

Dyspnea in Pulmonary Arterial Hypertension

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1. Introduction

Dyspnea is a complex sensation involving interaction of physiological, psychological, social, and environmental factors. Dyspnea in general is common across cardio-vascular and respiratory conditions and it is often difficult to clinically differentiate the exact cause of dyspnea in patients with heart or lung disease. Pulmonary hypertension in the absence of heart or lung disease, a condition called pulmonary arterial hypertension (PAH), is due to endothelial dysfunction and remodelling of small pulmonary arteries. Progressive dyspnea on exertion is a cardinal sign of PAH, which is often first diagnosed when in advanced stages. Improved understanding of pathogenic mechanisms underlying PAH and the related dyspnea should translate into new treatment options for symptom control and to prevent disease progression. This chapter reviews the current understanding of the etiology and pathogenesis of PAH and recent advances in management of this debilitating condition.

2. Pulmonary hypertension: Definition, classification and assessment of severity

Pulmonary hypertension was first described by Ernst von Romberg (von Romberg, 1891) and manifests as an increase in blood pressure in the pulmonary artery, vein, or capillaries. Elevated pulmonary vascular resistance and pressure lead to dyspnea, dizziness and fainting, all of which are exacerbated by exertion. Pulmonary hypertension leads to a progressive decrease in exercise tolerance, and ultimately to heart failure, with a median life expectancy from diagnosis of only 2.8 years. Pulmonary hypertension was previously defined as a mean pulmonary arterial pressure of 25 mmHg or more at rest, and/or 30 mmHg or more on light to moderate exercise. However, this definition has recently been revised with the exercise criterion in the previous definition being removed due to the difficulty of defining an exact upper limit of normal for pulmonary pressures during exercise. According to the most recent Dana Point revised classification (Simonneau et al., 2009; Galiè et al., 2009b), pulmonary hypertension is classified into five major groups: 1) pulmonary arterial hypertension (PAH), 2) pulmonary hypertension due to left heart disease, 3) pulmonary hypertension due to chronic lung disease and/or hypoxia, 4) pulmonary hypertension due to chronic thromboembolic disease and 5) pulmonary hypertension with unclear or multifactorial etiologies (Table 1).

1. PAH

- 1.1 Idiopathic PAH (IPAH)
- 1.2 Heritable
 - 1.2.1 BMPR2
 - 1.2.2 ALK-1, endoglin (with or without hereditary haemorrhagic telangiectasia)
 - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
 - 1.4.1 Connective tissue diseases
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
 - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis**2. Pulmonary hypertension due to left heart disease**

- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension**5. PH with unclear and/or multifactorial mechanisms**

- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

BMPR2: bone morphogenetic protein receptor, type 2; ALK-1: activin receptor-like kinase 1 gene; APAH: associated pulmonary arterial hypertension; PAH: pulmonary arterial hypertension. (Simonneau et al., 2009)

Table 1. Classification of Pulmonary Hypertension

PAH is defined by a mean pulmonary arterial pressure at rest equal or greater than 25 mm Hg in the presence of a normal pulmonary capillary wedge pressure (≤ 15 mm Hg) and

forms a distinct subgroup of pulmonary hypertension. PAH incorporates a number of different groups including familial/heritable PAH, idiopathic PAH and PAH associated with connective tissue disease, congenital heart disease, portal hypertension, or human immuno-deficiency virus (HIV) infection. Clinical severity of PAH is expressed in World Health Organisation (WHO) functional classes (FC), which mainly describe the severity of dyspnea experienced by patient (Barst et al., 2004) (Table 2). Assessment of severity is important as it guides clinical management and helps to determine prognosis (D'Alonzo et al., 1991). In untreated patients with PAH, historical data showed a median survival of 6 years for WHO-FC I and II, 2.5 years for WHO-FC III, and just 6 months for WHO-FC IV (D'Alonzo et al., 1991). Extremes of age (<14 yrs or >65 yrs), falling exercise capacity, syncope, haemoptysis and signs of RV failure all confer a worse prognosis in PAH. Patients with PAH in WHO-FC III or IV benefit from specific disease-modifying treatments and data to support improved outcomes from treatment of earlier stages of PAH are emerging.

Class	Symptomatic profile
Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause 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.

Table 2. WHO Classification of functional status of patients with pulmonary hypertension

3. Dyspnea and exercise intolerance in pulmonary arterial hypertension

Dyspnea is a complex sensation comprising at least three distinct sensations including air hunger, work/effort, and chest tightness. Dyspnea on exertion is a hallmark of PAH. The mechanism of dyspnea in pulmonary hypertension is complex and depends on the underlying condition and co-morbidities. It has been hypothesised that in pulmonary hypertension associated with pulmonary thromboembolism pressure, receptors or C fibers in the pulmonary vasculature or right atrium mediate the sensation of dyspnea (Manning & Schwartzstein, 1995). This mechanism may also operate in PAH since the severity of dyspnea in these patients is disproportionate to the impairment of left ventricular function, respiratory mechanics and gas exchange. In PAH dyspnea on exertion is usually associated

with little or no abnormalities in lung mechanics measured at rest (e.g., normal spirometry and lung volumes), while lung gas exchange may be abnormal (e.g., reduced diffusing lung capacity for carbon monoxide (DLco) (Chandra et al., 2010). Therefore, it is likely that exertional dyspnea in PAH results from complex interactions of signals from the central nervous system (i.e. autonomic centers in the brain stem and the motor cortex) and receptors in the upper airway, lungs, right atrium, pulmonary vessels and chest wall (Manning et al., 1995; O'Donnell et al, 2009). Cardiopulmonary exercise testing (CPET), which measures pulmonary gas exchange during exercise, demonstrates significant oxygen transport abnormalities, such as a decrease in peak oxygen uptake ($\dot{V}O_2$), a decreased slope of the increase in $\dot{V}O_2$ -work rate relationship and a low lactic threshold (Palange et al, 2007). In addition, patients with PAH often have a low \dot{V}_E and a normal breathing reserve at peak exercise. This reflects the fixed high physiological dead space consequent to reduced pulmonary perfusion. The alveolar-arterial O_2 difference is often widened during exercise; a right-to-left shunt may contribute to arterial hypoxemia during exercise in a proportion of patients with co-existent patent foramen ovale. Excessive \dot{V}_E at low absolute work rates may also reflect the influence of a premature lactic acidemia. Finally, the breathing pattern tends to be more rapid and shallow than normal; this pattern is not explained by restrictive mechanics and may result from activation of vagal-innervated mechanoreceptors in the right atrium, pulmonary vasculature and pulmonary interstitium. Importantly, with CPET it is possible to detect an abnormal increase in exercise ventilatory response relative to carbon dioxide output ($\dot{V}_E/\dot{V}CO_2$) that is associated with a proportional and sustained reduction in end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) (Riley et al., 2000). The degree of ventilatory and gas exchange inefficiency during exercise (i.e., the increase in $\dot{V}_E/\dot{V}CO_2$ and the drop in $P_{ET}CO_2$) correlates with the severity of the disease, and the level of $P_{ET}CO_2$ reduction may be a useful non-invasive screening tool for the selection of PAH patients for right heart catheterization (Yasunoby et al., 2005). Interestingly, differences in ventilatory and gas exchange adaptations to cycling and walking exercise have been described in PAH; walking, in particular, is more severely limited by high ventilatory response, arterial O_2 desaturation and dyspnea sensation compared to cycling (Valli et al., 2008).

Right heart catheterization with measurement of pulmonary artery pressure and cardiac output has traditionally been used to assess the severity of PAH and the response to interventions. However, catheterization is invasive and cumbersome, largely restricted to tertiary referral centers and not suitable for regular follow-up. Therefore, exercise testing has been used in its place as a surrogate marker to monitor disease severity and prognosis. Wensel et al. studied the prognostic value of $\dot{V}O_2$ peak in patients with PAH and reported that patients with $\dot{V}O_2$ peak ≤ 10.4 ml/min/kg have a 50% risk of early death at 1 year and 85% at 2 years (Wensel et al., 2002). Since CPET is not always available, field walking tests have been utilized to assess the degree of exercise intolerance in PAH (Steel, 1996). The degree of exercise impairment is judged by the measurement of distance covered during a fixed time period. The six minute walking test (6MWT), in which patients are free to choose the most convenient walking speed, is the most popular walking test (American Thoracic Society [ATS], 2002). The distance achieved in the 6MWT has been used as a primary endpoint in most randomised controlled trials of modern PAH therapies (Galiè et al., 2002). The 6MWT has good reproducibility and some studies have demonstrated a significant correlation between the 6MWT distance and peak oxygen uptake ($\dot{V}O_2$ peak) measured

during standard incremental protocols (Myamoto et al., 2000). Walk distance and oxygen desaturation during 6MWT in patients with PAH relate well to $V'O_2$ peak and appear to have a prognostic value (Myamoto et al., 2000; Paciocco et al., 2001). Unexplained dyspnea on exertion is the main symptom in the early stages of PAH and causes exercise intolerance. In PAH exercise intolerance correlates with the severity of the disease (Sun et al., 2002). Furthermore, the reduction of pulmonary vascular resistance and/or pulmonary arterial pressure with treatment (see below) is paralleled by changes in WHO FC and improvement in dyspnea on exertion as measured by the 6MWT.

4. Management of dyspnea in pulmonary hypertension

Treatment is determined by whether the pulmonary hypertension is arterial, venous, hypoxic, or thromboembolic and is first directed to the primary cause. Since pulmonary venous hypertension (Group 2) is synonymous with congestive heart failure, therapy of dyspnea aims to optimize left ventricular function through use of diuretics, beta blockers, and ACE inhibitors, and where relevant repair/replace dysfunctional heart valves. Similarly, in patients with lung disease and/or hypoxia (Group 3) therapy of dyspnea is usually directed at the underlying cause and correction of hypoxia.

PAH (Group 1) has no underlying cardiac or respiratory cause and most often is associated with scleroderma or idiopathic. While lifestyle changes, digoxin, diuretics, oral anticoagulants, and oxygen therapy were long considered appropriate treatments for PAH-associated dyspnea, these have never been proven to be beneficial in a randomized, prospective manner. As there is currently no cure, therapy of dyspnea in PAH is targeted at symptom control with the aim being to ease dyspneic symptoms thereby allowing patients to become more active, and to use treatments to reduce pulmonary vascular resistance and pressures and thereby slow disease progression.

As outlined in subsequent sections, four major classes of medications are available for treatment of PAH-associated dyspnea (Fig. 1) (Humbert et al., 2004b). Calcium channel blockers reduce contractility of pulmonary arterial smooth muscle thereby reducing pulmonary vascular resistance. Prostacyclin analogues induce pulmonary vasodilation by supplementing inadequate endothelial prostacyclin caused by under-activity of endothelial prostacyclin synthase. Endothelin receptor antagonists block the vasoconstrictor effects of endothelin on pulmonary smooth muscle. Phosphodiesterase 5 (PDE5) inhibitors promote the vasodilation activity of the nitric oxide pathway by reducing conversion of cyclic guanylate monophosphate (a nitric oxide second messenger) to 5'-guanylate monophosphate (an inactive product). By reducing pulmonary arterial pressures and resistance, these treatments reduce dyspnea and improve exercise tolerance in patients with PAH.

4.1 Calcium channel blockers

High-dose calcium channel blockers only showed benefit for symptom relief in about 10% of patients with idiopathic PAH, who achieved reduction in their mean pulmonary arterial pressure and pulmonary vascular resistance by > 20% as measured by Swan-Ganz catheterization during acute vasodilator challenge. In the absence of measurable improvement in pulmonary arterial pressure, calcium channel blockers are not indicated.

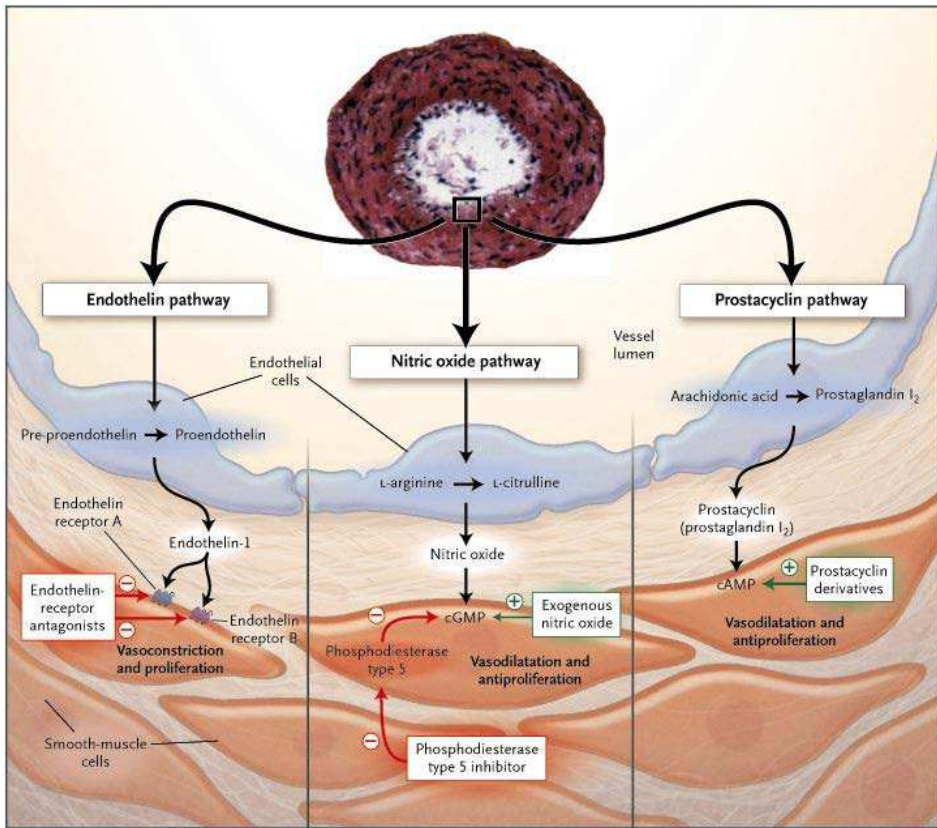


Fig. 1. Therapeutic Targets for Pulmonary Arterial Hypertension

Three major pathways involved in abnormal proliferation and contraction of the smooth-muscle cells of the pulmonary artery in patients with pulmonary arterial hypertension are shown. These pathways correspond to important therapeutic targets in this condition and play a role in determining which of four classes of drugs -- endothelin-receptor antagonists, nitric oxide, PDE5 inhibitors, and prostacyclin derivatives -- will be used. At the top of the figure, a transverse section of a small pulmonary artery (<500 μm in diameter) from a patient with severe pulmonary arterial hypertension shows intimal proliferation and marked medial hypertrophy. Dysfunctional pulmonary-artery endothelial cells (blue) have decreased production of prostacyclin and endogenous nitric oxide, with an increased production of endothelin-1 -- a condition promoting vasoconstriction and proliferation of smooth-muscle cells in the pulmonary arteries (red). Therapies interfere with specific targets in smooth-muscle cells in the pulmonary arteries. In addition to their actions on smooth-muscle cells, prostacyclin derivatives and nitric oxide have several other properties, including antiplatelet effects. Plus signs denote an increase in the intracellular concentration; minus signs blockage of a receptor, inhibition of an enzyme, or a decrease in the intracellular concentration; and cGMP cyclic guanosine monophosphate.

The criteria for vasoreactivity have recently changed. Only patients whose *mean* pulmonary artery pressure falls by > 10 mm Hg to < 40 mm Hg with an unchanged or increased cardiac output when challenged with adenosine, epoprostenol, or nitric oxide are considered "vasoreactive". Of these, only 50% may have sustained response to calcium channel blockers (Rich & Brundage, 1987; Sitbon et al., 2005) and can be treated with dihydropyridine calcium channel blockers (i.e. nifedipine, felodipine or amlodipine) or diltiazem. Verapamil is contraindicated because of its negative inotropic effect.

4.2 Prostacyclin analogues

Prostacyclin is a potent pulmonary vasodilator and inhibits platelet aggregation. It is a metabolite of arachidonic acid produced in the normal vascular endothelium. Reduced expression of prostacyclin synthase in patients with PAH causes prostacyclin deficiency. Epoprostenol is a potent, short-acting prostacyclin analogue that induces pulmonary vasodilation and is approved for treatment of patients with PAH in WHO FC III or IV. Epoprostenol is administered by continuous intravenous infusion through an indwelling central line. Unfortunately, it is expensive, inconvenient (patients need to carry a continuous infusion pump) and has significant dose-dependent adverse effects including flushing, headache, jaw and lower extremity muscular pain, diarrhea, nausea, and rash. Patients with PAH may live at distance from the nearest tertiary care facility and a well-established setting for ensuring continuous supply and supervision is critical, as sudden interruption of the epoprostenol infusion may cause rebound severe PAH and death. Despite the side effects and inconveniences with administration, epoprostenol has solid clinical evidence of efficacy in PAH. It has been shown to reduce dyspnea, improve exercise capacity, quality of life and survival in patients with PAH (Badesch et al., 2000; Barst et al., 1996; McLaughlin et al., 2002; Sitbon et al., 2002). Three-year survival of patients with PAH treated with epoprostenol was 63% (McLaughlin et al., 2002; Sitbon et al., 2002). Most patients experienced optimal benefit from epoprostenol at a stable dose of 25 to 40 ng/kg per minute, after incremental increases over the course of 6-12 months from an initial dosage of 2 to 6 ng/kg per minute.

Treprostinil is a prostacyclin analogue that is stable at room temperature and has a longer half-life than epoprostenol (3-4 hours). This allows it to be given intravenously or via a small subcutaneous catheter with a continuous pump. Treatment by either route improves the 6MWT distance in patients with PAH in WHO FC III or IV (Simonneau et al., 2002; Tapson et al., 2006). Three-year survival of patients with idiopathic PAH treated with subcutaneous treprostinil monotherapy has been reported as 71% (Barst et al., 2006a). Whilst short-term efficacy of intravenous treprostinil may equal epoprostenol; comparative survival data are lacking. The adverse effect profile of treprostinil is similar to epoprostenol. Frequent, severe pain at the site of infusion may limit the treprostinil dose that can be administered subcutaneously. This limitation may reduce treprostinil's efficacy because the effect on 6MWT distance is dose-dependent, and higher doses may require intravenous administration. Other clinical trials of treprostinil inhaled and oral formulations are ongoing. Some patients treated with epoprostenol may be switched to intravenous treprostinil with maintenance of 6MWT distance; although a larger dose of treprostinil is required (Gomberg-Maitland et al., 2005).

Iloprost is an inhaled prostacyclin analogue that was shown to improve dyspnea, exercise capacity and hemodynamics in patients with PAH. In a randomized, placebo-controlled, 12-week study, iloprost produced a placebo-corrected increase in 6MWT distance of 36 m in 207 patients with symptomatic idiopathic PAH, PAH associated with connective tissue disease or appetite suppressants, or pulmonary hypertension related to inoperable chronic thromboembolic disease (Olschewski et al., 2002). Long-term maintenance of improved exercise capacity and hemodynamics was observed with iloprost use (Hoepfer et al., 2000). Adverse effects of iloprost are similar to other prostacyclin analogues and include flushing, headache, and cough. A major downside for patients is that iloprost's short duration of action necessitates frequent 10-minute inhalations, 6 to 9 times per day.

4.3 Endothelin receptor antagonists (ERA)

By binding to endothelin receptors A and B, endothelin-1 triggers pulmonary vasoconstriction and stimulates vascular smooth muscle and fibroblast proliferation. Endothelin-1 levels are increased in PAH, and correlate with disease severity, suggesting that blockade of endothelin-1 should have beneficial effects. Bosentan is an orally-active, dual ERA that improves exercise capacity, quality of life, hemodynamics, and time to clinical worsening in PAH (Channick et al., 2001; Rubin et al., 2002). Two-year survival of patients with idiopathic PAH in whom bosentan was used as first-line therapy was 87% (McLaughlin et al., 2005; Provencher et al., 2006). Bosentan is currently approved for treatment of PAH patients in WHO FC III or IV. Adverse effects of bosentan include flushing, edema, nasal congestion, mild anemia, and teratogenicity. Dose-dependent elevation of liver transaminases occurs in about 10% of patients on bosentan, requiring monthly monitoring of liver function.

Ambrisentan and sitaxentan are ERA with relative selectivity for the endothelin receptor subtype A. Treatment with sitaxentan was efficacious for patients with PAH with low incidence of liver toxicity in initial reports (Barst et al., 2006b; Benza et al., 2008). However, it was recently removed from the market due to case reports of severe hepatitis and liver toxicity. Ambrisentan is another ERA with safer liver toxicity profile. It has been shown to improve symptoms, exercise capacity, and hemodynamics (Galiè et al., 2005a). Adverse effects of ambrisentan include flushing, edema, nasal congestion, and teratogenicity. Although associated with a low incidence of liver enzyme elevations, monthly liver function monitoring is still required (McGoan et al., 2009).

4.4 Phosphodiesterase 5 Inhibitors

Sildenafil, originally commercialized for erectile dysfunction, is a potent, highly specific inhibitor of PDE5 that has been shown to improve symptoms and functional capacity in PAH patients (Galiè et al., 2005b). Adverse effects associated with sildenafil include headache, flushing, dyspepsia, nasal congestion, and epistaxis. Nitrates are contraindicated in patients taking PDE5 inhibitors because the additive effects of the drugs can cause life-threatening hypotension.

Tadalafil, a long-acting PDE5 inhibitor, is the most recent oral agent for treatment of PAH (Rosenzweig, 2010). The Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) clinical trial examined the efficacy and tolerability of tadalafil for the treatment of

PAH over a period of 16 weeks (Galiè et al., 2009a). Tadalafil 40 mg showed significant improvement over placebo for six of eight SF-36 domains and EQ-5D index scores. Also, the tadalafil 40-mg group showed significant improvement over placebo on the 6MWT distance ($p < 0.001$), but no clear relationship was found between 6MWT distance and health-related quality of life (HRQoL). Results suggest that tadalafil may significantly improve HRQoL and exercise capacity in patients with PAH.

4.5 Combination treatments

Combinations of disease-modifying agents of various classes seems a logical next step in PAH management and is becoming standard care in many PAH centres. Clinical trial evidence for combination therapy is encouraging (Humbert et al., 2004a; McLaughlin et al., 2006; O'Callaghan & Gaine, 2007; Simonneau et al., 2008). The relatively small BREATHE-2 study (Humbert et al., 2004a) showed a trend to haemodynamic improvement with combination epoprostenol-bosentan as compared to epoprostenol alone. The STEP-1 study (Simonneau et al., 2008) addressed the safety and efficacy of 12 weeks therapy with inhaled iloprost plus bosentan and reported a non-significant increase of 26 m in the post-inhalation 6MWT distance ($p=0.051$). There was no improvement in pre-inhalation haemodynamics in the iloprost group after 12 weeks of treatment, but time to clinical worsening was significantly prolonged in the iloprost group (0 events *versus* 5 events in the placebo group; $p = 0.02$). In contrast, the COMBI trial which also studied the benefits of inhaled iloprost added to bosentan, was stopped prematurely after a planned interim analysis failed to show an effect on 6MWT distance or time to clinical worsening (Hoepfer et al., 2006). The TRIUMPH trial studied the effects of inhaled treprostinil in patients already treated with bosentan or sildenafil (McLaughlin et al., 2010). The primary end-point, change in 6MWT distance at peak exposure, improved by 20 m compared with placebo ($p<0.0006$). At trough exposure, *i.e.* after >4 hours post-inhalation, the difference was 14 m in favour of the treprostinil group ($p<0.01$). There were no significant differences in Borg dyspnea index, functional class and time to clinical worsening. The PACES trial addressed the effects of adding sildenafil to epoprostenol in 267 patients with PAH (Simonneau et al., 2008) and showed significant improvements after 12 weeks in 6MWT distance and time to clinical worsening.

Additional data are available for the combination of ERA and PDE5 inhibitors. In the subgroup of patients enrolled in the EARLY study (Galiè et al., 2008) (bosentan in WHO FC II PAH patients already on treatment with sildenafil), the haemodynamic effect of the addition of bosentan was comparable with that achieved in patients without background sildenafil treatment. A pharmacokinetic interaction has been described between bosentan and sildenafil, which act as inducers or inhibitors of cytochrome P450 CYP3A4, respectively. The co-administration of both results in a decline of sildenafil and increase in bosentan plasma levels (Paul et al., 2005). So far there is no indication that these interactions are associated with reduced safety (Humbert et al., 2007), but whether the clinical efficacy of sildenafil is significantly reduced is still controversial. No pharmacokinetic interactions have been reported between sildenafil and the two other available ERAs, sitaxentan and ambrisentan. In the PHIRST study (Galiè et al., 2009a) the combination of tadalafil and bosentan resulted in an improvement of exercise capacity of borderline statistical significance.

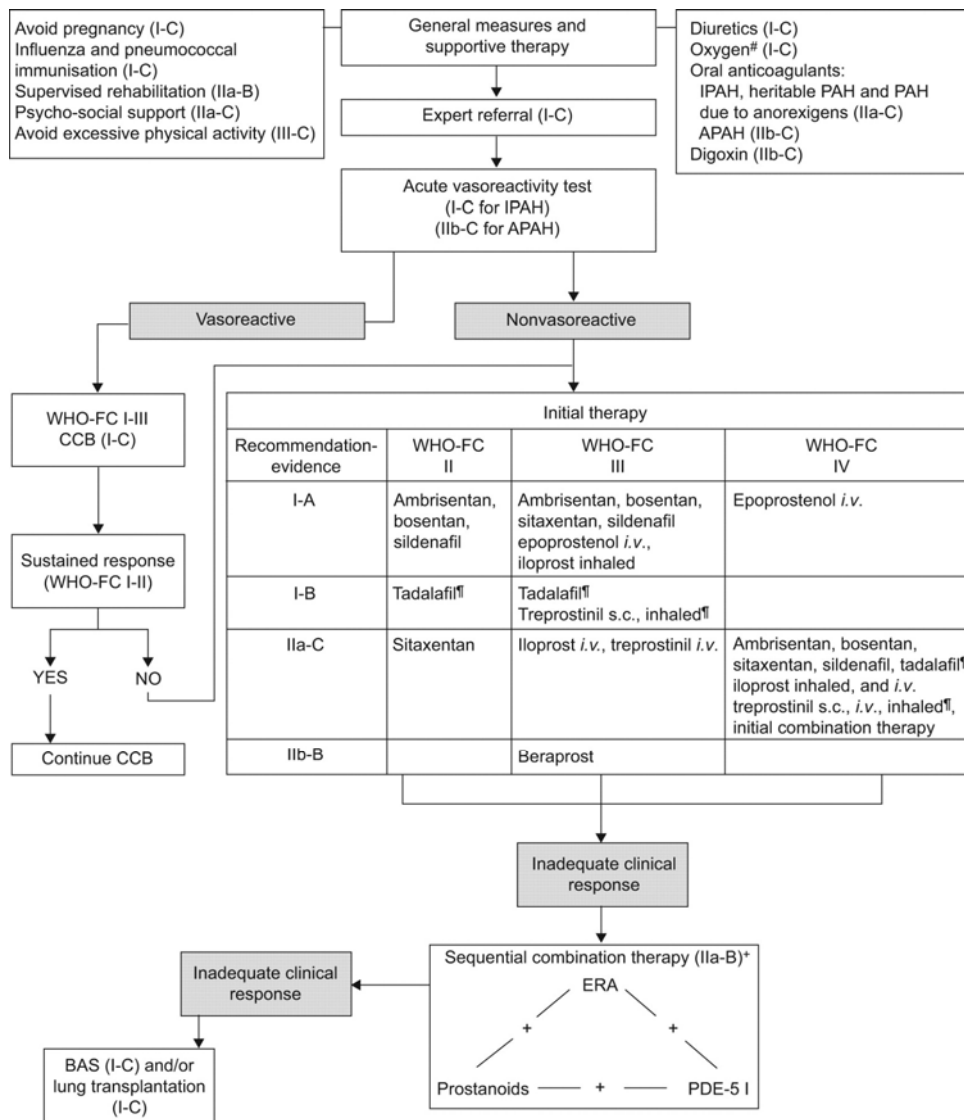


Fig. 2. Treatment algorithm for PAH-associated dyspnea
Evidence-based treatment algorithm for treatment of dyspnea caused by pulmonary arterial hypertension (group 1 patients only). APAH: associated pulmonary arterial hypertension; BAS: balloon atrial septostomy; CCB: calcium channel blocker; ERA: endothelin receptor antagonist; IPAH: idiopathic pulmonary arterial hypertension; PAH: pulmonary arterial hypertension; PDE-5 I: phosphodiesterase type-5 inhibitor; s.c.: subcutaneously; WHO-FC: World Health Organization functional class. #: to maintain arterial blood O₂ pressure >8 kPa (60 mmHg); [¶]: under regulatory review in the European Union; +: IIa-C for WHO-FC II.

In summary, whether the response to monotherapy is sufficient or not can only be decided on an individual basis. Combination therapy is recommended for PAH patients not responding adequately to monotherapy and ideally should be instituted by experienced centres (Fig. 2).

5. Palliative and supportive treatments for residual dyspnea in treated progressive pulmonary hypertension

Since PAH is not a curable disease, many patients inevitably progress to WHO-FC IV with severe dyspnea. This necessitates additional palliative and supportive treatments. Exercise training, atrial septostomy and opioids are some of the interventions that may have a role in improving symptoms and exercise tolerance in patients with progressive PAH.

Exercise in the form of respiratory and physical training appears efficacious as part of the management of PAH. When superimposed on an optimal stable drug regimen, 15 weeks of respiratory and physical training led to an average increase of 111 m in 6MWT distance, in addition to improvements in other measures of exercise tolerance and quality of life (Mereles et al., 2006). This is a major benefit when put in the perspective of expensive PAH medications that may deliver more modest 20-40 m improvements in 6MWT distance.

Atrial septostomy performed by graded balloon dilatation may be suitable for selected patients with severe PAH. In patients with medically treated severe progressive PAH, atrial septostomy improved clinical symptoms and dyspnea, cardiac index, exercise endurance and systemic oxygen transport (Reichenberger et al., 2003; Sandoval et al., 1998).

Transplantation is an important option for selected PAH patients. Up to 25% of patients with PAH fail to improve on disease-specific therapy and the prognosis of patients who remain in WHO FC III or IV is poor. International guidelines to aid referral and listing have been published by the International Society for Heart and Lung Transplantation (Orens et al., 2006). Both heart-lung and double-lung transplantation have been performed for PAH and each centre has developed its own strategy for the choice of the type of transplantation in the individual patient. However, due to the shortage of donor organs, most patients are considered for double-lung transplantation. While right ventricular afterload is immediately reduced after double-lung transplantation, right ventricular systolic and left ventricular diastolic functions do not improve immediately and hemodynamic instability is a common problem in the early post-operative period. The overall 5-year survival following transplantation for PAH is 45-50%, with evidence of sustained improvement in dyspnea and quality of life (Trulock et al., 2006).

In parallel with attempts to treat the underlying pathology causing dyspnea, the sensation of breathlessness itself must be ameliorated. For many patients there comes a point when there are no further identifiable reversible components of PAH and the treatment focus needs to move to reducing the subjective sensation of breathlessness (Davis, 1994). Like pain, dyspnea has a sensory and an affective dimension. Therefore, treatment strategies in dyspnea should be similar to those used in pain. Recent neuroimaging studies suggest that neural pathways involved in pain and dyspnea sensation may be shared and, therefore, similar neurophysiological and psychological approaches used to understand and manage pain can be applied to dyspnea (Nishino, 2011). Previous randomised controlled trials have

reported the effectiveness of sustained-release morphine in patients with refractory dyspnea, including those with severe COPD (Abernethy et al., 2003; Poole et al., 1998) and chronic heart failure (Johnson et al., 2002). Currently there is no data on use of opioids to relieve dyspnea in patients with progressive advanced PAH and clinical trials are on-going. Effective and predictive treatment of dyspnea remains elusive and a better understanding of the pathophysiology and neurophysiology of dyspnea may lead to more effective treatments.

6. Conclusion

Etiological diagnosis and assessment of pulmonary hypertension WHO functional class is critical for management. Despite recent advances in understanding and treatment of PAH it remains a progressive and incurable disease, with dyspnea and exercise intolerance being the major causes of distress to sufferers. More effective palliation of dyspnea in patients with PAH depends on better understanding of its mechanisms. More randomised clinical trial evidence on combination and palliative treatments is needed to improve management of dyspnea in patients with advanced PAH.

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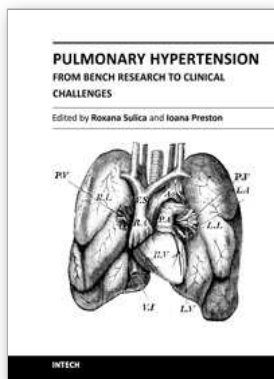
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The textbook "Pulmonary Hypertension - From Bench Research to Clinical Challenges" addresses the following topics: structure and function of the normal pulmonary vasculature; dysregulated cellular pathways seen in experimental and human pulmonary hypertension; clinical aspects of pulmonary hypertension in general; presentation of several specific forms of pulmonary hypertension, and management of pulmonary hypertension in special circumstances. The textbook is unique in that it combines pulmonary and cardiac physiology and pathophysiology with clinical aspects of the disease. First two sections are reserved for the basic knowledge and the recent discoveries related to structure and cellular function of the pulmonary vasculature. The chapters also describe dysregulated pathways known to be affected in pulmonary hypertension. A special section deals with the effects of hypoxia on the pulmonary vasculature and the myocardium. Other three sections introduce the methods of evaluating pulmonary hypertension to the reader. The chapters present several forms of pulmonary hypertension which are particularly challenging in clinical practice (such as pulmonary arterial hypertension associated with systemic sclerosis), and lastly, they address special considerations regarding management of pulmonary hypertension in certain clinical scenarios such as pulmonary hypertension in the critically ill.

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