An official European Respiratory Society statement: pulmonary haemodynamics during exercise

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ABSTRACT There is growing recognition of the clinical importance of pulmonary haemodynamics during exercise, but several questions remain to be elucidated. The goal of this statement is to assess the scientific evidence in this field in order to provide a basis for future recommendations.

Right heart catheterisation is the gold standard method to assess pulmonary haemodynamics at rest and during exercise. Exercise echocardiography and cardiopulmonary exercise testing represent non-invasive tools with evolving clinical applications. The term "exercise pulmonary hypertension" may be the most adequate to describe an abnormal pulmonary haemodynamic response characterised by an excessive pulmonary arterial pressure (PAP) increase in relation to flow during exercise. Exercise pulmonary hypertension may be defined as the presence of resting mean PAP <25 mmHg and mean PAP >30 mmHg during exercise with total pulmonary resistance >3 Wood units. Exercise pulmonary hypertension represents the haemodynamic appearance of early pulmonary vascular disease, left heart disease, lung disease or a combination of these conditions. Exercise pulmonary hypertension is associated with the presence of a modest elevation of resting mean PAP and requires clinical follow-up, particularly if risk factors for pulmonary hypertension are present. There is a lack of robust clinical evidence on targeted medical therapy for exercise pulmonary hypertension.

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Introduction

Acute and chronic alterations of pulmonary haemodynamics are of major clinical relevance [1]. An abnormal pulmonary haemodynamic response to exercise may be present in various cardiac and pulmonary conditions and may cause dyspnoea, which is one of the most frequent symptoms in both respiratory and cardiovascular medicine. The importance of pulmonary haemodynamics during exercise has been recognised, but this topic was not extensively discussed at recent pulmonary hypertension world conferences [1–3]. Accordingly, many questions, including the choice of diagnostic tools, the criteria for an abnormal response, or the clinical and prognostic relevance of pulmonary haemodynamics during exercise in different patient groups remain to be elucidated. Therefore, the goal of this statement has been to review the available literature and to assess the scientific evidence in the field of pulmonary haemodynamics during exercise. In addition, several areas have been identified where further research is needed. The current statement may provide a basis for future recommendations in clinical practice guidelines.

Methods and process

This task force is an international and multidisciplinary effort supported by the European Respiratory Society (ERS). 15 members were pulmonologists, four were cardiologists and two were physiologists. The chairs (P. Herve and H. Olschewski) and coordinator (G. Kovacs) selected the other task force members based on their expertise in pulmonary exercise haemodynamics. Conflicts of interest of all task force members were declared and managed according to ERS rules (for full disclosure, see online supplementary material). An early face-to-face meeting of the chairs took place in Graz (Austria) in May 2015. At this meeting, suggestions were made on the formation of 10 working groups within the task force and the specific questions to be addressed within the groups (table 1). Following that, the literature search and the review of the relevant studies between 1945 and 2015 were performed within the working groups using the MEDLINE database. The search was restricted to articles available in English, reporting on human studies performed in adults. A secondary search reviewed the reference list of relevant papers. From 2016 onwards, task force members were asked to provide additional key literature they were aware of. At the first task force meeting (Amsterdam, the Netherlands; September 2015), the results of the individual reviews were presented and discussed by the whole panel. Based on these discussions, each group assembled the most important statements ("claims") addressing a specific area and the statements were evaluated by all task force members for correctness and importance. Based on this grading, the first draft of the manuscript was written. This draft was discussed at the second task force meeting (Lausanne, Switzerland; April 2016); the main points of the statement were finalised together and studies published after the first task force meeting were included. The final document combines an evidence-based approach relying on the reviewed publications with the clinical expertise of the task force members.

Assessment of pulmonary haemodynamics during exercise

Clinical relevance

Based on the reviewed literature, the assessment of pulmonary haemodynamics during exercise provides important additional information to resting haemodynamics in several clinical situations (table 2). This

TABLE 1 Main topics of pulmonary exercise haemodynamics discussed by the working groups

Requirement for a definition of normal *versus* abnormal exercise haemodynamics
Assessment of exercise haemodynamics by right heart catheter
Assessment of exercise haemodynamics by echocardiography
Assessment of exercise haemodynamics by CPET
Exercise haemodynamics in healthy subjects
Exercise haemodynamics in patients at risk of pulmonary hypertension
Exercise haemodynamics in patients with borderline PAP elevation
Exercise haemodynamics in manifest pulmonary hypertension
Pulmonary exercise haemodynamics in patients with left heart disease
Pulmonary exercise haemodynamics in patients with lung disease
Pressure–flow relationship and ventriculo-arterial coupling during exercise

CPET: cardiopulmonary exercise testing; PAP: pulmonary arterial pressure.

applies to patients without overt pulmonary or cardiac disease by the unmasking of occult pulmonary vascular or left heart disease, or to patients with known chronic lung or heart limitations but unexplained dyspnoea. Pulmonary haemodynamics during exercise may be helpful to discriminate between group 1 and group 2 pulmonary hypertension during the diagnostic work-up [1, 4–7]. This discrimination can be very difficult if only resting haemodynamics are available and the pulmonary arterial wedge pressure (PAWP) is close to 15 mmHg or if the clinical characteristics of the patient primarily suggest heart failure with preserved ejection fraction despite normal resting PAWP. Furthermore, pulmonary haemodynamics during exercise may be used for the risk stratification and follow-up of pulmonary arterial hypertension (PAH) patients and as a useful tool in clinical research, in order to better understand the characteristics of the pulmonary circulation and its interaction with the heart. This may lead to the development of better methods to assess right ventricular contractile reserve and to predict right ventricular failure. Current cardiology guidelines recommend exercise echocardiography in symptomatic patients with mild mitral stenosis, low flow/low gradient aortic stenosis and asymptomatic severe aortic insufficiency and mitral regurgitation, in order to refine the indications for valve surgery [8, 9].

Safety

Based on the experience of the panel members and current guidelines for exercise tests [10], the risk/benefit ratio of the assessment of pulmonary haemodynamics during exercise is unfavourable in patients with unstable disease or patients with decompensated right heart failure. Based on personal experience of the task force members, the investigation of pulmonary haemodynamics during exercise appears to have no additional risk compared to resting right heart catheterisation (RHC) [11] or echocardiography and cardiopulmonary exercise testing in expert centres. However, there is a paucity of large-scale published data for this specific question. Most task force members agreed that from an ethical point of view it is difficult to justify invasive exercise examinations in healthy controls or in patients who have not undergone a thorough work-up at rest.

Exercise RHC

In order to reliably assess pulmonary haemodynamics during incremental exercise, the measurement of mean pulmonary arterial pressure (PAPm), PAWP and cardiac output (CO) are necessary at each exercise level. This allows the calculation of total pulmonary resistance (TPR = PAPm/CO) and pulmonary

TABLE 2 Possible clinical relevance of pulmonary haemodynamics during exercise

Decision on valve surgery/intervention: symptomatic mild mitral stenosis and low flow/low gradient aortic stenosis, asymptomatic severe aortic insufficiency and mitral regurgitation
Unmasking of abnormal physiology during exercise suggestive of occult pulmonary vascular or left heart disease or early pulmonary vascular disease in patients at risk of PAH
Diagnostic work-up of patients with known chronic pulmonary or cardiac disease, but still unexplained dyspnoea
Diagnostic work-up of pulmonary hypertension: discrimination between group 1 and group 2 pulmonary hypertension in patients with ambiguous test results
Risk stratification in PAH: assessment of prognosis
Follow-up in PAH patients: assessment of treatment efficacy (exercise capacity and right ventricular function)

PAH: pulmonary arterial hypertension.

vascular resistance (PVR = (PAPm−PAWP)/CO) at each exercise level as well as the PAPm/CO slope. The additional repeated determination of right atrial pressure (RAP) may help detecting changes in intrathoracic pressure during exercise [12]. RHC is the gold standard method to assess pulmonary haemodynamics at rest and during exercise (table 3) [1]. Although the method is very well established and widely used, some practical issues may be challenging, in particular if exercise causes movement artifacts and large breathing efforts cause large intrathoracic pressure swings.

The accurate assessment of PAWP is essential at rest and during exercise, as this is the key parameter to differentiate between pulmonary vascular and left heart diseases. In addition, it is essential for the calculation of PVR. The assessment of PAWP may be technically challenging, especially during exercise. A common pitfall is an incompletely wedged balloon, creating a hybrid tracing of pressures between pulmonary arterial pressure and PAWP, leading to an overestimation of PAWP. The calculation of TPR does not necessitate PAWP assessment, which reduces the sources of error as compared to PVR.

In line with current recommendations [1], for both rest and exercise it is important that the zero reference level is set at the left atrial level. In the supine position this corresponds to the midthoracic level [1, 13, 14]. If a non-supine position is used, a general rule of providing a reference point has been suggested as the intersection of 1) the frontal plane at the midthoracic level; 2) the transverse plane at the level of fourth anterior intercostal space; and 3) the midsagittal plane [15, 16] (figure 1).

When a fluid-filled catheter is used for the examination, the pressure reading corresponds to the difference between the pressure in the vessel and the pressure at zero level, irrespective of the position of the catheter tip in the vessel [17]. PAPm can be measured reliably by fluid-filled catheter, but due to aliasing artifacts, the systolic and diastolic pressures may be better assessed by micromanometer-tipped catheter. When a micromanometer-tipped catheter is used, the position of the catheter tip corresponds to the zero level. Therefore, it makes a difference if the catheter tip is placed into an upper or a lower lung region. In order to get values from tip catheters corresponding to a fluid-filled catheter, the tip should be positioned at the midthoracic (left atrial) level, or the pressure should be corrected by the vertical distance from this level.

Intrathoracic vascular pressure readings correspond to the algebraic sum of transmural vascular pressure and intrathoracic pressure (P_{it}). P_{it} depends on the alveolar pressure, actual lung volume, lung compliance, body position and indirectly on respiratory phase and age [18]. Respiratory pressure swings increase with

TABLE 3 Major statements regarding exercise right heart catheterisation

Essential measurements and calculations at each exercise level	Measurement of PAPm, PAWP and CO Calculation of TPR (PAPm/CO) and PVR ((PAPm − PAWP)/CO) as well as the PAPm/CO slope
Supplementary measurements	Assessment of RAP during increasing exercise levels Systemic and pulmonary arterial blood gas analysis at least at peak exercise
Zero reference level	At the left atrial level for both rest and exercise Supine position: midthoracic level at the insertion of the 4th rib to the sternum Non-supine position: intersection of the frontal plane at the midthoracic level, the transverse plane at the level of fourth anterior intercostal space and the midsagittal plane
Dealing with respiratory swings	During exercise: averaging pulmonary pressure values over several respiratory cycles Comparing exercise and resting haemodynamics: all conditions (body position, zero level and respiratory averaging) must be exactly the same at rest and during exercise
Exercise duration and performance	Incremental exercise tests (step or ramp protocol) with repeated haemodynamic measurements may provide most clinical information on the pulmonary circulation For reaching a steady state for oxygen uptake on a given exercise level (step protocol), generally 3–5 min are needed; however, for practical reasons, shorter time intervals may be chosen (*e.g.* 2-min steps aiming for a duration of the exercise time of ~10 min) Prolonged exercise tests of the pulmonary circulation have not been evaluated for the detection of early pulmonary vascular disease or left heart conditions Isometric exercise has little or no effect on CO, and may considerably change pleural pressure and systemic vascular pressure and resistance and is not suitable to challenge the pulmonary circulation
Safety	Risk/benefit ratio of the assessment of pulmonary haemodynamics during exercise is unfavourable in patients without thorough resting haemodynamic examinations, patients with unstable disease or patients with decompensated right heart failure From an ethical point of view, it may be difficult to justify invasive exercise examinations in healthy controls or in patients who did not undergo a thorough diagnostic work-up at rest

PAPm: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; TPR: total pulmonary resistance; PVR: pulmonary vascular resistance; RAP: right atrial pressure.

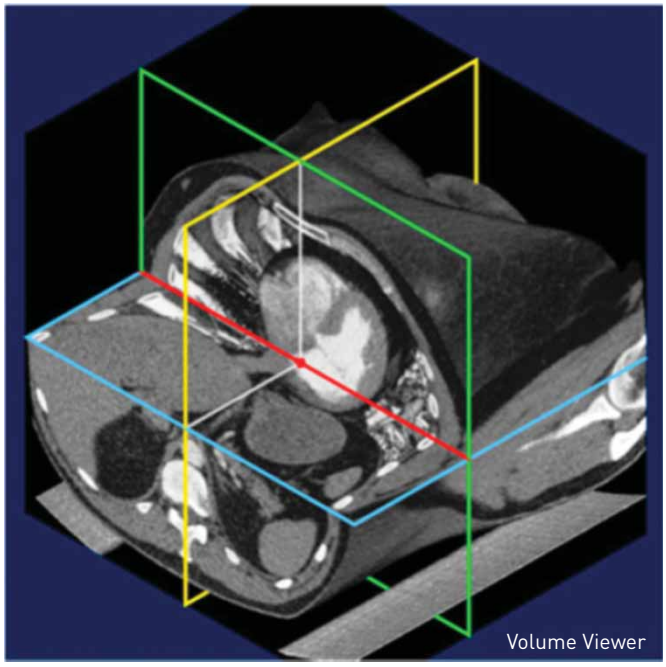

FIGURE 1 Suggested zero reference point (red point) defined by the intersection of the frontal plane (blue) at the midthoracic level, the transverse plane (green) at the level of fourth anterior intercostal space, and the midsagittal plane (yellow). In this patient, the reference point would be within the left atrium. The zero reference level in the non-supine patient is suggested to be set at the height of the zero reference point. Reproduced from [16] with permission from the publisher.

increasing tidal volume, ventilatory flow, pulmonary elastance and airway resistance [19]. During exercise, where ventilatory flow and tidal volume increase considerably, in the absence of pleural pressure measurements reliable assessment of pulmonary pressure values is only possible when these are averaged over several respiratory cycles, as performed in previous studies [16, 19, 20]. Any breath-hold manoeuvre, with or without Valsalva manoeuvre, should be avoided, because this may cause sudden changes in heart rate and CO during low levels of exercise [21–23]. If exercise haemodynamics are to be compared with resting haemodynamics, all conditions of measurement (body position, zero level and respiratory averaging) must be performed in exactly the same way at rest as they are during exercise.

CO corresponds to the total pulmonary blood flow if there is no shunt blood flow and no significant bronchial arterial to pulmonary arterial collateral blood flow. The gold standard for determination of CO is the direct Fick principle, while thermodilution is considered to be a reliable alternative method both at rest and during exercise. For application of the Fick principle, oxygen saturations and haemoglobin concentrations must be measured and not calculated from the partial pressures of oxygen in arterial and mixed venous blood. In addition, oxygen consumption must be directly measured and not taken from tables relying on standardised resting conditions in healthy subjects. Pulmonary blood flow is strongly dependent on the respiratory cycle, but CO, as determined by thermodilution or the Fick principle, corresponds to the average blood flow over several respiratory cycles. At rest, repeated thermodilution assessments and averaging of the measurements are needed. During exercise, it may be difficult to obtain multiple measurements due to rapidly changing haemodynamics with increasing workload, but it seems reasonable to obtain at least two measurements at each step.

In most exercise studies, incremental work (ramp or step protocol) has been used. In case of a step protocol, haemodynamic measurements were performed towards the end of each exercise level. For reaching a steady state in oxygen consumption on a given exercise level, generally 3–5 min are needed; however, for practical reasons, mostly shorter time intervals have been chosen (*e.g.* 2-min steps aiming for a duration of the exercise time of ~10 min), which appears to be a good compromise. In addition to the haemodynamic measurements, systemic and pulmonary arterial blood gas analysis was performed at least at rest and at peak exercise. In some studies, prolonged exercise was performed at a constant submaximal level [24–27]. Such prolonged exercise tests have not been performed in patients with pulmonary vascular or left heart disease, so it is difficult to make statements on their utility for detection of abnormalities of the pulmonary circulation. There is a paucity of data on isometric exercise. This has little or no effect on CO, and may change intrathoracic and systemic arterial pressure and systemic vascular resistance.

Therefore, isometric exercise is not suitable to challenge the pulmonary circulation [4, 5]. In exercise studies with cycle ergometry, a venous approach *via* the jugular or the cubital vein for the insertion of the pulmonary artery catheter are advantageous as compared to the femoral approach and should be preferred.

Exercise Doppler echocardiography

Echocardiography is considered to be the most important non-invasive method of investigating the pulmonary circulation at rest. Echocardiography allows the estimation of several important variables, including the pulmonary arterial pressure, left ventricular filling pressure and CO. These parameters may also be assessed during exercise [28–31]. From the methodological point of view it needs to be emphasised that haemodynamics change very rapidly after cessation of exercise, making measurements performed after this time point less valuable. Relying on echocardiography, PAPm may be calculated from estimated systolic PAP values (0.61 × systolic PAP + 2) [32, 33]; left ventricular filling pressure may be estimated from the ratio of Doppler mitral E flow–velocity wave and tissue Doppler mitral annulus flow E′ early diastolic velocity (1.9 + 1.24 E/E′) [34]; and CO from the left ventricular outflow tract cross-sectional area multiplied by the pulsed Doppler velocity time integral [35]. Alternative formulas might also be adequate. Although these methods provide accurate estimates of haemodynamics (no relevant bias at Bland–Altman analysis when compared with invasive measurements), they suffer from insufficient precision (relatively wide limits of agreement at Bland–Altman analysis) [36]. This reduces the value of these methods if individual data are to be evaluated. In particularl, the precision of echocardiography to estimate PAPm, left ventricular filling pressure or CO during exercise is currently unknown, necessitating further validation studies against RHC [37–39].

Exercise echocardiography was performed in several studies in patients at risk of pulmonary hypertension [40–45]. These studies are important as they delivered information on exercise haemodynamics within these patient groups and may form a basis for long-term observation studies determining potential prognostic parameters. Unfortunately, only few of these studies compared haemodynamic data during exercise assessed by echocardiography and the gold standard, RHC [36, 37].

Currently, exercise echocardiography is recommended by cardiology guidelines in symptomatic patients with mild mitral stenosis, low flow/low gradient aortic stenosis [8] and asymptomatic severe aortic insufficiency and mitral regurgitation, in order to refine the indications for valve surgery [9]. It is considered to be reasonable that dedicated investigators perform exercise echocardiography in patients with dyspnoea of unknown aetiology and normal resting echocardiographic results. In addition, the technique should be considered in subjects at risk of PAH (such as systemic sclerosis (SSc)) [46]. This method requires the use of a semirecumbent left-tilted ergometer and an intense training period of the investigator. According to the current European pulmonary hypertension guidelines, the "clinical value of exercise echocardiography is uncertain, particularly with regards to its use for the identification of cases with pulmonary hypertension limited to exercise due to the lack of validated criteria and prospective confirmatory data" [1].

Exercise echocardiography may contribute to the assessment of right ventricular function during exercise [47]. In patients with severe PAH, both a diminished increase in systemic arterial pressure [48] and a diminished systolic PAP increase as assessed by exercise echocardiography, suggesting a reduced contractile reserve of the heart [49] were independent indicators of a poor prognosis. Exercise is the most commonly used "stress" modality, but hypoxia and pharmacological stress (dobutamine) have also been employed [29, 50].

An emerging method for the assessment of pulmonary haemodynamics during exercise is cardiac magnetic resonance imaging (MRI), delivering information on right ventricular function and the characteristics of the pulmonary vessels [51–54].

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is a useful tool to assess functional variables such as oxygen uptake (peak V'_{O_2}), heart rate and ventilation at peak exercise [10, 55]. In addition, the method allows for a detailed analysis of the gradual changes of many cardiorespiratory variables during increasing exercise intensities and may help clinicians distinguish between normal and abnormal haemodynamic responses to exercise [56–64]. CPET may suggest reduced stroke volume, impaired chronotropic response, exercise-induced hypoxaemia (including right–left shunt), reduced muscular oxygen extraction and increased ventilatory demand due to increased dead space and hyperventilation in patients with pulmonary vascular disease [61]. In patients with pulmonary hypertension there was an excellent correlation between resting PAPm and the minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) slope [57] and end-tidal carbion dioxide tension [60], although only the V'_E/V'_{CO_2} slope appears to have

prognostic relevance in PAH [65]. Due to different response profiles, CPET helps differentiate PAH from pulmonary veno-occlusive disease [66] and chronic thromboembolic pulmonary hypertension [67–69] and allows for the assessment of exercise-limiting factors in pulmonary hypertension patients with concomitant chronic obstructive pulmonary disease (COPD) [70, 71], interstitial lung disease [72] or left heart disease [73–75]. Peak V'_{O_2} has been shown to have prognostic relevance in idiopathic PAH, where peak V'_{O_2} <10.4 $L \cdot min^{-1} \cdot kg^{-1}$ is strongly associated with worse survival [48, 49, 76]. In addition, a recent study demonstrated that a peak V'_{O_2} >18.7 $L \cdot min^{-1} \cdot kg^{-1}$ ruled out PAH in patients with SSc [77]. In addition, CPET can be used in combination with direct haemodynamic measurements (RHC or exercise echocardiography), providing detailed information on both the degree of cardiac impairment and pulmonary pressure abnormalities [49, 64, 76, 78–81].

Requirement for a definition of normal *versus* abnormal exercise haemodynamics

In order to distinguish normal and pathological patterns of pulmonary haemodynamics, the response of healthy subjects to exercise needs to be defined. This was identified as an issue at early scientific meetings after the introduction of the RHC technique. In 1961 at a World Health Organization (WHO) expert committee meeting on chronic cor pulmonale in Geneva [82] exercise haemodynamics was discussed; however, due to the "lack of standardisation of available figures" normal values have not been established. In 1973, at the WHO meeting on primary pulmonary hypertension [83] a "latent form of pulmonary hypertension" was described, which "becomes apparent only when there is an increase in blood flow", and based on expert opinion ("mean pulmonary arterial pressure (PAPm) does not normally exceed 30 mmHg during exercise"), the definition of pulmonary hypertension was supplemented with an "exercise-part". This included a threshold for PAPm (30 mmHg), but did not integrate any further parameters such as age, work rate or CO. The haemodynamic definition of pulmonary hypertension, including the exercise-part, has been adopted at later consensus conferences [84] and widely used by clinicians. Pulmonary exercise haemodynamics became one of the major issues discussed during the 4th Pulmonary Hypertension World Conference in Dana Point (2008) [2], where the exercise-part of the pulmonary hypertension definition was challenged. Based on a large meta-analysis [20] of almost 1200 healthy subjects it became evident that the normal response of pulmonary pressure to exercise is dependent on age and the level of exercise, and therefore no single pressure threshold can be set to define pathological changes. Accordingly, the exercise-part of the pulmonary hypertension definition was abandoned and additional studies were suggested before implementing an updated exercise-part of the pulmonary hypertension definition.

Meanwhile, the introduction of a multitude of therapeutic options for pulmonary hypertension and growing awareness led to an increasing number of pulmonary hypertension patients and a remarkable increase in the median age of the incident patients [85, 86]. Particularly in the advanced age groups, there are many patients with severe dyspnoea on exertion, but only moderately elevated resting PAP values. These patients may even present with PAPm values <25 mmHg at rest, but a steep pressure increase during exercise. The same applies for patients with scleroderma and patients with chronic thromboembolic pulmonary disease. More than ever before, the increased incidence of such forms of pulmonary vascular disease which may be characterised by changes in pulmonary haemodynamics during exercise necessitates appropriate operational definitions of normal *versus* abnormal exercise haemodynamics.

The task force members agreed that the term "exercise pulmonary hypertension" is adequate to describe an abnormal pulmonary haemodynamic response characterised by an excessive increase in PAP in relation to flow during exercise. Therefore, this preliminary term is used in this statement. The term "exercise-induced pulmonary hypertension" was felt to be inappropriate by the majority of task force members, because this term might suggest that exercise causes pulmonary hypertension. There is currently no widely accepted haemodynamic definition for exercise pulmonary hypertension. Subjects with exercise pulmonary hypertension have a resting PAPm <25 mmHg and represent the haemodynamic appearance of early pulmonary vascular disease, left heart disease, lung disease or a combination of these.

Exercise haemodynamics in healthy subjects; the recognition of abnormal exercise haemodynamics

Based on invasive haemodynamic measurements, an increase of PAP and PAWP, a modest decrease of TPR and a very modest decrease of PVR may be observed in healthy subjects at progressing exercise levels [87, 88] (table 4). In subjects aged <50 years, an 85% increase in CO was associated with a 41% increase in PAPm, a 25% decrease in TPR ($p<0.0001$) and a 12% decrease in PVR ($p<0.01$) [87].

As exercise intensity is the main determinant of CO during dynamic exercise, both the PAPm/CO slope and the PAPm/workload slope may be more suitable than PAPm alone to distinguish between normal and abnormal pulmonary haemodynamics during exercise [4, 5, 78, 87, 89–92]. Therefore, during increasing

TABLE 4 Major statements regarding pulmonary haemodynamics during exercise in healthy subjects

At progressing exercise levels and CO, a steady increase of PAPm and PAWP, a modest decrease of TPR and a very modest decrease of PVR can be observed
The PAPm/CO slope appears to be largely independent of sex, although minor differences may be present
The elevation of PAPm (the PAPm/CO slope) during exercise is largely dependent on age
There are very few data available on pulmonary haemodynamics during exercise in overweight subjects
Body position has an influence on pulmonary haemodynamics: in the upright as compared to the supine position, PAPm, PAWP, stroke volume and CO are lowered, whereas heart rate, PVR and arterio-venous oxygen difference are increased both at rest and mild exercise levels. Posture-induced haemodynamic differences decrease during increasing levels of exercise
Most haemodynamic data during exercise were assessed by means of cycle ergometry. No direct comparison of haemodynamics between treadmill and cycle ergometry is available

CO: cardiac output; PAPm: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; TPR: total pulmonary resistance; PVR: pulmonary vascular resistance.

exercise levels, PAPm (and PAWP) changes should always be provided in relation to the respective increase in CO or workload.

CO is the main factor determining the pressure difference across a given blood flow resistance. Although it may not be perfectly accurate, the resistance of the lung to pulmonary blood flow can be calculated in analogy to an Ohm's resistor with

$$PVR = TPG/CO = (PAPm - PAWP)/CO$$

where TPG is the average transpulmonary pressure gradient and

$$TPG = PAPm - PAWP \text{ and } PAPm = TPG + PAWP$$

TPR refers to

$$TPR = PAPm/CO$$

and includes both the serial resistances of the pulmonary vasculature and the heart. Indeed, TPR corresponds to the sum of PVR and the PAWP/CO ratio with

$$TPR = PAPm/CO = TPG/CO + PAWP/CO = PVR + PAWP/CO$$

KOVAKS *et al.* [87] proposed the term "left ventricular filling resistance" for the PAWP/CO ratio. One of the main confounders for determination of the PAWP/CO ratio, and therefore for the PAPm/CO ratio, is intrathoracic pressure, which can change significantly during exercise, particularly in patients with obstructive lung diseases. TPG/CO is not directly affected by changes in intrathoracic pressure because PAPm and PAWP are affected in the same way; however, it may be difficult to assess accurately if there are large respiratory swings.

An analysis based on a retrospective cohort and healthy subjects from the scientific literature revealed haemodynamic criteria predicting diseases of the pulmonary vessels or the heart [89]. When the controls and healthy subjects were compared to patients with a resting PAPm $\leqslant$20 mmHg, but suffering from either pulmonary vascular or cardiac diseases, an abnormal haemodynamic response defined by PAPm >30 mmHg and TPR >3 Wood units at peak exercise [89] predicted the disease with high sensitivity and specificity (figure 2). Among all parameters tested, these criteria were the best to distinguish controls and healthy subjects from patients with pulmonary vascular disease or left heart failure, therefore they may be used to define exercise pulmonary hypertension (figure 3 and table 5). Alternatively, a PAPm/CO slope >3 Wood units may be used to define exercise pulmonary hypertension [4, 5] if multipoint PAPm/CO relationships are available. A third method which uses a two-point measurement of the PAPm/CO slope from resting and peak exercise haemodynamics has also been proposed [93]. In a recent analysis, the three methods described were compared and a very high diagnostic accuracy for all three methods was found [94], all of them representing a significant advancement compared to merely relying on pulmonary arterial pressure for the diagnosis of exercise pulmonary hypertension. Regarding the classification of patients for

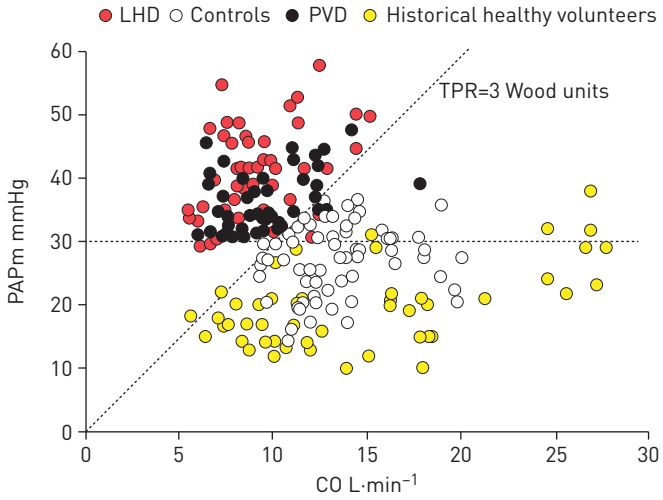

FIGURE 2 Relationship between mean pulmonary arterial pressure (PAPm) and cardiac output (CO) during peak exercise. Individual data points represent PAPm and CO reached at maximal exercise stratified by subjects with pulmonary vascular disease (PVD), left heart disease (LHD), control subjects and historical healthy volunteers. Note that the total pulmonary resistance (TPR) line with a slope of 3 Wood units differentiated the diseased (PVD and LHD) and nondiseased groups (controls and historical volunteers). Reproduced from [89].

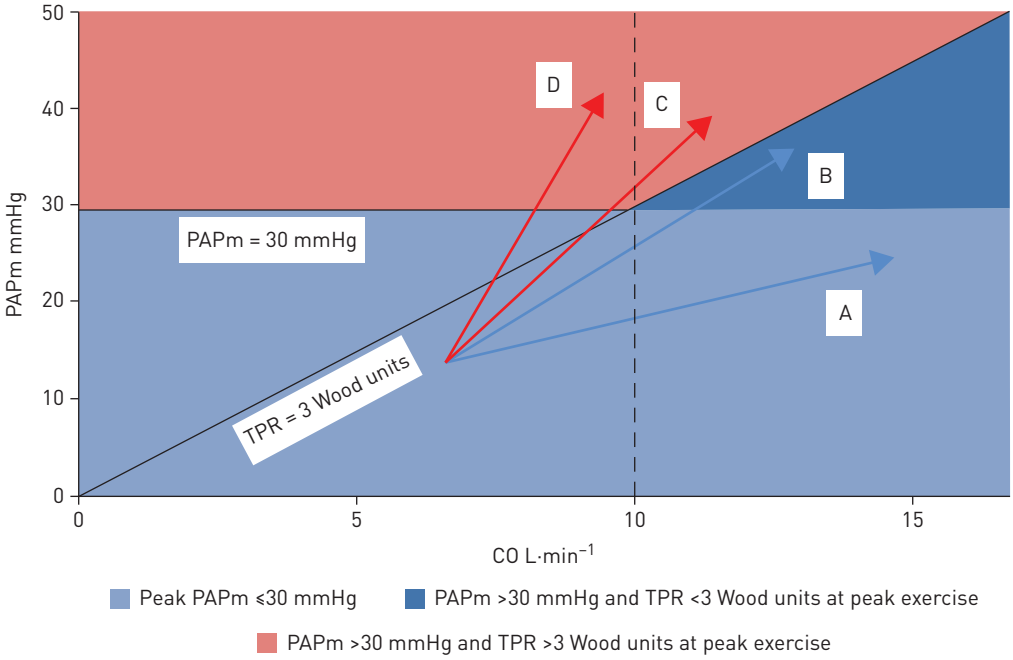

FIGURE 3 Definition of exercise pulmonary hypertension according to the task force proposal. The definition is based on the relationship between mean pulmonary arterial pressure (PAPm) and cardiac output (CO) at peak exercise by Herve *et al.* [89]. The light blue area represents peak PAPm values ⩽30 mmHg (normal range according to previous exercise pulmonary hypertension definition). The dark blue triangle represents PAPm values >30 mmHg, but total pulmonary resistance (TPR) <3 Wood units at peak exercise. Reaching this area was considered pathological according to the previous definition of exercise pulmonary hypertension, but normal based on the proposal of this task force. The red area represents values with PAPm >30 mmHg and TPR >3 Wood units at peak exercise, corresponding to exercise pulmonary hypertension proposed by the task force. Line A represents a patient with a mild increase of PAPm and normal pulmonary haemodynamics during exercise. Line B represents a patient with a steeper PAPm/CO ratio and PAPm >30 mmHg, but TPR <3 Wood units during exercise. In this case, the criteria of the proposed definition of exercise pulmonary hypertension are not fulfilled. Lines C and D represent patients with PAPm >30 mmHg and TPR >3 Wood units at peak exercise and thus fulfilling the proposed criteria of exercise pulmonary hypertension.

TABLE 5 Major statements regarding an abnormal pulmonary haemodynamic response during exercise

The PAPm/CO relationship or ratio may be more suitable than PAPm alone to distinguish between normal and abnormal pulmonary haemodynamics during exercise
Exercise pulmonary hypertension may be defined by the presence of resting PAPm <25 mmHg and PAPm >30 mmHg at peak exercise while TPR is >3 Wood units
The reliable diagnosis of exercise pulmonary hypertension necessitates right heart catheterisation
Various cut-offs from 20 mmHg to 25 mmHg have been considered as the upper limit of normal for PAWP during exercise, but the evidence supporting these thresholds is scarce, requiring further studies in this field. From a theoretical point of view, the PAWP/CO relationship and the LVEDP/CO relationship might better discriminate between physiological and pathological responses of the left ventricle than PAWP and LVEDP alone
Very limited data are available from elderly and non-Caucasian subjects to distinguish normal from pathologic haemodynamics during exercise
Exercise pulmonary hypertension is a condition representing the haemodynamic appearance of early pulmonary vascular disease, left heart disease, lung disease or a combination of these conditions
The prognostic relevance of exercise pulmonary hypertension and its predictive value for the future development of manifest pulmonary hypertension needs to be assessed in large prospective studies
There is a lack of robust clinical evidence on targeted medical therapy for exercise pulmonary hypertension

PAPm: mean pulmonary arterial pressure; CO: cardiac output; TPR: total pulmonary resistance; PAWP: pulmonary arterial wedge pressure; LVEDP: left ventricular end-diastolic pressure.

presence or absence of exercise pulmonary hypertension, concordant classification among the three methods was found in 80.5–85.8% of cases. The first method may be the simplest one. The second method using the PAPm/CO slope has the advantage of avoiding reliance on peak exercise haemodynamic values during which respiratory swings are often accentuated and the dependence on exercise-limiting factors like joint pain preclude maximum challenge of the cardiovascular system.

Based on the significant correlation of CO with body surface area (BSA) [18], it may be reasonable to consider cardiac index values instead of CO where small subjects (or children) or large overweight subjects are concerned. In the original data of Herve *et al.* [89], relying on patients with an average BSA of 1.9 m^2, the c-statistics were not improved by using cardiac index instead of CO. Therefore, the routine use of cardiac index instead of CO is not justified based on the existing data.

There is no consensus on the normal PAWP and left ventricular end-diastolic pressure (LVEDP) elevation during exercise. Various cut-offs from 20 mmHg to 25 mmHg (depending on the method of measurement) have been considered as upper limit of normal for PAWP [6, 95, 96] during exercise, but the evidence supporting these thresholds is scarce, requiring further studies in this field. From a theoretical point of view, the PAWP/CO relationship and the LVEDP/CO relationship might better discriminate between physiological and pathological responses of the left ventricle than PAWP and LVEDP alone. This relationship may rely heavily on age and training in healthy controls [97]. The assessment of PAWP or LVEDP during exercise is technically challenging, and as a confounder the reading depends on changes in intrathoracic pressures. However, currently there is no suitable alternative to these measures for assessment of pulmonary venous pressure during exercise.

Currently, the reliable diagnosis of exercise pulmonary hypertension necessitates RHC. Exercise pulmonary hypertension is a condition representing the haemodynamic appearance of early pulmonary vascular disease, left heart disease, lung disease or the combination of these conditions. Depending on the cause, besides the elevation of PAPm, the elevation of PAWP and/or intrathoracic pressure may be present. It should be mentioned that only a very limited number of elderly and non-Caucasian subjects were included in the available RHC studies. Therefore, it would be important to confirm the suggested haemodynamic definitions of exercise pulmonary hypertension in populations that have been underrepresented. In addition, it would be important to test them for their clinical (dyspnoea and exercise limitation) and prognostic relevance and for their predictive value for the future development of manifest pulmonary hypertension in prospective studies.

In studies with individual haemodynamic data during exercise, a linear PAPm–CO relationship has been documented in the majority of healthy subjects [98]. This seems to exclude both significant distensibility/recruitment of vessels and active vasodilatation. However, reflected waves and a vortex formation in the pulmonary arterial Windkessel area [99] might increase pulmonary vascular resistance by the same amount as it is decreased by distensibility and recruitment. Alternative modelling has determined the distensibility factor α, employing a dedicated mathematical model [5, 100–102], where α is the percentage change in diameter per mmHg increase in distending pressure. In order to achieve reliable results, the number of PAPm − CO points should be four or more [4].

The elevation of PAPm with increasing exercise levels and CO is dependent on age [20, 88]. Older subjects have a significantly steeper PAPm/CO slope than younger subjects, even if they are apparently healthy [87, 88, 103–108]. This can be explained partly by a steeper PAWP/CO slope, which corresponds to changed diastolic characteristics of the left ventricle during exercise [87] and potentially by decreased resistive vessel distensibility.

The PAPm/CO slope appears to be independent of sex, although minor differences may be present [20, 88]. Echocardiographic estimations have suggested that premenopausal females have a more distensible (higher α) pulmonary circulation than age-matched males, but no different linear approximations of PAPm − CO plots (or TPR) [30]. Conversely, healthy male subjects of sub-Saharan ancestry may have less distensible pulmonary resistive vessels (lower α) than age-matched European Caucasian controls [109]. These studies must be interpreted with caution, because they had no transpulmonary pressure gradient measurement readings and had to rely on echo-based PAPm and CO estimations. Indeed, these echocardiographic assessments need further validation studies against RHC [37–39].

There are very few data available on pulmonary haemodynamics during exercise in overweight subjects [110]. Body position has an influence on pulmonary haemodynamics. In the upright as compared to the supine position at rest PAPm, PAWP, stroke volume and CO are lowered, whereas heart rate, PVR and arterio-venous oxygen difference are increased [95, 111–116]. The posture-induced differences in haemodynamics smooth out during increasing levels of exercise, and during maximal exercise there are no major differences in haemodynamics, apart from the effects of different peak exercise levels in the different postures [117, 118]. No direct comparison of haemodynamics between treadmill and cycle-ergometry is available [20].

During exercise, highly trained athletes may easily exceed a PAPm of 30 mmHg due to a large increase in CO (to values >30 $L \cdot min^{-1}$), which becomes possible due to a large increase in stroke volume with no change in peak heart rate [95, 112].

Relationship between resting and exercise PAP and resting PAPm above the upper limit of normal, but not fulfilling the criteria of pulmonary hypertension (21–24 mmHg)

According to some studies there is a significant correlation between resting and exercise PAP, as well as resting and exercise PAWP measured at RHC [44, 91, 119, 120]. However, resting PAP alone was not sufficiently accurate to predict a strong PAP increase in relatives of patients with idiopathic and familiar PAH and in asymptomatic carriers of BMPR-2 mutations [29, 121].

A special haemodynamic condition may be represented by a mild elevation of PAPm values above the upper limit of normal, but not fulfilling the criteria of pulmonary hypertension (21–24 mmHg) [20, 122]. This condition has been called a "borderline elevation of PAPm" in a number of studies [91, 123–129]. Data suggest that this is a clinically relevant condition which may be caused by several factors including pulmonary vascular, parenchymal and left heart diseases or sleep-associated disorders [91, 125–127]. It is characterised by decreased exercise capacity and associated with an increased risk of hospitalisation and mortality compared to patients with normal resting haemodynamics, and may thus represent a marker of a poor prognosis [91, 123, 126]. In patients undergoing RHC due to symptoms or risk factors for pulmonary hypertension, exercise pulmonary hypertension was closely associated with a mild (21–24 mmHg) elevation of PAPm at rest [91, 120, 128, 130], with one invasive haemodynamic study showing that 86% of such patients display concurrent "exercise pulmonary hypertension" as discussed earlier [120]. In patients with SSc, modest elevations in PAPm (21–24 mmHg) and an elevated resting TPG were associated with an increased risk of future progression to manifest PAH [127, 129]. The natural history of such a modest elevation in PAPm in the context of other clinical conditions is poorly defined at present.

Pulmonary haemodynamics during exercise in special patient groups

Patients at risk of PAH or pulmonary hypertension

Certain conditions are associated with a significantly increased risk of PAH, in particular SSc, which is often used as a model to investigate the development of PAH and recognise early markers of PAH development [38, 39]. Based on recent studies, exercise pulmonary hypertension may represent early pulmonary vascular involvement in SSc and may be predictive for development of PAH [129, 131–135]. In SSc, an abnormal PAP increase during exercise may result from pulmonary vasculopathy [37, 41, 43], but also from parenchymal lung disease and left heart disease [43, 130, 133, 134, 136–138]. It is unclear which clinical factors best predict the development of manifest PAH and an indication for targeted therapy.

In addition, abnormal haemodynamic responses, measured either by exercise Doppler echocardiography or by RHC during exercise have been reported in family members of idiopathic or heritable PAH patients [29, 121, 139, 140], in patients susceptible to high-altitude pulmonary oedema [28], in chronic

thromboembolic disease [53, 89, 141], post-repair congenital heart disease (closed atrial septal defect) [134], lung disease [93, 142, 143], chronic heart failure [78] and valvular heart disease patients [144, 145]. It is not clear whether any of these conditions is associated with PAH.

Patients exposed to high altitude and those susceptible to high-altitude pulmonary oedema

Exposure to hypobaric hypoxia at high altitude is associated with an increase in PAP and CO. During these circumstances, exercise is associated with lower peak workload, oxygen uptake and possibly a lower maximal CO due to a reduced stroke volume at similar maximal heart rates as compared to sea level [146–150]. Those susceptible to high-altitude pulmonary oedema may have a hypertensive pulmonary arterial pressure response during exercise at sea level and this response may allow discrimination between susceptibles and nonsusceptibles [28, 151]. An increase in pulmonary capillary pressure (postcapillary vascular constriction) may be involved in the mechanisms connecting the exercise-induced PAP response to high-altitude pulmonary oedema [151].

Patients with manifest precapillary pulmonary hypertension

There is growing evidence that exercise haemodynamics have prognostic relevance in patients with pulmonary hypertension. According to the most recent publications, in patients with PAH, peak exercise cardiac index, the pressure–flow relationship during exercise and the right ventricular contractile reserve were associated with survival [152–154] and a strong linear correlation was found between heart rate and PAP during exercise [155]. In PAH patients on targeted PAH therapy, the beneficial effects of therapy on haemodynamics may be better recognised during exercise than at rest [156, 157].

Ventriculo-arterial coupling (VAC) represents an interesting haemodynamic measure to characterise the interaction between the right ventricle and the pulmonary vasculature, although in a recent MRI study, pressure-derived estimates of RV-arterial coupling were not associated with mortality [158, 159] while simpler measures like right ventricular ejection fraction were. This suggests that further investigations are warranted to decipher the clinical value of VAC. In a recent study, using a simplified measure of VAC during exercise in PAH patients, VAC was deteriorated due to the inability to further increase contractility [160]. By simplification, the stroke volume at rest and stroke volume responses during exercise may be indicative of ventriculo-arterial coupling [3].

Patients with left heart disease

In patients with left heart disease, PAWP and left ventricular end diastolic pressure may be within the normal range at rest, but usually show an abnormal increase during exercise. Therefore, exercise haemodynamics may unmask left heart disease [6]. The abnormal PAP increase in relation to flow driven by the increase in PAWP, assessing left ventricular filling pressure, may become a limiting factor for the maximal CO and workload [161].

Patients with left ventricular disease may present with isolated postcapillary pulmonary hypertension or combined pre- and postcapillary pulmonary hypertension, leading to different haemodynamic patterns [1]. The assessment of TPG or diastolic PAP-PAWP gradient or PVR may be helpful to distinguish between these entities; however, there are limited studies addressing this question during exercise [6, 78]. The precise assessment of diastolic PAP during exercise is difficult with fluid-filled catheters due to less reliable tracings as compared to micromanometer-tipped catheters. Haemodynamic changes during exercise are further influenced by the impact of dynamic variation in left atrial pressure and its influence on pulmonary arterial compliance [162–164]. In patients with established heart failure due to either heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), exercise induces a steep increase in PAPm (>5 $mmHg \cdot L^{-1} \cdot min^{-1}$) [78, 98, 165]. Both HFpEF and HFrEF patients had reduced pulmonary vascular distensibility (α), as shown in exercise RHC studies [166]. Furthermore, HFpEF patients, in addition to a limited left ventricular reserve, display an impaired right ventricular reserve during exercise which is associated with high filling pressures and reduced CO responses, indicative of abnormal right ventricular/pulmonary artery coupling [167]. Echocardiography studies additionally identified mitral regurgitation, decreased left ventricular contractile reserve and intraventricular dyssynchrony as major contributors to the abnormal PAP increase in HFrEF [168, 169], while in HFpEF, the PAP increase was most closely associated with the degree of diastolic left ventricular dysfunction [165].

Patients with lung disease

Abnormal PAP increase during exercise is very frequent in patients with lung diseases [93, 143]. In these patients, both the abnormal increase of PAP and of PAWP may be influenced by an increase in intrathoracic pressure swings and average intrathoracic pressure during exercise [143, 170, 171]. The increase in stroke volume during exercise appears lower compared to healthy controls [172] and changes

in pulmonary haemodynamics correlate with exercise capacity [173]. According to a recent study, patients with interstitial lung disease and increased PAPm/CO slope during exercise have a decreased exercise tolerance, but cannot be reliably identified by lung function test or exercise desaturation [142]. In addition, in COPD patients, the haemodynamic response to exercise was associated with limitation of physical capacity [143, 173] and with the consecutive development of pulmonary hypertension [174]. The assessment of haemodynamics may be challenging due to respiratory pressure swings that impede the reading of PAP, PAWP and RAP. The end-expiratory measurement of pressures may massively overestimate the transmural pressures in all these locations [19]. Breath-hold manoeuvres are not feasible and will cause rapid changes in CO and all other measures. Digital averaging of the pressure readings over several respiratory cycles may be the only way to reliably read the pressures despite large respiratory pressure swings. However, this will not avoid the overestimation of the transmural pressures in cases of increasing intrathoracic pressures due to air trapping during exercise [175].

Prognostic relevance of exercise pulmonary hypertension

Exercise pulmonary hypertension is a clinically relevant entity [91, 126, 127, 131–134] and in certain conditions (*e.g.* SSc [131] and COPD [174]) may be predictive for the development of pulmonary hypertension. However, in general, the natural history of exercise pulmonary hypertension is unknown. In a small recent study, exercise pulmonary hypertension in scleroderma was associated with increased mortality as compared to patients with normal exercise haemodynamics [176], and in patients with myelodysplastic syndrome, a strong increase in PAP during exercise was associated with an increased hospitalisation rate [177]. Two small pilot studies showed improvement in haemodynamic end-points in patients with SSc and exercise pulmonary hypertension on targeted PAH therapy [178, 179]. However, there is a lack of robust multicentre data for prognosis and controlled prospective studies are needed before any recommendations can be made on medical treatment. Patients with exercise pulmonary hypertension require ongoing clinical follow-up, particularly if established risk factors for pulmonary hypertension are present.

Conclusion

The assessment of pulmonary haemodynamics during exercise in addition to resting haemodynamics may provide important additional information on the cause of dyspnoea and may have prognostic value. Exercise pulmonary hypertension is characterised by an excessive increase in PAP in relation to pulmonary blood flow during exercise requiring clinical follow-up, particularly in patients with established risk factors for pulmonary hypertension, such as scleroderma. Further research regarding the prognostic relevance of pulmonary haemodynamics during exercise in specific patient groups is warranted.

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