Pulmonary hypertension: the importance of correctly diagnosing the cause

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ABSTRACT Pulmonary hypertension (PH) is a complex condition that can occur as a result of a wide range of disorders, including left heart disease, lung disease and chronic pulmonary thromboembolism. Contemporary PH patients are older and frequently have a multitude of comorbidities that may contribute to or simply coincide with their PH. Identifying the cause of PH in these complicated patients can be challenging but is essential, given that the aetiology of the disease has a significant impact on the management options available. In this article, we present two cases that highlight the difficulties involved in obtaining a precise diagnosis of the cause of PH within the setting of multiple comorbidities. The importance of performing a comprehensive, multidimensional diagnostic work-up is demonstrated, in addition to the need to specifically consider cardiopulmonary haemodynamic data in the context of the wider clinical picture. The article also illustrates why achieving an accurate diagnosis is necessary for optimal patient management. This may involve treatment of comorbidities as a priority, which can ameliorate the severity of PH, obviating the need to consider PH-targeted medical treatment.

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Introduction

An accurate and timely diagnosis of pulmonary hypertension (PH) and identification of the specific underlying cause of PH is essential to ensure that patients can be treated as early as possible with interventions that are appropriate for their diagnosis. Many effective PH-targeted therapies are available [1, 2] and when used in patients with appropriate types of PH, predominantly those with World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH), these therapies can lead to significant improvements in functional capacity, quality of life and outcome [1, 2]. As the underlying cause and recommended management approach varies between patients, PH-targeted therapies are not suitable for all PH patients [1, 2]. For example, PH-targeted pharmacotherapies have not been shown to be effective for WHO Group 2 PH (PH due to left heart disease (LHD)) or WHO Group 3 PH (PH due to lung disease and/or hypoxia) [3].

As the appropriate treatment differs between PH patients [1, 2], it is important to correctly identify the cause of PH in each patient. However, obtaining a definitive diagnosis can be difficult due to the increasing age of PH patient populations and the fact that these patients frequently present with significant comorbidities, such as obesity, systemic hypertension, diabetes and underlying respiratory disorders [4, 5].

Editorial comment in *Eur Respir Rev* 2016; 25: 361–363.

Received: Aug 19 2016 | Accepted after revision: Oct 18 2016

Conflict of interest: Disclosures can be found alongside this article at err.ersjournals.com

Provenance: The *European Respiratory Review* received sponsorship from Actelion Pharmaceuticals Ltd, Allschwil, Switzerland, for the publication of these peer-reviewed articles.

This article highlights the challenges associated with identifying the specific cause of PH in patients with significant comorbidities, and the importance of careful integration and interpretation of various multidimensional diagnostic tests in order to achieve this. Two patient cases are presented to illustrate the complexity of making a specific diagnosis of the cause of PH and the importance of achieving an accurate diagnosis in order to appropriately manage the disease.

Case 1

A 57-year-old male with newly identified PH was referred for assessment and treatment by the specialist PH clinic. He complained of a 1-year history of dyspnoea after walking up less than one flight of stairs, fatigue and ankle oedema, but no chest pain or orthopnoea. The patient had long-standing morbid obesity (body mass index (BMI) ~55 kg·m^{-2}), type 2 diabetes mellitus, systemic hypertension and obstructive sleep apnoea syndrome, and had previously been treated for atrial flutter. At the time of assessment, he was treated with two antihypertensive drugs, an antiarrhythmic drug and a diuretic. As shown in table 1, echocardiography indicated a high probability of PH and a normal left ventricular ejection fraction. Pulmonary function tests (PFTs) and blood gas analysis revealed no sign of lung disease. Pulmonary emboli were excluded by nuclear ventilation/perfusion (V'/Q') lung scanning. Functional capacity was maintained, as shown by the 6-min walking distance (table 1). PH was confirmed by right heart catheterisation (RHC) (table 1). Although the pulmonary artery wedge pressure (PAWP) was close to the cut-off point of ⩽15 mmHg commonly accepted to identify pre-capillary pulmonary hypertension (which includes PAH), as opposed to post-capillary pulmonary hypertension (which includes PH-LHD) [1, 2], it was considered unreliable due to the patient's obesity. Therefore, left heart catheterisation (LHC) was performed, which demonstrated an elevated left ventricular end-diastolic pressure (LVEDP) and an elevated diastolic pressure gradient (DPG = diastolic pulmonary arterial pressure (PAP) – LVEDP). This led to a final diagnosis of combined post- and pre-capillary pulmonary hypertension (Cpc-PH) (figure 1), in the context of heart failure with preserved ejection fraction (HFpEF) and obesity. The patient's obesity was subsequently treated successfully by bariatric surgery, which considerably improved his PH.

Case 2

A 37-year-old female was referred to the specialist PH clinic with severe PH and right ventricular (RV) failure. She had recently been admitted to hospital with fatigue, dyspnoea and severe oedema, which had worsened over a period of 6 months. She was a former smoker of half a pack of cigarettes per day for

TABLE 1 Cardiopulmonary and physiological parameters in case 1 at assessment

Parameter	Assessment
6MWD m	470
Echocardiography #	
TRV m·s^{-1}	4.51
RVSP mmHg	91
TAPSE mm	>18
LVEF	Normal
Right heart catheterisation	
Systolic/diastolic PAP mmHg	100/38
Mean PAP mmHg	61
PAWP mmHg	16
DPG mmHg	22
CO L·min^{-1}	8.31
CI L·min^{-1}·m^{-2}	3.2
PVR Wood units	5.45
RAP mmHg	14
S_{vO_2} %	67
Left heart catheterisation	
LVEDP mmHg	19
DPG mmHg	23

6MWD: 6-min walking distance; TRV: tricuspid regurgitation velocity; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; LVEF: left ventricular ejection fraction; PAP: pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; DPG: diastolic pressure gradient; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; RAP: right atrial pressure; S_{vO_2}: mixed venous oxygen saturation; LVEDP: left ventricular end diastolic pressure. #: right ventricular size and right ventricular systolic function were not assessable due to poor imaging quality.

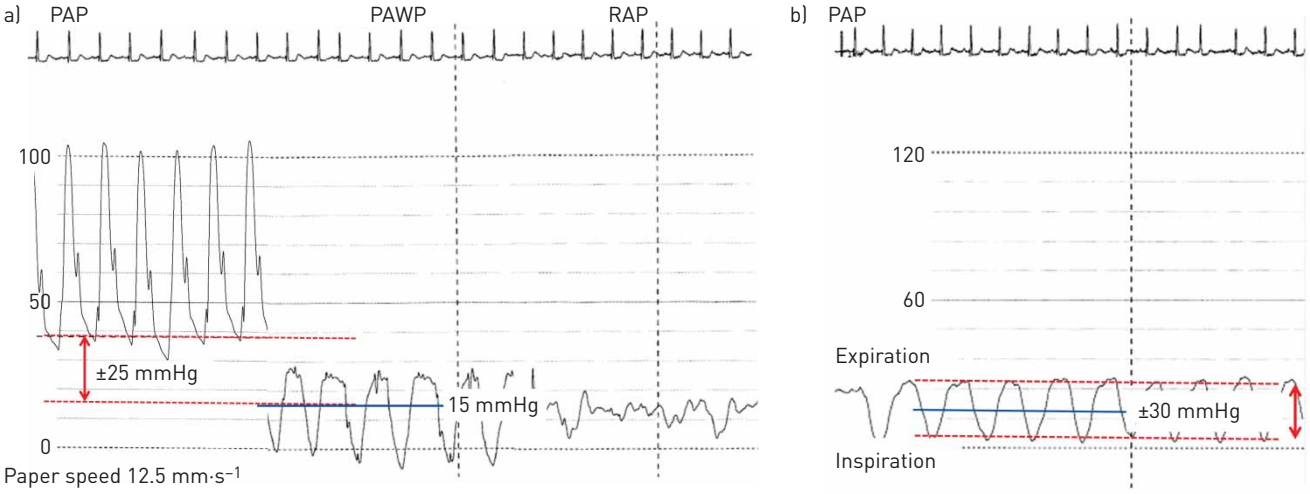

FIGURE 1 Pulmonary artery catheterisation haemodynamic tracings for case 1. a) The increase in pulmonary arterial pressure (PAP) is associated with an increase in the gradient between pulmonary artery diastolic pressure and pulmonary arterial wedge pressure (PAWP) to 25 mmHg. b) Marked respiratory variation in PAWP was observed. RAP: right atrial pressure.

15 years but had no other history of cardiac or respiratory disease and no personal or family history of thromboembolism. On examination, she had severe kyphoscoliosis, moderate–severe peripheral oedema, marked jugular venous pressure elevation and evidence of PH. Echocardiography confirmed severe PH with no evidence of underlying LHD or right–left shunt on contrast bubble study (table 2). Measurement of arterial blood gases revealed chronic, compensated respiratory acidosis and marked hypoxaemia. PFTs indicated mild restrictive lung disease. Nuclear V'/Q' lung scanning demonstrated ventilation heterogeneity due to kyphoscoliosis, with matched small, multifocal nonsegmental perfusion defects, not suggestive of chronic pulmonary emboli. An overnight polysomnogram revealed hypoventilation with rising arterial carbon dioxide tension (P_{aCO_2}) levels and marked hypoxaemia, but no central or obstructive apnoea events. She was diagnosed with chronic respiratory failure due to kyphoscoliosis, exacerbated by nocturnal hypoventilation, and resulting in significant chronic hypoxaemia and severe pre-capillary PH, most likely WHO Group 3 PH due to lung disease and/or hypoxia. She was initiated on continuous noninvasive face-mask ventilation, supplemental oxygen and diuretics. After 2 weeks in hospital, she was transitioned to home and continued on nocturnal noninvasive ventilation. 6 months later, she was markedly improved clinically and had achieved near-normal daytime P_{aCO_2} levels with resolution of hypoxaemia, as well as marked improvement in her PH with no evidence of RV failure.

Discussion

In this article, two cases have been selected to illustrate the complex and challenging approach to making an accurate diagnosis of the cause of PH and the importance of this to ensure appropriate management. The main points that will be considered are: first, multiple potential contributing illnesses and mechanisms should be considered before making a specific diagnosis of the cause of PH; second, comorbidities can complicate the specific diagnosis of PH; third, a multifactorial diagnostic work-up is necessary to correctly determine PH aetiology; and fourth, accurate diagnosis is essential to ensure appropriate management.

Multiple potential causes of PH to consider when making a specific diagnosis of PH

A number of diverse conditions can cause PH and this is illustrated by the clinical classification, which categorises PH into five distinct groups: WHO Group 1 (PAH), WHO Group 2 (PH-LHD), WHO Group 3 (PH due to lung disease and/or hypoxia), WHO Group 4 (chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions) and WHO Group 5 (PH with unclear or multifactorial mechanisms) [1, 2]. Before reaching any specific PH diagnosis in an individual patient, clinicians should consider all potential comorbid conditions that can lead to the development of PH [1, 2].

Obesity is an independent risk factor for PH [6, 7] and may directly contribute to the development of PH [8]. Indeed, it has been estimated that up to 5% of otherwise healthy individuals with a BMI >30 kg·m^{-2} have moderate or severe PH [8]. The mechanism by which PH occurs in obese patients may simply be due to the fact that obese patients are at increased risk of other conditions that can cause PH, including LHD, pulmonary thromboembolism and sleep-disordered breathing [8]. Obesity is particularly common in the USA, Canada and the UK [9–11], and is expected to become more frequent in other developed [9] and

DOI: 10.1183/16000617.0104-2016

TABLE 2 Cardiopulmonary and physiological parameters in case 2 at diagnosis and 6 months following initiation of chronic noninvasive ventilation

Parameter	Baseline	Post-noninvasive ventilation
Echocardiography		
TRV $m \cdot s^{-1}$	4.3	3.3
RVSP mmHg	90	48
RV size	Moderate dilation	Normal
RV systolic function	Moderate dysfunction	Normal
TAPSE mm	14	18
Arterial blood gas		
pH	7.37	7.39
P_{aCO_2} mmHg	75	46
P_{aO_2} (mmHg)	52	67
HCO_3^- $mEq \cdot L^{-1}$	42	27
Pulmonary function tests		
FEV_1 % of predicted	53	59
FVC % of predicted	56	62
FEV_1/FVC	0.79	0.78
TLC % of predicted	56	60
D_{LCO} (%)	42	65
Right heart catheterisation		
Systolic/diastolic PAP mmHg	80/32	
Mean PAP mmHg	47	
PAWP mmHg	12	
DPG mmHg	20	
CO/CI $L \cdot min^{-1}$	3.8/2.2	
PVR Wood units	9.3	
RAP mmHg	13	
S_{vO_2} %	62	

TRV: tricuspid regurgitation velocity; RVSP: right ventricular systolic pressure; RV: right ventricle/ventricular; TAPSE: tricuspid annular plane systolic excursion; P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}: arterial oxygen pressure; HCO_3^-: bicarbonate ion; FEV_1: forced expiratory volume in the 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; PAP: pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; DPG: diastolic pressure gradient; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; RAP: right atrial pressure; S_{vO_2}: mixed venous oxygen saturation.

developing [11] countries. Therefore, it is clear that in the coming years, specialist PH centres will be seeing more obese patients with PH, like the patient illustrated in case 1.

Several types of lung diseases can lead to pre-capillary PH (WHO Group 3 PH due to lung disease and/or hypoxia) [1, 2]. Sleep-disordered breathing is one example, and can include obstructive sleep apnoea and nocturnal hypoventilation, which can be related to obesity [8, 12]. Sleep-disordered breathing is very common in obese patients, and screening for sleep disorders should be part of a routine work-up in obese patients with PH [13]. Hypoventilation both during daytime and nocturnally can also arise due to skeletal deformities such as kyphoscoliosis, as illustrated by case 2. Kyphoscoliosis is an abnormal curvature of the spine in both the anterior and lateral directions, which results in reduced chest wall compliance [14]. As such, respiratory difficulties are common in patients with significant kyphoscoliosis and chronic respiratory failure can develop [14]. PH is a common complication of severe kyphoscoliosis, developing as a result of hypoxaemia due to hypoventilation, and to a lesser extent, hypercapnia [14]. PH is also common in patients with chronic advanced lung diseases, including pulmonary fibrosis and chronic obstructive pulmonary disease, especially when both conditions are present [15]. Comorbid PH and chronic lung disease is associated with increased mortality and reduced functional status, as well as quality of life, highlighting the clinical need to accurately and completely diagnose all respiratory conditions in patients suspected of having PH [16, 17].

CTEPH is an important cause of pre-capillary PH [18]. Diagnosis of this form of PH is crucial, as it can often be cured by pulmonary endarterectomy (PEA) [1, 2, 18, 19], and can also be treated with PH-specific medications [1, 2, 18]. Patients with recurrent or multiple pulmonary emboli are at risk of CTEPH [20, 21], despite effective anticoagulation. It is recommended that specific diagnostic testing is conducted to investigate the presence of CTEPH in all patients being assessed for PH [1, 2, 18, 22].

PH is a common complication of LHD, including systolic and diastolic left ventricular (LV) dysfunction and left-sided valvular disease, although the exact prevalence of PH among patients with LHD is unknown [23–26]. PH-LHD is caused by passive backward transmission of elevated filling pressures (*i.e.* LVEDP), and is associated with more severe symptoms, worse exercise capacity and a negative impact on clinical outcomes [23]. There are no approved therapies for PH-LHD [23]; studies have not established any benefit of PH-specific medications in patients with PH-LHD, and conversely, have reported significant adverse effects [1–3]. As a result, distinguishing PH-LHD from PAH is essential but this can be challenging [23, 27], particularly when PH is due to occult LHD (such as HFpEF as seen in case 1). One factor that contributes to the challenge of differentiating between PH-LHD and PAH is the changing demographics of PAH populations. Historically, PH-LHD patients were considered as being typically older than PAH patients [1, 2]; today, PAH populations have a higher mean age than those in the past [28]. As the age of PAH patients increases, the likelihood of confusing PH-LHD with PAH also becomes higher. In part due to their increasing age, PAH patients today also have more comorbidities than in the past [4, 29]. Indeed, recent registry data indicate that a significant proportion of PAH patients now have a comorbidity profile similar to that found in PH-LHD patients, including obesity, diabetes and atrial fibrillation. Case 1 provides an example of a patient with PH-LHD due to HFpEF with exactly such a comorbidity profile: he was morbidly obese and had been previously diagnosed with a number of chronic conditions, including type 2 diabetes mellitus and systemic hypertension. In these patients, it is important to carefully define the haemodynamic profile, using LHC in cases of uncertainty, to clearly distinguish between a diagnosis of PAH or PH-LHD.

Multifactorial diagnostic assessment of patients with suspected PH

Given the multiple potential causes of PH and the impact that the specific PH diagnosis can have on the most appropriate treatment, clinicians should perform a comprehensive multifactorial work-up to correctly determine the precise cause of PH.

Once PH is suspected, echocardiography is recommended to assess heart structure and function, and to determine the probability of PH [1, 2]. In case 1, echocardiography revealed a tricuspid valve regurgitation velocity that was above the upper limit of normal of 3.4 $m \cdot s^{-1}$ recommended in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines [1, 2], and which indicates a high probability of PH. Furthermore, elevated right ventricular systolic pressure is an important clue to the presence of clinically significant PH. In some cases, a structural left heart abnormality can be detected by echocardiography, raising suspicion of PH-LHD [1, 2]. However, echocardiographic parameters suggestive of PH-LHD are not easily measurable in all patients with LHD [25]. In particular, echocardiographic findings of HFpEF are often subtle and can easily be missed [26]. This was observed in the patient in case 1; although he was ultimately diagnosed with LHD, he had no obvious echocardiographic left-sided cardiac abnormalities, and both left ventricular ejection fraction and left atrial size were normal. In patients with obesity, good quality echocardiographic images can be difficult to obtain, and this was observed for case 1. Indeed, echocardiographic images are classified as being "nondiagnostic" in up to 30% of obese patients [30, 31].

Rigorous evaluation of the potential contribution of significant lung disease is indicated during diagnostic work-up. PFTs should be conducted to provide a specific assessment of lung function and to establish important obstructive or restrictive lung disease. Indeed, for the patient in case 2, PFTs indicated moderate restrictive lung disease, which helped to reach the final diagnosis of WHO Group 3 PH due to lung disease and/or hypoxia. Measurement of arterial blood gases established the presence of resting hypoxaemia, which was also essential in order to support this cause of PH. Moreover, the presence of daytime or nocturnal elevated P_{aCO_2} levels confirms hypoventilation, which is an important risk factor for WHO Group 3 PH [1, 2].

Thoracic computed tomography (CT) imaging is a valuable tool in the diagnostic approach to PH [1, 2]. CT findings can suggest the presence of PH, including main or hilar pulmonary artery enlargement, RV enlargement, or reflux of contrast material into the inferior vena cava or hepatic veins, and can also indicate the presence of significant underlying lung disease as a cause of PH [1, 2]. In case 1, a contrast-enhanced thoracic CT scan showed relatively small lungs (possibly due to the patient's morbid obesity) and large hilar pulmonary arteries but no evidence of parenchymal lung disease.

It is strongly recommended that in all patients with PH, the potential contribution of chronic pulmonary emboli should be examined using a V'/Q' lung scan [1, 2, 18]. Mismatched segmental perfusion defects indicate the possibility of CTEPH [1, 2], whereas a normal or low-probability V'/Q' scan allows CTEPH to be excluded, as in both cases presented.

Identifying the underlying cause of PH can be aided by performing exercise testing. Exercise testing with a 6-min walk test objectively assesses functional capacity in PH patients, confirming clinical severity of symptoms and exercise limitation, but does not provide any information regarding the specific cause of PH. Moreover, 6-min walk distance values both at baseline and during follow-up can predict the risk of death in

 DOI: 10.1183/16000617.0104-2016

many types of PH [32, 33]. As such, clinical practice guidelines recommend baseline and serial assessment of exercise capacity with a 6-min walk test [1, 2]. More information can be provided by cardiopulmonary exercise testing (CPET), which is becoming increasingly utilised in clinical practice, and is now considered the gold standard test for evaluating the causes of dyspnoea and exercise intolerance [34, 35]. CPET can be particularly useful in the differential diagnosis of PH as the pattern of cardiopulmonary and gas-exchange responses can distinguish between pulmonary and cardiac limitations to exercise [35]. It must be cautioned that the proper performance and accurate interpretation of CPET in patients with PH requires significant technical and scientific expertise, as well as critical monitoring of patients in order to ensure safety.

The role of heart catheterisation in PH diagnosis

In order to definitively diagnose the cause of PH, guidelines recommend that RHC should be performed [1, 2]. This is particularly critical for the diagnosis of pre-capillary forms of PH, such as PAH, that can be treated with PH-specific medications. Despite the guideline recommendations, some patients are diagnosed with PH and treated with PH-specific medications without undergoing RHC as part of their assessment [36], and this can lead to inaccurate diagnoses and adverse outcomes [37]. One reason for not performing RHC may include concerns regarding the safety of the procedure [38] as cardiorespiratory, hypotensive or device-related complications can occur [39, 40]. Despite these concerns, RHC is considered to be safe at expert centres, with low morbidity and mortality rates of 1.1% and 0.055%, respectively [39]. Underuse of RHC may also be due to a lack of technical training or knowledge. The complexities of the technique, along with a lack of standardisation, can make RHC vulnerable to technical or data interpretation errors [40, 41]. To address this, guidance on optimising RHC is available and provided in table 3. Additional practical recommendations related to the specific measurement or derivation of certain haemodynamic variables have also recently been published [40]. Adoption of a standardised protocol for RHC, as well as ensuring that staff are appropriately trained, can improve the accuracy of RHC measurements and, therefore, of PH diagnosis [1, 2, 29, 40–45].

By RHC, PH is defined as a mean PAP $\geqslant$25 mmHg, and can be further differentiated into pre-capillary PH and post-capillary PH on the basis of the PAWP, such that PAWP $\leqslant$15 mmHg defines pre-capillary PH and PAWP >15 mmHg indicates post-capillary PH [1, 2]. Post-capillary PH can exist in an isolated form or as Cpc-PH [1, 2]. The haemodynamic distinction of the latter type is made based on PH in the presence of PAWP >15 mmHg, as well as findings of an elevated pulmonary vascular resistance (>3 Wood units) and/or an increased DPG (PAPdiastolic − PAWP $\geqslant$7 mmHg) [1, 2]. In patients with post-capillary PH, the additional pre-capillary component can be due to underlying lung disease [1, 2] or as a result of a pulmonary vascular remodelling process in the setting of chronic LHD, as in mitral stenosis, LV systolic

TABLE 3 Potential sources of error when performing right heart catheterisation and guidance on how to minimise the impact of these errors

Potential error class	Potential error	Risk	Solution
Measurement	Catheter balloon over-inflation	False high or low PAWP readings [41]	Half inflation of the balloon (diameter ~0.9 cm, 0.75 mL air) [42]
		Pulmonary arterial rupture [41]	Avoid repeated inflations and deflations of the balloon [29]
	Catheter balloon under-inflation	False elevation of PAWP readings [41]	Half inflation of the balloon (diameter ~0.9 cm, 0.75 mL air) [42]
	Use of end-expiratory PAWP readings	Misdiagnosis of patients with a pre-capillary phenotype [43, 44]	Average PAWP readings across respiratory cycles [44]
	Analysing single cycle	Potential data inaccuracy [44]	Mean values of multiple respiratory cycles should be used [44]
	Variation in the location of the pressure transducer	Nonuniformity of the pressure transducer setting and zero levelling [29, 45]	Standardised location of pressure transducer according to guideline recommendations [1, 2, 40, 44] or adoption of micromanometer-tipped catheters [44]
Data interpretation	Failure to review traces	Data inaccuracy (measurement artefacts) [41]	Each trace should be scrutinised to ensure that it is not affected by artefacts [41]
Technical	Incorrectly maintained or calibrated equipment	Errors in data acquisition [41]	Equipment maintained to a high standard and regular calibration [41]
	Inadequate flushing of the catheter	Dampened waveforms [41]	Adequate flushing [41]

PAWP: pulmonary arterial wedge pressure.

dysfunction or HFpEF [23–25]. In case 1, RHC revealed the presence of significant PH (table 1), with elevated PAP (normal mean PAP ⩽20 mmHg [1, 2, 29]) and increased pulmonary vascular resistance (normal ⩽1.5 Wood units [46, 47]). In addition, a PAWP of 16 mmHg was measured (figure 1a), which is close to the cut-off point of ⩽15 mmHg described above [1, 2]. However, because of the obesity, there were marked respiratory swings in the RHC trace which can affect the accuracy of the PAWP reading (figure 1b). If the PAWP value is unreliable or if there are significant risk factors for LHD (both of which occurred in case 1), the current ESC/ERS guidelines state that LHC should be considered to directly measure LVEDP [1, 2]. LVEDP is the gold standard measurement for distinguishing between pre- and post-capillary PH. In contrast, PAWP is only an estimate and can be affected by many factors, including respiratory swings [40]. The LHC results in case 1 revealed an elevated DPG. The degree of elevation of mean PAP in this patient could not be explained entirely by the PAWP and LVEDP values, suggesting the presence of a pre-capillary component to this patient's PH. Therefore, the most appropriate diagnosis for the patient in case 1 was WHO Group 2 PH-LHD with Cpc-PH, complicated by morbid obesity. The post-capillary component was a result of HFpEF. The pre-capillary component was likely the result of pulmonary vascular remodelling in the setting of HFpEF.

Invasive measurement of cardiopulmonary haemodynamics during exercise rather than at rest as described above may provide additional diagnostic value. Patients with HFpEF in the early stages of the disease may have normal haemodynamic values at rest or may have haemodynamic values suggestive of PH (defined as high resting PAP, but with normal PAWP and/or LVEDP [⩽15 mmHg]). However, when the cardiovascular system is stressed and cardiac output increases during exercise, pathological changes in systolic PAP, mean PAP and PAWP may occur [48]. Haemodynamic testing during exercise can therefore "unmask" diastolic dysfunction, aiding the early diagnosis of HFpEF [49]. Exercise haemodynamics are especially useful in obese patients [49] who, as seen in case 1, often present with unreliable PAWP values. As invasive exercise testing is not universally available, fluid loading can be used as an alternative method of stressing the cardiovascular system, although it may be less sensitive than exercise testing [48]. Currently, the methodology of haemodynamic exercise testing in the diagnosis of PH is not standardised and guidelines do not recommend it as a routine diagnostic test [1, 2, 49]. A recent publication has suggested a diagnostic algorithm for interpreting the haemodynamic and ventilatory data that CPET with invasive haemodynamic assessment provides [50], which may help to standardise this technique in the future.

To identify the correct cause of PH, particularly in the setting of patients who have multiple comorbidities, a comprehensive, multidimensional diagnostic methodology is required, as illustrated by the two cases presented. Due to the increasing complexity of diagnosing PH, it is recommended that patients presenting with suspected PH are referred to a specialist PH centre [15]. Furthermore, clinicians working outside of these centres are encouraged to discuss complex cases with PH specialists to aid a timely and accurate diagnosis.

The implications of PH diagnosis on patient management

Failure to reach a correct diagnosis of the cause of PH in an individual patient can result in patients receiving inappropriate treatments for their specific type of PH. PH-targeted medications are approved and effective in patients with PAH [1, 2], but are not indicated for many of the other forms of PH.

For patients with PH-LHD, PH-specific therapies are not recommended or approved [1–3] as they have demonstrated a lack of efficacy in patients with HFpEF and those with PH due to systolic LV dysfunction [51–54]. Moreover, in patients with heart failure and a reduced ejection fraction, PH-specific therapies have increased the occurrence of adverse events [55] or hastened disease progression as a consequence of fluid retention [56]. Similarly, the use of drugs approved for PH is not recommended in patients with PH due to lung diseases [1, 2]. This highlights the critical importance of differentiating PAH from WHO Group 2 PH-LHD or WHO Group 3 PH due to lung disease and/or hypoxia prior to initiating PH-targeted medical therapy. The optimal management of CTEPH patients is different again to that of other forms of PH, with surgical PEA being the treatment of choice in eligible patients [1, 2]. Medical treatment of CTEPH patients with PH-targeted therapy may be justified for inoperable patients or for patients with persistent or recurrent PH following PEA [1, 2].

For the management of PH in WHO Groups 2 and 3, treatment of the underlying cause/comorbidity is essential and is recommended in the ESC/ERS guidelines for PH [1, 2]. Treatment of comorbidities in PH patients is important as it has been demonstrated that certain comorbidities are associated with worse outcomes in patients with PH. For example, long-term survival appears worse in PH patients with diabetes in comparison to PH patients without diabetes [57]. Furthermore, a recent meta-analysis has demonstrated that bariatric surgery leads to short-term clinical improvements in PH in obese patients [58]. In alignment with this, in case 1, the patient underwent a sleeve gastric band procedure, which led to significant improvements in his condition. 2 years after surgery, the patient's BMI had reduced to 36.6 $kg \cdot m^{-2}$. Follow-up echocardiography indicated that he was largely cured of his PH. There was a qualitative improvement in RV

 DOI: 10.1183/16000617.0104-2016

size/left ventricle compression and right atrium size. Treatment of underlying chronic hypoventilation due to kyphoscoliosis using noninvasive ventilation also markedly improved PH in case 2. This is in line with previous data on the treatment of chronic hypoventilation syndromes using ventilation therapy. In a retrospective analysis that assessed patients with daytime PH due to hypoventilation, noninvasive ventilation was found to significantly improve haemodynamics and exercise capacity [59].

In addition to highlighting the benefits of treating comorbidities, case 1 also illustrates how failure to reach a definitive diagnosis can have significant implications for the management of PH patients. Undiagnosed conditions can result in patients being rejected for potentially beneficial procedures. The patient in case 1 had previously been refused bariatric surgery, as there was a perceived risk of operating in the setting of an unidentified cardiopulmonary condition. Following successful diagnosis of PH, and discussions between specialist surgical and cardiology staff, the original decision not to operate was overturned as surgeons felt that the PH was reversible.

Conclusion

As illustrated in this review, the accurate diagnosis of the underlying cause of PH is associated with a number of challenges. There are multiple cardiac and pulmonary conditions that can contribute to the development of PH, and the frequency and variety of comorbid conditions complicates the diagnostic approach to a PH patient. It is, however, essential that the type of PH is correctly identified, in order to ensure that patients are optimally managed.

Acknowledgements

We would like to thank James Glasper (nspm Ltd, Meggen, Switzerland) for medical writing assistance, funded by Actelion Pharmaceuticals Ltd (Allschwil, Switzerland).

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 DOI: 10.1183/16000617.0104-2016