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Making a diagnosis in PAH

J.S.R. Gibbs

ABSTRACT: Poor survival among patients with untreated pulmonary arterial hypertension (PAH) means that timely and accurate diagnosis is of paramount importance. However, the nonspecific nature of PAH symptoms, which include breathlessness and fatigue, make PAH a considerable diagnostic challenge. As a result, many patients are passed among different physicians and are only correctly diagnosed at relatively advanced stages of disease, when they are already significantly compromised and are finding even the basic activities of daily living difficult. Over recent years, the advent of targeted therapies has changed PAH from a rapidly fatal disease to a serious but treatable condition. This makes the need for obtaining a rapid and accurate diagnosis all the more urgent.

The diagnostic process itself requires a reason for clinical suspicion and a series of investigations that are intended to confirm the diagnosis, to establish the cause of pulmonary hypertension and to determine the severity. The present paper reviews the routine investigations available to the physician to diagnose PAH, including electrocardiography, chest radiography, transthoracic Doppler echocardiography and right heart catheterisation, and highlights some of the diagnostic pitfalls encountered *en route* to an accurate diagnosis of PAH.

KEYWORDS: Diagnosis, pulmonary arterial hypertension

Significant research over the last few years has turned pulmonary arterial hypertension (PAH) from a progressive fatal disease to a serious but treatable condition. To capitalise fully on the recent advances made in the treatment of PAH, accurate diagnosis is critical. Due to the nonspecific nature of the symptoms of PAH, the condition remains a major diagnostic challenge.

For patients with untreated idiopathic PAH (iPAH), the historical median survival after diagnosis is 2.8 yrs [1], whilst for patients with PAH associated with systemic sclerosis (SSc), this figure falls to only 1 yr [2, 3]. Despite the shortcomings of historical data, the relatively poor prognosis and predicted survival (fig. 1) lend urgency to the speed of accurate diagnosis so that targeted therapy can be initiated promptly.

The symptoms, which include breathlessness, fatigue, angina, syncope, cough, fluid retention and exercise-induced nausea and vomiting, are nonspecific. The diagnosis is often delayed for $\geqslant$2 yrs [4, 5], with too many patients being diagnosed only in an advanced stage of the disease [5]. In the UK, 40% of PAH patients will have seen four or more doctors, 50% will have waited >1 yr to be diagnosed, and 30% will wait >2 yrs to be given the correct diagnosis [6]. Physician awareness needs to improve so that delays in diagnosis can be reduced.

Compounding this, the rarity of PAH, which is estimated to affect 30–50 people per million [7], means that many other conditions, such as asthma, chronic obstructive pulmonary disease, chronic heart failure and even lack of fitness are likely to be considered before PAH. Consequently, most PAH patients present relatively late on in the course of their disease, in World Health Organization functional classes III or IV. At this stage patients are already significantly compromised and are finding even the basic activities of daily living difficult.

DIAGNOSING PAH

When making a diagnosis it is important to remember that PAH occurs at any age. The recently defined clinical classification of pulmonary hypertension (PH), agreed in Venice in 2003 [8], is important because it is based on the aetiology of disease according to similar pathology in similar parts of the circulation.

PAH represents one of the five categories of PH in the clinical classification (table 1). PAH is further subdivided into three main subgroups: iPAH, familial PAH and PAH associated with other conditions, such as connective tissue disease. Determining the precise aetiology is critical; for example, patients with left heart disease may

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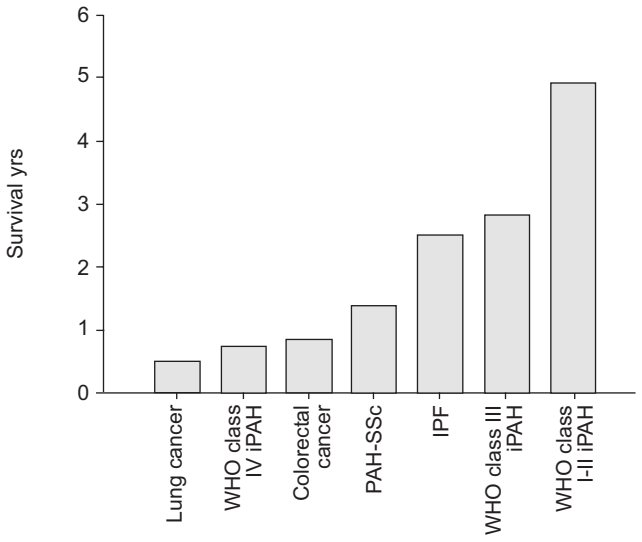

FIGURE 1. Median survival of untreated idiopathic pulmonary arterial hypertension (iPAH) and pulmonary arterial hypertension associated with systemic sclerosis (PAH-SSc) patients in different World Health Organization (WHO) functional classes compared with other chronic conditions. IPF: idiopathic pulmonary fibrosis.

deteriorate if given medications that are targeted at PAH. For patients with chronic thromboembolic PH, pulmonary endarterectomy should be offered to those with proximal disease.

The diagnostic approach to PAH has been described in the European Society for Cardiology guidelines [9]. The diagnostic process itself requires a reason for clinical suspicion and a series of investigations that are intended to confirm the diagnosis, to establish the cause of PH, and to determine its severity.

Routine investigations include ECG, chest radiography and transthoracic Doppler echocardiography (TTE). A combination of ECG and chest radiography will afford a diagnosis of PH in 80–90% of cases. Doppler echocardiography is the investigation of choice for patients considered at risk of developing PAH, such as those with a family history or SSc [10, 11]. Doppler echocardiography uses the peak tricuspid regurgitant (TR) jet velocity, which measures the pressure difference between the right ventricle and the right atrium, to estimate systolic pulmonary arterial pressure (systolic P_{pa}) using the modified Bernoulli equation [12]. This requires measurement of right atrial pressure. Right atrial pressure is estimated from the diameter of the inferior vena cava and the response to sharp inspiration or ''sniff''. Mild PAH defined by echocardiography is an estimated systolic P_{pa} of 36–50 mmHg, corresponding to a peak TR jet velocity in the region of 2.8–3.4 $m \cdot s^{-1}$ with normal right atrial pressure.

In addition to noting the peak TR jet velocity, it is important to look for corroborative evidence of PH on the echocardiogram. This includes enlargement of the right atrium and right ventricle, interventricular septal deviation to the left in both systole and diastole, pericardial effusion and mid-systolic pulmonary valve closure. In patients with end-stage disease, the estimated systolic P_{pa} may underestimate the severity of their disease. In these patients, a failing right ventricle will result in an elevated right atrial pressure, resulting in a reduced pressure gradient between the right ventricle and right atrium. Successful treatment in such patients will improve right ventricular function. As a consequence, the pressure difference will increase, associated with a rise in peak TR velocity.

Ventilation/perfusion lung scanning, high-resolution and contrast computed tomography of the chest, lung function, abdominal ultrasound and cardiac catheterisation with vasoreactivity testing are used to refine the diagnosis.

Invasive right heart catheterisation (RHC) is safe in patients with PAH and is the only way to make a definitive diagnosis. Using RHC, PAH is defined as a mean pulmonary arterial pressure ($\bar{P}_{pa}$) of >25 mmHg at rest or >30 mmHg during exercise with a pulmonary capillary wedge pressure of $\leqslant 15$ mmHg and pulmonary vascular resistance of >3 Wood units. The validity of considering RHC as the only definitive means of diagnosing PAH is apparent by plotting the estimated systolic P_{pa} based on measured peak TR jet velocity against the measured $\bar{P}_{pa}$ according to RHC in patients with SSc (fig. 2) [13]. Figure 2 demonstrates that not all patients with PAH defined according to RHC have corresponding systolic P_{pa} values that would be considered indicative of PAH by echocardiography. Consequently, both false positives and false negatives are possible and if there is any doubt a confirmatory RHC should be undertaken.

COMMON DIAGNOSTIC PITFALLS

If a patient is clinically stable and has PH but is in atrial fibrillation, it is unlikely that iPAH is the diagnosis. A more likely diagnosis is heart disease or thromboembolic disease. The reason for this is that patients with iPAH do not tolerate the loss of atrial transport that occurs during atrial fibrillation. The sinus beat that contracts the atrium is responsible for 25–30% of the cardiac output. Atrial fibrillation will usually result in rapid deterioration and death if restoration of sinus rhythm is delayed in iPAH.

It is important to look at left atrial size on echocardiography (fig. 3). Some patients with left heart disease in sinus rhythm will have ''good'' systolic left ventricular function according to echocardiography. This does not exclude diastolic dysfunction, which can be assessed by left atrial size and Doppler measures of left ventricular filling.

Another cause of atrial enlargement in sinus rhythm is atrial septal defect (ASD). ASDs are easily missed on TTE but can be picked up with contrast echocardiography and careful imaging in a subcostal view. As the level of PAH increases and the right heart starts to fail, movement of blood across the defect is reduced and it becomes harder to find the defect. Remarkably, at >50 yrs of age the $\bar{P}_{pa}$ (in mmHg) of a patient with an ASD is half the age of the patient (in yrs). All patients presenting with mild PAH and ASD should be offered defect closure.

Another pitfall is pulmonary veno-occlusive disease (PVOD). Treatment with vasodilators in such patients may result in the rapid onset of pulmonary oedema and death. Whereas high-resolution computed tomography (HRCT) of the lungs in

TABLE 1 Venice classification of pulmonary hypertension (PH)

Group I: PAH
Idiopathic PAH
Familial PAH
PAH associated with:
Connective tissue disease
Congenital systemic-to-pulmonary shunts
Portal hypertension
HIV infection
Drugs and toxins
Other (*e.g.* thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
PAH associated with significant venous or capillary involvement:
Pulmonary veno-occlusive disease
Pulmonary capillary haemangiomatosis
Persistent PH of the newborn
Group II: PH associated with left heart diseases
Group III: PH associated with respiratory diseases and/or hypoxaemia (including COPD)
Group IV: PH due to chronic thrombotic and/or embolic disease
Group V: Miscellaneous group
e.g. sarcoidosis, histiocytosis X and lymphangiomatosis

PAH: pulmonary arterial hypertension; COPD: chronic obstructive pulmonary disease.

iPAH looks relatively normal, in a patient with PVOD HRCT is likely to show interlobular septal thickening and a ground-glass appearance (fig. 4). These findings are consistent with pulmonary venous hypertension, which, in the absence of left heart disease, makes the likely diagnosis PVOD.

In proximal thromboembolic disease, the presence of webs in pulmonary arteries is usually diagnostic. In distal thromboembolic disease, computed tomography pulmonary angiography may show no evidence of thromboembolic disease. Only ventilation/perfusion scanning to reveal mismatched ventilation/perfusion defects will afford the diagnosis in this situation.

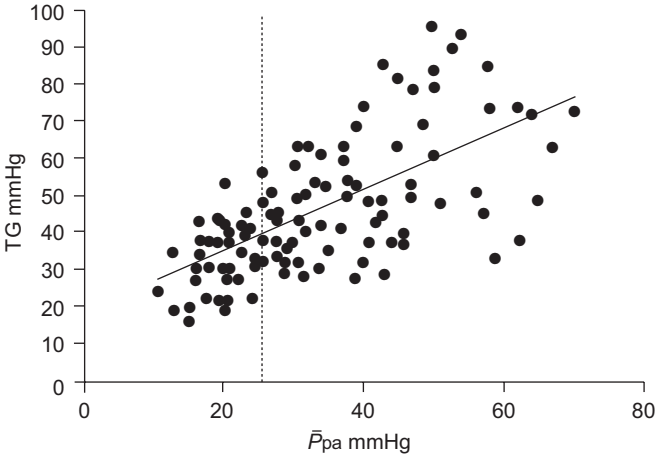

FIGURE 2. Correlation of tricuspid regurgitant (TR) jet velocity with measured mean pulmonary arterial pressure ($\bar{P}_{pa}$) by right heart catheterisation in patients with systemic sclerosis. Plot of the systolic pulmonary arterial pressure estimated from echocardiographic measurement of the TR jet velocity (tricuspid gradient (TG)) *versus* the $\bar{P}_{pa}$ measured by right heart catheterisation. ·····: normal $\bar{P}_{pa}$ (25 mmHg). r^2=0.4515. Reproduced from [4] with permission from the publisher.

THE IMPORTANCE OF PATIENT FOLLOW-UP

Following initiation of treatment, it is essential that the patient continues to be monitored vigilantly to evaluate treatment efficacy and tolerability and ensure that appropriate treatment goals are met. This allows treatment to be modified and

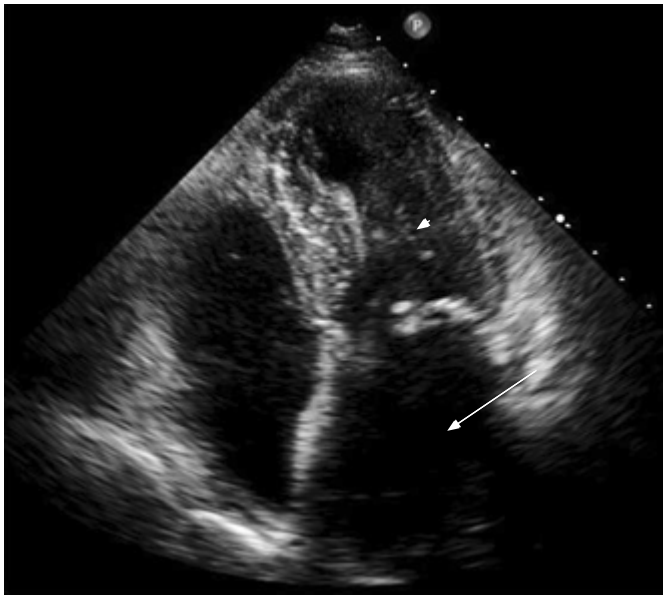

FIGURE 3. Four-chamber view of the heart showing left ventricular hypertrophy and left atrial enlargement in a patient with long-standing systemic hypertension. The patient had pulmonary hypertension caused by diastolic left ventricular dysfunction.

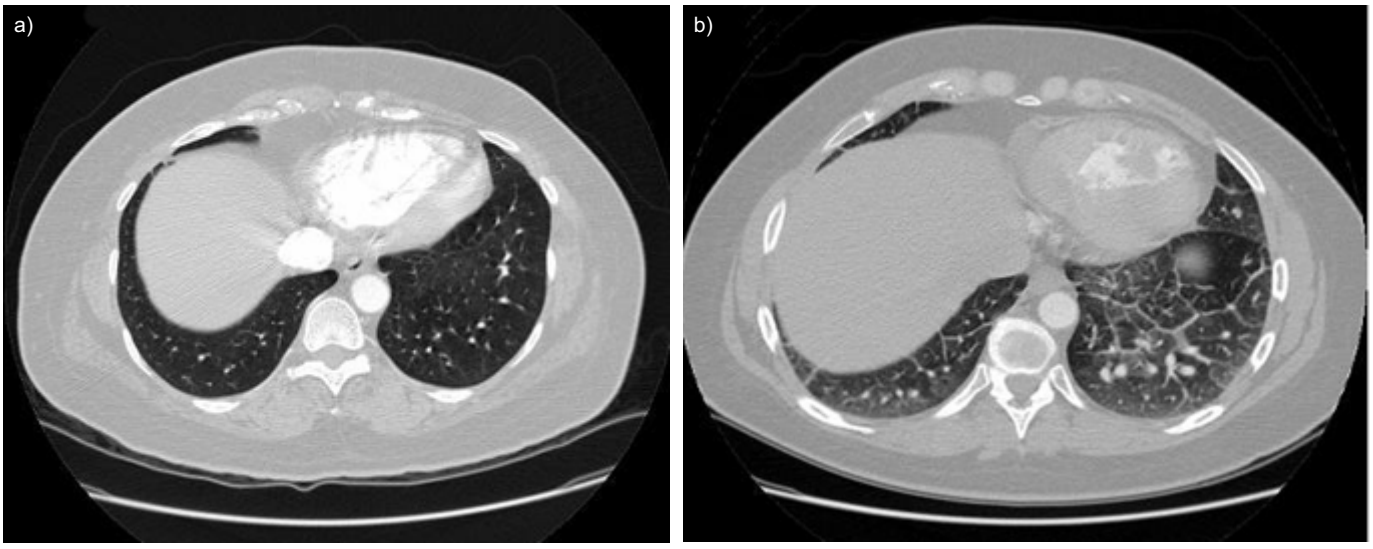

FIGURE 4. High-resolution computed tomography scans of the chest in pulmonary arterial hypertension. a) Normal lung appearances in a patient with idiopathic pulmonary arterial hypertension. b) Lung appearances of pulmonary veno-occlusive disease with interlobular septal thickening against a ground-glass background.

tailored to meet the individual needs of the patient as well as for a quantitative assessment of progress. Symptoms and their severity, physical examination, quality of life measurement and exercise capacity measured by the 6-min walk test (6MWT), should be monitored every 3 months. These are further supported by serial echocardiography, cardiac catheterisation, biomarkers and cardiac magnetic resonance imaging.

The 6MWT in particular has been shown to correlate with survival. One study showed that after 3 months of treatment, PAH patients who could walk ⩾380 m had a significantly longer cumulative survival compared with those who walked <380 m (p=0.0005; fig. 5) [14].

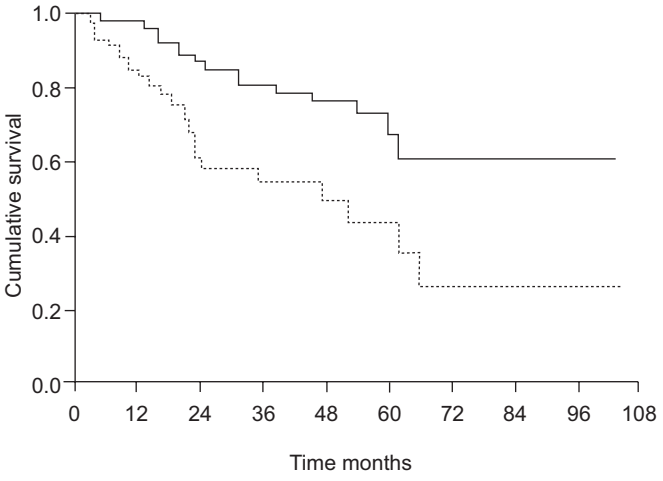

FIGURE 5. Correlation of 6-min walking distance (6MWD) with survival after 3 months of treatment with epoprostenol. Kaplan–Meier survival estimates of 156 patients with pulmonary arterial hypertension, according to 6MWD performed after 3 months of epoprostenol therapy. Survival rates for patients walking ⩾380 m (——) were 99%, 88% and 81% at 1, 2 and 3 yrs, respectively, compared with values of 86%, 64% and 56% for patients walking <380 m (·····; p=0.0005). Reproduced from [14] with permission from the publisher.

Echocardiography is useful for detecting changes in cardiac structure and function following medical intervention [15]. Doppler-derived measurements have been shown to correlate with symptoms and survival in patients with PH [16] and have been used as a substudy of the Bosentan Randomized Trial of Endothelin Antagonist THErapy (BREATHE-1) study [15].

Novel, noninvasive tools such as measurement of biochemical markers (pro-N-terminal brain natriuretic peptide (BNP) and troponin, for example) offer promising approaches for the assessment of PAH. In addition to being elevated in patients with PAH [17], plasma BNP levels correlate with the degree of right ventricular dysfunction in patients with PH [18, 19].

CONCLUSIONS

The outlook for patients with pulmonary arterial hypertension has improved considerably in recent years with the introduction of diagnostic and treatment guidelines. Owing to the difficulty in obtaining an accurate diagnosis in some patients, and choosing the most appropriate treatment and monitoring strategies, it is recommended that all patients be referred to specialist centres at the time of diagnosis. Continued improvements in disease detection, diagnosis and treatment will offer a better future outlook for patients.

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