REVIEW

Severe paediatric pulmonary hypertension: new management strategies

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Pulmonary hypertension is a significant complication in many paediatric disease states. This article discusses current understanding of pulmonary hypertension and includes definition, diagnosis, and management. A description of the latest advances in targeted pharmacological therapy in children is also provided as well as impact on morbidity and mortality.

Previously, the diagnosis of pulmonary hypertension in children carried a poor prognosis. In a 1965 series of 35 patients with primary pulmonary hypertension, none survived greater than 7 years. Further, 22 of 35 patients died in the first year after the onset of symptoms.[1] In 1995, prognosis was still poor, with the median survival in a series of 18 children with primary pulmonary hypertension being 4.12 years.[2] Recent advances in the understanding of the vascular biology of the normal and hypertensive pulmonary circulations have led to a broader pharmaceutical armoury against pulmonary hypertension. As a result, preliminary studies have been promising. For example, there was 90% survival at 4 years in children with severe idiopathic pulmonary hypertension treated with prostacyclin.[3]

Pulmonary hypertension may be an idiopathic or primary phenomenon—that is, without an underlying cause, or secondary to a specific disease process. Idiopathic pulmonary arterial hypertension (IPAH) is a rare and poorly understood condition and is diagnosed by excluding conditions responsible for secondary pulmonary hypertension. Without appropriate treatment, the natural history of IPAH is progressive and fatal. In contrast, the natural history of pulmonary hypertension from congenital heart disease has a broad range of survival, ranging from months to decades.

The selection of appropriate therapies is complex, requiring familiarity with the disease process, complicated delivery systems, dosing regimens, medication side effects, and complications. This article will discuss current diagnosis and treatment of children with primary and secondary pulmonary hypertension.

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DEFINITION

Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mm Hg at rest, or greater than 30 mm Hg during exercise.[4] In 1998 the World Health Organisation proposed a new classification of pulmonary hypertension and this was updated in 2003 (box 1). This classification is appropriate to both the paediatric and adult age group.

DIAGNOSTIC EVALUATION

As the most successful strategy in the treatment of pulmonary hypertension is to treat the underlying cause, the workup of pulmonary hypertension involves a complete history and examination (box 2) and extensive evaluation (box 3), aiming to exclude all known aetiologies of pulmonary hypertension (box 1). Idiopathic pulmonary arterial hypertension is defined as a diagnosis of exclusion.[3] The history and physical examination should be undertaken with attention to aetiology (boxes 1 and 2). Symptoms may include exertional dyspnoea, reducing exercise tolerance, orthopnoea, atypical chest pain, and haemoptysis. Syncope in this condition is a worrying sign of end stage disease.

Non-invasive diagnostic studies are important in the evaluation of pulmonary hypertension (box 3). Cardiac catheterisation is important to evaluate pulmonary artery pressure and resistance as well as to determine reactivity of the pulmonary vasculature. Further, as respiratory disease is an important cause of pulmonary hypertension, extensive evaluation of the lung should be undertaken (box 3).

Congenital heart disease

A variety of congenital cardiac lesions cause pulmonary hypertension (box 4). The age at which these lesions cause irreversible pulmonary vascular disease varies. In general, patients with ventricular septal defect or patent ductus arteriosus do not develop irreversible pulmonary vascular changes before 1 year of age. Children with Down's syndrome may have an increased risk of pulmonary hypertension. Furthermore, infants with an atrial septal defect or ventricular septal defect with chronic lung disease have an increased risk for the early development of severe pulmonary vascular disease. Patients with atrioventricular septal defect may develop irreversible pulmonary vascular disease earlier than patients with other left-to-right shunt lesions.

Patients with cyanotic congenital cardiac lesions may also develop pulmonary hypertension. Hypoxaemia with increased shunting is a potent stimulus for the rapid development of pulmonary vascular disease. Examples include transposition of the great arteries, truncus arteriosus, and univentricular heart with high flow. Total correction of many cardiac lesions in the first months of life may prevent the late

Box 1: WHO classification of pulmonary hypertension

1. Pulmonary arterial hypertension

- 1.1 Idiopathic pulmonary hypertension
- 1.2 Familial
- 1.3 Associated with:
  - (a) Collagen vascular disease
  - (b) Congenital systemic to pulmonary shunts
  - (c) Portal hypertension
  - (d) HIV infection
  - (e) Drugs (anorexigens)/toxins
  - (f) Other thyroid disorders: Gaucher disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies
- 1.4 Persistent pulmonary hypertension of the newborn
- 1.5 Pulmonary veno-occlusive disease

2. Pulmonary hypertension with left heart disease

- 2.1 Left sided atrial or ventricular heart disease
- 2.2 Left sided valvular disease

3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Sleep disordered breathing
- 3.4 Alveolar hypoventilation disorders
- 3.5 Chronic exposure to high altitude
- 3.6 Neonatal lung disease
- 3.7 Alveolar-capillary dysplasia
- 3.8 Other

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

- 4.1 Thromboembolic obstruction of proximal pulmonary arteries
- 4.2 Obstruction of distal pulmonary arteries
  - Pulmonary embolism (thrombus, tumour, and/or parasites)
  - In situ thrombosis

5. Miscellaneous, e.g. sarcoidosis

development of pulmonary hypertension. Finally, palliative shunting operations for certain cardiac anomalies designed to increase pulmonary blood flow may lead to the development of pulmonary hypertension.

Eisenmenger syndrome

Eisenmenger syndrome describes pulmonary hypertension with a reversed central shunt.[5] In general, the term ''Eisenmenger syndrome'' is used for shunts distal to the tricuspid valve. Increased pulmonary vascular resistance, and bidirectional or right-to-left shunting through a systemic-to-pulmonary connection, such as a ventricular septal defect, patent ductus arteriosus, univentricular heart, or aortopulmonary window characterises this syndrome. The shunt is initially left-to-right, but as the underlying condition continues to increase pulmonary vascular resistance, there is a reversal of the shunt, leading to cyanosis, and erythrocytosis. In general, the prognosis of patients with Eisenmenger syndrome is much better than for patients with idiopathic pulmonary arterial hypertension. Syncope, right heart failure, and severe hypoxemia have been associated with a poor prognosis. Phlebotomy may be utilised in Eisenmenger syndrome and should be reserved for temporary relief of major hyperviscosity symptoms or to improve perioperative haemostasis. Non-cardiac operations on Eisenmenger patients are associated with a high mortality rate, and should be managed by a multidisciplinary team experienced in the care of patients with pulmonary hypertension.

Box 2: History and examination

History
Diet pill use; contraceptive pill; methamphetamine use
Onset and length of pulmonary hypertension
Family history of pulmonary hypertension
Prior cardiac and other surgeries

Symptoms
Chest pain; dyspnoea; shortness of breath; syncope

Physical examination
Loud second heart sound; systolic murmur of tricuspid regurgitation or diastolic murmur of pulmonary insufficiency; palpable second heart sound; peripheral oedema; jugular venous distension

Idiopathic pulmonary arterial hypertension

Primary or idiopathic pulmonary arterial hypertension is a rare disease, which occurs most frequently in young adult females.[6] Idiopathic pulmonary arterial hypertension is characterised by progressive and sustained increases of pulmonary artery pressure without a defined aetiology.

From 6% to 12% of cases of IPAH may be familial in origin with an autosomal dominant pattern of inheritance involving the phenomenon of genetic anticipation. Recently, the gene for familial primary pulmonary hypertension was found to lie within chromosome 2q33. This causes defects in the bone morphogenetic protein receptor II (BMPR2) and may lead to uncontrolled proliferation of vascular smooth muscle.[7–9] Clinical and genetic screening of first degree relatives may be considered to help identify, early, at-risk individuals. Clinical screening includes a chest *x* ray, ECG, echocardiogram, and possibly exercise test. Genetic screening involves analysis for BMPR2 mutations. However, the absence of the mutation does not exclude IPAH.[8]

Respiratory disease

Lung disease is an important factor in the aetiology of pulmonary hypertension in some patients. Resulting complications include pulmonary vasoconstriction or thromboembolic changes, which increase pulmonary pressure and lead to right ventricular hypertrophy and possibly right sided heart failure. Right ventricular function is usually normal until the disease progresses in severity. In most cases, the reversal of the hypoxic state leads to reversal of pulmonary hypertension. However, the development of cor pulmonale carries a poor prognosis.

Treatment of cor pulmonale depends on the exact aetiology of the lung disease, as well as disease severity. Night time oxygen administration may alleviate hypoxia without hypercapnia. In patients with cystic fibrosis, calcium channel blockers have not shown proven effectiveness and may

Box 3: Diagnostic evaluation of pulmonary hypertension

- Chest radiograph (signs of cardiomegaly and enlarged pulmonary arteries)
- ECG (right ventricular hypertrophy and ST-T changes)
- Echocardiogram
  - (right ventricular hypertrophy, exclude congenital heart disease, left ventricular diastolic dysfunction, quantify right ventricular systolic pressure)
- Cardiac catheterisation with acute vasodilator testing
  - (evaluate pulmonary artery pressure and resistance and degree of pulmonary reactivity)
- Liver evaluation
  - Liver function tests with gamma glutaryl transferase
  - Abdominal ultrasound (porto-pulmonary hypertension)
  - Hepatitis profile
- Complete blood count, urinalysis
- Hypercoagulable evaluation
  - DIC screen
  - Factor V Leiden
  - Antithrombin III
  - Prothrombin mutation 22010
  - Protein C
  - Protein S
  - Anticardiolipin IgG/IgM
  - Russel viper venom test
- Collagen vascular workup—looking for autoimmune disease
  - Antinuclear antibody with profile (DNA, Smith, RNP, SSA, SSB, centromere, SCL-70)
  - Rheumatoid factor
  - Erythrocyte sedimentation rate
  - Complement
- Lung evaluation
  - Pulmonary function tests with DLCO/bronchodilators (to exclude obstructive/restrictive disease)
  - Sleep study and pulse oximetry (degree of hypoxia or diminished ventilatory drive)
  - CT/MRI scan of chest (evaluation of thromboembolic disease or interstitial lung disease)
  - Ventilation perfusion test
  - Lung biopsy
- Six minute walk test/cycle ergometry
- HIV test
- Thyroid function tests
- Toxicology screen (cocaine/methamphetamine and HIV testing)

Box 4: cardiac lesions associated with pulmonary hypertension

- Left-to-right shunts
  - Ventricular septal defect
  - Atrioventricular septal (canal) defect
  - Patent ductus arteriosus
  - Atrial septal defect
  - Aorto-pulmonary window
- Increased pulmonary venous pressure
  - Cardiomyopathy
  - Coarctation of the aorta (left ventricular diastolic dysfunction)
  - Hypoplastic left heart syndrome
  - Shone complex
  - Mitral stenosis
  - Supravalvar mitral ring
  - Cor triatriatum
  - Pulmonary vein stenosis/veno-occlusive disease
  - Total anomalous pulmonary venous return
- Cyanotic heart disease
  - Transposition of the great arteries
  - Truncus arteriosus
  - Tetralogy of Fallot (pulmonary atresia/VSD)
  - Univentricular heart (high-flow with/without restrictive atrial septum)
- Anomalies of the pulmonary artery or pulmonary vein
  - Origin of a pulmonary artery from the aorta
  - Unilateral ''absence'' of a pulmonary artery
  - Scimitar syndrome
- Palliative shunting operations
  - Waterston anastamosis
  - Potts anastamosis
  - Blalock-Taussig anastamosis

worsen oxygenation.[10 11] For patients with end stage lung disease from cystic fibrosis, lung transplantation is an option. Disorders of respiratory mechanics may also lead to hypoxia, and the development of pulmonary hypertension.

Thromboembolic disease

Thromboembolic disease as a cause of pulmonary hypertension in children is uncommon. However, an accurate diagnosis is essential for treatment.[12] Predisposing factors include collagen vascular disease, hypercoagulation disorders (see box 1), bacterial endocarditis, as well as a right atrial shunt (cerebral ventricular) for hydrocephalus. Likewise, the use of oral contraceptive agents may cause hypercoagulation leading to pulmonary thromboembolic phenomena. Diagnosis involves a high index of suspicion, as well as evaluation by ventilation perfusion scanning and CT scanning. In adults with chronic thromboembolic pulmonary hypertension, pulmonary thromboendarterectomy has been shown to improve survival and quality of life.

THERAPEUTIC CONSIDERATIONS

General principles

Most children with mild pulmonary hypertension do not require treatment other than treating the underlying aetiology. Therefore, a complete evaluation for the causes of pulmonary hypertension is important. Other general principles include avoidance of pregnancy and avoiding the use of birth control pills.

Operability

In patients with congenital heart disease, the timing of surgery depends on several factors. These include age, lesion, vasoreactivity at cardiac catheterisation, findings on lung biopsy, and pulmonary wedge angiography.[13–15]

Vasodilator therapy

Despite appropriate surgical correction, pulmonary hypertension and pulmonary vascular disease may progress. As vasoconstriction is an important component in the development of medial hypertrophy, vasodilators are frequently used to decrease pulmonary artery pressure, improve cardiac output, and potentially reverse some of the pulmonary vascular changes noted in the lung. Figure 1 shows our long term strategy for the treatment of pulmonary hypertension. Children who respond acutely to vasodilator testing with nitric oxide or epoprostenol should initially be treated with calcium channel blockers, such as nifedipine or diltiazem. Children who do not respond to acute vasoreactivity testing should be treated with other forms of therapy. Right heart failure (RHF) in the presence of a non-reactive pulmonary vasculature mandates treatment with continuous intravenous epoprostenol. In the absence of RHF, other agents may be trialled first. Bosentan, treprostinil, and iloprost have been studied and approved for treatment of pulmonary arterial hypertension. Other investigational drugs, such as sildenafil or sitaxsentan, are being assessed. For patients with severe disease, combination therapy may be considered but has not been well studied.

Before starting vasodilator therapy, vasodilator responsiveness should be assessed in a controlled situation, ideally in the cardiac catheterisation unit. A positive response is defined by assessing the change of cardiac and pulmonary catheter data to vasodilators (box 5).[16] The younger the child at the time of testing, the greater the likelihood of acute pulmonary vasodilatation in response to vasoreactivity testing.[6] Many oral and inhaled vasodilators have been used for testing of vasodilator responsiveness.[15 17]

Nitric oxide

The use of newer vasodilator agents, particularly nitric oxide, has been an important advance in determining vasoreactivity.

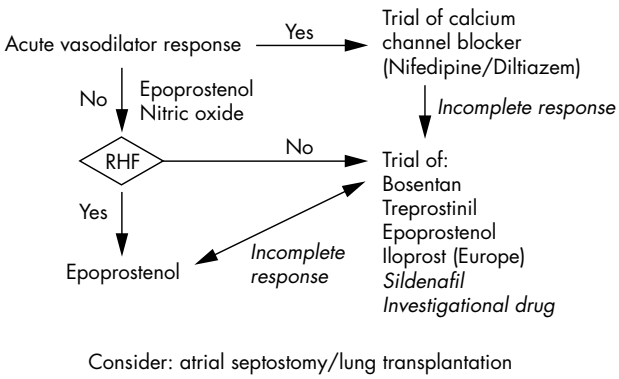

Figure 1 Algorithm of the treatment of paediatric pulmonary arterial hypertension.

Box 5: Positive response to vasodilators

Patients responding positively to acute vasodilator testing are defined as those who show all of the following:

- Decrease in the mean pulmonary artery pressure and resistance by 20%, or greater, with a fall to near normal levels (<40 mg Hg)
- Experience no change or an increase in their cardiac index
- Exhibit no change or a decrease in the ratio of pulmonary vascular resistance to systemic vascular resistance
- Normal right atrial pressure and cardiac output

Inhaled nitric oxide therapy improves gas exchanges and selectively lowers pulmonary vascular resistance in several clinical diseases, including idiopathic pulmonary hypertension and congenital heart disease.[15 17–24] Inhaled nitric oxide bypasses the damaged endothelium seen in pulmonary hypertensive disorders, and diffuses to the adjacent smooth muscle cell, where it activates soluble guanylate cyclase resulting in an increase in cGMP and vasodilatation (fig 2). Phosphodiesterase type 5 (PDE 5) degrades cGMP within vascular smooth muscle, and may limit vasodilatation. Sildenafil blocks PDE5 causing vasodilatation. Currently, either nitric oxide or prostacyclin is recommended as the agents of choice for evaluating pulmonary vasoreactivity (fig 1).

Recent studies have begun to explore the role of chronic nitric oxide in the treatment of pulmonary hypertensive disorders.[20 25 26] Although iNO therapy causes sustained decreases in pulmonary vascular resistance, adverse haemodynamic effects may complicate iNO therapy after abrupt withdrawal.[27 28] Inhibition of phosphodiesterase type 5 (see later), which degrades cGMP within vascular smooth muscle, causes vasodilatation and may attenuate the rebound effect.[29 30]

Calcium channel blockers

The use of calcium channel blockers to evaluate vasoreactivity may be problematic as these drugs can cause a decrease in

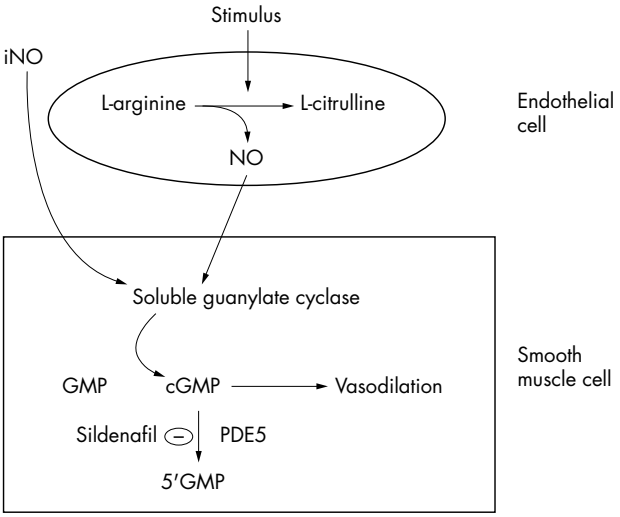

Figure 2 Inhaled nitric oxide (iNO) bypasses the damaged endothelium seen in pulmonary hypertensive disorders.

cardiac output. In addition, such deleterious effects may be prolonged due to the relatively long half life of calcium channel blockers. Consequently, increased right atrial pressure and low cardiac output are contraindications to acute or chronic calcium channel blockade.

Our preference is to perform an acute trial of calcium channel blocker therapy only in those patients who are responsive to nitric oxide or prostacyclin. Likewise, patients who do not have an acute vasodilatory response to short acting agents and who are then placed on calcium channel blocker therapy are unlikely to benefit from this form of therapy.[16] At least 60% of children with severe pulmonary hypertension are non-responsive to acute vasodilator testing, and are candidates for other forms of therapy, but not calcium channel antagonists.

Prostacyclin

Adults with IPAH and children with congenital heart disease show an imbalance in the biosynthesis of thromboxane A_2 and prostacyclin. Likewise, adults and children with severe pulmonary hypertension show diminished prostacyclin synthase expression in the lung vasculature.[31] Prostacyclin administered over the long term, utilising intravenous epoprostenol, has been shown to improve survival and quality of life in adults and children with primary pulmonary hypertension (fig 3).[16 32] Recent studies have shown improved outcome in patients who were previously poor candidates for calcium channel blockers, or thought to be candidates only for lung transplantation. Survival in these patients has markedly improved using the targeted approach to therapy outlined above. Using this strategy, five year survival in patients with primary pulmonary hypertension who were not candidates for calcium channel blocker therapy may be higher than 80% in children (fig 3).[16]

The use of prostacyclin in patients with congenital heart disease is promising.[33] Disadvantages of prostacyclin analogues, such as epoprostenol, include the dose dependent side effects of the drug (nausea, anorexia, jaw pain, diarrhoea, musculoskeletal aches and pains) and side effects due to the method of delivery. The drug must be given through a central line and thus potential complications include clotting, haemorrhage, cellulitis, and sepsis. Furthermore, the delivery of the product to the patient is continuous with abrupt cessation causing acute deterioration and in some cases death. In patients with residual shunting, continuous prostacylin may result in worsening cyanosis and complications of cerebrovascular accidents.

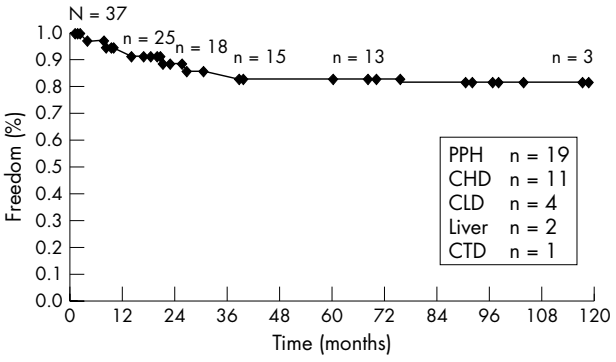

Figure 3 Kaplan-Meier curves of long term prostacyclin treatment in children with pulmonary hypertension at The Children's Hospital Heart Institute/Paediatric Heart Lung Center, Denver, Colorado. PPH, primary pulmonary hypertension; CHD, congenital heart disease; CLD, chronic lung disease; Liver, liver disease; CTD, connective tissue disease.

Alternative delivery routes for prostacyclin analogues

Success of epoprostenol (a synthetic analogue of natural prostacyclin) therapy, coupled with limitations of its delivery has led to the utilisation of prostacyclin analogues with alternative delivery routes.

Treprostinil, a subcutaneous prostacyclin analogue, has a half life of 45 minutes with a similar side effect profile to prostacyclin. Importantly, it can also cause pain and erythema around the infusion site, thus limiting its usefulness in young children. Treprostinil has been tested in a multicentre international placebo controlled randomised study and was found to have beneficial effects on haemodynamics and exercise tolerance, the latter being dose dependent.[34]

An inhaled prostacylin analogue, iloprost, has undergone initial trials with significant beneficial effects on symptomatology and quality of life.[35] Iloprost has a half life of 20–25 minutes and therefore 6–9 inhalations a day are required to be clinically effective. The advantage of an inhaled prostacylin is that it can cause selective pulmonary vasodilatation without affecting systemic blood pressure. Additionally inhaled prostacyclin analogues can improve gas exchange and pulmonary shunt in cases of impaired ventilation/perfusion by redistributing pulmonary blood flow, from non-ventilated to ventilated, aerosol accessible lung regions.[36] A recent randomised controlled trial of aerosolised prostacyclin therapy was shown to improve oxygenation in children with acute lung injury.[37]

Beraprost, an orally active prostacyclin analogue, is fast acting and has a half life of 35–40 minutes; it has beneficial effects, which may be attenuated with increasing length of treatment.[38]

Endothelins

Another target for treatment of pulmonary hypertension is the vasoconstrictor peptide endothelin (ET). The endothelins are a family of isopeptides consisting of ET-1, ET-2, and ET-3. ET-1 is a potent vasoactive peptide produced primarily in the vascular endothelial cell, but also may be produced by smooth muscle cells. Two receptor subtypes, ET_A and ET_B, mediate the activity of ET-1. ET_A receptors on vascular smooth muscle mediate vasoconstriction. ET_B receptors on smooth muscle cells mediate vasoconstriction, whereas ET_B receptors on endothelial cells cause release of nitric oxide (NO) or prostacyclin (PGI2) and act as clearance receptors for circulating ET-1 (fig 4). ET-1 expression is increased in the pulmonary arteries of patients with pulmonary hypertension. Bosentan, a dual ET receptor antagonist, lowers pulmonary artery pressure and resistance and improves exercise tolerance in adults with pulmonary arterial hypertension.[39] In children with pulmonary arterial hypertension related to congenital heart disease or IPAH, bosentan lowered pulmonary pressure and resistance, and was well tolerated.[40]

Selective ET_A receptor blockade is also possible using sitaxsentan, an ET receptor antagonist with high oral bioavailability, a long duration of action, and high specificity for the ET_A receptor. Sitaxsentan may benefit patients with pulmonary arterial hypertension by blocking the vasoconstrictor effects of ET_A receptors while maintaining the vasodilator/clearance functions of ET_B receptors. Sitaxsentan given orally for 12 weeks was seen to have beneficial effects on exercise capacity and cardiopulmonary haemodynamics in patients with pulmonary arterial hypertension that was idiopathic, or related to connective tissue disease or congenital heart disease.[41] Further studies using selective ET_A receptor blockade in postoperative congenital heart disease[42 43] have been reported.

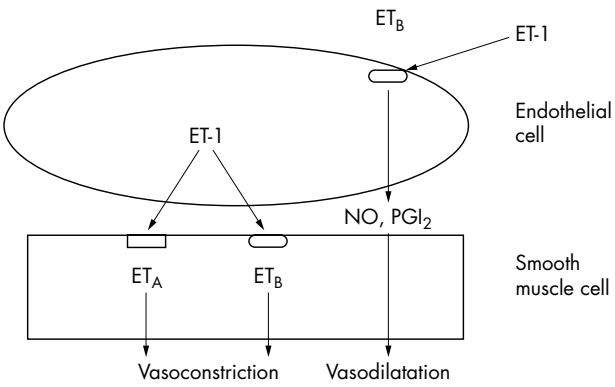

Figure 4 Endothelin-1 (ET-1) is a potent vasoactive peptide produced primarily in the vascular endothelial cell, but also may be produced by smooth muscle cells.

Recently, bosentan has been successfully used in children on long term epoprostenol therapy. Specifically concomitant use of bosentan allowed for a decrease in epoprostenol and its associated side effects, and discontinuation of epoprostenol in some children with normal pulmonary artery pressure.[44]

Phosphodiesterase-5 inhibitors

Specific phosphodiesterase-5 inhibitors, such as sildenafil, also have a role in treatment of pulmonary hypertension. These drugs promote an increase in cGMP levels and thus cause pulmonary vasodilatation (fig 2). Sildenafil is as effective a pulmonary vasodilator as inhaled NO and may be preferred because it does not increase pulmonary wedge pressure.[3 45] Sildenafil may also be useful in the setting of inhaled nitric oxide therapy withdrawal,[30] in postoperative pulmonary hypertension,[46 47] or in the presence of pulmonary hypertension related to chronic lung disease.[48] In some settings, sildenafil may worsen oxygenation.[46] Studies examining the use of such oral phosphodiesterase-5 inhibitors over the long term are ongoing.

Anticoagulation

Anticoagulation may be required because some causes of pulmonary hypertension may be associated with low cardiac output leading to sluggish blood flow through the pulmonary artery which may predispose to the development of pulmonary thrombi. In adults with IPAH, use of warfarin improves survival. However, the use of chronic anticoagulation has not been studied widely in children, but is usually recommended. The use of anticoagulation agents in patients with Eisenmenger syndrome is controversial. In primary pulmonary hypertension the aim is to keep the INR at 1.5–2.0. Risks of anticoagulation in other forms of pulmonary hypertension must be weighed against advantages.

Atrial septostomy

The general indications for atrial septostomy include pulmonary hypertension refractory to chronic vasodilator treatment[49] and in symptomatic low cardiac output states. Syncope and intractable right heart failure are indications for patients who are treated with vasodilators and remain refractory. Risks associated with this procedure include a worsening of hypoxaemia with resultant right ventricular ischaemia and worsening right ventricular failure, increased left atrial pressure, and pulmonary oedema.

Transplantation

For patients who do not respond to prolonged vasodilator treatment, or with certain lesions, such as pulmonary vein stenosis, lung transplantation may be offered.[50–52] Cystic fibrosis accounts for the majority of lung transplants, with primary pulmonary hypertension as an indication for transplantation in 14–17% of patients. For certain patients, including those with congenital heart disease, heart-lung transplantation may be necessary.

CONCLUSION

Advances in the understanding of the pulmonary vasculature have led to improved survival in children with severe pulmonary hypertension. The timely diagnosis of paediatric pulmonary hypertension is of paramount importance because treatment strategies improve morbidity and mortality. An extensive evaluation is performed in children with severe pulmonary hypertension, as the most successful strategy involves treatment of any underlying disorders. Further, a targeted approach to treatment includes acute vasodilator testing at cardiac catheterisation to determine long term therapy. In patients reactive to acute vasodilator testing with short acting vasodilators, such as inhaled nitric oxide, calcium channel blockers have been shown to provide effective therapy. In those patients not reactive to acute vasodilator testing, one should consider other forms of therapy, such as epoprostenol.

Newer treatment strategies in children include the use of endothelin receptor antagonists, inhaled nitric oxide, prostacylin analogues, and phosphodiesterase inhibitors. Recent advances have given the clinician more options in the management of a once uniformly fatal condition; however, more work is required to understand the role of new treatments for children with pulmonary hypertension in different clinical settings.

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