitate rebound PAH.[44] The latter may be avoided by the use of phosphodiesterase inhibitors (see below), prostacyclins (see below) or discontinuation of NO followed by resumption of treatment at half the dose.[47] Despite this, there is no clear evidence that short-term use of NO causes significant cardiac and respiratory complications.[48]

NO administration has been shown to reduce the need for extracorporeal membrane oxygenation (ECMO) treatment in term or near term neonates with hypoxic respiratory failure.[42] However, a recent Cochrane review found that there was no significant difference in short-term post-operative mortality or mean PA pressure with administration of inhaled NO compared to placebo or conventional management (hyperventilation, use of sodium bicarbonate, intravenous inotropes and vasodilatory agents, and sedatives).[49] Current European guidance suggests that there is insufficient evidence at present to recommend the use of prophylactic post-operative inhaled NO in patients with congenital heart disease at risk of PAH.[50] However, there is sufficient evidence to support a trial of NO therapy (with a starting dose of 20 ppm, increasing to 40 ppm if there is no response) in patients with significant peri-operative PAH.[50] Treatment should be discontinued after 30 minutes if there has been no clinically significant response.

Extracorporeal membrane oxygenation (ECMO)

The use of extracorporeal membrane oxygenation (ECMO) has been associated with complications including interstitial and alveolar hemorrhage and secondary epithelial alterations.[51] For this reason, since the establishment of inhaled NO therapy as a treatment for pediatric PAH, the use of ECMO has significantly decreased.[52] Despite this, there are still some incidences in which ECMO therapy is necessary, such as those infants with severe respiratory or cardiac disease in addition to pulmonary arterial hypertension; one study of children with hypoxemic respiratory failure found that treatment with NO alone was successful in only 29% cases.[53]

Maintenance therapies

Aims of maintenance therapies for pediatric pulmonary hypertension will generally be to lower PA pressure in order to reduce or reverse the rate of progression of PVD, and thus to obtain functional improvement in terms of increased activity levels.

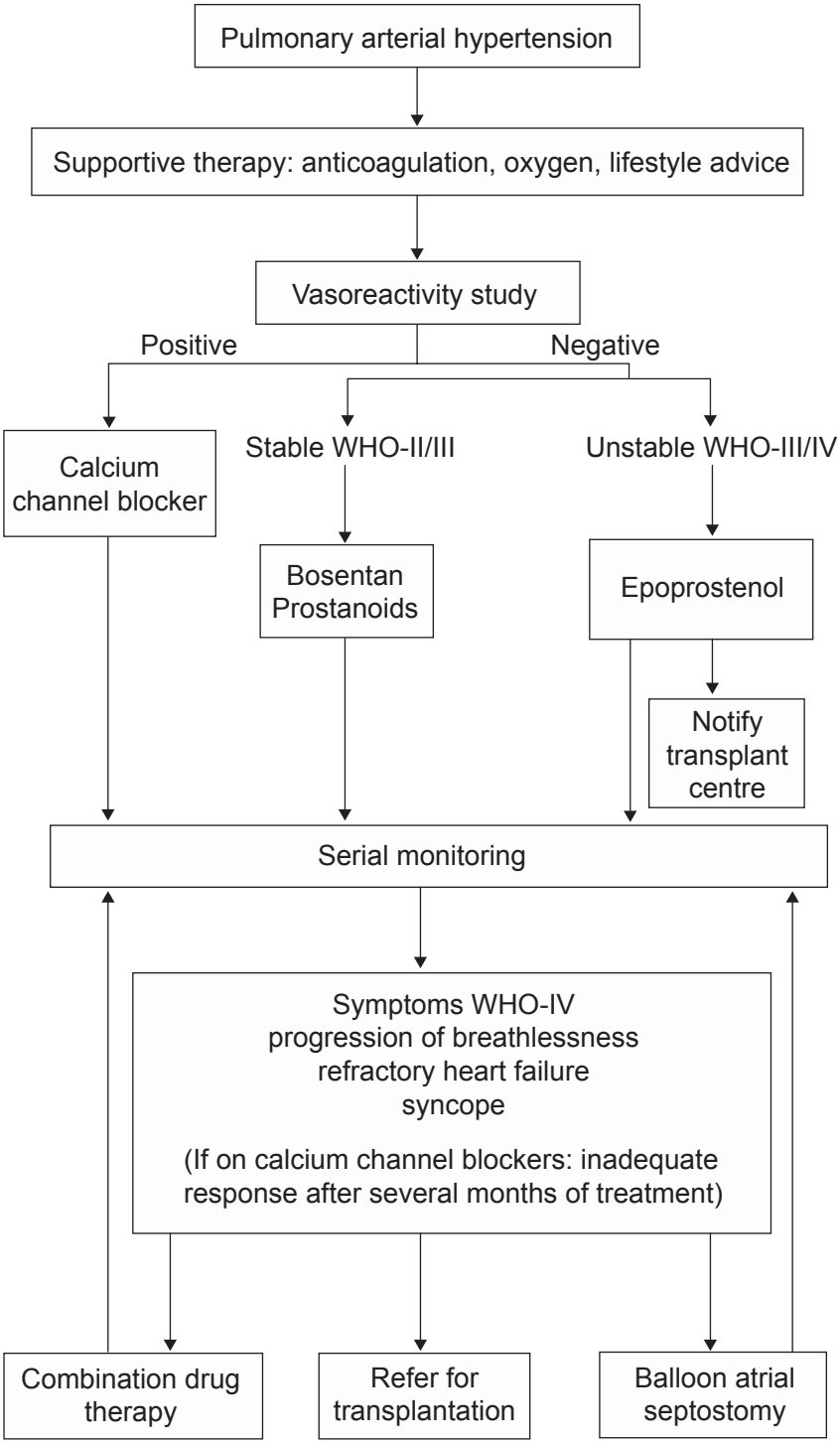

Figure 1 Current British Cardiovascular Society (BCS) algorithm for the management of PAH in children.
Abbreviation: WHO, World Health Organization.

Current guidelines state that the choice of therapy should be based on WHO functional class and response to vasodilator testing during cardiac catheterization.[15] The age of the child is also an important factor, as several drugs used to treat adults are unsuitable for use in young children; subcutaneous treprostinil frequently causes significant pain, and unwell children may be unable to tolerate inhaled doses of iloprost every 2–3 hours.[15]

In the UK, current statistics suggest that only a minority of patients are responsive to vasoreactivity studies and

treatment with calcium channel antagonists (see below).[15] Therefore, the majority of children are treated with specific disease-targeted therapies, such as intravenous epoprostenol (the only drug for children tested in a placebo-controlled trial),[54] bosentan,[55] and sildenafil. Choice of drug is dependent upon a number of factors, including side effect profile, route of administration, patient preferences, and physician experience.[33]

Calcium channel antagonists

The calcium channel antagonist, nifedipine is one of the oldest agents used for PAH,[56,57] and amlodipine has been suggested to be beneficial for IPAH.[58] An initial trial of these agents should be carried out, and calcium channel antagonists should only be continued in those patients who demonstrate an adequate vasodilator response (defined by a decrease in mean PA pressure and PVR by >20%).[59] These patients may need no further medication.[56,58] However, calcium channel antagonists are only efficacious in 5%–10% of children and adults, whereas nonresponders demonstrate a continually rising PVR. Some patients may switch from being 'responders', demonstrating a stable response to calcium channel blockers for a period of several years, to 'nonresponders,' who suddenly require additional medication.

Phosphodiesterase inhibitors

Sildenafil, a phosphodiesterase inhibitor, given orally, has been shown to be a potent and selective pulmonary vasodilator.[60] Sildenafil works by selectively inhibiting phosphodiesterase V (PDE V),[61] which is responsible for cGMP breakdown in lung tissue. The resultant increase in cGMP leads to calcium-mediated relaxation of vascular smooth muscle. These effects on pulmonary vasculature appear to occur independently of the cause of PAH, suggesting a role in the management of IPAH.[62]

An initial small-scale pilot study suggested that sildenafil improves hemodynamics and exercise capacity in children with primary pulmonary hypertension and PAH secondary to congenital heart disease.[63] Since then, research has suggested that sildenafil works by improving endothelial-dependent vasodilatation, and by reducing plasma concentrations of endothelin-1 and von Willebrand factor, mediating a fall in PA pressure and PVR.[64] In IPAH and Eisenmenger's syndrome, there are reduced levels of endothelial progenitor cells; sildenafil has been hypothesized to increase numbers of these cells in the long term, thereby reducing endothelial dysfunction.[65] Another study found that patients with PAH secondary to congenital heart defects treated with sildenafil had improved exercise capacity, WHO functional class and hemodynamics.[66] Similarly, Baharani and colleagues found that patients with CHD had significant improvements in six-minute walking distance (6-MWD) and systolic PA pressure when treated with sildenafil in comparison with placebo.[67] Sildenafil has been suggested to improve mean PA pressure, PVR, and exercise tolerance in PAH.[68] Research has suggested that there is a direct dose-response relationship between sildenafil and exercise capacity, measured by 6-MWD; one study observed a significant improvement in 6-MWD in patients taking 50 mg sildenafil three times daily (tds) compared to 25 mg tds or 12.5 mg tds.[69]

Sildenafil has also been shown to work synergistically with NO, enhancing the efficacy of exogenous NO, which further increases vasodilatation.[70] This combined approach enables transfer of patients from intensive care, and facilitates weaning from high doses of nitric oxide, by reducing the rebound effect commonly seen with discontinuation of inhaled NO.[18,71] In the long-term, sildenafil demonstrates marked down-regulatory responses which may limit its use,[67] although this may be lessened when administered alongside NO. Side-effects of sildenafil may include nausea, abdominal discomfort, headache, dizziness and flushing[72] and potentially, in the long-term, memory loss.[73]

More recently, research has suggested that another PDE type 5 inhibitor, vardenafil, may be more effective than sildenafil *in vitro*.[74,75] These studies have suggested that vardenafil acts directly to reduce calcium influx in the pulmonary artery, in addition to its vasodilatory effects via cGMP.

Endothelin receptor antagonists

Endothelin 1 (ET-1) acts on ET_A and ET_B receptors to promote mitosis of pulmonary artery smooth muscle cells; activation of ET_A and ET_B on smooth muscle cells causes vasoconstriction, whereas activation of ET_B on the endothelial cell releasing NO causes vasodilatation. This is thought to contribute significantly to the imbalance between vasodilatation and vasoconstriction in pulmonary hypertension[76] and high levels of ET-1 have been found in the lung and circulation of patients with PAH.[77,78]

Bosentan, a nonselective (endothelin receptor A and B) antagonist has been shown to reduce mean PA pressure and PVR, and increase quality of life in patients with IPAH.[17] One study found that in pediatric patients with congenital heart disease or connective tissue disease, treatment with bosentan for a median period of 14 months improved WHO functional class in 46%.[79] Bosentan has also been found to be effective in patients with Eisenmenger's syndrome, reducing PA pressure

and PVR and improving exercise capacity, without reducing oxygen saturations (the BREATHE-5 trial).[80,81] However, bosentan has been shown to cause hepatic dysfunction in some patients; a recent study identified deranged liver function tests in 2.7% of children under 12 years of age on bosentan therapy, compared to 7.8% of those aged over 12 years.[82] There is some evidence to suggest that in the long-term, there is a progressive decline in the beneficial treatment effects of bosentan, particularly in children.[83]

Sitaxsentan, a more ET_A selective ERA has been investigated in recent trials. Research has suggested that that it may play an important role in the management of PAH associated with connective tissue diseases, and it may have a more prolonged action than bosentan in children with congenital heart disease.[84,85] One study of 247 patients found that use of sitaxsentan 100 mg once daily improved exercise capacity and WHO functional class in adult patients with PAH, and it has reduced hepatic toxicity compared to bosentan.[86] As well as bosentan, sitaxsentan has also been shown to be effective in patients with Eisenmenger's syndrome.[87] Data on the use of sitaxsentan is limited in children at the current time.

Ambrisentan, another selective ERA antagonist has recently been shown to improve exercise capacity in patients with PAH compared to placebo, and is well-tolerated.[88]

Prostacyclin agonists

Prostacyclin (PGI_2) is an endogenous vasodilatory mediator in the pulmonary vasculature; prostacyclin agonists act via cyclic AMP-dependent pathways in smooth muscle cells. Its effects include reducing PVR, inhibiting platelet aggregation, and reducing smooth muscle cell proliferation. In patients with pulmonary hypertension, pulmonary endothelial cells have decreased expression of prostacyclin synthase[89] and urinalysis demonstrates a decrease in stable prostacyclin metabolites.[26]

Preliminary results of treatment with prostacyclins have been promising. Barst and colleagues[90] found a 90% survival rate at four years for children with severe IPAH treated with prostacyclin, and studies have suggested that prostacyclins improve hemodynamic function and quality of life.[91] Prostacyclins have been shown to work synergistically with NO, since they act through a different pathway and hence the therapeutic effects are additive. Therefore, these drugs may also be used when NO treatment has failed, when weaning from NO (as also occurs with sildenafil), or when therapeutic resistance has occurred.[47,92] They may be administered intravenously (epoprostenol, treprostinil), by inhalation (iloprost) or orally (beraprost). However, the side-effects of prostacyclin agonists have limited their use to some extent; adverse events associated with epoprostenol include flushing, jaw pain, headaches, rashes and thrombocytopenia.[93] Epoprostenol requires a continuous infusion and has a short half-life (<6 minutes). Interruption of the infusion can lead to rapid increases in PVR, hemodynamic collapse and death.[93]

Epoprostenol has been shown to improve the survival of patients with IPAH in the long-term,[94] and is the gold standard starting treatment for patients with severe IPAH. It also has a role acutely in neonates with persistent pulmonary hypertension of the newborn (PPHN), post-operatively in children with heart disease, and in patients with IPAH, to reduce PVR prior to cardiac catheterization. However, epoprostenol has dose-limiting effects, and may cause severe rebound pulmonary arterial hypertension.[95]

Treprostinil was originally used as a subcutaneous infusion, which has a longer half-life and increased stability, so does not have to be kept in cooled storage.[96] However, this route of administration is extremely painful, which has limited its use in the pediatric population. In recent research, intravenous preparations of treprostinil have been investigated, which have been suggested to cause fewer adverse effects than epoprostenol. However, whilst successful transfer rates have been achieved, high central-line infection rates were seen.[97]

Beraprost, an oral preparation, is well-tolerated and widely used in parts of Europe and in Japan, but research has suggested it is less efficacious than intravenous preparations.[98,99]

The inhaled form, iloprost, is easy to administer, has fewer side-effects as it acts directly on the lungs[100] and it avoids the potential risks of infection seen with indwelling central lines.[95] Iloprost must be administered approximately every two hours, and therefore has a greater role in the acute setting. It has been shown to be effective in improving hemodynamic parameters, exercise tolerance and quality of life in patients with PAH.[101,102]

Novel therapies

Rho-kinase inhibitors

Developments in recent years have suggested that a new class of drug, rho kinase inhibitors, may be beneficial in the treatment of pediatric PAH.[103,104] Rho kinase causes vasoconstriction of vascular smooth muscle through phosphorylation and consequent inhibition of myosin phosphatase.[105] It has also been shown that rho kinase acts by activation of the enzyme myosin light chain kinase (MLCK), which causes

phosphorylation of the hyper-constrictive segments of arteries *in vitro*.[106] Animal models have suggested that activation of rho kinase is associated with pulmonary vasoconstriction and proliferation, impaired endothelial vasodilatation and pulmonary remodelling, and that administration of its antagonists reverse these processes.[107,108] Preliminary results have suggested that administration of intravenous fasudil, a selective rho-kinase inhibitor, may cause acute pulmonary vasodilatation and reduction in PA pressure in patients with severe PAH refractory to other therapies.[103,109]

Vasoactive intestinal peptide

Recent research investigating the role of vasoactive intestinal peptide (VIP) in rats has produced promising results.[110] This study showed that ET_A antagonists, ET_B antagonists, and VIP all prevented the pulmonary vasoconstriction caused by ET1. Unlike ET_A and ET_B antagonists, VIP did not induce an increase in airway resistance and thus this peptide may exert protective effects against both the vascular and bronchial adverse effects of ETI. This may therefore have a role in patients with PAH and co-existing chronic lung disease. Clearly therefore, *in vivo* experimentation is now needed.

Estradiol derivatives

There has been limited investigation into the use of 2-ethoxyestradiol, a nonestrogenic metabolite of estradiol in the treatment of PAH.[111] This study found that 2-ethoxyestradiol lowered right ventricle (RV) peak systolic pressure and consequently led to reduced vascular remodelling and mortality in rats with PAH. This suggests that *in vitro* anti-proliferative agents including synthetic analogues of estradiol metabolites may be protective against development of PVD.

Apoptosis and gene therapy

Limited research has suggested that modulation of the process of apoptosis (programmed cell death) involved in the process of vascular remodelling in PAH could be one possible therapeutic opportunity.[112,113] For example, survivin (also known as Birc5), is one of a family of genes known to inhibit apoptosis; the use of molecular antagonists of survivin to increase cell death and prevent vascular remodelling may, in the future, hold therapeutic potential.[114] Similarly, preliminary research has suggested that the use of the 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase inhibitor, pravastatin, and the Cox-2 inhibitor, celecoxib, prevent the development of monocrotaline-induced PAH in rats.[115,116] Simvastatin has been found to be ineffective in this respect *in vitro*.[117]

Serotonin pathways

Research has found that patients with PAH have increased plasma serotonin levels,[118] and that over-expression of the serotonin transporter gene (SERT) increases PA pressure.[119] Hypoxia and monocrotaline-induced PAH in animals has been shown to be inhibited by the selective serotonin reuptake inhibitor (SSRI), fluoxetine.[120,121] So far however, studies in humans have not produced statistically significant results.[122]

L-Arginine

An alternative approach to inhaled NO therapy is to increase endogenous NO synthesis. Plasma L-arginine is a substrate for endothelial nitrogen oxide synthase,[123] and experimental[124] and clinical[125] data have suggested that patients with a left-to-right shunt lesion may be deficient in L-arginine, both pre- and post-operatively. However, research has suggested that low levels of plasma arginine do not correlate with the degree of post-operative PAH[126]. Further trials are needed to ascertain whether peri-operative therapy with L-arginine may be beneficial.

Anticoagulation

Whilst most children with PAH will not be treated with anticoagulation, it is recommended that those at high risk of thromboembolism (such as patients with IPAH and reduced cardiac output, indwelling venoatrial shunt or severe polycythemia), should be prescribed warfarin.[127]

Other therapies

Although rare, children with systemic sclerosis and coexisting pulmonary hypertension should be treated with corticosteroids, which appear to slow disease progression in this group.[128]

Combination treatment

Currently, there is some debate as to the optimal management of patients who demonstrate clinical deterioration despite maximal targeted therapy with one agent. The use of combination therapies has been widely adopted across the US and Europe, but currently, there is little clear consensus as to the most effective and safe combinations.[129] In Switzerland and other countries, combination therapies involving two or three of bosentan, iloprost, and sildenafil are commonly used but their relative merits are not yet clarified.[130]

Combination of sildenafil with an endothelin receptor antagonist (notably bosentan) has been recently validated in several trials, improving hemodynamic variables, exercise capacity, and quality of life in patients with IPAH

or PAH unresponsive to monotherapy.[131–133] Limited trials of treatment with bosentan and a prostacyclin agonist such as epoprostenol or iloprost have suggested this may be an effective combination.[134,135] Inhaled prostacyclin and milrinone have also been postulated to work synergistically to reduce PVR.[136]

However, the pharmacokinetics involved are complex; at steady state, when used in combination, bosentan reduces the maximum plasma concentration of sildenafil, and sildenafil increases the concentration of bosentan.[137] Further research is therefore needed to establish the clinical applications for these complex drug interactions. It is also important to note that dual treatments combine the adverse effects of both drugs, and thus the incidence of side-effects may be increased.[138]

Management of refractory pulmonary hypertension

Those patients who remain symptomatic despite medical therapies may require more invasive forms of management.

Atrial septostomy

Children with PAH and without adequate right to left shunting across the atria commonly develop recurrent syncopal episodes.[12] Atrial septostomy, either by cardiac catheterization or surgically, has been shown to be beneficial in patients experiencing recurrent syncope, by creating a left to right shunt and consequently maintaining cardiac output.[139] In turn, this procedure has been suggested to reduce the signs and symptoms of right heart failure.[141–144] Improved survival rates have also been demonstrated following atrial septostomy; Kerstein and colleagues[139] demonstrated increased survival at one and two years, 87% and 76%, respectively.

Lung transplantation

Lung transplantation is currently only considered as a last resort,[145] in part due to concerns regarding long-term survival rates; one study found that survival rates were 77% at one year, 62% at two years, and 55% after five years.[146] Since 1986, over 1055 children have undergone transplantation worldwide.[147] Between January 1990 and June 2006, there were 977

Table 5 Key trials of pharmacological agents for the management of pediatric PAH

First Author/year	Official acronym	Number of patients	Active drug	Comparator	Study period (weeks)	Outcome* (active drug versus comparator)
Rubin et al 1990[150]	–	23	Epoprostenol	Randomized controls	8	Net benefit
Barst et al 1996[151]	–	81	Epoprostenol	Randomized controls	12	Net benefit
Badesch et al 2000[152]	–	111	Epoprostenol	Randomized controls	12	Net benefit
Channick et al 2001[153]	–	32	Bosentan	Placebo	12	Net benefit
Langleben et al 2002[154]	–	71	Terbogrel	Placebo	12	Net harm
Simonneau et al 2002[96]	–	470	Treprostinil	Placebo	12	No difference
Galie et al 2002[155]	ALPHABET	130	Beraprost	Placebo	12	No difference
Olschewski et al 2002[101]	AIR	203	Iloprost	Placebo	12	Net benefit
Rubin et al 2002[156]	BREATHE-1	213	Bosentan	Placebo	16	Net benefit
Barst et al 2003[99]	–	116	Beraprost	Placebo	36	Net benefit
Sastry et al 2004[157]	–	22	Sildenafil	Placebo	12	Net benefit
Humbert et al 2004[158]	BREATHE-2	33	Epoprostenol + bosentan	Epoprostenol + placebo	16	Net benefit
Barst et al 2004[159]	STRIDE-1	178	Sitaxsentan	Placebo	12	Net harm
Galie et al 2005[160]	SUPER-1	278	Sildenafil	Placebo	12	No difference
Wilkins et al 2005[161]	SERAPH	26	Bosentan	Sildenafil	16	Net benefit
Singh et al 2006[162]	–	20	Sildenafil	Placebo	8	Net benefit
Galie et al 2006[80]	BREATHE-5	20	Sildenafil	Placebo	8	Net benefit
Barst et al 2006[163]	STRIDE-2	185	Sitaxsentan	Placebo	18	Net benefit
McLaughlin et al 2006[164]	STEP	67	Inhaled iloprost	Placebo	12	Net benefit
Hoeper et al 2006[165]	COMBI	40	Inhaled iloprost	Placebo	12	Net benefit
Galie et al 2008[88]	ARIES	394	Ambrisentan	Placebo	12	No difference
Galie et al 2008[148]	EARLY	185	Bosentan	Placebo	12	Net benefit
Simonneau et al 2008[138]	PACES	267	Sildenafil	Placebo	16	Net benefit

Notes: *The outcome variables are risk of death or hospitalization due to complications of PH.
Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

pediatric lung transplantation; of these, the primary indication in 104 patients (10.6%) was IPAH, 34 (3.5%) due to CHD, 18 for PVD (1.8%), and 17 (1.7%) for Eisenmenger's syndrome.[147] However, the use of lung transplantations is restricted by waiting times, risks of surgery, and the problems accompanying transplant rejection, and thus cannot be considered as a viable treatment option earlier in the course of disease.

Treatment outcomes and prognosis

Currently, there is no PAH-specific quality of life measure, although recent studies of outcomes in pediatric patients suggest that although physical activity is limited to approximately 50% of normal, psychological scores are 80%–90% of normal.[147,148] These scores do not correlate with age, time since diagnosis, PVR or cause of PAH.

Treatment with disease-targeted therapies for secondary and idiopathic PAH has been shown to improve survival in a number of studies;[15,129] a number of recent trials have investigated the relative efficacy of management options in pulmonary arterial hypertension (Table 5).[149]

A recent meta-analysis of trials of modern treatment modalities including phosphodiesterase inhibitors, endothelin receptor antagonists and prostacyclin agonists found that overall, active treatment resulted in reduction in mortality of 43% (risk ratio 0.57, 95% confidence interval [CI] 0.35–0.92; p = 0.023) (Figure 2).[149]

Survival rates are typically higher in those with secondary PAH compared to IPAH, and for those with IPAH, combination therapy is more effective than monotherapy.[141,166] Children with postoperative PAH have previously had particularly poor outcomes, and therefore early detection in these patients is crucial.[15] There is currently limited evidence regarding the optimal management of patients with pulmonary venous hypertension, and for patients with other forms of pulmonary hypertension.

Conclusion

Advances in available therapeutics for pulmonary hypertension have improved survival in pediatric patients. General supportive care, early diagnosis and prompt surgery for patients with PAH secondary to CHD is crucial.

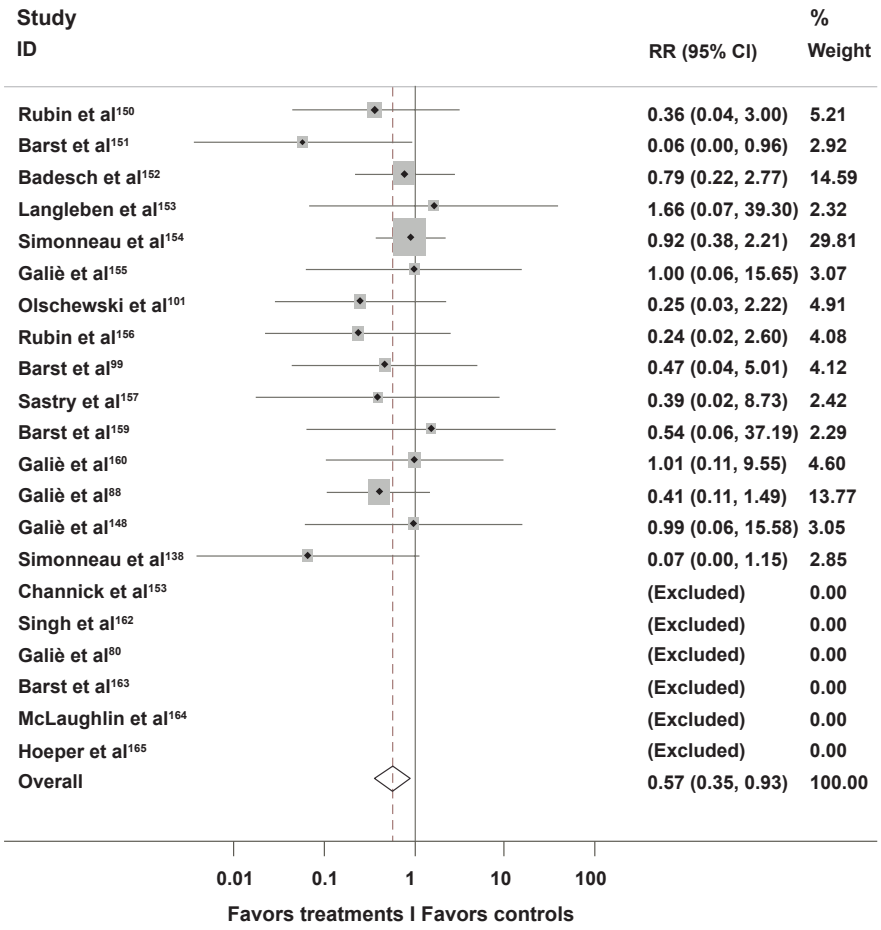

Figure 2 Meta-analysis of active treatment versus placebo in trials of current management strategies in pulmonary arterial hypertension.

An individualized approach must be taken in deciding treatment options, depending on the symptoms, clinical signs, and hemodynamic status of each patient.

Following this, treatment options are complex and current BCS guidelines suggest that treatment should universally depend upon the NYHA functional class and response to vasodilator therapy.[15] Acutely, treatment options include oxygen therapy, NO and ECMO. Current maintenance therapies include calcium channel antagonists, phosphodiesterase inhibitors, endothelin receptor antagonists and prostacyclin agonists, with or without anticoagulation. For patients who remain symptomatic or whom demonstrate equivocal hemodynamic response to therapy with a single agent, combination therapy may be considered. Atrial septostomy and lung transplantation are generally considered as the next stage in patients who have been unresponsive to medical therapy. A recent systematic review of oral treatment methods in PAH highlighted the problems of small sample size and limited follow-up period in many of the available studies this is particularly problematic in pediatric populations.[167] More *in vivo* research is needed to assess the efficacy of the increasing number of novel therapies.

Disclosure

Dr. Hawkins reports no conflict of interest in this work. Dr. Tulloh has received lecture fees and honoria from Actelion, Pfizer and GlaxoSmithkline.

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