Peer reviewed article

Pulmonary hypertension

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Summary

Pulmonary arterial hypertension (PAH) must be classified into primary pulmonary hypertension and PAH related to other diseases such as collagen vascular diseases, HIV infection or portal hypertension. PAH must also be differentiated from other entities, in particular pulmonary hypertension secondary to thromboembolic diseases, requiring specific approaches. All PAH results in similar histological remodelling of pulmonary arteries, with thickening of the intima, proliferation of the media and plexogenic lesions. Today the physiopathology of these lesions is much better understood and has resulted in new therapies involving substances such as prostacyclins, endothelin receptor antagonists or phosphodiesterase inhibitors, aimed not only at dilating arteries but also at preventing their remodelling. Thromboendarterectomy, septostomy and transplantation remain the only option where medical treatment has failed.

Key words: pulmonary hypertension; prostacyclin; endothelin receptor antagonists; phosphodiesterase inhibitors; septostomy; transplantation; thromboendarterectomy

Introduction

Pulmonary arterial hypertension (PAH) has often been misdiagnosed in the past, due to the poor specificity of symptoms early in the disease until the appearance of right heart failure. Although primary pulmonary hypertension (PPH) remains a rare disease, in recent times PAH related to other diseases has been better recognised. These forms are related to systemic connective tissue diseases, thromboembolic disease, congenital heart disease, portal hypertension or HIV infection, or are secondary to the use of drugs as anorexigens. They all result in an indistinguishable histological picture [1, 2].

Improved understanding of the pathogenesis of PPH has produced new treatments, not only for PPH but for PAH related to other diseases. Genetic predisposition has been found in familial PPH, a disease transmitted as an autosomal trait with a low penetrance of 10–20%. A heterozygous germ line mutation in bone morphogenetic protein (BMP) receptor II, a member of the TGF beta family, has been identified in 60% of familial PPH and in 25% of sporadic cases. These alterations may result in altered vascular growth and remodelling. In addition, there is strong evidence that alterations of endothelial function cause or contribute to vasculopathy: unbalance in the production of vasoactive substances and mitogens, including excessive production of endothelin-1 (ET-1); and diminished production of prostacyclin and nitric oxide (NO). Additionally, altered smooth muscle K-channel activity has been demonstrated in PPH, resulting in membrane polarisation and increased intracellular calcium concentrations which probably contribute to vasoconstriction and smooth muscle cell proliferation. It has also been suggested that inflammation may contribute to production of cytokines, providing a further stimulus for growth. As will be discussed later, serotonin and a serotonin transporter gene have recently been implicated in this process as well. Although the sequence of events still needs to be elucidated, these observations provide a strong rationale for the newer, targeted approaches to therapy with agents which affect not merely vasomotor but also vascular growth and remodelling.

To determine the therapeutic options, a precise diagnosis of pre- or postcapillary pulmonary hypertension is required, as well as testing of the reversibility of PAH by initial catheterisation. After this, non-invasive evaluation using echo-Doppler, combined with a walking test (easier to perform than cardiopulmonary exercise testing), suffice in most situations to follow up the therapeutic effect. In view of the many new forms of treatment and various ongoing clinical trials, it is suggested that patients with pulmonary hypertension be managed in cooperation with an experienced centre. In Switzerland, the Swiss Working Group for Pulmonary Hypertension (SAPH) constitutes a collective of experts in this field (www.saph.ch).

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Diagnosis and screening for pulmonary arterial hypertension

The standard definition of PAH is based on catheter-derived assessment of mean pulmonary artery pressure (PAP) exceeding 25 mm Hg at rest or 30 mm Hg during exercise. However, invasive assessment is not suitable for screening or follow-up of individuals at high risk for PAH. Doppler echocardiography provide reliable assessment of right ventricular systolic pressure, from the maximum velocity of the jet of tricuspid regurgitation according to the Bernouilli equation. During the Second World PPH Symposium at Evian in 1998, mild pulmonary hypertension was defined arbitrarily as the presence of tricuspid jet velocity between 2.8 and 3.4 meters/second, which corresponds to a pulmonary artery systolic pressure (PASP) between 36 and 51 mm Hg, assuming a fixed right arterial pressure of 5 mm Hg. On the basis of existing evidence, including the Massachusetts General Hospital database, it appears that tricuspid jet velocity exceeding 2.8 m/sec at rest, and PASP greater than 36 mm Hg, can justifiably be considered elevated except in elderly and/or very obese patients.

Screening may be appropriate in groups of patients at increased risk of developing pulmonary hypertension. In such instances the screening should start with a search for clinical signs or symptoms consistent with PAH. Trans-thoracic echocardiography is then the preferred screening test for the presence of PAH. However, screening by echocardiography every 3–5 years has been suggested in the first relatives of families with documented PPH; in scleroderma, screening is suggested every year in view of the high prevalence of pulmonary hypertension in these patients and the arrival of potentially effective therapies [3]. This is even more important in patients with limited cutaneous systemic sclerosis, where the incidence of PAH is even higher. Similar systematic screening is not recommended for systemic lupus, rheumatoid arthritis or other connective tissue diseases, in view of the lower prevalence of PAH.

Because PAH involves a high risk of morbidity and mortality during liver transplantation, transthoracic echocardiography should be performed in all patients when evaluated for liver transplantation. Transthoracic echocardiography is not recommended routinely in patients with HIV infection, a history of intravenous drug use or a history of appetite suppressor drug use, unless symptoms consistent with PAH are found.

Practical approach to differential diagnosis of PAH

The classification of PAH proposed by the Evian Conference in 1998 is shown in table 1. The diagnosis of PAH may be initially suspected on the basis of patients' complaints or a constellation of risk factors which warrant screening, as previously stated. In some cases suspicion arises by chance,

Table 1

Classification of pulmonary hypertensive diseases (adapted from WHO, Evian 1998).

I Pulmonary arterial hypertension
Primary pulmonary hypertension (sporadic or familial)
Associated with:
collagen vascular disease
congenital shunts
portal hypertension
HIV
drugs
others
II Pulmonary venous hypertension
Left myocardial or valvular diseases
Extrinsic compression of pulmonary veins
Pulmonary veno-occlusive disease
Others
III Pulmonary hypertension associated with respiratory disorders or hypoxaemia
IV Pulmonary hypertension secondary to embolic diseases
V Pulmonary hypertension secondary to disorders affecting the pulmonary vasculature
Inflammatory:
schistosomiasis
sarcoidosis
Pulmonary capillary haemangiomatosis

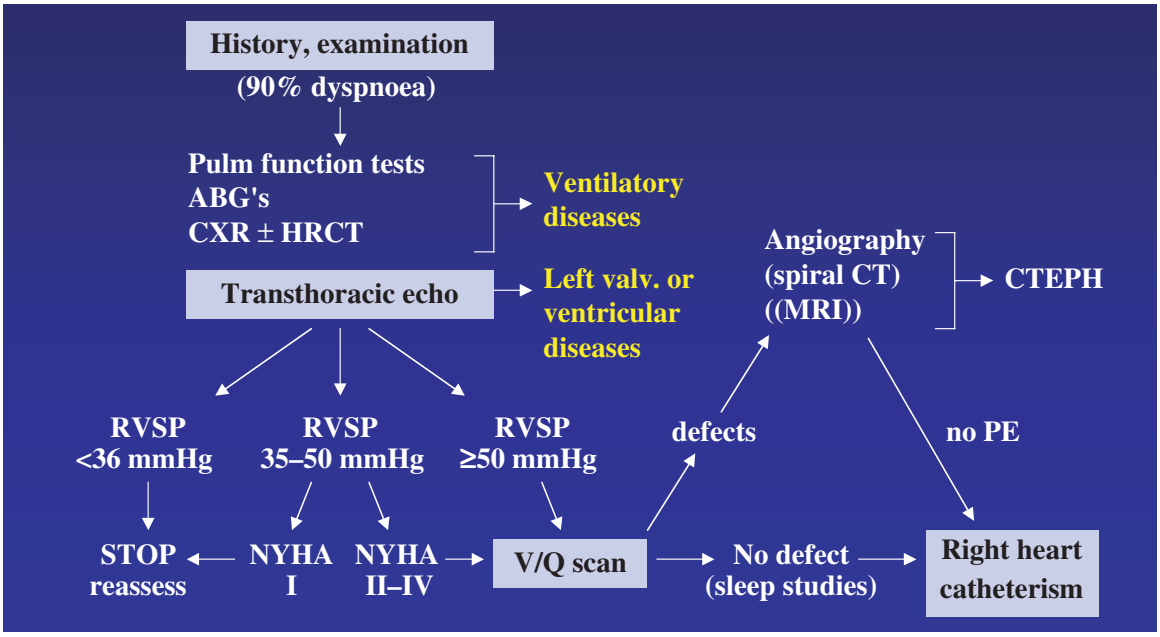

Figure 1

Algorithm for diagnosis of pulmonary hypertension. Abbreviations: ABG: arterial blood gases; CXR: chest x-ray; HRCT: high resolution CT; RVSP: right ventricular systolic pressure; NYHA: New York Heart Association; V/Q: ventilation/perfusion; MRI: magnetic resonance imaging; PE: pulmonary emboli; CTEPH: chronic thromboembolic pulmonary hypertension.

e.g. when an electrocardiogram (ECG), echocardiogram or chest x-ray is done for an unrelated condition.

After the first suspicion, a thorough history and examination, which should include the family case history, clinical examination and basic diagnostic workup by means of x-ray, ECG, echocardiography and, in the case of dyspnoea, pulmonary function testing, should be completed. Pulmonary radioisotope scan (ventilation/perfusion) should be performed if pulmonary hypertension is confirmed, to rule out chronic thromboembolic disease. Additional imaging techniques such as spiral CT scan or angiography, if the radioisotope scan is abnormal, can complement the examination (fig. 1), since the sensitivity of the diagnostic methods appears to differ between chronic and acute cases of pulmonary embolism. In chronic thromboembolic pulmonary hypertension (CTEPH), perfusion radioisotope scanning shows almost always typical segmental defects, without a concordant reduction in ventilation, which are difficult to differentiate from acute emboli. On the other hand, sometimes neither spiral CT nor pulmonary angiography show thrombi even where radioisotope scan results are unequivocal. In this case, supraselective angiography will be superior to other methods in detecting small artery occlusions [4]. Angiography is the procedure of choice when thromboendarterectomy is considered.

Where PAH is confirmed, testing for viral infections such as HIV and hepatitis is mandatory. Testing for autoantibodies should include antinuclear antibodies and extractable nuclear antigens (Scl 70, Centromere, Ssa, SSb and Jo-1 antibodies) and also the antibodies typical of autoimmune thyroiditis. The latter are found with relative frequency in patients with primary pulmonary hypertension.

According to the current classification, autoimmunological findings like these are in accordance with the diagnosis of primary pulmonary hypertension. However, these findings warrant further diagnostic measures (micro-angioscopy, barium swallow test, Schirmer's test, urinalysis) to rule out connective tissue disease.

The spectrum of other diseases is very wide and involves entities such as sleep apnoea syndrome; liver disease with portal hypertension; sarcoidosis; Behçet's disease; bilharziosis or thrombocythaemia. The differential blood count combined with general inflammation markers is recommended as general screening with other appropriate screening tests on an individual basis.

Right heart catheterisation is not usually recommended for mild pulmonary hypertension, especially if symptoms are minor; after this, a follow-up examination after one year is appropriate (fig. 1). Right heart catheterisation should be undertaken if moderate or severe pulmonary hypertension (PASP ≥50 mm Hg) is suspected involving significant functional limitations. Right heart catheterisation should be performed at least once to confirm the pre- or postcapillary nature of PAH and to test its reversibility when calcium channel blockers are considered.

Conventional PAH therapies

The 1-, 3- and 5-year survival rates in the patients included in the National Institute of Health register on PPH are 77%, 41% and 27% respectively. Current experience in expert reference centres is that the death rate has decreased by half, with improved quality of life, in pure PPH as well as more broadly defined PAH. This is related to the improvement in conventional therapies and even more to new advances such as the prostacyclin therapies or endothelial receptor antagonists.

Present-day conventional therapies in PAH can be summarised as follows: careful physical activity is encouraged provided there is no anginal pain or syncope, since it has not been shown to aggravate the disease and prevents deconditioning and debilitation. Because of the risk associated with pregnancy, and since there is no proof of adverse side effects of hormonal contraception in otherwise anticoagulated PAH patients, low-dose hormonal preparations are prescribed for women with child-bearing potential.

Patients are advised to avoid altitudes above 1500 metres and air travel without supplemental oxygen, since hypoxia may aggravate PAH. Indications for supplemental oxygen are otherwise limited to profoundly hypoxaemic patients with demonstrated saturation improvement under oxygen. Anticoagulation is indicated and titrated for an international normalised ratio (INR) between 2 and 3. Diuretics are given if oedema is present and adapted to prevent an excessive decrease in right ventricular preloads, as monitored by echocardiography. Inotropic therapy with cardiac glycosides may be considered in the presence of excessive tachycardia (more than 110–120 beats/minute). Inotropic therapy with intravenous dobutamine must be instituted in an intensive care setting to deal with episodes of right heart failure, and with dopamine or if necessary norepinephrine when systemic blood pressure becomes too low.

One subgroup of patients with PPH clearly benefits from calcium channel blockers. In the initial study of Rich [5] the "calcium antagonist responders" treated with high-dose calcium antagonists had a considerably improved prognosis compared with non-responders. Recently it has been reported that the extent of vasodilatation possible with calcium antagonists can be predicted by observing the response to inhaled NO [6, 7]. This makes it possible to avoid lengthy and dangerous testing with increasing doses of calcium antagonists. Inhaled NO is then given during catheterisation and, in the event of a major fall (more than 30%) in pulmonary resistance to below 800 dyn.s.cm^{-5}, high-dose therapy with calcium channel blockers is indicated.

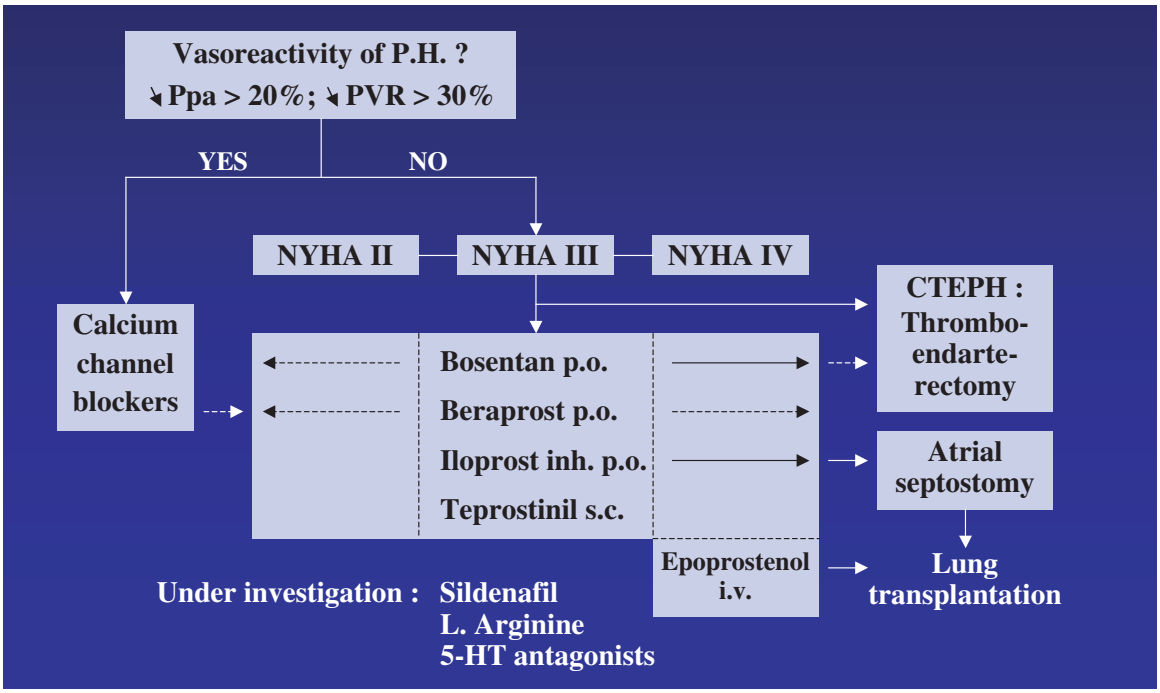

Figure 2

Treatment of pulmonary hypertension. Abbreviations: PH: pulmonary hypertension; Ppa: pulmonary artery pressure; PVR: pulmonary vascular resistance; p.o.: per os; s.c.: subcutaneous; CTEPH: chronic thromboembolic pulmonary hypertension; 5-HT: serotonin.

New therapies in PAH

A better understanding of the pathogenesis of PAH and PPH has changed the focus of drug treatment from purely chronic vasodilator therapy to the evaluation of agents which may reverse the vasoproliferative effects and produce regression of pulmonary vascular hypertrophy and remodelling.

Prostacyclins

Prostacyclin I_2 (PGI_2) is known as the most potent pulmonary vasodilator, exerting its effect through activation of adenylate cyclase. It has also been shown to inhibit platelet aggregation and smooth muscle proliferation. Epoprostenol was the first preparation proposed for intravenous use. Because of its short half-life (3–5 minutes), it must be administered continuously. Since its first long-term use in patients with PPH, reported by Higenbottam [8], it has been shown to be life-saving. After several reports in 1996, a controlled trial over 12 weeks reported a significant improvement in physical capacity and prognosis compared with the control group [9]. The FDA approved this substance in 1995 for use in the therapy of PPH of NYHA class III and IV. Shortly afterwards the substance was also approved in the USA for the treatment of patients with collagen vascular diseases and PAH [10]. Other favourable reports have led to the use of this therapy in various associated forms of pulmonary arterial hypertension such as HIV [11], cirrhosis of the liver [12] and Eisenmenger's syndrome [13].

There is no general agreement regarding the practical administration of PGI_2 intravenously. While in the USA the dosage is regularly increased to induce some side effects, in the UK there is a tendency to wait with a dose until worsening of the clinical condition. The stable analogue iloprost is also used for continuous infusion as an alternative to epoprostenol which offers considerable practical advantages (chemical stability, longer half-life).

Major side effects are local infections sometimes accompanied by sepsis, pain in the lower extremities or Sudeck's syndrome. Less serious side effects such as headache, flushing, diarrhoea, jaw pain and flatulence are very frequent.

Treprostinil is a stable tricyclic benzidine analogue of prostacyclin with 30–80 minutes' half-life, given intravenously or subcutaneously. It has been used subcutaneously in a large study of patients with PPH, PAH-related congenital heart disease and connective tissue disease.

It brought about a significant improvement in exercise capacity, functional class, haemodynamics and quality of life over 12 weeks. Improvement in exercise capacity was greater in the sicker patients and was dose-related but independent of disease aetiology [14]. Long-term improvement of haemodynamics and functionality was observed at 12 months' follow-up. Subcutaneous catheters and microinfusion pumps were used. The most common side effect attributed to treprostinil was dose-limiting pain and redness at the infusion site (85%), leading to premature discontinuation of the drug in 8% of patients.

Inhaled iloprost selectively dilates the pulmonary vessels in the ventilated areas of the lung. A single inhalation of iloprost has been shown to induce vasodilatation lasting 60–120 minutes. Several uncontrolled studies in various forms of PAH showed a long-term functional and haemodynamic improvement with no apparent tolerance. A long-term randomised, placebo controlled 12-week study on PPH, PAH related to connective tissue disease and chronic thromboembolic pulmonary hypertension has recently been conducted. At 12 weeks again, a small but significant improvement was recorded in the six-minute walk test, Mahler Dyspnoea Transition Index and NYHA class, with improvement of haemodynamic variables and no indication of tachyphylaxis. Side effects were aggravated cough, headache, flush and jaw pain. The major limitation was the repetitive inhalation – 6–9 times daily [15] – required.

Oral beraprost is the first orally active prostacyclin analogue with a half-life of 35–40 minutes after a single oral administration. A recent large-scale study has confirmed its efficacy in regard to several clinical criteria, but with no improvement in haemodynamics or NYHA functional class. This may have been related to side effects during the titration period, including nausea and diarrhoea [16].

Anti-endothelins

Endothelin 1 (ET-1) is a potent vasoconstrictor and pro-proliferative substance. Increased expression of ET-1 in vascular endothelial cells and increased levels of plasma ET-1 have been demonstrated in patients with PPH.

Bosentan, an orally active dual receptor antagonist, has been evaluated in a large randomised 16-week trial with NYHA class III and IV PPH and PAH related connective tissue disease [17]. Bosentan increased exercise capacity, delayed time to clinical worsening and improved the Borg dyspnoea score. A reversible dose-related increase in liver enzymes was noted in about 15% of the patients and necessitated medication ending in 4% of the highest dose treatment group (250 mg/bd). A new multidrug approach combining epoprostenol and bosentan is currently under investigation.

Phosphodiesterase inhibitors

Phosphodiesterases are a superfamily of enzymes which inactivate cyclic adenosine monophosphate and cyclic guanosine monophosphate, the second messenger of prostacyclin and nitric oxide.

Inhibition of phosphodiesterases may augment and prolong prostanoid and nitric oxide-re-

lated vascular effects. The novel selective phosphodiesterase-5 inhibitor, sildenafil, has been approved for treatment in erectile dysfunction. Sildenafil causes only very minor systemic haemodynamic effects in healthy humans. Sildenafil was recently shown to be a potent pulmonary vasodilator which acted synergistically with inhaled iloprost in 30 patients with PPH and PAH related to connective tissue disease and chronic thromboembolic disease [18]. However, long-term controlled clinical trials are needed before their use in the management of PAH can be advocated.

L-arginine

L-arginine is the substrate used by our metabolism to generate NO. A small trial over a week has shown a slight improvement in PAPm of 9% and in PVR of 16% in 19 patients with PAH tested orally with L-arginine [19]. Here also, long-term controlled trials are needed to rule out potential long- term side effects related to toxic NO radicals.

Serotonin inhibitors

Serotonin (5-HT) has been implicated in the pathogenesis of PAH, particularly in patients exposed to anorexigens working as serotonin reuptake inhibitors. It acts directly on cell receptors to induce contraction, but can also stimulate smooth muscle cell proliferation. Selective pulmonary serotonin receptor antagonists reduce PAH in rats. Likewise, serotonin transporter inhibitors such as fluoxetin are capable of abolishing completely the serotonin-induced growth of pulmonary artery smooth muscle cells [20]. A fluoxetin phase II pilot study is planned to start soon.

Atrial septostomy

Atrial septostomy (AS) has long been used as a palliative procedure for certain congenital cardiac anomalies in children, and has been extended to PPH only recently. The goal is to decrease right ventricle afterload and increase left ventricle preload. Improved filling of the left ventricle will improve cardiac output.

The drop in systemic arterial oxygen saturation induced by right-left shunting will be compensated by increased cardiac output and systemic oxygen transport will increase. The current indications for AS are recurrent syncopal episodes or severe ascites, and clinical deterioration despite maximum drug treatment. In a review of 62 cases Rothman et al. reported mortality of 15%, and long-term improvement was reported in 70% of the patients with resolution of ascites, oedema, and syncopal episodes [21].

Transplantation

Historically, heart-lung transplantation was the first and only procedure in these patients. Many authors reserved this procedure for patients with special indications, such as Eisenmenger's syndrome caused by complex congenital heart disease. Bilateral lung transplantation is currently considered the procedure of choice by most centres, also compared with unilateral lung transplant. It is indeed easier to manage, in the immediate post-operative period, with fewer ventilation/perfusion mismatches, and it enables more marginal donors' lung to be utilised with better overall pulmonary function. However, the perioperative risk remains the highest amongst all lung transplant recipients in the NIH registry. Regarding the timing of transplant, most centres choose it if patients with NYHA class III and IV fail to benefit from a 3-months course of vasodilator therapy, since improvement in NYHA to class II and a decrease in PVR of 30% has been associated with 5-year survival of 90%, versus approx. 0% survival in patients showing no such improvement on epoprostenol (ref. Sitbon JACC, in press).

Some centres use haemodynamic criteria for listing, such as right atrial pressure of more than 15 mm Hg, PVR of 4–15 Wood units, mixed oxygen saturation of less than 63% or a cardiac index of less than 2.1 l/min/m^2. A six-minute walking test of more than 332 meters is associated with a good prognosis and this simple exercise test is both reproducible and correlates reasonably well with the haemodynamics [22]. One important outstanding issue is the potential delay on the waiting list for patients with disease refractory to the new drug therapies.

Thromboembolectomy

Chronic thromboembolic pulmonary disease can be diagnosed only six months after acute pulmonary embolism effectively treated by anticoagulation, since in 20% of patients 40% of the vascular bed is still occluded beyond the third month of anticoagulation following an acute event. However, most patients are detected in the course of investigating progressive dyspnoea of unknown aetiology.

If pulmonary radioisotope scan is the most sensitive tool for CTEPH diagnosis, selective pulmonary angiography is still the examination of choice, compared to CT-scan acquisitions, in delineating the vascular obstruction.

The place of drug therapy, apart from anticoagulation, is not yet well established. Prostacyclins have been used with uneven results from patient to patient. Thromboendarterectomy is, in the long term, more successful than transplantation. Well-trained centres show 80% 5-year survival compared to 30% survival for conservative treatment in patients with a mean PAP of 45–50 mm Hg (fig. 3) [23].

Thromboendarterectomy is performed by angioscopy during circulatory arrest, with a body temperature reduced below 30 °C. This procedure involves 6–8% mortality in expert centres [4], and initial cases in which it has been performed successfully have been reported from Zurich, Lausanne and Geneva.

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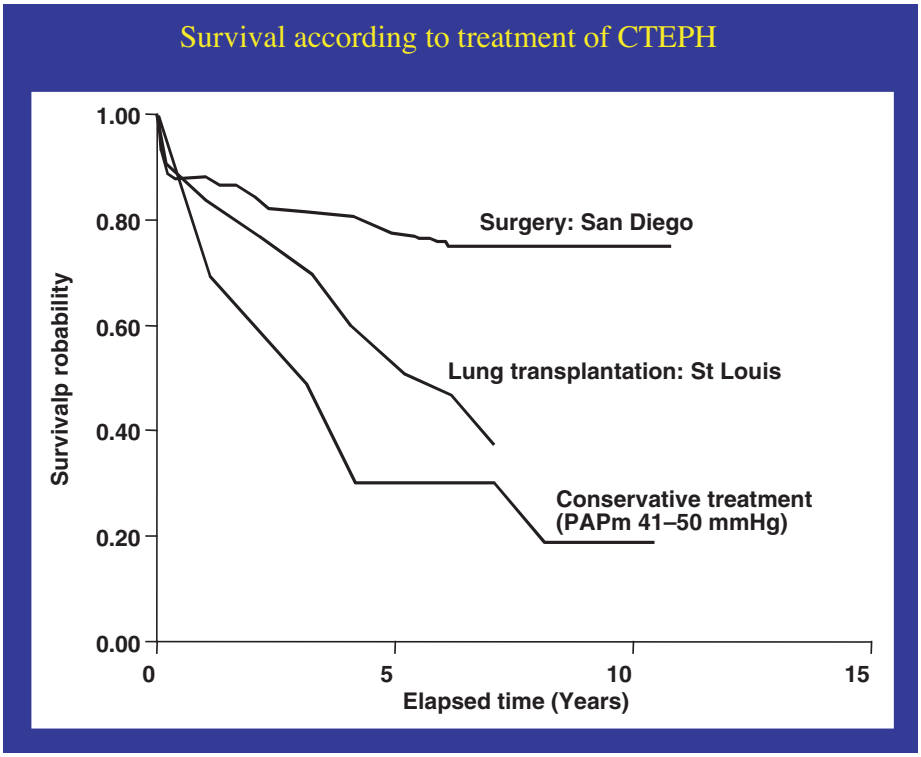

Figure 3

Survival with chronic thromboembolic disease. Historical survival of patients with severe pulmonary hypertension is compared with survivals recently published after transplantation or thrombo-embolectomy.

References

1 Heath D. The pathology of pulmonary hypertension. Eur Respir Rev 1993;3:555–8.
2 Humbert M, Nunes H, Sitbon O, Parent F, Herve P, Simmoneau G. Risk factors for pulmonary arterial hypertension. Clin Chest Med 2001;22(3):459–75.
3 Lee P, Langevitz P, Alderdice CA, Aubrey M, Baer PA, Baron M, et al. Mortality in systemic sclerosis (scleroderma). Q J Med 1992;82:139–48.
4 Fedullo P, Auger WR, Channick RN, Kerr KM, Rubin LJ. Chronic thromboembolic pulmonary hypertension. Clin Chest Med 2001;22(3):561–81.
5 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76–81.
6 Ricciardi MJ, Knight BP, Martinez FJ, Rubenfire M. A safe and effective agent for predicting response to nifedipine. J Am Coll Cardiol 1998;32:1068–73.
7 Sitbon O, Brenot F, Denjean A, Bergeron A, Parent F, Azarian R, et al. Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension. A J Respir Crit Care 1995; 151:384–9.
8 Higenbottam T, Wheeldon D, Wells F, Wallwork J. Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). Lancet 1984;1:1046–7.

9 Barts RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296–301.

10 Allen SW, Chatfield BA, Koppenhafer SA, Schaffer MS, Wolfe RR, Abman SH. Circulating immunoreactive endothelin-1 in children with pulmonary hypertension. Am Rev Respir Dis 1993;148:519–22.

11 Petipretz P, Brenot F, Azarian R, Parent F, Rain B, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection. Circulation 1994;89:2722–7.

12 Kuo PC, Plotkin JS, Gaine S, Schroeder RA, Rustgi VK, et al. Portopulmonary hypertension and the liver transplant candidate. Transplantation 1999;67(8):1087–93.

13 Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation 1999;99:1858–65.

14 Simonneau G, Barst R, Galie N, et al. Continuous subcutaneous infusion of Treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2002;165:800–4.

15 Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, et al. Inhaled Iloprost for severe pulmonary hypertension. N Engl J Med 2002;347:322–9.

16 Galie N, Humbert M, Vachery JL, Vizza CD, Kneussl M, Manes A, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol 2002;39:1496–502.

17 Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896–903.

18 Ghofrani H, Wiedermann R, Rose F, Olschewski H, Schermuly R, Weissmann N, et al. Combination therapy with oral Sildenafil and inhaled Iloprost for severe pulmonary hypertension. Ann Intern Med 2002;136:515–22.

19 Nagaya N, Uematsu M, Oya H, Sato N, Sakamaki F, Kyotani S, et al. Short-term oral administration of L-Arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. Am J Respir Crit Care Med 2001; 163:887–91.

20 Eddahibi S, Humbert M, Fadel E, Raffestin B, Darmon M, Capron F, et al. Hyperplasia of pulmonary artery smooth muscle cells is causally related to overexpression of the serotonin transporter in primary pulmonary hypertension. Chest 2002; 121(Suppl.3):97S–98S.

21 Rothman A, Sklanski MS, Lucas VW, Kashani IA, Shaughnessy RD, Channick RN, et al. Atrial septostomy as a bridge to lung transplantation in patients with severe pulmonary hypertension. Am J Cardiol 1999;84:682–6.

22 Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Am J Respir Crit Care Med 2000;161:487–92.

23 Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Chest 1982;81:151–8.

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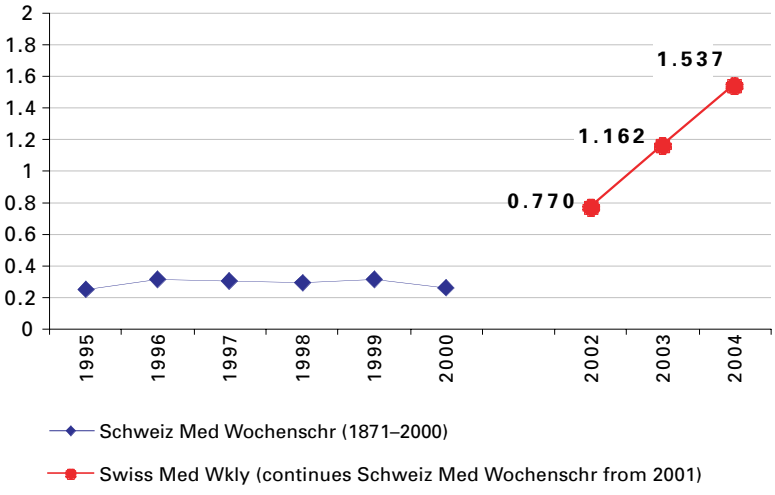

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