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Review

The Role of Exercise Testing in the Modern Management of Pulmonary Arterial Hypertension

Martin K. Johnson * and Stephen Thomson

Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Agamemnon Street, Clydebank G81 4DY, UK; E-Mail: stephenthomson1@nhs.net

*Author to whom correspondence should be addressed; E-Mail: mjohnson4@nhs.net; Tel.: +44-0-141-951-5497; Fax: +44-0-141-951-5948.

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Abstract: A culture of exercise testing is firmly embedded in the management of pulmonary arterial hypertension (PAH) but its clinical relevance and utility have recently been under some debate. The six minute walk test (6MWT) has been used as a primary outcome measure to enable the licensing of many of the medications used for this condition. Recent reviews have questioned the validity of this test as a surrogate of clinical outcomes. At the same time, other questions are emerging where exercise testing may be the solution. With the rise in understanding of genetic markers of idiopathic PAH (IPAH), the screening of an otherwise healthy population for incipient pulmonary hypertension (PH) will be required. The proliferation in treatment choices and identification of populations with PH where PAH treatment is not indicated, such as left heart and lung disease, requires more definitive differentiation from patients with PAH. There is a continuing question about the existence and clinical relevance of exercise induced PAH as a cause of unexplained dyspnoea and fatigue and as a latent phase of resting PH. This review presents a summary and critical analysis of the current role of exercise testing in PAH and speculates on future trends.

Keywords: pulmonary arterial hypertension; exercise testing; activity monitoring

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1. Introduction

Exercise can be viewed as the process of transferring oxygen from atmosphere to capillaries and its utilisation there by exercising muscles. The movement of oxygen from the lungs to the capillaries is a convective process described mathematically by the Fick equation which states

$$VO_2 = CO \times (C_aO_2 - C_vO_2) \quad (1)$$

where VO_2 is oxygen uptake, CO is cardiac output and C_aO_2-C_vO_2 is the arteriovenous difference in oxygen content. This equation can be expanded as follows:

$$VO_2 = SV \times HR \times Hb \times (S_aO_2 - S_vO_2) \quad (2)$$

where SV is stroke volume, HR heart rate, Hb blood haemoglobin concentration and S_aO_2-S_vO_2 the difference in oxygen saturation between arterial and mixed venous blood. Severe exercise intolerance due to impairment of oxygen transport is a hallmark of pulmonary arterial hypertension (PAH) and the reasons for that are evident from inspection of the Fick equation. In subjects with PAH, maximum SV is severely reduced [1], peak predicted HR is often not reached [2], relative anaemia is a common finding [3] and desaturation on exercise is present in the majority of cases due to a combination of precipitate fall in mixed venous oxygen saturation (S_vO_2) and ventilation-perfusion mismatch [4].

There are other factors which can in general limit exercise such as ventilatory limitation and peripheral muscle dysfunction but their contribution to impairment of exercise capacity in PAH is less relevant. Ventilatory capacity can be reduced in PAH, where mild obstruction and restriction have been found at rest [5,6] and dynamic hyperinflation with reduced end exercise inspiratory capacity on exercise [7,8]. More striking in these patients is markedly increased ventilatory demand due to reduced ventilatory efficiency. The pathophysiological reasons for this can be illustrated by considering the ratio of ventilation (V_E) to carbon dioxide production (VCO_2) which is given by the following expression derived from the Bohr equation:

$$\frac{V_E}{VCO_2} = \frac{k}{P_aCO_2 \times \left(1 - \frac{V_D}{V_T}\right)} \quad (3)$$

where k is a constant, P_aCO_2 is the arterial carbon dioxide concentration and V_D/V_T is the ratio of dead space to tidal volume. In PAH, inefficient ventilation, *i.e.*, the requirement for a high ventilation to remove the carbon dioxide produced by respiration, is due to a combination of both increased dead space and a lowered set point for arterial carbon dioxide concentration [9]. Despite this reduced ventilatory capacity and increased demand, ventilatory limitation is said not to occur in PAH unless there is concomitant lung disease. Peripheral muscle dysfunction has been shown in PAH in the form of reduced capillary density and oxidative enzymes in muscle biopsies of these patients [10]. This abnormality can lead to impairment of extraction of oxygen from muscle capillaries and should be reflected in abnormally high values of S_vO_2 at end-exercise [11]. However, data from studies in heart failure [12] and published in abstract form in PAH [13] suggest that this is not the case. Thus, although muscle dysfunction is present in PAH, the diffusion capacity for oxygen from the capillaries to the mitochondria still more than matches the reduced level of oxygen delivery to the capillaries.

Since exercise limitation is present in the majority of patients with this condition, exercise testing has been widely used as a means of investigating its severity and assessing for change. The most commonly used tests have been incremental cardiopulmonary exercise tests (CPETs) and six minute walk tests (6MWTs) but these have both had their critics. When the former was used as the primary outcome measure in a trial of sitaxentan, it proved negative, whereas 6MWT, as the secondary outcome measure, was positive [14]. The failure of CPET to show a signal was attributed to its complexity and hence the quality of test performance [15]. Recently an attempt was made to quantify what proportion of the treatment effect of disease targeted therapy was captured by changes in 6MWT distance (6MWD) [16]. This proved surprisingly low at 22.1%, supporting earlier studies which suggested that changes in 6MWD were not of prognostic value [17].

There is opportunity for development in the application of exercise testing techniques in PAH. There has been interest in both invasive and non-invasive measurements of exercise haemodynamics since this is one of the cardinal impairments of pathophysiology in this condition. Attempts have been made to enhance the value of CPET and 6MWT by modifications of protocol or measurement of additional variables. Finally studies are emerging of the use of activity monitoring in PAH under the premise that this test will more closely reflect clinical reality. The aim of this review is to summarise the current status of exercise testing in PAH and to highlight recent advances.

2. Exercise Haemodynamics

2.1. Invasive Measurement

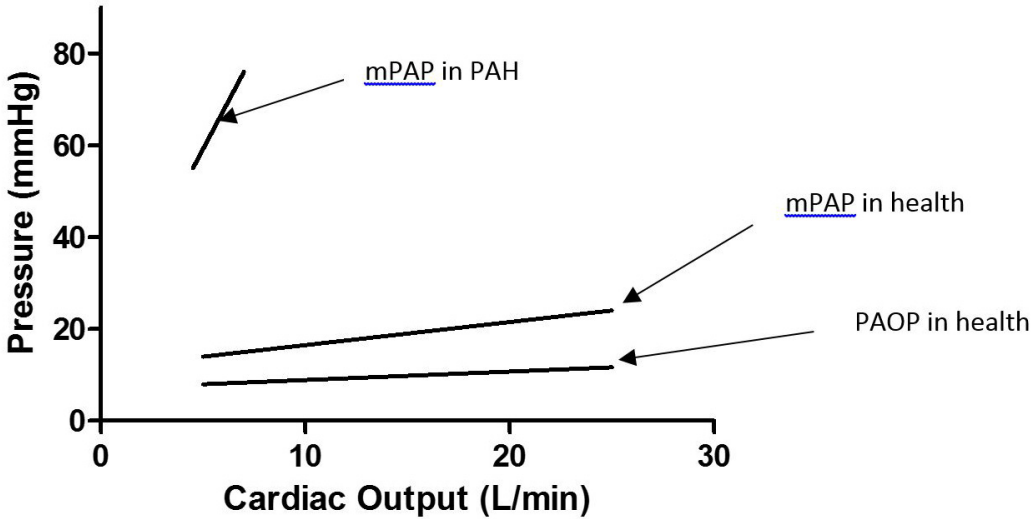
The measurement of the pressure-flow behaviour of the pulmonary circulation during exercise by right heart catheterisation (RHC) continues to be of interest despite the invasive process involved [1,18,19]. It provides information which cannot be accurately acquired by other routes. Potential roles include differentiating between pulmonary venous and pulmonary arterial hypertension, investigation of exertional dyspnoea defying diagnosis by non-invasive tests and accurate assessment of treatment effect on pulmonary artery haemodynamics.

Mean pulmonary artery pressure (mPAP), CO, pulmonary vascular resistance (PVR) and pulmonary artery occlusion pressure (PAOP) are interlinked by the equation

$$PVR = \frac{(mPAP - PAOP)}{CO}. \quad (4)$$

Figure 1 contrasts the typical results seen for mean pulmonary artery pressure (mPAP) during exercise in healthy individuals and those with PAH. In health both mPAP and PAOP rise with exercise. The estimated range of normality for mPAP change on exercise is 0.5–3.0 mmHg.min.L^{-1} [20] whereas the normal range for PAOP change is less certain, one estimate being 0.3–1.93 mmHg.min.L^{-1} [19]. During supine exercise PVR falls slightly [21,22] and S_vO2 falls from 75% at rest to 25% at maximal exercise [23]. By contrast in PAH there is a very steep rise in mPAP over a much more limited CO response. The data for PVR and PAOP in PAH are very limited. In the study by Janicki *et al.* [24] which included a mixture of subjects with PAH and pulmonary hypertension (PH) related to lung disease, PAOP rose from 8 mmHg at rest to 18 mmHg on exercise with PVR unchanged. As discussed earlier, there has been controversy over the S_vO2 values achieved at maximal exercise in PAH. In a recent study of patients with precapillary pulmonary hypertension the mean S_vO2 on maximal supine exercise was low at 22% [13].

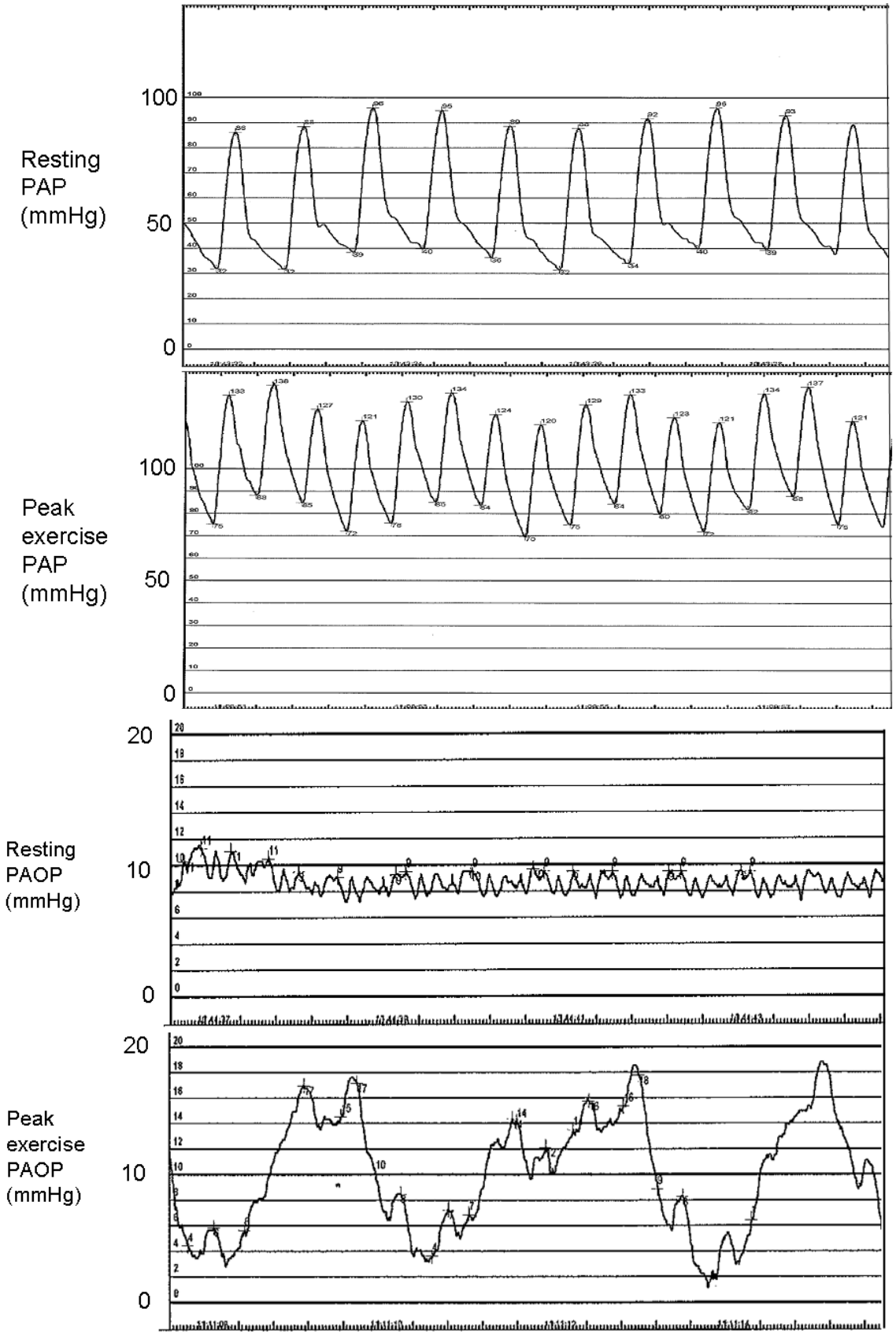
Figure 1. Mean data for healthy subjects taken from Kovacs *et al.* [22]. Mean data for subjects with pulmonary arterial hypertension (PAH) adapted from Provencher *et al.* [25]. Exercise performed in the supine position. mPAP: mean pulmonary artery pressure, PAOP: pulmonary artery occlusion pressure.



There are obvious issues with the widespread utilisation of exercise haemodynamics. Firstly, it is an invasive test and therefore not well suited to serial measurements. There is no standardised exercise protocol followed in the studies which have investigated its use [26]. Difficulties arise in interpreting measurements at peak exercise due to the swings in pressure traces caused by increasing respiratory efforts, particularly marked with PAOP [27] but also noticeable in mPAP (see Figure 2). To overcome this problem which leads to exaggerated end-expiratory pressures, it has been suggested that pulmonary vascular pressures measured during exercise should be averaged over the respiratory cycle [18]. Lastly, exercise haemodynamics are most easily performed in the supine position but this does not lead to the same results as erect exercise. In particular, for any workload HR is lower and SV higher in the supine position [22] and the peak workrate achievable higher when erect [28].

There is a role for exercise haemodynamics in established PH. It has provided insights into the physiological behaviour of the pulmonary circulation during exercise in these patients [29]. It can provide **diagnostic** information to differentiate between clinical classes of PH. Borlaug *et al.* [30] demonstrated that patients with pulmonary venous hypertension showed a marked increase in PAOP during exercise which could be used to discriminate between this condition and PAH. There is some, albeit limited, evidence for the **prognostic** value of exercise haemodynamics. Provencher *et al.* [25] showed that exercise haemodynamic variables could predict change in 6MWD on therapy whereas resting values did not. In a mixed population of subjects with PAH and chronic thromboembolic pulmonary hypertension, Blumberg *et al.* [31] showed that exercise cardiac index and the pressure/flow relationship were significant prognostic indicators. They may have greater sensitivity than resting values to detect treatment effect. Castelain *et al.* [29] demonstrated that pressure-flow slopes improved with epoprostenol whereas resting haemodynamic values did not.

Figure 2. Right heart catheterisation traces of pulmonary artery pressure (PAP) and pulmonary artery occlusion pressure (PAOP) at rest and at peak exercise. Note both the significant elevation of PAP and the marked respiratory swing, most prominently affecting PAOP, which develops on exercise.



There may be a role for exercise haemodynamics in evaluating subjects with dyspnoea or fatigue that is defying diagnosis particularly if combined with VO_2 measurements. In subjects with normal resting measurements, elevated pulmonary artery pressure on exercise has been associated, not only with an impaired exercise capacity and CO response and higher values of PVR, but also with symptoms, reduced peak VO_2, abnormal gas exchange and reduced quality of life [32–34]. Such results support exercise induced PAH (EIPAH) as a true pathophysiological entity which may be responsible for some cases of unexplained exercise intolerance. Since the concept of EIPAH was discouraged in the guidelines from Dana Point (2008) [35] and this advice was repeated in Nice (2013) [36], there has been neither consensus as to whether this is a true precursor of resting PAH nor a widely accepted haemodynamic definition by which to identify it. In a recent review, Naeije *et al.* [20] have proposed that either an mPAP of 30 mmHg at a CO of less than 10 $L.min^{-1}$ (which approximately corresponds to a PVR greater than 3 Wood units) or a slope of mPAP-CO greater than 3 $mmHg.min.L^{-1}$ could be used as diagnostic criteria for this condition.

Exercise haemodynamics may also have a role in identifying EIPAH in subjects with substantial risk factors for PAH as early data suggest treatment may be indicated for this group. One fifth of patients with systemic sclerosis and EIPAH developed resting PAH after a mean follow up of 2.3 years [37]. Exercise haemodynamic measurements in scleroderma patients with borderline resting measurements [38,39] show a greater increase in mPAP on exercise. In this group there was progression in mPAP and PVR on serial measurements over a year and bosentan appeared to attenuate that change [40]. Finally Saggar *et al.* [41] showed an improvement in exercise haemodynamics in an open label trial of ambrisentan in patients with scleroderma and EIPAH.

2.2. Non-Invasive Measurements

For greater utilisation of exercise haemodynamics to occur, the technique for measuring them should be non-invasive and there are a number of candidates for this.

Transthoracic echocardiogram (TTE) surpasses RHC in the amount of information it supplies [42]. Not only can it give estimates of pressure and flow but it can also be used to evaluate right ventricular function. Its major problem, as with all indirect techniques, is the potential for error in patients with challenging anatomy (e.g., concomitant lung disease, obesity) or arising from inter-operator variability.

There are a number of studies illustrating the feasibility of TTE during exercise in PAH and other conditions. These have shown the ability to estimate systolic pulmonary artery pressure (sPAP) [43–48], PAOP by inference from E/e' ratio [49,50], CO from left ventricular outflow velocity-time integral [43,44], resistance [43,44], distensibility [43,44,51] and right ventricular function assessed by tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular systolic velocity [52]. mPAP can be deduced from sPAP using one of the equations derived for this relationship [53,54]. Formal validation of non-invasive with invasive measurements during exercise has been limited [55–57].

Early data show encouraging results for the use of exercise TTE in subjects at risk of PAH. Grunig *et al.* [58] looked at relatives of patients with IPAH or familial PAH with and without bone morphogenetic protein receptor 2 gene mutations and found a greater prevalence of a hypertensive tricuspid regurgitant velocity response in affected kindreds. Multiple studies have shown a high prevalence of TTE determined EIPAH in scleroderma patients [45,59–63]. Of these, Steen *et al.* [61]

was the only one to proceed to RHC in those subjects with EIPAH and confirmed the non-invasive results in 81% of cases.

Cardiac magnetic resonance (CMR) is a more complex imaging technique which also has potential to provide noninvasive haemodynamic data. It is more accurate than TTE in measuring CO [64] and similarly provides information on right ventricular function, resting values of which have been shown to be superior to PVR for predicting prognosis [65]. However, unlike TTE it cannot provide information on pressure and a significant minority of subjects fail to tolerate the test because of claustrophobia [66]. Additionally exercise measurements so far in PAH have been taken in the immediate post-exercise phase because of the difficulty in cycling whilst inside the bore of the scanner [67]. The validity of this is questionable as values of pressure and flow post-exercise fall rapidly [44,68]. This technique needs to be evaluated with imaging performed during exercise to assess its full value. The feasibility of such measurements has been illustrated in other conditions [64].

Simpler physiological measurements have also been used to estimate exercise haemodynamic variables. The **inert gas rebreathing** technique utilises the high solubility in blood of gases such as acetylene or nitrous oxide to estimate pulmonary blood flow [69]. This technique gives no information on pulmonary artery pressure or other aspects of right ventricular function. It is simple to perform during exercise with a measurement possible every few minutes allowing for a washout period. Its major limitation is in patients with lung disease where ventilation heterogeneity leads to poor mixing of inspired gases and inaccurate results [70]. It is also compromised where there is significant intracardiac shunting.

Nevertheless, the feasibility of the technique to estimate SV during exercise in PAH and detect the effects of disease targeted therapy on exercise SV, have both been demonstrated [67,71]. Lee *et al.* [71] also showed that, if SV is the variable of interest, then changes in supine resting SV provided as much information as erect exercise values, indicating the importance of preload as a stressor for assessing the pulmonary circulation. Validation data for use of the technique in PAH are limited to resting data [70,72].

Impedance cardiography or **bioimpedance** uses the change in thoracic impedance as the fluid content of the chest varies during the cardiac cycle to estimate SV [73]. This technique is attractive as it has the potential to provide a continuous measurement of CO at rest or during activity. However, measurements are not possible in a quarter of patients and the quantitative validity of the data in the remaining proportion cannot be relied upon. Relative changes in measurements of cardiac index were able to identify subjects severely affected by PAH [74]. **Bioreactance** is a version of the technique which looks at phase rather than amplitude changes of alternating current and voltage applied across the thorax. Its signal is proportional to aortic blood flow and performed well in quantitative terms when validated against thermodilution and indirect Fick in a broad population of PH patients [75].

3. Cardiopulmonary Exercise Testing

Improvement in equipment design and widespread adoption of breath by breath measurement techniques have made CPET relatively easy to perform and widely available [76]. The minimum dataset collected during exercise includes V_E, oxygen and carbon dioxide content of inspired and expired air, HR and oxygen saturation (S_pO_2). With these measurements the characteristic pathophysiological response of PAH patients can be seen, *i.e.*, profound exercise limitation marked by

impairment of oxygen transport and inefficient gas exchange with very high ventilatory demand [77–85]. In an incremental CPET, the oxygen transport abnormality is reflected in a low VO_2 at anaerobic threshold, low VO_2 - workrate slope, low peak oxygen (O_2) pulse (defined as the ratio of peak VO_2 to peak HR) and a steep HR-VO_2 response, combined on occasions with a HR response which fails to reach predicted maximum. The gas exchange response is even more striking with high ventilatory equivalents (V_E/VCO_2 and V_E/VO_2) and low end-tidal carbon dioxide ($P_{et}CO_2$) combined with desaturation (see Figure 3). These features can be exaggerated by the use of walking rather than cycling exercise which causes more hypoxaemia [86] and are more prominent in the presence of a right to left shunt such as through a patent foramen ovale [87].

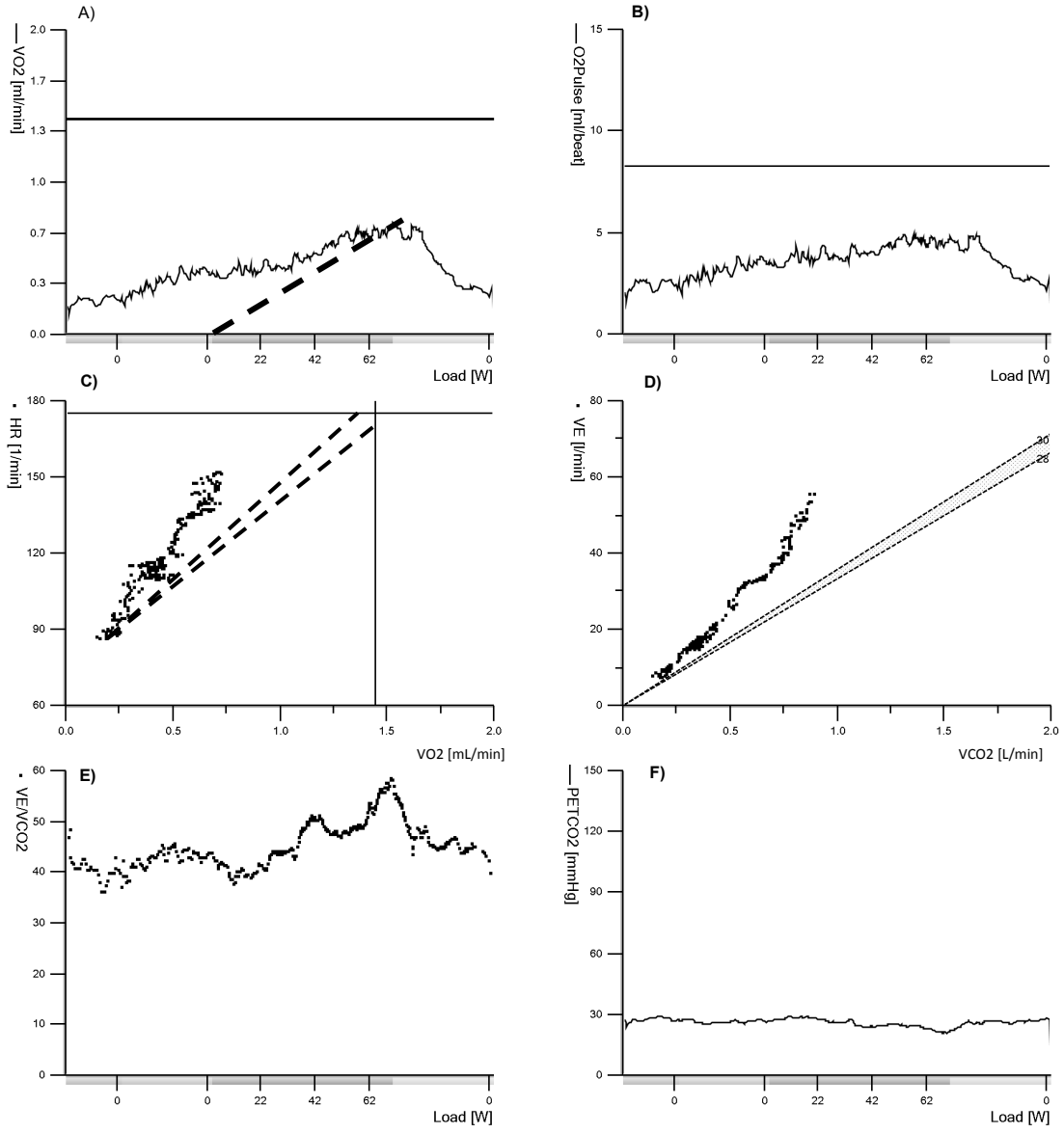
The exercise response of disease are more subtle. Table 1 lists a number of studies which have examined this issue. Although PAH patients is very readily distinguished from normal subjects. However, differences in CPET results between PAH and other conditions complicated by PH such as left heart problems, hypoxic lung disease and chronic thromboembolic group mean measurements can differentiate between these conditions, using CPET results to make a definitive diagnosis for an individual is not often possible because of the overlap in the range of the abnormal variables. Thus CPET can suggest the presence of PH in an associated condition but is insufficient without other investigations to make a diagnosis of PAH. One study [88] has proposed an algorithm for diagnosing a pulmonary vascular problem which uses a decision tree based upon peak VO_2, VO_2 at anaerobic threshold (AT), breathing reserve and V_E/VCO_2 at AT. This achieved a sensitivity of 79%, specificity of 88% and accuracy of 85% of detecting a "pulmonary vascular limit" as the cause of exercise impairment. One major issue with this study was that the definition of "pulmonary vascular limit" used in the study was not a standard one and so these results need further confirmation.

Several CPET variables have been demonstrated to have prognostic value for patients with PAH although some of the studies are limited by small numbers and lack of multivariate analyses [89,90]. Themes emerging from the heterogeneous results are summarised in Table 2. Of note both oxygen transport (peak VO_2, O_2 pulse, peak HR) and gas exchange variables (V_E/VCO_2 at AT) are represented in the table. A further study looked at prognostic information contained in change in variables following treatment with change in peak VO_2 being predictive on multivariate analysis [91]. Only one study looked at "Time To Clinical Worsening" [92] as the prognostic outcome rather than death and this showed that peak VO_2 was predictive.

CPET variables in some but not all studies have been able to detect a change pre and post approved disease targeted therapy in patients treated for PAH. In an uncontrolled study in 16 subjects Wax *et al.* [93] showed an improvement in peak VO_2 on intravenous prostacyclin therapy. In an uncontrolled study in 11 subjects [94] Wensel *et al.* was able to show an increase in peak VO_2 and reduction in V_E/VCO_2 slope with nebulised iloprost. In a controlled study of 28 subjects [95] Oudiz et al was able to show changes at AT in V_E/VCO_2 ratio and $P_{et}CO_2$ with sildenafil. The largest treatment study utilising a CPET variable as a primary outcome measure [14] looked at the use of sitaxentan in 178 subjects. This failed to show an increase in the primary outcome measure (% predicted peak VO_2) despite a positive exercise based secondary outcome measure (6MWD) which eventually lead to the drug's approval. The reason for the failure of VO_2 as an outcome measure has been attributed to the complexity of CPET and the multicentre design of STRIDE-1 [15]. It has been postulated that this lead to inaccurate results at the less experienced sites and failure of the outcome measure to show a signal. As support for this a single

centre study in PAH subjects [96] achieved excellent reproducibility of CPET variables on repeated testing with coefficients of variation of 5.8%, 3.3%. 5.2% 6.5%, 1.0%, 2.8% and 3.3% respectively for peak values of VO_2, HR and O_2 pulse and AT values of VO_2, $P_{et}O_2$, $P_{et}CO_2$ and V_E/VCO_2.

Figure 3. Typical CPET responses of a patient with PAH. The solid lines in (**A**), (**B**) and (**C**) indicate the predicted peak values of the respective variables. The dashed line in (**A**) represents a VO_2/WR slope of 10 mL.W./min^{-1} – a healthy response would parallel this line. Note the shallower VO_2/WR slope and reduced peak VO_2 in PAH. Reduced peak oxygen pulse is seen in (**B**). Steep heart rate response and V_E/VCO_2 slope are evident in (**C**) and (**D**) respectively with the predicted response corridors indicated by dashed lines. (**E**) displays a markedly elevated ventilatory equivalent of CO_2 while (**F**) shows reduced end-tidal CO_2, demonstrating key elements of the abnormal gas exchange response in PAH.



Screening of at risk populations for the presence of resting PH is best performed by TTE. However, if it becomes important to detect EIPAH, then this may be an appropriate indication for CPET. Studies

which examined CPET variable abnormalities in EIPAH are listed in Table 3. The ability of CPET to detect these differences adds support to the concept of EIPAH as a genuine pathophysiological entity.

The safety of maximal incremental CPET in PAH subjects has been questioned. Multiple studies in adults [83,96,97] and children [89,98,99] have suggested that this is not a problem. In the largest study looking at CPET in high risk cardiovascular patients (n = 5060 CPET events) [97], adverse event rate was 0.16% with no fatalities. In a study dedicated to PAH [96], there were no events in 242 tests.

Table 1. Studies comparing cardiopulmonary exercise test (CPET) variable responses in PAH with left heart, hypoxic lung and chronic thromboembolic disease or in these conditions complicated by PH.

Study	Population	Finding
Left Heart Disease		
Deboeck 2004 [100]	LHD (19), PAH (19)	Matched for peak VO_2, PAH patients have • higher dyspnoea scores • higher V_E/VCO_2 at AT and peak • lower peak O_2 pulse • lower peak S_pO_2 • lower VO_2-WR slope above AT
Hansen 2007 [101]	Normal (25), COPD (25), LHD (25), IPAH (25)	Matched for peak VO_2, lower peak $P_{et}CO_2$ in PAH
Groepenhoff 2010 [102]	PAH (28), LHD (18)	Matched for peak VO_2, PAH patients have • lower peak S_pO_2 • lower SV • steeper HR-VO_2 slope • higher peak RER
Nishio 2012 [103]	LHD (20), PAH (20)	Matched for NYHA FC, peak VO_2 lower and V_E/VCO_2 slope higher in PAH. Peak VO_2 correlated with PVR in PAH and PAOP in LHD. V_E/VCO_2 slope correlated with PAOP in LHD
Guazzi 2013 [104]	LHD (293); (134 had PH on TTE)	Presence of PH associated with high V_E/VCO_2 slope, low peak $P_{et}CO_2$ and presence of oscillatory breathing
COPD		
Hansen 2007 [101]	Normal (25), COPD (25), LHD (25), IPAH (25)	Matched for peak VO_2, PAH patients have lower peak $P_{et}CO_2$, higher peak P_eCO_2 and higher peak P_eCO_2/ $P_{et}CO_2$ ratio
Vonbank 2008 [105]	COPD (42); PH determined by RHC present in 32	Not matched for peak VO_2 (lower in PH). Presence of PH during exercise associated with • high VO_2-WR slope • high V_E/VCO_2 • high $P_{(a-et)}CO_2$

Table 1. *Cont.*

Study	Population	Finding
Boerrigter 2012 [106]	COPD (47); (stratified for severity of PH determined at RHC – no PH (24), mPAP 25-39 mmHg (14), mPAP ≥ 40 mmHg (9)	As PH severity increased, • reduced peak S_vO_2 • reduced peak P_aCO_2 • reduced peak S_pO_2 • increased breathing reserve • increased peak RER • reduced peak $P_{et}CO_2$ • increased V_E/VCO_2 slope – switch from ventilatory to cardiovascular limitation profile
IPF		
Glaser 2009 [107]	IPF (34); PH determined by TTE and confirmed by RHC in 16	Not matched for peak VO_2 (lower in PH). Presence of PH associated with • higher dyspnoea scores • higher V_E/VCO_2 slope • higher$P_{(a\text{-}ET)}CO2$ at AT
van der Plas 2013 [108]	IPF (38) ; mPAP ≥ 40 mmHg on TTE in 11	V_E/VCO_2 at AT higher in group with mPAP ≥ 40 mmHg
CTEPH		
Zhai 2011 [9]	PAH (77), CTEPH (50)	CTEPH patients had • higher peak V_E, lower BR, higher peak RR • higher V_E/VCO_2 slope and V_E/VCO_2 at AT and lower $P_{et}CO2$ at AT • higher V_D/V_T, lower P_aO_2 and P_aCO_2 at peak exercise
McCabe 2013 [109]	CTEPH (15), CTED (15)	Not matched for peak VO_2. CTEPH patients had • higher V_E/VCO_2 slope and V_E/VCO_2 at AT and lower $P_{et}CO_2$ at AT • higher V_D/V_T, Aa gradient, lower P_aO_2 at peak exercise

CPET: cardiopulmonary exercise test; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; LHD: left heart disease; COPD: chronic obstructive pulmonary disease; IPAH: idiopathic pulmonary arterial hypertension; RHC: right heart catheterisation; TTE: transthoracic echocardiogram; mPAP: mean pulmonary artery pressure; IPF: idiopathic pulmonary fibrosis; CTEPH: chronic thromboembolic pulmonary hypertension; CTED: chronic thromboembolic disease; VO_2: oxygen uptake; V_E: ventilation; VCO_2: carbon dioxide production; O_2 pulse: oxygen pulse; S_pO_2: oxygen saturation; WR: workrate; $P_{et}CO_2$: end-tidal carbon dioxide; SV: stroke volume; HR: heart rate; RER: respiratory exchange ratio; NYHA FC: New York Heart Association functional class; PAOP: pulmonary artery occlusion pressure; P_eCO_2: mixed-expired carbon dioxide; $P_{(a\text{-}et)}CO_2$: arterial to end-tidal carbon dioxide pressure difference; S_vO_2: mixed venous oxygen saturation; P_aCO_2: arterial partial pressure of carbon dioxide; Aa gradient: Alveolar-arterial gradient; P_aO_2: arterial partial pressure of oxygen.

Table 2. Studies of prognostic value of CPET variables in PAH subjected to multivariate analysis.

Significant CPET Variables	Studies
Peak VO_2	Wensel 2002 (absolute value) [110], Wensel 2013 (% predicted) [111]
Peak systolic BP	Wensel 2002 [110]
V_E/VCO_2 at AT	Oudiz 2010 [112], Deboeck 2012 [92]
Δ O_2 pulse	Groepenhoff 2008 [113]
Peak HR / ΔHR	Groepenhoff 2013 [91] / Wensel 2013 [111]
Change in peak VO_2 with treatment	Groepenhoff 2013 [91]
Presence of right to left shunt	Oudiz 2010 [112]

CPET: cardiopulmonary exercise test; PAH: pulmonary arterial hypertension; VO_2: oxygen uptake; BP: blood pressure; V_E: ventilation; VCO_2: carbon dioxide production; AT: anaerobic threshold; Δ O_2 pulse: increase in oxygen pulse during exercise; HR: heart rate; ΔHR: increase in HR during exercise.

Table 3. Studies showing CPET variable abnormalities in exercise induced PAH (EIPAH).

Study	Population	Finding in EIPAH
Tolle 2008 [34]	Unexplained dyspnoea and fatigue with EIPAH (n = 78)	Reduced peak VO_2, increased peak Aa gradient
Dumitrescu 2010 [114]	Scleroderma (n = 30)	Lower VO_2 at peak and AT, lower peak O_2 pulse; lower VO_2 – WR slope, higher V_E/VCO_2 and lower $P_{et}CO_2$ at AT
Fowler 2011 [33]	Dyspnoea in scleroderma, family history of PAH, borderline PH (sPAP 35-45 mmHg on resting TTE) (n = 57)	Elevated V_E/VCO_2 and reduced $P_{et}CO_2$ at AT
Schwaiblmair 2012 [115]	Borderline PH (mPAP 21-24 mmHg on RHC) (n = 53)	Reduced peak VO_2, increased V_E/VO_2 at AT, increased V_D/V_T, increased Aa gradient, increased $P_{(a-et)}CO_2$

CPET: cardiopulmonary exercise test; EIPAH: exercise induced pulmonary arterial hypertension; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; sPAP: systolic pulmonary arterial pressure; TTE: transthoracic echocardiogram; mPAP: mean pulmonary arterial hypertension; RHC: right heart catheterisation; VO_2: oxygen uptake; Aa gradient: alveolar-arterial pressure gradient; AT: anaerobic threshold; O_2 pulse: oxygen pulse; WR: workrate; V_E: ventilation; VCO_2: carbon dioxide production; $P_{et}CO_2$: end-tidal partial pressure of carbon dioxide; V_D/V_T: ratio of dead space volume to tidal volume, $P_{(a-et)}CO_2$: arterial to end-tidal carbon dioxide pressure difference.

In summary, studies of CPET in PAH have been encouraging but not unconditionally so. The test can discriminate readily between subjects with PAH and normals but overlap of CPET variable responses between PAH and other comorbidities such as heart and lung disease can reduce its usefulness as a discriminator between differential diagnoses. Several of the CPET variables have prognostic value but studies have had heterogeneous results and they are not as strongly predictive as simpler variables (6MWD). CPET variables can detect treatment effect but larger studies were perhaps compromised by the complexity of the test. Finally CPET variables can detect abnormalities present in

EIPAH but this condition is of uncertain clinical significance.

Several approaches for enhancing the utility of CPET in PAH have been proposed. One suggestion has been to use submaximal rather than maximal testing [71,116–118]. This simplifies the test, removing the subjective element of maximal effort, making it shorter and potentially more reliable to administer, and may not lose any of the responsiveness. Whilst most studies have concentrated solely on measurement of gas exchange variables in this context ($P_{et}CO_2$, V_E/VCO_2), Lee *et al.* [44] looked at isotime measurement of the complete array of CPET variables after three minutes of low level steady state exercise. They found that whereas both oxygen transport (VO_2, O_2 pulse) and gas exchange variables (V_E/VCO_2 at AT) distinguished between different severity of PAH, only the former showed change pre and post treatment.

Another approach has been to introduce new CPET variables often based upon pattern of variable response rather than peak values [119]. Oxygen uptake kinetics are slower in these patients and represent one potential avenue which could be explored via time constants or post-exercise VO_2 decline. Autonomic imbalance with increased sympathetic and reduced parasympathetic activity can be present leading to delay in heart rate recovery (HRR). The latter was shown to be reduced in PAH [2] and had prognostic significance on multivariate analysis when only CPET variables were considered [120]. Oxygen uptake efficiency slope (OUES) [121] which represents the slope of a plot of VO_2 against log V_E is thought to encapsulate in one variable a measure of oxygen transport and gas exchange. It can be used as an estimate of peak VO_2 which requires only submaximal effort [121,122]. It has recently been shown to be of prognostic value in PAH [123].

4. Field Exercise Tests

The application of field exercise tests in subjects with PAH has been overwhelmingly dominated by the 6MWT which has as outcome measurement 6MWD. As its name implies, this is a fixed time walking test whose major requirement is a quiet 30 m corridor. There is detailed guidance on how the test should be performed [124] and its reproducibility and validation are well documented. Deboeck *et al.* [125] demonstrated the physiological response to the test in PAH subjects to be a submaximal test performed using predominantly aerobic metabolism. In common with other conditions [126], the 6MWD in PAH correlates with both the peak VO_2 achievable and the VO_2 attained during the test [125,127]. The product of 6MWD and weight improves the correlation [15,125,128]. 6MWD correlates with resting haemodynamics including CO and total pulmonary resistance but not mPAP [127]. It also correlates with New York Heart Association Functional Class [127] and quality of life [129]. Similarly change in six minute walk distance (Δ6MWD) following PAH treatment correlated with changes in cardiac index, PVR [130] and quality of life [129].

The short, fixed duration of administration makes it highly convenient for routine clinical use. Unfortunately it also has significant drawbacks. It can be surprisingly difficult to locate a 30 m corridor sufficiently quiet for regular use. Comorbidity with the pulmonary vascular axis which is particularly relevant in associated forms of PAH, such as scleroderma, compromise the reliability of the results [131,132]. The test has a ceiling effect as the linear relationship between peak VO_2 and 6MWD is lost in less impaired subjects [71,133–136]. This makes it more responsive to change in more severely affected individuals and vice versa in fitter individuals. Additionally there is a learning

effect [137] of approximately 2 to 4% between three consecutive daily walks, seen both at baseline and at two months follow up in healthy individuals. There was, however, no learning effect seen between two walks performed two months apart.

The major strength of the 6MWT is the ability of a baseline measurement to predict prognosis in IPAH which has resulted in its inclusion in several PH registry models for predicting survival including the French PH registry [138], the risk calculator derived from REVEAL (the North American database) [139] and the Scottish Composite Score [140]. This was also demonstrable in a meta-analysis of the many treatment trials in PAH [141]. It retains significance in multivariate analyses even when other strong predictors are included such as patient demographics [127,140], baseline haemodynamics from right heart catheterisation or CMR [140,142,143], CPET variables [92,113] and presence of pericardial effusion [127]. Absolute values of 6MWD measured following PAH treatment retain prognostic power but do not improve on the baseline measurement [144]. The prognostic power is reduced and may be lost in cases of associated PAH such as connective tissue disease [37,92].

Changes are seen in 6MWD with PAH treatment and it has been used as a surrogate outcome measure to obtain registration for most of the medications now used in this condition [145,146]. Although Δ6MWD correlates with change in haemodynamics following PAH treatment [130], it has proven very difficult to demonstrate any prognostic power of Δ6MWD with therapy despite being sought by several studies and meta-analyses [17,141,142,144,147]. The mechanism of this phenomenon has been explored recently by two further studies. In a meta-analysis of 22 PAH treatment studies, Savarese *et al.* [130] demonstrated that the change in haemodynamics seen with PAH treatment and correlating with Δ6MWD did not predict subsequent clinical events. In a pooled analysis of ten PAH treatment studies submitted to the US Food and Drug Administration (2404 patients), Gabler *et al*. [16] found that, despite a significant improvement in 6MWD, it accounted for only 22.1% of the treatment effect and they concluded that it was at best a modest surrogate endpoint for clinical events. To explain this anomaly it has been hypothesised that treatment improves both right ventricular function and haemodynamics but that only the former is strongly linked to clinical outcome [65]. Consequently Δ6MWD which correlates more strongly with change in haemodynamics [130] than change in right ventricular function [148] is poorly linked to clinical outcomes.

Given the poor performance of Δ6MWD in predicting clinical outcome, it is unknown whether this represents an insurmountable drawback or whether change in implementation of the test can improve its performance. Use of minimal important differences may be of some value here as there will then be confidence that changes in 6MWD, although not prognostic, do have some bearing on the morbidity experienced by the patient. Estimates of this for the 6MWT in PAH subjects have suggested an increase in 6MWD of between 26 and 42 m to be clinically relevant [16,149,150]. Alternatively, absolute rather than predicted values of 6MWD are commonly used as targets in clinical practice, which may obscure prognostic information as the distance covered by a 2 m tall 30 year old male will be very different from that expected from a 1.5 m 70 year old female. However, analysis of the relative performance of absolute and % predicted 6MWD did not show any difference in the ability of the two values to predict prognosis [151].

Measurements of HR and S_pO_2 routinely made during the 6MWT may confer additional value on the test. It has been shown that, as in left heart disease, patients with PAH have altered autonomic nervous system activity, the degree of which may reflect disease severity [152]. Such abnormalities

may be visible in heart rate response during recovery from exercise and readily measured in variables such as HRR1, which is the fall in HR during the first minute of recovery. Minai *et al.* [153] have measured this following a 6MWT in idiopathic PAH and found it to complement the ability of 6MWD to predict clinical worsening. Similarly in an older study with a limited multivariate analysis on a small cohort (n = 34) [154], the size of fall in S_pO_2 during the 6MWT was found to be of prognostic value with a 27% increase in risk of death over the study period (1992–1997) for each percentage point fall in saturation. The relevance of this in the modern treatment era is uncertain.

Waiting in the wings should the recent fall in fortune of the 6MWT prove irretrievable, there are a number of alternative exercise test candidates vying to displace it from its central position in the clinical management of PAH. **Treadmill** based walks have been proposed by several authors [155–158]. This is a convenient method of administering an exercise test not requiring a corridor with well-established protocols (such as Naughton-Balke) developed primarily for cardiac stress testing. The physiological stress imposed by such protocols is incremental in nature and avoids the ceiling effect issue seen with the 6MWT. Because of the fixed position of the subject, it can be combined with gas exchange measurements which moves it in complexity towards a formal CPET. S_pO_2 and other gas exchange measurements obtained during cycle and treadmill ergometry testing are not directly comparable because treadmill exercise leads to more desaturation and increased ventilatory inefficiency [86]. Changes in performance on treadmill testing were found to correlate with change in haemodynamics following PAH treatment [155] and treadmill exercise capacity was a predictor of mortality on multivariate analysis [156]. The REVEAL risk equation for PAH contains 6MWD. A study [158] which replaced this with treadmill test performance improved the predictive value of the equation. A treadmill version of the 6MWT has been developed where the speed of the treadmill is increased every 30 s following patient instructions [157] until a maximum is reached. If indicated by the subject, the speed can be decreased before the end of the test is reached. The outcome of the test is the distance walked on the treadmill in 6 min.

Shuttle walk tests are popular field exercise tests which require only a 10 m corridor. The incremental shuttle walk test imposes a linear physiological stress avoiding a ceiling effect and has been used by some PH groups [159,160]. The walk distance achieved correlates more strongly with peak VO_2 than 6MWD [160] but this is unsurprising given that it is an incremental test whereas the 6MWT is not. Endurance protocols are generally thought to be more sensitive ways of detecting a treatment effect than incremental tests [161]. There is only one study [162] comparing the relative ability of 6MWT, endurance shuttle walk test and constant load cycle ergometry CPET to detect treatment effect in PAH. The results suggest that the 6MWT is the most reproducible and responsive of the three.

Step climbing tests have received some attention in PAH studies. Again this test has a very small footprint and, because of the fixed location of the test, it can be combined with more elaborate gas exchange measurements. Fox *et al.* [163] found that step test performance was impaired in PAH and was correlated with functional class and 6MWD. Bernstein *et al.* [164] assessed the use of change in $P_{et}CO_2$ measurements during a step test in patients with scleroderma with and without established PAH. They found a correlation with mPAP determined by RHC in a subset of the patients and the measurement performed well as a screening test for PH in this group.

Activity monitoring is topical in many disease groups as daily activity is possibly a measurement more relevant to the burden of disease experienced by the patient than the performance of an exercise

test. Both Mainguy *et al.* [165] and Pugh *et al.* [166] demonstrated a reduction in daily life physical activities and increased sedentary time in PAH. Preliminary data published by Ulrich *et al.* [167] have suggested poorer survival in those with reduced daytime activity and Frantz *et al.* [168] provided evidence that treatment can improve activity levels.

5. Future of Exercise Testing in PAH

There are roles for all the modes of exercise testing discussed above in the management of PAH and a summary of what these may be in the future is suggested in Table 4.

Table 4. Likely future Indications for exercise testing modalities in management of PAH.

	Invasive Haemodynamics	Non-invasive haemodynamics	CPET	Field tests
Screening	-	++	++	-
Diagnosis	++	+	+	-
Prognosis	+	+	+	++
Follow-up	-	++	+	++

- little or no role; + some role; ++ major role.

Invasive exercise haemodynamics remains the reference standard for investigating the possible diagnosis of EIPAH and its use in this context will hopefully answer the question of the clinical relevance of this condition. It is also useful as a test of last resort in the investigation of subjects with unexplained dyspnoea or fatigue. It will not have a major role in screening or follow-up of subjects and in that area it is likely that non-invasive methods of determining cardiac haemodynamics will increase their foothold.

CPET is a cumbersome tool to use routinely. Its areas of growth are likely to include screening for subclinical disease and a focussing of the test towards follow up of fitter patients less well served by field tests. It is also likely that there will be increasing use of new variables such as OUES and HRR1 and application of cut-down submaximal tests more convenient for widespread clinical use.

Given the major investment so far in 6MWTs and their acknowledged prognostic power in the more impaired patients, it seems unlikely that they will be replaced by alternative field tests. It is possible that more use will be made of additional variables such as HRR1. The major growth in this area may be in activity monitoring, particularly given the flexibility of this mode of measurement and its link with rehabilitation programmes.

6. Conclusion

Exercise testing occupies a major role in the management of PAH. Critical review of its current utilisation shows scope for improvement of its implementation and expansion in the indications (screening, diagnosis, prognosis, monitoring of outcomes) for which it is used. This applies to a wide range of tests from invasive haemodynamics through to activity monitoring over prolonged periods. We predict continued and growing research interest in this modality of assessment of PAH.

Author Contributions

MKJ performed the literature review and wrote the article. ST produced the figures and reviewed the text.

Conflicts of Interest

The authors declare no conflict of interest.

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