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Recognition and Management of Pulmonary Hypertension

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Contents

Abstract

Pulmonary hypertension (mean pulmonary arterial pressure >20mm Hg at rest or >30mm Hg during exercise) occurs (i) as primary pulmonary hypertension (no known underlying cause), (ii) as persistent pulmonary hypertension of the newborn or (iii) secondary to a variety of lung and cardiovascular diseases. In the last 10 to 15 years there have been significant advances in the medical management of this debilitating and life-threatening disorder. The main drugs in current use are anticoagulants (warfarin, heparin) and vasodilators, especially oral calcium antagonists, intravenous prostacyclin (prostaglandin I_2; epoprostenol) and inhaled nitric oxide.

Calcium antagonists, (e.g. nifedipine, diltiazem) are used chiefly in primary pulmonary hypertension. They are effective in patients who give a pulmonary vasodilator response to an acute challenge with a short acting vasodilator (e.g. prostacyclin, nitric oxide or adenosine), and are used in doses greater than are usual in the treatment of other cardiovascular disorders.

Prostacyclin, given by continuous intravenous infusion, is effective in patients

even if they do not respond to an acute vasodilator challenge. The long term benefit in these patients is thought to reflect the antiproliferative effects of the drug and/or its ability to inhibit platelet aggregation. It is used either as long term therapy or as a bridge to transplantation.

Inhaled nitric oxide, which is used mainly in persistent pulmonary hypertension of the newborn, has the particular benefit of being pulmonary selective, due to its route of administration and rapid inactivation.

Anticoagulants have a specific role in the treatment of pulmonary thromboembolic pulmonary hypertension and are also used routinely in patients with primary pulmonary hypertension.

Nondrug treatments for pulmonary hypertension include (i) supplemental oxygen (≥15 h/day), which is the primary therapy in patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease and (ii) heart-lung or lung transplantation, which nowadays is regarded as a last resort.

Different types of pulmonary hypertension require different treatment strategies. Future advances in the treatment of pulmonary hypertension may come from the use of drug combinations, the development of new drugs, such as endothelin antagonists, nitric oxide donors and potassium channel openers, or the application of gene therapy.

During the last 10 to 15 years there have been important advances in our understanding of pulmonary hypertension and in the medical management of patients with this disorder. These advances reflect both improvements in diagnosis and the development of new treatments. This article reviews both drug and nondrug treatments of pulmonary hypertension as practised in the 1990s, with occasional reference to earlier work to provide a historical perspective when appropriate. Each of the drug groups in current use is discussed separately, and treatment strategies for 5 important subtypes of pulmonary hypertension are addressed.

1. Recognition of Pulmonary Hypertension

1.1 Definition

The pulmonary vascular bed is a high flow, low pressure circulation system. Normal values of pulmonary artery pressure (PAP) are: systolic 22mm Hg, diastolic 10mm Hg, mean 15mm Hg.[1] Pulmonary hypertension is said to exist when mean PAP is >25mm Hg at rest or >30mm Hg with exercise.[2] The associated increase in pulmonary vascular resistance (PVR) leads to right ventricular hypertrophy and eventually right heart failure.

Pulmonary hypertension can occur as a secondary consequence of a variety of other diseases, the most important of which are listed in table I. When pulmonary hypertension cannot be attributed to any other underlying cause it is termed primary pulmonary hypertension. Primary pulmonary hypertension is rare (incidence 1 to 2 per million in the general population), affects more women than men (1.7 : 1), sometimes has a familial link (6% of patients) and has a poor prognosis (median survival after diagnosis 2 to 3 years); patients typically have mean PAP >60mm Hg.[2,3] Secondary pulmonary hypertension is more common but the elevations in PAP are generally less severe (mean PAP rarely >40mm Hg).[3] The treatment strategies for different types of pulmonary hypertension vary (section 4).

The increase in PAP in pulmonary hypertension is due to a combination of pulmonary vasoconstriction and pulmonary vascular remodelling (fixed obstruction of the pulmonary vessels). It is now understood that dysfunction of the vascular endothelium contributes to both these abnormalities in that the balance is disturbed between vasoconstric-

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Table I. Some common causes of secondary pulmonary hypertension

Persistent fetal circulation (persistent pulmonary hypertension of the newborn)
Congenital heart disease (left to right shunts; Eisenmenger's syndrome)
Left heart disease
Chronic obstructive pulmonary disease
Acute respiratory insufficiency [e.g. adult respiratory distress syndrome; (ARDS)]
Chronic pulmonary thromboembolism
Collagen vascular disease (e.g. scleroderma)
Pulmonary venous occlusive disease
Cirrhosis
Post surgical (involving cardiopulmonary by-pass)

tors and vasodilators and between mitogenic and antimitogenic factors derived from the endothelium.[4-6] The relative importance of vasoconstriction and vascular remodelling varies depending on the cause of the pulmonary hypertension and the stage of progression of the disease; it also influences the most appropriate choice of treatment.

1.2 Diagnosis

The most common presenting feature of patients with pulmonary hypertension is dyspnoea.[2] Other symptoms include fatigue, reduced exercise tolerance, syncope, chest pain, cyanosis and peripheral oedema. Clinical diagnosis is based initially on a combination of physical examination, chest radiograph, electrocardiogram and Doppler echocardiography (table II). Definitive diagnosis of pulmonary hypertension depends on right heart catheterisation and direct measurement of PAP, right atrial pressure, pulmonary capillary wedge pressure and cardiac output. Pulmonary angiography, isotope ventilation-perfusion lung scans, lung function tests, measurement of arterial blood gases, blood coagulation profiles and screens for collagen vascular disease are used to help classify the particular type of pulmonary hypertension.[7] The procedures employed in the diagnosis of pulmonary hypertension have been reviewed in detail elsewhere.[2,7-9]

2. Drug Treatments

2.1 Anticoagulants

Anticoagulants have a specific role in chronic thromboembolic pulmonary hypertension[10] and acute pulmonary thromboembolism. There is also clinical evidence that anticoagulant therapy increases the survival of patients with primary pulmonary hypertension[11,12] and anorectic drug-induced pulmonary hypertension.[13] The survival rate of patients with primary pulmonary hypertension receiving oral anticoagulants was approximately double that of patients not receiving this therapy, e.g. 3-year survival was increased from 31 to 62%.[11] Hence anticoagulants are used routinely in primary pulmonary hypertension as an adjunct to other therapies (section 4.1).

The rationale behind the use of anticoagulants in primary pulmonary hypertension is that the inactive lifestyle, compromised pulmonary blood flow and venous insufficiency of these patients predispose them to pulmonary thromboembolism. Furthermore, it has been shown that patients with primary pulmonary hypertension have abnormalities in blood coagulation, such as increased thrombin activity (measured as an increase in fibrinopeptide) and a decrease in thrombomodulin.[10] Also, the production of endothelium-derived nitric oxide and prostacyclin (prostaglandin I_2; epoprostenol), which normally inhibit platelet aggregation, is re-

Table II. Diagnosis of pulmonary hypertension

Presenting symptoms	Dyspnoea, fatigue, reduced exercise tolerance, syncope
Physical examination	Prominent P2 heart sound, tricuspid regurgitation murmur, atrial (S3) or ventricular (S4) heart sound
Chest x-ray	Enlarged main pulmonary artery, enlarged hilar vessels
Electrocardiogram	Right axis deviation, right ventricular hypertrophy
Doppler echocardiography	Right ventricular enlargement, paradoxical septal motion, partial systolic closure of pulmonary valve, elevated right ventricular systolic pressure
Right heart catheterisation	Increased pulmonary artery pressure, increased right atrial pressure

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duced in patients with pulmonary hypertension (sections 2.2.2 and 2.2.3).

The main drug used is warfarin, which belongs to the coumarin group of anticoagulants and is orally administered. It acts by preventing the reduction of vitamin K, thereby inhibiting the formation of vitamin K–dependent clotting factors. Also used is heparin, which inhibits thrombin by enhancing the action of antithrombin III and also inhibits platelet aggregation. It is administered intravenously and is used prior to warfarin in patients being treated for acute or chronic pulmonary thromboembolism (section 4.4) because the effects of warfarin may take several days to develop.

2.2 Vasodilators

The use of vasodilators in the treatment of pulmonary hypertension is based on the premise that pulmonary vasoconstriction contributes to the elevation in PAP. Vasodilators can be expected to be most effective in the earlier stages of the disease before fixed vascular obstruction predominates. Short acting vasodilators are used as screening agents to identify patients who are potentially responsive to long term vasodilator therapy. The goals of long term vasodilator therapy are to reduce PVR and PAP and increase cardiac output without causing any reduction in systemic vascular resistance or oxygen saturation. It is important that both PAP and PVR are reduced, i.e. that any reduction in PVR is not simply a reflection of increased cardiac output.[11]

The 3 main types of vasodilator currently used in pulmonary hypertension are calcium antagonists, prostacyclin and nitric oxide. The mechanisms of action of these drugs, at the cellular level, are illustrated in figure 1.

2.2.1 Calcium Antagonists

The use of calcium antagonists in the treatment of pulmonary hypertension dates back to the early 1980s.[14-16] They cause vasodilation by inhibiting the influx of calcium into the smooth muscle cell via voltage-operated (L-type) calcium channels (fig. 1). Their effect is most pronounced when there is a state of elevated vasomotor tone involving influx of extracellular calcium. Therefore, in patients with pulmonary hypertension, the effects of calcium antagonists are generally somewhat greater on the pulmonary vasculature (where tone is elevated) than on the systemic blood vessels (where tone is normal). This results in some measure of pulmonary vascular selectivity in patients with pulmonary hypertension,[17] such that relatively few patients who respond to calcium antagonists have to be excluded from treatment because of systemic hypotension.[18]

There are 3 major subclasses of calcium antagonists: dihydropyridines (e.g. nifedipine), benzothiazepines (e.g. diltiazem) and phenylalkylamines (e.g. verapamil). In pulmonary hypertension, diltiazem and the dihydropyridines are used in preference to verapamil because of the more pronounced cardiac depressant effects of the latter drug.[19]

The greatest success with calcium antagonists has been achieved in primary pulmonary hypertension.[11,17] Their value in the treatment of secondary pulmonary hypertension is less clear and may vary depending on the nature of the underlying disease. For example, calcium antagonists have been shown to be beneficial in pulmonary hypertension secondary to connective tissue vascular disease[20] but not always of benefit in patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease (COPD),[21] where the drugs may have an adverse effect on ventilation/perfusion matching.[22] In secondary pulmonary hypertension, in contrast to primary pulmonary hypertension, the effectiveness of calcium antagonists may depend on the initial level of PAP i.e. the higher the initial level of PAP, the less effective the drug.[18,20,21]

When first used in pulmonary hypertension, calcium antagonists were administered at dosages similar to those used for other cardiovascular disorders.[14-16] The early short term studies demonstrated only modest beneficial effects on PAP and PVR; follow-up studies on patients with a response to short term therapy failed to show long term clinical benefits.[23] Subsequent experience has shown that better results are achieved with higher dosages

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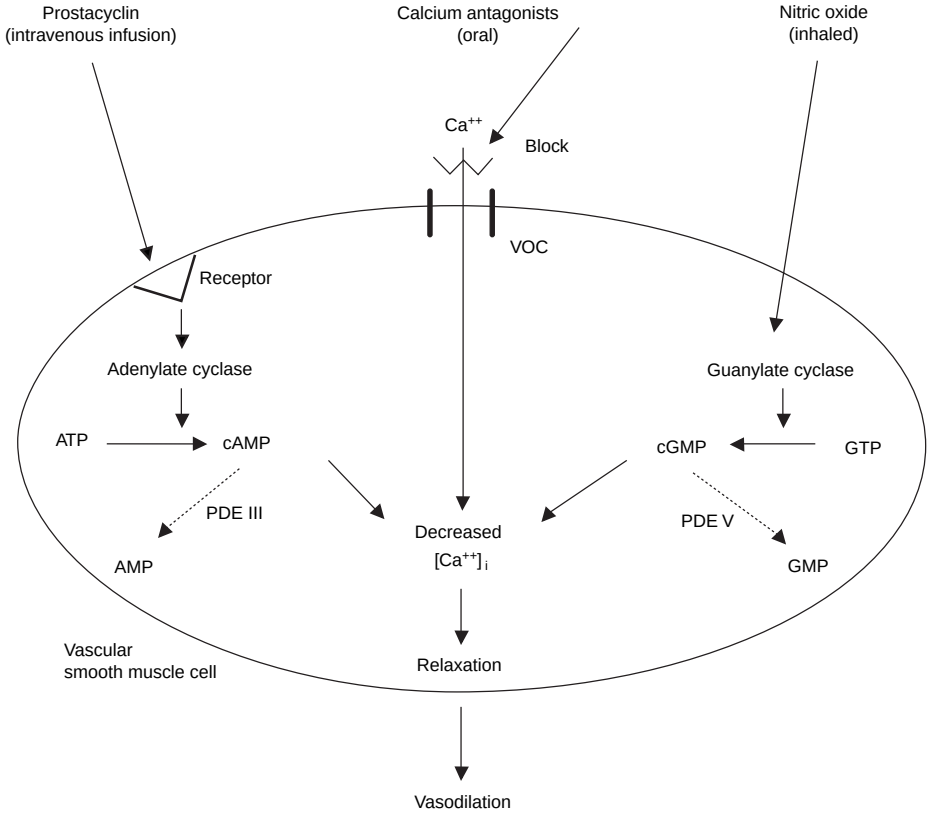

Fig. 1. Mechanisms of action of vasodilator drugs used in the treatment of pulmonary hypertension. Calcium antagonists inhibit the influx of Ca^{++} into the vascular smooth muscle cell through voltage operated calcium channels (VOC), thereby reducing the intracellular free Ca^{++} concentration, $[Ca^{++}]_i$. Prostacyclin (prostaglandin I_2; epoprostenol) activates specific cell membrane receptors linked to adenylate cyclase which catalyses the formation of cAMP from ATP. Nitric oxide diffuses into the cell and directly activates soluble guanylate cyclase which catalyses the formation of cGMP from GTP. cAMP and cGMP cause a reduction in $[Ca^{++}]_i$ by a variety of mechanisms, and are broken down by PDE III and PDE V, respectively. A reduction in $[Ca^{++}]_i$ leads to relaxation of the vascular smooth muscle cell and results in vasodilation. Prostacyclin and nitric oxide increase cAMP and cGMP, respectively, whatever the resting state of the vascular smooth muscle cell. Calcium antagonists act preferentially on cells in which there is an increase in Ca^{++} influx and an associated elevation in vascular tone. **ATP** = adenosine triphosphate; **Ca^{++}** = calcium ion; **cAMP** = cyclic adenosine monophosphate; **cGMP** = cyclic guanosine monophosphate; **GTP** = guanosine triphosphate; **PDE** = phosphodiesterase.

of the drugs (e.g. nifedipine ≤240 mg/day; diltiazem ≤900 mg/day).[17,24] Furthermore, a procedure is now advocated whereby the drugs are titrated to maximal physiological response so that the optimal dose for each individual is determined[17] (section 4.1). Used in this way, calcium antagonists are the most effective oral vasodilator agents in patients with pulmonary hypertension.

The long term value of calcium antagonists has recently been summarised in a meta-analysis of 8 long term trials.[25] This study showed that (i) a reduction in PAP occurred in 7 out of 8 trials; (ii) the greatest reduction in PAP occurred in patients given the highest dosages; and (iii) the reduction in PAP corresponded with subjective clinical improvement.[25]

A 5-year follow-up study on 64 patients provides the clearest evidence for the long term benefit of calcium antagonists in primary pulmonary hypertension.[11] In this study, 94% of patients who

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responded to calcium antagonists survived for 5 years, compared with a 5-year survival rate of 38% recorded in the National Institutes of Health Registry for patients with primary pulmonary hypertension not treated with calcium antagonists.

Nifedipine is the most widely used calcium antagonist, but longer acting dyhydropyridines requiring once-a-day administration have also been tested. In a recent crossover study, various dosages of amlodipine and a slow-release formulation of felodipine were compared in patients with pulmonary hypertension secondary to COPD.[26] These drugs produced similar reductions in PAP, but patients recorded fewer adverse effects with amlodipine. A daily dose of amlodipine 2.5mg was recommended.

Although calcium antagonists are clearly beneficial in pulmonary hypertension, these drugs can have severe adverse outcomes if used improperly. It is therefore recommended that the initial calcium antagonist treatment of patients with pulmonary hypertension be limited to specialised centres with broad experience in their use.[17] Patients with pulmonary hypertension and severe clinical right heart failure (i.e. with right atrial pressure >20mm Hg and cardiac output <2 L/min) are unsuitable for treatment with calcium antagonists because of concerns about the negative inotropic effects of these drugs.

2.2.2 Prostacyclin

Prostacyclin was first reported to reduce PAP in a patient with primary pulmonary hypertension as long ago as 1980.[27] The pulmonary vasodilator effect of prostacyclin was subsequently confirmed in 7 patients with primary pulmonary hypertension and it was suggested that prostacyclin might be useful in screening patients with pulmonary hypertension for vasodilator capacity and also for the short term management of seriously ill patients.[28]

Prostacyclin is a product of arachidonic acid metabolism. It is a potent vasodilator produced mainly by the vascular endothelium and it acts via specific prostacyclin receptors linked to adenylate cyclase; hence it increases intracellular levels of cyclic 3′,5′-adenosine monophosphate (cAMP; fig. 1). There is evidence in the literature of impaired prostacyclin production in patients with pulmonary hypertension[6,29] and hence prostacyclin may act in part to replace deficiencies in this endogenous vasodilator. Additional actions of prostacyclin which may be beneficial in pulmonary hypertension include inhibition of both platelet aggregation and smooth muscle proliferation.[30,31]

As with calcium antagonists, the most extensive long term use of prostacyclin has been in patients with primary pulmonary hypertension. Iloprost, a stable prostacyclin analogue has also been shown to be beneficial.[32] In these patients prostacyclin reduces PAP and PVR,[33-35] and improves right heart function and structure,[30] mixed venous O_2 saturation and exercise capacity.[35] More importantly, it improves long term survival[1,34,36-39] and hence has been used as a bridge to heart-lung transplantation.[33,36,38] More recently, an increase in long term survival has been observed even in patients who did not show an initial acute vasodilator response to prostacyclin.[33,34] This increase is thought to result from the non-vasodilator actions of prostacyclin, i.e. inhibition of pulmonary vascular growth and remodelling[34,35] and of thrombus formation.[32,34]

Other forms of pulmonary hypertension in which prostacyclin or iloprost have been shown to lower PAP include the following:

- persistent pulmonary hypertension of the newborn,[40]
- pulmonary hypertension crises after heart surgery in infants,[41,42]
- adult respiratory distress syndrome (ARDS),[43] or
- pulmonary hypertension secondary to connective tissue diseases in adults.[44,45]

Prostacyclin was not successful in patients with pulmonary hypertension secondary to COPD.[46]

Since prostacyclin has a very short half-life in the circulation (2 to 3 minutes), long term treatment requires continuous administration. Generally it is given by a portable infusion pump connected to a catheter inserted into the jugular or subclavian vein. Problems associated with this method of

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administration include the risks of sepsis, thrombus formation and malfunctioning of the pump.[31] Prostacyclin is not selective for the pulmonary circulation and hence, when given intravenously, adverse effects reflecting peripheral vasodilation are often seen, including hypotension, flushing, warmth and headaches.[31,47] A major disadvantage of prostacyclin is that it is very expensive.[48]

The dosage for long term infusion of prostacyclin is determined from the results of an acute challenge in which the starting dose is 2 ng/kg/min with increments of 2 ng/kg/min every 10 to 15 minutes until adverse effects are seen, or until a maximum dose of 15 to 20 ng/kg/min is reached.[31] The starting dose for long term intravenous infusion is usually 60 to 80% of the maximum tolerated dose in this acute challenge.[31] Tolerance often develops to prostacyclin, with a return of symptoms, but this can be overcome by increasing the dosage up to 100 to 150 ng/kg/min. In the aggressive dosage strategy recently reported by McLaughlin and colleagues,[35] the dosage was increased regularly even if symptoms had not returned, unless the occurrence of adverse effects indicated otherwise; the goal was to maintain patients on the highest dosage tolerated. These investigators have suggested that as PVR returns to normal following long term prostacyclin, the drug could possibly be withdrawn or replaced with calcium antagonists.[35]

Ways of overcoming the problems associated with continuous intravenous infusion and the lack of pulmonary selectivity of prostacyclin are to administer the drug by inhalation in aerosol form or to administer an oral analogue. Studies have shown that aerosolised prostacyclin is successful in lowering PAP and PVR in primary and secondary pulmonary hypertension in patients of all ages.[49-55] Aerosolised iloprost has also been successful and has the added benefit of a longer duration of action.[53] Advantages of this method are pulmonary selectivity and minimisation of ventilation-perfusion mismatch,[51-53] as well as ease of administration. However, frequent doses are still required[53] and there is concern over the effects the highly alkaline glycine buffer vehicle will have on large and small airways.[52] An alternative to intravenous prostacyclin infusion is the orally active prostacyclin analogue, beraprost. Beraprost, has a half-life of 1 hour and therefore must be given several times a day.[56]

2.2.3 Inhaled Nitric Oxide Gas

Inhaled nitric oxide gas was first administered to patients with pulmonary hypertension in 1991.[57] In 8 patients with primary pulmonary hypertension, inhalation of 40 ppm nitric oxide produced a decrease in PVR without any reduction in systemic vascular resistance. Inhaled nitric oxide gas has subsequently been shown to lower PVR in a wide range of clinical settings characterised by pulmonary hypertension, e.g. COPD, congenital heart disease, ARDS, persistent pulmonary hypertension of the newborn and after the use of cardiopulmonary bypass during open heart surgery.[58]

The rationale behind the use of nitric oxide is that this substance is an important endothelium-derived vasodilator[59] which, in the pulmonary circulation, contributes to the normally low pulmonary vascular tone.[60] Endothelial nitric oxide is also important in the transition from fetal to adult pulmonary circulation.[61] There is evidence to suggest that the endothelial nitric oxide pathway is impaired in various types of pulmonary hypertension, e.g. primary pulmonary hypertension,[4,62] persistent pulmonary hypertension of the newborn,[63] pulmonary hypertension associated with systemic sclerosis[64] and pulmonary hypertension seen after cardiopulmonary bypass.[65] Therefore, inhaled nitric oxide can be seen as replacing deficient, or augmenting existing, endothelial nitric oxide. Another site of nitric oxide production is the nose; healthy individuals normally inhale small amounts of nitric oxide. Thus, in intubated patients, inhaled nitric oxide given therapeutically may substitute for nitric oxide of nasal origin.

Nitric oxide causes relaxation of vascular smooth muscle by activating soluble guanylate cyclase and increasing intracellular cyclic 3′,5′-guanosine monophosphate (cGMP; fig. 1). It does this whatever the state of the vascular smooth muscle and hence it is not inherently selective for the pulmonary cir-

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culation in patients with pulmonary hypertension. However, pulmonary selectivity is achieved by virtue of the route of administration (inhalation), together with particular physicochemical properties of nitric oxide, i.e. it is highly lipid soluble and rapidly bound by oxyhaemoglobin. Therefore, nitric oxide rapidly diffuses from the alveoli to the pulmonary vascular smooth muscle but is inactivated before it can reach the systemic circulation.[66] Inhaled nitric oxide has the further advantage that it increases partial arterial oxygen pressure (PaO_2) because it selectively reaches well ventilated regions of the lung, i.e it does not have an adverse effect on ventilation/perfusion matching.

The widest use of nitric oxide in pulmonary hypertension has been in neonatal medicine. In full term or near full term neonates with hypoxic respiratory failure, administration of nitric oxide has been shown to produce a significant improvement in PaO_2, reduce the fraction of inspired oxygen level required and decrease the need for extra corporeal membrane oxygenation (ECMO).[67,68] For those infants who subsequently require ECMO, the improved oxygenation at the initiation of ECMO may be beneficial.[69] The hypoxaemic neonates who appear to benefit from nitric oxide are those who also have pulmonary hypertension, provided that the pulmonary hypertension is not of pulmonary venous origin or associated with left heart dysfunction.[70,71]

Despite the many reports of the short term therapeutic benefits of nitric oxide in term or near term neonates, there are occasions when the initial response is not sustained.[72] There is also conflicting evidence as to whether the use of nitric oxide prevents ongoing medical and neurodevelopmental problems or has any significant effect on overall mortality.[73,74] More long term studies are required to resolve this issue.

The therapeutic benefits of nitric oxide in adults are less clear than in infants. In patient with ARDS, nitric oxide has been reported to be effective in improving oxygenation and reducing PAP.[75-77] However, more recent studies have shown that only about 50% of patients had an improvement in oxygenation and/or a decrease in PVR; patients with septic shock were less likely to respond,[78] and the greatest benefit was in patients with the most severe hypoxaemia.[79] Furthermore, recent prospective trials have shown that nitric oxide does not appear to reduce mortality in ARDS patients[77,80] and a European multicentre trial in these patients has been stopped. In patients with COPD, nitric oxide reduced PAP but PaO_2 was improved only during exercise.[81] One valuable use of nitric oxide in adult pulmonary hypertension is as a screening agent for selecting patients for oral vasodilator therapy (section 4.1).

Nitric oxide has been used perioperatively in both adults and children undergoing various forms of heart and lung surgery. Perioperative nitric oxide is valuable in circumstances where PVR is elevated, whether this is due to the use of cardiopulmonary bypass, which causes endothelial dysfunction,[65] or to pulmonary vascular hypertrophy. Hence, it is useful in children undergoing corrective cardiac surgery for congenital cardiac defects[82,83] and in adults undergoing lung or heart/lung transplantation.[84] In these situations, administration of nitric oxide for a few days can reduce PAP[85] and improve oxygenation[65,86] until abnormalities are corrected.

The most common doses of nitric oxide in use are in the range of 10 to 40 ppm. An early dose-response study in neonates showed no difference in response with doses over the range of 5 to 80 ppm[87] and these investigators suggest that doses of ≤20 ppm should be adequate. In a more recent study in children with pulmonary hypertension there was a dose-response relationship at doses of ≤40 ppm; 80 ppm was of no further benefit.[88] On occasions, a dose as low as 4 ppm can be effective.[74]

There are various potential problems with the use of nitric oxide and these have recently been reviewed.[89] They include (i) increased bleeding times (due to inhibition of platelet aggregation and adhesion), (ii) negative inotropic effects and (iii) the formation of potentially toxic products, e.g. peroxynitrite, nitrogen dioxide and methaemo-

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globin. Particular consideration should be given to methaemoglobinaemia in near term and preterm infants in whom methaemoglobin reductase activity may be reduced. Despite the potential problems associated with nitric oxide, the question of whether there is a case for the use of domiciliary nitric oxide in extreme cases of pulmonary hypertension (e.g. to replace domiciliary oxygen) has recently been raised.[90]

2.2.4 Other Vasodilators

Numerous vasodilators other than calcium antagonists, prostacyclin and nitric oxide have also been tested in pulmonary hypertension, but most of these are no longer in common use.[1] Those that may still have a place in the therapy of pulmonary hypertension include alprostadil (prostaglandin E_1), adenosine, phosphodiesterase (PDE) inhibitors and magnesium.

Alprostadil, like prostacyclin (section 2.2.2), is a product of arachidonic acid metabolism and causes vasodilation by increasing intracellular cAMP. It is metabolised in the lung and hence when given by inhalation selectively reduces PAP without causing systemic hypotension.[91] Inhaled alprostadil has recently been shown to reduce PVR and improve arterial oxygenation in patients with ARDS.[91,92] However, in some ARDS patients pulmonary metabolism of alprostadil may be impaired and systemic hypotension may still occur.[93]

Adenosine causes vasodilation by acting on specific receptors linked to adenylate cyclase. It has been shown to lower PAP and PVR in patients with primary pulmonary hypertension[94] but its use is limited because of its very short duration of action (half-life 10 sec) and low solubility.[95] However, it is valuable for testing vasoreactivity before starting long term vasodilator treatment since it is less expensive than prostacyclin[95,96] and may be more convenient than nitric oxide. It can also be used to treat perioperative pulmonary hypertensive crises[97,98] and in some patients may be of benefit if used in conjunction with calcium antagonists.[99] It is not orally active and is given by continuous intravenous infusion; it has been suggested that oral analogues of adenosine need to be developed.[99]

PDE inhibitors act by inhibiting one or more of the enzymes responsible for the breakdown of cAMP and/or cGMP (fig. 1). Therefore PDE inhibitors cause vasodilation by increasing the amount of these cyclic nucleotides. There is a limited amount of data available about PDE inhibitors used specifically to treat pulmonary hypertension. Indirect studies have shown that theophylline, when used as a bronchodilator to treat symptoms of COPD, also reduced PAP and PVR.[100,101] Dipyridamole (a PDE-V inhibitor) and enoximone (a PDE-III inhibitor) have both been used specifically to lower PAP in patients with pulmonary hypertension secondary to COPD.[102,103] More recently, the PDE-III inhibitors, milrinone and amrinone have been used successfully in patients with pulmonary hypertension after cardiac surgery.[104-106] Since PDE inhibitors are not selective for the pulmonary circulation, they have the potential to produce systemic hypotension, although this effect could be balanced by a positive inotropic effect.

Magnesium is thought to produce vasodilation by blocking calcium channels[107] and has been shown to improve arterial oxygenation in infants with pulmonary hypertension.[108,109] Hence, intravenous magnesium sulphate could be useful in infants with pulmonary hypertension when a therapy of short duration and low cost is required.[110] Magnesium is thought to have beneficial properties other than vasodilation, including the ability to enhance nitric oxide synthase activity, activate adenylate cyclase and release prostacyclin.[107] Beneficial effects of magnesium have also been reported when it is used in conjunction with the endothelium-dependent vasodilator ATP in the treatment of children with pulmonary hypertension secondary to congenital heart defects.[110]

2.3 Miscellaneous Drugs

An alternative approach to lowering PAP and PVR has been to use drugs that specifically interfere with endogenous vasoconstrictor mechanisms. Drugs in this category include α-adrenoceptor

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antagonists, serotonin (5-hydroxytryptamine; 5-HT) antagonists, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists.

The α-adrenoceptor antagonist, tolazoline, first used in neonatal pulmonary hypertension in the 1960s, is still in current use,[111] despite the advent of nitric oxide. The most common route of administration is intravenous. The dosages generally used (1 to 10 mg/kg/h) can cause severe systemic adverse effects, but lower doses (0.5 mg/kg/h) may overcome this problem.[42] Recently, tolazoline has been administered endotracheally to infants with persistent pulmonary hypertension of the newborn and was successful in improving arterial oxygenation;[111,112] it was more successful in preterm than in term infants.[111] Other α-adrenoceptor antagonists that have been used are prazosin and urapidil. In adult patients with pulmonary hypertension secondary to COPD, each of these drugs was successful in lowering mean PAP, but systemic effects occurred.[113,114]

There are isolated reports of the use of the 5-HT antagonist ketanserin in patients,[115-117] but the results have not always been encouraging. Ketanserin is a 5-HT_{2A} receptor-selective antagonist. Since human pulmonary arteries possess 5-HT_1-like receptors, antagonists at this subclass of receptors may be an alternative.[118]

Drugs affecting the renin-angiotensin pathway have been tried with mixed success in patients with pulmonary hypertension. Angiotensin II is a potent pulmonary vasoconstrictor and smooth muscle mitogen; drugs that inhibit either the formation (ACE inhibitors) or action (angiotensin receptor antagonists) of this peptide may prove to be of some benefit. To date, the main ACE inhibitor to have been used in patients with pulmonary hypertension is captopril, but unfortunately studies carried out in the 1980s were mostly of short term treatment and met with limited success.[119] When long term treatment with captopril was used, it was successful in reducing PAP and PVR in patients with secondary pulmonary hypertension.[120-122] The success in long but not short term studies may indicate that the benefit of ACE inhibitors depends on their ability to reduce vascular remodelling, as shown in animal models of pulmonary hypertension.[123] Therefore, the key to the use of ACE inhibitors in pulmonary hypertension may be prolonged rather than short term treatment (as with prostacyclin; section 2.2.2). The angiotensin receptor antagonist, losartan, when tested in patients with secondary pulmonary hypertension, successfully reduced PAP and PVR.[124,125]

3. Nondrug Treatments

3.1 Supplemental Oxygen

Oxygen acts as a selective pulmonary vasodilator. Continuous administration of oxygen was tested in patients with pulmonary hypertension secondary to COPD in the 1960s, and found to reduce PAP.[126,127] In subsequent controlled trials, continuous oxygen had variable effects on PAP and PVR, but consistently increased survival.[128-130] The treatment did prevent further increases in PAP,[129,130] as confirmed in a recent study,[131] and reduce polycythaemia.[128] In another study, oxygen treatment was shown to improve exercise tolerance.[132] Interestingly, post mortem histological analysis of the pulmonary blood vessels from patients who did not survive after continuous oxygen therapy indicated that there was no relation between severity of pulmonary vascular remodelling and responsiveness to oxygen.[133] The precise mechanism whereby long term oxygen therapy reduces mortality is debatable; increased oxygen utilisation at peripheral tissues and prevention of worsening pulmonary hypertension may be more important than reversal of existing elevations in PAP.

The daily duration of long term oxygen treatment is important; the longer the duration the greater the benefit.[3] Nocturnal oxygen alone (i.e. 12 h/day) was shown to be less effective in improving survival than treatment for 19 hours daily or more[128] and a minimum of 15 hours daily is recommended.

In addition to its use in patients with pulmonary hypertension secondary to COPD, supplemental

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oxygen is indicated in any patient with pulmonary hypertension accompanied by oxygen desaturation, as assessed by overnight oximetry.

3.2 Transplantation and Thromboendarterectomy

Heart-lung transplantation (HLT) leading to long term survival in patients with pulmonary hypertension was first achieved in 1981.[134] Initially, HLT was the only method used. However, in the 1990s there has been a shift away from HLT towards lung transplantation (single or bilateral), with HLT reserved for patients with left ventricular failure or Eisenmenger's syndrome.[135] In other patients, lung transplantation is satisfactory because right heart function improves once PAP is lowered.

Patients with a range of different types of pulmonary hypertension have been successfully transplanted.[136] Patient selection is based on a range of factors including age (≤50 years), severity of disease (mixed venous oxygen saturation <63%; right atrial pressure >6mm Hg; cardiac index <2.8 L/min/m^2), absence of renal and liver dysfunction, and absence of infection or psychological factors.[136] Transplantation nowadays is reserved for patients who do not respond to drug therapy with vasodilators. Survival rates of 60 to 86% after 1 year and 44 to 72% after 4 years are reported.[137,138] The major long term problem is obliterative bronchiolitis, which leads to graft rejection in 30% of patients.[136] The occurrence of obliterative bronchiolitis is closely associated with the incidence and severity of episodes of rejection. Transbronchial biopsy is now routinely used to detect rejection at an early stage, so that immunosuppressive therapy can be increased if necessary. The other major cause of death is infection, and prophylaxis with cotrimoxazole (trimethoprim-sulfamethoxazole) is routine.[136] Patients who survive transplantation enjoy a good quality of life.

The other surgical procedure employed in pulmonary hypertension is thromboendarterectomy, which is used occasionally for patients with thromboembolic pulmonary hypertension (section 4.4). The need for this procedure is rare and the risks of surgery are great if carried out by inexperienced surgeons.

4. Management Strategies

4.1 Primary Pulmonary Hypertension

Primary pulmonary hypertension was once considered to be universally fatal, with transplantation being the only real therapeutic option for patients with this disease. Now, with advances and refinements in the use of vasodilator drugs, transplantation should be considered as a last resort.[139]

The vasodilators of choice in the treatment of primary pulmonary hypertension are oral calcium antagonists or intravenous prostacyclin. In addition, it is recommended that all patients be given anticoagulants in conjunction with vasodilator treatment. Detailed flow charts showing strategies for selecting the most appropriate treatment for individual patients are to be found in recent reviews on the management of primary pulmonary hypertension.[24,140] A simplified flow chart is given in figure 2.

Once primary pulmonary hypertension has been definitively diagnosed, an acute challenge with a short acting vasodilator is performed, followed by complete haemodynamic assessment involving measurements of cardiac output, PAP, capillary wedge pressure and oxygen saturation (central venous and peripheral arterial). Based on the results of this acute challenge, patients are classified as 'responders' or 'nonresponders'.

The definition of a positive response in the acute challenge is still somewhat controversial, but is generally taken as a >20% reduction in PVR together with a reduction in PAP. Those with a positive response to the acute challenge (indicative of the presence of active vasoconstriction) are candidates for therapy with oral calcium antagonists. The dosage of calcium antagonists should be determined using a procedure in which the drug is titrated to a concentration that provides a maximum physiological response, as described in detail by Rich and colleagues.[11,18]

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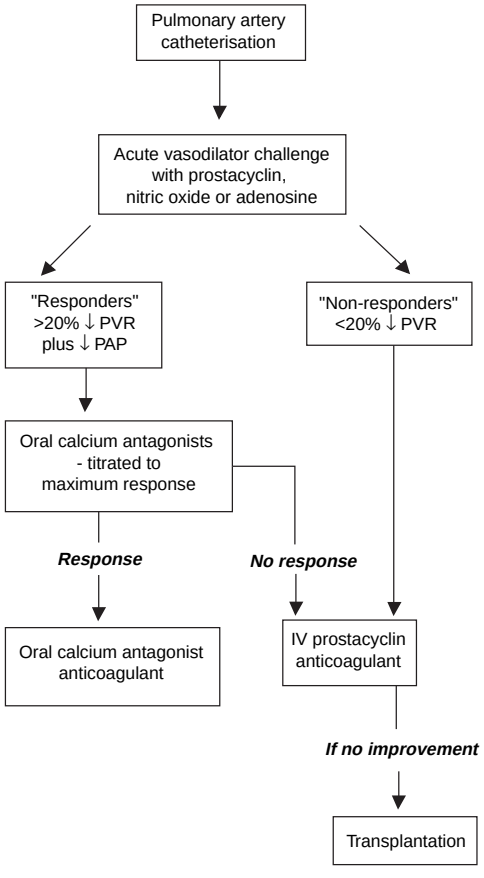

Fig. 2. Treatment strategy for primary pulmonary hypertension. **NO** = nitric oxide; **PAP** = pulmonary artery pressure; **PVR** = pulmonary vascular resistance.

Nonresponders to the initial acute challenge, or those who respond to the acute challenge but then fail to respond to the subsequent administration of an oral calcium antagonist, are candidates for continuous prostacyclin infusion, either as a long term therapy or as a bridge to transplantation. Where appropriate, patients receiving calcium antagonists may be given supportive therapy with diuretics, if there is severe peripheral oedema, and/or digoxin, to counteract any negative inotropic effects of the calcium antagonists. Drugs recommended for the acute vasodilator challenge are: intravenous prostacyclin (starting dose 2 ng/kg/min; increments of 2 ng/kg/min at 10-minute intervals; maximum dose 12 ng/kg/min); intravenous adenosine (starting dose 50 μg/kg/min; increments of 50 μg/kg/min at 2-minute intervals; maximum dose 500 μg/kg/min); inhaled nitric oxide (starting concentration 10 ppm for 10 minutes followed by 20 ppm for a further 10 minutes).[48,140]

4.2 Persistent Pulmonary Hypertension in the Neonate

The use of inhaled nitric oxide has revolutionised the management of term or near term neonates with persistent pulmonary hypertension of the neonate, but a correct diagnosis is essential before nitric oxide is used.[71] Thus, neonates with hypoxaemic respiratory failure must first be classified according to whether or not they have elevated PAP, based on echocardiographic evidence of increased right ventricular pressure or right to left shunts. It is then necessary to exclude those patients whose elevated PAP is due to cardiac structural abnormalities. The remaining patients are potential candidates for nitric oxide therapy.

Nitric oxide would normally be started if administration of oxygen, conventional ventilation and high frequency oscillatory ventilation (HFOV) fail to cause adequate increases in oxygen saturation (fig. 3). The use of HFOV prior to nitric oxide has the advantage of recruiting alveoli and hence optimising the effects of nitric oxide. An appropriate starting concentration of nitric oxide is in the range of 5 to 10 ppm, with subsequent increases to 20 or even 40 ppm as required. 80 ppm is associated with the risk of methaemoglobinaemia and is not recommended. Nitrogen dioxide levels are constantly monitored and should not exceed 2 ppm.

It is essential to wean the infant off nitric oxide slowly since abrupt withdrawal can lead to rebound pulmonary hypertension. Treatment should be continued until withdrawal of nitric oxide causes no decline in oxygenation. The duration of treatment is generally a few days, but treatment periods of several weeks have been reported.[141] With the advent of nitric oxide therapy, the need for ECMO has all but disappeared. In preterm (as opposed to

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term) infants, the use of nitric oxide poses particular problems, such as the possibility of increasing the severity of any intracranial haemorrhage or increasing pulmonary oedema,[142] and should be approached with caution. In these patients, endotracheal tolazoline may be of value.[111] In some centres, prostacyclin has been used as an alternative to nitric oxide.[40]

4.3 Pulmonary Hypertension Secondary to Chronic Obstructive Pulmonary Disease

Treatment of pulmonary hypertension secondary to COPD is warranted because survival in patients with COPD is inversely related to their PAPs.[1] A treatment strategy for pulmonary hypertension in patients with COPD is summarised in figure 4. In patients with COPD, the severity of hypoxaemia, rather than lung function tests, provide the most accurate indication of concomitant pulmonary hypertension.[143] The presence of pulmonary hypertension can be confirmed with Doppler echocardiography.

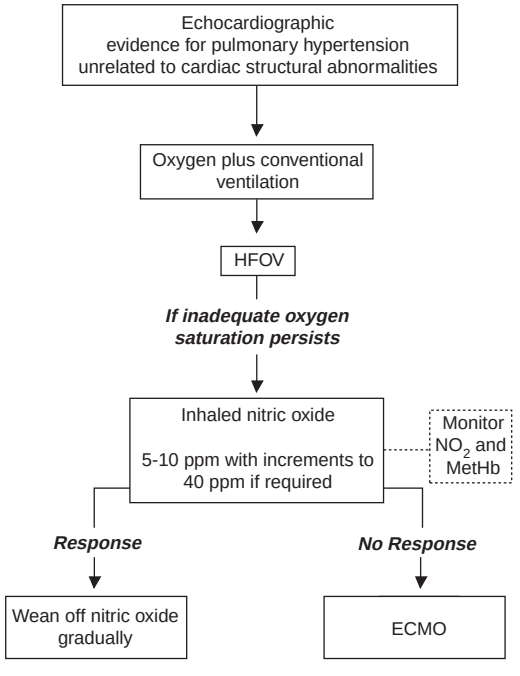

Fig. 3. Treatment strategy for persistent pulmonary hypertension of the newborn. **ECMO** = extracorporeal membrane oxygenation; **HFOV** = high frequency oscillatory ventilation; **MetHb** = methaemoglobin; **NO** = nitric oxide; **NO_2** = nitrogen dioxide.

The most important factor in pulmonary hypertension associated with COPD is alveolar hypoxia. Therefore, the first approach to therapy is to improve lung function and gas exchange with drugs such as bronchodilators or steroids.[3,48] If hypoxaemia persists after 3 to 4 weeks of this treatment, long term domiciliary oxygen therapy is indicated.[143] Domiciliary oxygen is administered via a nasal cannula for 15 to 19 hours daily. In some patients, increasing the flow rate at night may be helpful to compensate for desaturation during sleep.[3]

If pulmonary hypertension still persists despite long term oxygen therapy, the use of vasodilators (section 2.2) may be justified, but it is recommended that reactivity to vasodilators first be tested by means of an acute challenge with a short-acting vasodilator[3] as described in section 4.1. The problem with vasodilators is that they often exacerbate the hypoxaemia due to an adverse effect on ventilation/perfusion matching. The one vasodilator that does not have this disadvantage is inhaled nitric oxide. A recent study demonstrated a greater improvement in oxygenation with nitric oxide plus oxygen than with oxygen alone.[144] However if nitric oxide is to be used outside the intensive care setting, careful monitoring of toxic byproducts (section 2.2.3) will be necessary. Extreme cases that do not respond to these treatment strategies may be considered for single or double lung transplantation.

4.4 Thromboembolic Pulmonary Hypertension

Acute and chronic pulmonary thromboembolism are 2 distinct clinical conditions, the first common and the second rare. Both conditions are associated with elevations in PAP; in chronic pulmonary thromboembolism there is also pulmonary vascular remodelling and right ventricular hypertrophy.[145] Definitive diagnosis of pulmonary thromboembolism is important and is achieved with iso-

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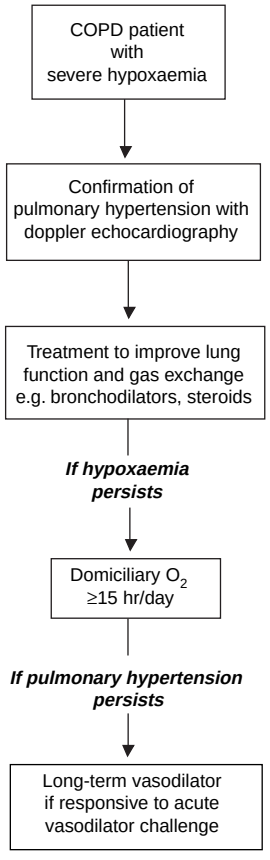

Fig. 4. Treatment strategy for pulmonary hypertension secondary to chronic obstructive pulmonary disease (COPD).

tope ventilation-perfusion scans, pulmonary angiography and Doppler echocardiography.[146]

The management of acute pulmonary thromboembolism requires immediate commencement of anticoagulant therapy with intravenous heparin (loading dose 500U followed by continuous intravenous infusion of 1000 to 2000 U/h to maintain activated partial thromboplastin time of 1.5 to 2.5 times the control value). At the same time, oral warfarin is commenced, and the heparin is discontinued once the international normalised ratio (INR) is within the range 2.0 to 3.0. The duration of anticoagulant therapy is still controversial, but is in the order of months. Whether or not thrombolytic therapy, in addition to anticoagulant therapy, is of any value is still a matter of debate.

In patients with chronic pulmonary thromboembolism and associated ventilatory and pulmonary haemodynamic abnormalities, surgery (i.e. thromboendarterectomy) is the most effective treatment. The surgery is followed by indefinite anticoagulant therapy, initiated with subcutaneous or intravenous heparin and continued with oral warfarin.

Patients not suitable for thromboendarterectomy can be considered for lung transplantation; those not suitable for either type of surgery are maintained on oral warfarin, with or without insertion of a filter into the inferior vena cava.

4.5 Eisenmenger's Syndrome

Children who have congenital heart disease that allows excessive pulmonary blood flow at high pressure are at risk of developing structural changes to the pulmonary vasculature. These changes result in progressive loss of luminal cross-sectional area. PVR inevitably rises and the left to right shunt eventually reverses, causing progressive cyanosis.[147] Once the pulmonary vascular changes have become severe, surgical correction of the anatomical abnormality of the heart does not result in resolution of the pulmonary hypertension. Patients with this problem typically die in their third or fourth decade. In general, heart and lung transplantation is the only effective form of treatment.[147]

5. Future Directions

The therapeutic management of pulmonary hypertension has progressed rapidly in the 1990s, and there are now several treatment strategies that improve both symptoms and haemodynamic variables. Furthermore, the survival of patients with pulmonary hypertension has increased not only following lung transplantation (section 3.2), but also as a consequence of treatment with anticoagulants (section 2.1), calcium antagonists (section 2.2.1) or prostacyclin (section 2.2.2).[8]

However, there is still no ideal treatment for this debilitating disease and alternatives are still required. Strategies for the future include (i) improved methods of administering current drugs, (ii) the use of currently available drugs in combination

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instead of alone, (iii) the development of new drug groups and (iv) gene therapy.

Improved methods of administration include pulsed delivery of nitric oxide,[148,149] and delivery of nitric oxide in conjunction with partial liquid ventilation.[150-152]

Examples of drug combinations that have been shown to be effective, either in human trials or animal experiments, include adenosine with calcium antagonists,[99] beraprost with nitric oxide[153] and PDE-V inhibitors with nitric oxide.[154,155]

New drug groups that are under development and that have been shown to be effective in animal models of pulmonary hypertension include potassium channel openers,[156,157] endothelin antagonists[158,159] and novel nitric oxide donor drugs.[160] A particularly promising group of nitric oxide donors are the NONOates, which can be designed to generate nitric oxide at predictable rates.[161]

The possibilities for gene therapy are still in their infancy,[162] but it was recently shown that aerosolised recombinant adenoviruses carrying the human constitutive nitric oxide synthase gene into rats lungs attenuated hypoxic induced increases in PAP.[163]

Any or all of these advances could be of benefit to patients with pulmonary hypertension in the 21st century.

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