RECOMMENDATIONS

Management of pulmonary hypertension

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Pulmonary arterial hypertension (PAH) is a potentially lethal disease mainly affecting young females. Although the precise mechanism of PAH is unknown, the past decade has seen the advent of many new classes of drugs with improvement in the overall prognosis of the disease. Unfortunately the therapeutic options for PAH in South Africa are severely limited. The Working Group on PAH is a joint effort by the South African Heart Association and the South African Thoracic Society tasked with improving the recognition and management of patients with PAH. This article provides a brief summary of the disease and the recommendations of the first meeting of the Working Group.

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Lack of awareness of pulmonary arterial hypertension (PAH) on the part of both patients and caregivers, and failure of public and private funders to provide resources for the management of the disease, have meant that patients have little or no access to any of the treatments approved by international guidelines.

Recognising the plight of patients with PAH, interested individuals were invited to participate in the First Joint South African Heart Association (SA Heart)/South African Thoracic Society (SATS) Working Group Meeting, held at O R Tambo Airport, Johannesburg, South Africa (SA), on 23 May 2014. The meeting received official recognition from both SA Heart and SATS. The members of the Working Group Writing Committee of SA Heart/SATS wrote this article and are listed above as authors.

1. Format of the joint Working Group Meeting

The meeting was co-chaired by Prof. M R Essop (cardiologist) and Dr P Williams (pulmonologist). Two international experts representing Europe and North America participated in the lectures and discussions. Prof. N Galie from Bologna University, Italy, is chairman of the European Guideline Committee on PAH and guest editor of the *Journal of the American College of Cardiology* supplement on the Proceedings of the 5th World Society of Pulmonary Hypertension. Prof. D Badesch from the Division of Pulmonary Sciences, Critical Care Medicine and Cardiology, University of Colorado, USA, is an author of the American Guidelines on PAH. Both have published extensively and have been senior investigators in pivotal trials on PAH. In addition, representatives of patient interest groups and medical funders were invited to give their perspective.

The Joint SA Heart/SATS Working Group Committee concluded that local medical expertise should remain current and not lag behind other developing nations. While PAH remains an uncommon disease, it affects mainly younger people and has a prognosis worse than those of most malignancies, and therefore merits treatment. Although treatment is expensive, it is probably in proportion to that of other diseases with a poor prognosis. The prognosis of PAH is steadily improving as a result of advances in medical therapy, and SA patients should have access to these. In this regard, there is an urgent need for introduction and registration of at least one drug from each of the four major therapeutic classes.

Consequently, the Committee unanimously resolved to: (*i*) increase awareness of PAH, promoting education and research and establishing databases and registries; (*ii*) provisionally adopt the European Guidelines for PAH[1] as a working document for SA while making amendments pertinent to the practice of medicine in this country; (*iii*) engage with funders to provide essential therapies to patients with PAH; (*iv*) inform the Medicines Control Council of the need to expedite approval of essential therapies and encourage suppliers of such therapies to provide these at an optimal cost given SA's financial constraints; and (*v*) serve as arbitrator when there are conflicting views on how a patient with PAH should be managed best.

2. Pulmonary arterial hypertension

PAH is a disorder of the pulmonary arterioles characterised by endothelial proliferation, fibrointimal hyperplasia and *in situ* thrombosis with progressive obstructive vasculopathy, pulmonary hypertension and eventually right ventricular failure and death. Despite significant progress, there are large gaps in the understanding

of the pathogenic mechanisms and determinants of progression of PAH. The grim prognosis highlights the need for earlier recognition, intensive management, and further clinical and laboratory research.

The recently published classification of PAH, representing consensus of the 5th World Symposium held in Nice, France, in 2013, recognises five groups of pulmonary hypertension.[2] The term PAH is reserved specifically for group 1 (Table 1).

2.1 Aetiology of PAH

About 20% of patients with idiopathic PAH and 80% of those with heritable PAH have a mutation of the bone morphogenetic protein receptor (*BMPR2*) gene, a member of the super-family of TGF proteins. Although the exact mechanism by which *BMPR2* mutations result in the PAH phenotype is unclear, inhibition of apoptosis with clonal proliferation of endothelial cells is thought to play a role.

Autoimmune diseases most frequently associated with PAH include scleroderma and lupus erythematosus. Not infrequently, idiopathic PAH may be associated with low positive titres of autoantibodies, making it difficult to distinguish it from PAH secondary to autoimmune disease. Consultation with a rheumatologist in these cases is essential.

Table 1. The Nice classification of pulmonary hypertension[5]

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.3 Drug- and toxin-induced PAH
   - 1.4 PAH associated with:
     - 1.4.1 Autoimmune disease
     - 1.4.2 HIV
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart disease
     - 1.4.5 Schistomiasis
   - 1' Pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis
   - 1" Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow obstruction and familial cardiomyopathies
3. Pulmonary hypertension due to lung diseases 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 lung diseases
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disease, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders
   - 5.4 Others: tumour obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

PAH occurs in 0.5% of patients with HIV and is associated with a poor prognosis.

2.2 Epidemiology of PAH

Ascertaining the true incidence of PAH is difficult, as the onset is insidious and the diagnosis challenging. Furthermore, symptoms and signs of right ventricular dysfunction and reduction in cardiac output occur when the disease is already advanced. The estimated prevalence of PAH in the developed world ranges from 5 to 15 per million adults.[3] There is no reason to believe that the prevalence in SA is any different. With the huge burden of HIV, a cause of PAH indistinguishable from the idiopathic type, it is likely that there is a large undiagnosed population with this disease.[4]

2.3 Diagnosis of PAH

A diagnostic algorithm is shown in Fig. 1.

Symptoms of PAH include dyspnoea, fatigue, chest pain, syncope and ankle swelling. Clinical signs lack sensitivity, but in advanced disease include tachycardia, left parasternal heave, loud pulmonary component of the second heart sound, murmurs of tricuspid or pulmonary regurgitation, and evidence of systemic venous congestion. Electrocardiography characteristically shows right axis deviation and right ventricular hypertrophy. The proximal pulmonary arteries are dilated on the chest radiograph, with attenuation of distal vessels together with evidence of right atrial and ventricular enlargement. Echocardiography remains the most useful investigation, allowing measurement of pulmonary artery systolic pressure, exclusion of left heart disease and congenital shunts, and assessment of right ventricular function. Cardiac catheterisation is the gold standard for diagnosis of PAH and in addition allows assessment of disease severity, exclusion of category 2 pulmonary hypertension caused by left heart disease, and testing of pulmonary vasoreactivity.

2.4 Treatment of PAH

PAH patients with vasoreactivity are treated with high-dose calcium channel blockers such as nifedipine. Four classes of drugs are available for non-reactive patients, including the prostacyclin agonists, endothelin receptor blockers, PDE5 inhibitors, and most recently agents that increase availability of cyclic guanosine monophosphate. Combinations of these various classes of drugs seem to be the way forward, but the optimal permutation is still the subject of ongoing research. Other treatments include diuretics, digitalis and

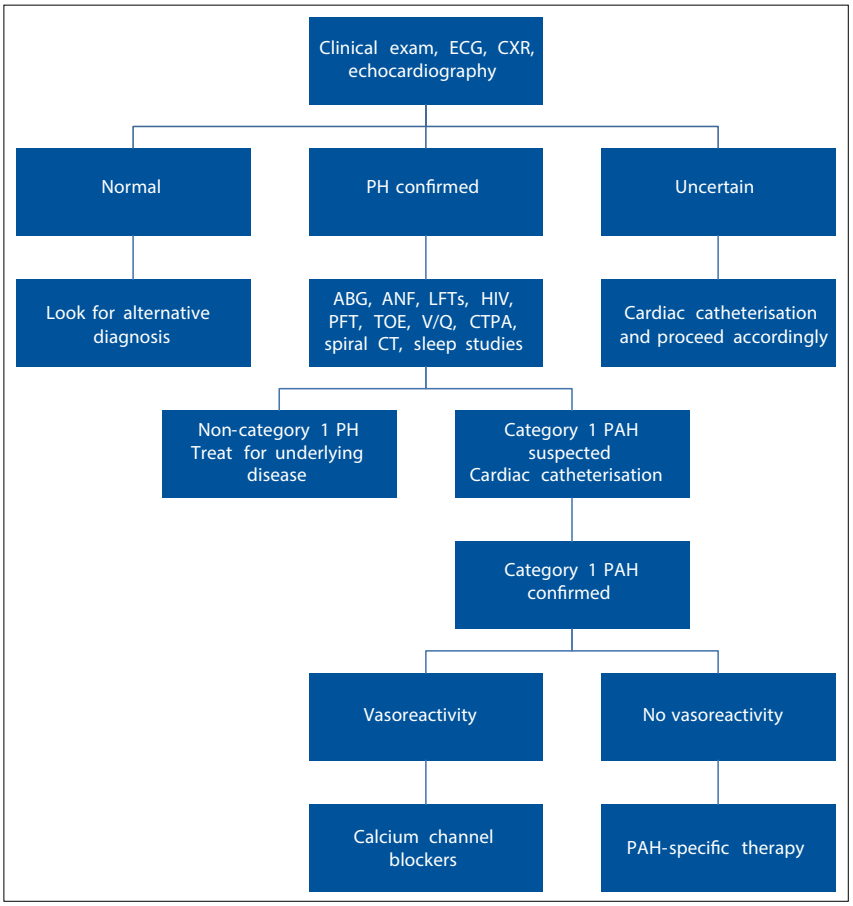

Fig. 1. Diagnostic algorithm for patients with suspected pulmonary hypertension. (ECG = electrocardiography; CXR = chest radiograph; PH = pulmonary hypertension; ABG = arterial blood gas; ANF = antinuclear factor; LFTs = liver function tests; PFT = pulmonary function tests; TOE = transoesophageal echocardiography; V/Q = ventilation-perfusion scan; CTPA = CT pulmonary angiogram; CT = computed tomography.)

ambulatory oxygen with sequential lung transplantation for class 4 patients resistant to all pharmacological agents.

2.5 Prognosis of PAH

Modern targeted pharmacological therapy for PAH has reduced mortality by about 40%. Nevertheless, survival is 58% at 5 years, indicating a need for more effective disease-modifying therapies.

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