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REVIEW

Exercise Pulmonary Hypertension

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ABSTRACT

The clinical value of pulmonary hemodynamics during exercise has not been fully explored. In the last decade, several studies investigated the prognostic and diagnostic relevance of exercise hemodynamics and novel hemodynamic variables including the mean pulmonary arterial pressure (mPAP)/cardiac output (CO) slope and the pulmonary arterial wedge pressure (PAWP)/CO slope have been analyzed. These parameters describe the effects of pulmonary blood flow on the pulmonary pressure and were shown to be of prognostic relevance. In addition, they may also serve as tools to differentiate early forms of pulmonary vascular from left heart diseases. Right heart catheterization remains the gold standard to assess pulmonary hemodynamics both at rest and during exercise, while exercise echocardiography represents a promising non-invasive research tool. In this review, we provide an overview of the growing body of evidence on the clinical relevance of pulmonary hemodynamics during exercise and discuss its potential future role.

Keywords: Exercise pulmonary hypertension. Methodology. Right heart catheterization. Survival.

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INTRODUCTION

History of exercise pulmonary hypertension and its first definition

Since the introduction of right heart catheterization (RHC) into the clinical practice in the 1940s, there has been a continuous interest in pulmonary hemodynamics during exercise[1]. The relevance of exercise hemodynamics was already mentioned at the WHO Meeting on Cor Pulmonale in 1960[2], and later at the first WHO Meeting on Pulmonary Hypertension in 1973[3]. At this conference, based on the available studies and expert opinion, it was postulated that "mean pulmonary arterial pressure (mPAP) does not normally exceed 30 mmHg during exercise"[3]. Accordingly, in the National Institute of Health (NIH) registry, primary pulmonary hypertension was hemodynamically defined as mPAP > 25 mmHg at rest or > 30 mmHg during exercise[4], and in 2004, the term "exercise pulmonary hypertension" (exercise PH), defined as mPAP > 30 mmHg on effort, was officially introduced in the European Society of Cardiology (ESC) guidelines on pulmonary arterial hypertension[5]. A few years later, however, it was recognized that even healthy subjects frequently exceeded this threshold at high levels of exercise and that exercise hemodynamics are strongly dependent on age[1,6]. Therefore, it is not possible to generally distinguish a normal from an abnormal hemodynamic response to exercise by a single mPAP threshold. As a result, the hemodynamic definition of exercise PH was abandoned from the following ESC/ERS PH guidelines[7,8] and has not been reintroduced until today.

Proposed new definition(s) of exercise pulmonary hypertension

In order to recognize an abnormal reaction to exercise, a "normal" hemodynamic response needs to be defined. This issue was addressed by several studies investigating pulmonary exercise hemodynamics, providing evidence for the normal ranges of pulmonary hemodynamics during exercise. As exercise hemodynamics are strongly dependent on the level of exercise, for any potential new definition of exercise PH, the relation to cardiac output (CO) or, to be more exact, to pulmonary blood flow (PBF) for a given mPAP increase has been emphasized[9]. Based on the available data, two potential hemodynamic definitions have been considered.

1) mPAP > 30 mmHg + total pulmonary resistance (TPR) > 3 Wood units (WU) at peak exercise

Herve et al.[10] investigated n = 169 patients with dyspnea on effort, but normal resting mPAP (≤ 20 mmHg) and pulmonary arterial wedge pressure (PAWP < 15 mmHg) and free from overt cardiopulmonary disease. Patients were stratified according to their response to exercise as controls, pulmonary vascular disease (PVD) or left heart disease (LHD). Controls were defined by normal lung function, normal echocardiography, no significant parenchymal lung disease on thoracic computed tomography (CT) scan, normal ventilation-perfusion scintigraphy, no known risk factors for PH, normal resting hemodynamics and PAWP < 20 mmHg during exercise. The diagnosis of PVD was made in patients with PAWP < 20 mmHg during exercise, based on either 1) previous

invasive confirmation of resting pre-capillary PH, or 2) evolution to resting pre-capillary PH during follow-up, or 3) documentation of pulmonary chronic thromboembolic disease by positive ventilation–perfusion scintigraphy with vascular obstruction on pulmonary angiography, or 4) lung biopsy consistent with diagnosis of pulmonary veno-occlusive disease. The LHD group had peak PAWP ≥ 20 mmHg during exercise, mainly due to heart failure with preserved ejection fraction (HFpEF) or valvular heart disease. From all analyzed hemodynamic parameters, peak mPAP and peak total pulmonary resistance (TPR) had the highest diagnostic accuracy for differentiating controls from PVD or LHD, while resting hemodynamics had low diagnostic sensitivity and specificity. Area-under-the-curve values for TPR at peak exercise reached 0.99 and for mPAP at peak exercise 0.98 with best cut-offs of 2.97 WU for TPR and 31 mmHg for mPAP (Fig. 1). By combining these parameters, a diagnostic accuracy with an overall sensitivity of 93% and specificity of 100% could be achieved. For practical reasons, cut-offs were rounded and a TPR > 3 WU in combination with mPAP > 30 mmHg was proposed as a potentially suitable definition for exercise PH[10].

This definition and its association with mortality were investigated in n = 72 patients with systemic sclerosis (SSc) who underwent exercise right heart catheterization. In that study, SSc patients with exercise PH had significantly worse transplant-free survival as compared to patients without exercise PH, but a similar outcome compared to patients with manifest resting PH (mPAP ≥ 25 mmHg at rest)[11]. This study underlines the prognostic value of this potential definition for exercise PH.

2) mPAP/CO slope > 3 mmHg/L/min

The second suggestion to define abnormal pulmonary hemodynamics during exercise was an mPAP/CO slope > 3 mmHg/L/min[12]. This suggestion was based both on invasive[13] and non-invasive data[14], showing that healthy subjects normally do not present with values above this threshold. This proposed definition has later been used in the largest currently available study on the prognostic relevance of exercise PH in patients with dyspnea, confirming its prognostic relevance[15]. The mPAP/CO slope may be calculated either from multipoint mPAP/CO relationships or from two-point measurements including resting and peak exercise values, only[16,17]. In direct comparison, both methods showed high diagnostic accuracy for exercise PH[18].

Both proposed exercise PH definitions incorporate the relation of mPAP and pulmonary blood flow during exercise and suggest similar cut-offs, although there is a minor difference: while the definition of Herve et al. focuses only on hemodynamics during peak exercise, the mPAP/CO slope > 3 mmHg/L/min definition displays the transition from rest to any exercise level. As a potential advantage, the latter definition may reveal abnormal hemodynamics even in those subjects who are strongly limited in their exercise capacity by muscular, orthopedic, or neurologic factors and are not able to sufficiently increase their pulmonary blood flow and pressures on effort.

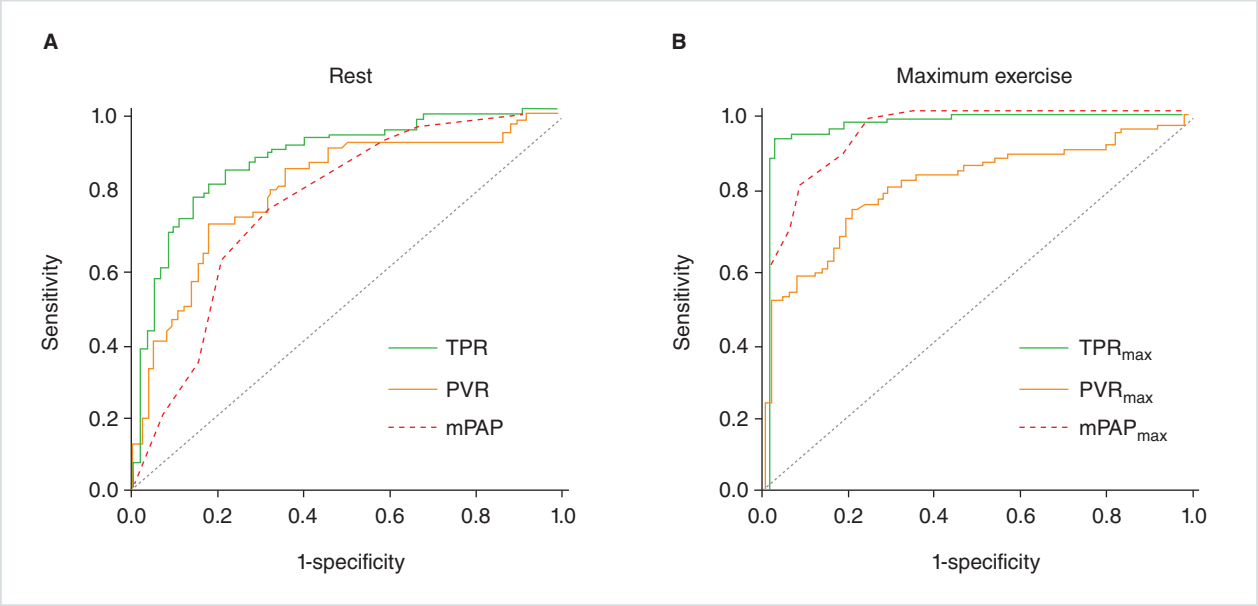

Figure 1. Receiver operating characteristic curves of pulmonary hemodynamic variables at rest and maximum exercise for discriminating controls versus disease group (pulmonary vascular disease and left heart disease). **A:** overall, resting hemodynamic variables performed poorly compared to exercise hemodynamic variables. **B:** for exercise hemodynamic variables the performance of total pulmonary resistance (TPR) and mean pulmonary artery pressure (mPAP) obtained at maximal exercise (TPR_{max} and $mPAP_{max}$, respectively) were superior to pulmonary vascular resistance (PVR) at maximal exercise (PVR_{max}) *(reproduced with the authors' authorisation [Herve et al., 2015])*[10].

CLINICAL RELEVANCE – WHY DO EXERCISE INVESTIGATIONS MATTER?

Early recognition of cardiopulmonary diseases based on pulmonary exercise hemodynamics

It has been postulated that exercise hemodynamics may uncover the early stages of cardiopulmonary diseases. Historic studies in healthy subjects suggested an upper limit of normal PAWP and left ventricular end-diastolic pressure (LVEDP) during exercise of < 20-23 mmHg[19,20] and < 25 mmHg[21,22].

In addition, a recent study in a large group of patients with unexplained dyspnea and suspected HFpEF, a PAWP at peak exercise > 25.5 mmHg/W/kg was associated with a 5.44-fold increased mortality risk (Fig. 4)[23], while another study found that HFpEF patients (resting PAWP ≥ 15 mmHg and left ventricular ejection fraction > 50%) had significantly steeper PAWP/CO slopes as compared to patients with dyspnea and normal resting PAWP (median (IQR) 3.1 (2.3–4.6) vs. 1.7 (1.2–2.6) mmHg/L/min). In this second study, a PAWP/CO slope > 2 mmHg/L/min was suggested as the upper limit of normal and was significantly associated with increased cardiovascular mortality and hospitalization[24].

Accordingly, the actual consensus from the Heart Failure Association and the European

Society of Cardiology (ESC) for the diagnosis of HFpEF has recommended RHC during exercise for the structured work-up of suspected HFpEF[25]. While a resting PAWP > 15 mmHg is confirmative of HFpEF, the increase of normal resting PAWP above 25 mmHg during exercise may correspond to an early stage of HFpEF in patients, who are compensated at rest[25].

Early pulmonary vascular disease might also be recognized based on the changes in pulmonary hemodynamics during exercise. However, probably due to the much lower incidence of PVD as compared to HFpEF, it has been difficult to provide evidence on which hemodynamic variable is the best predictor of future pre-capillary PH. Based on theoretical considerations, the pulmonary vascular resistance (PVR) or the transpulmonary gradient (TPG) during exercise, or the TPG/CO slope may represent such parameters[26,27].

Prognostic implications of exercise hemodynamics

Two large studies investigated the prognostic relevance of pulmonary hemodynamics during exercise in patients with exercise dyspnoea. Ho and colleagues[15] included n = 714 subjects and analysed the association between exercise PH (defined as mPAP at rest ≤ 20 mmHg but mPAP/CO slope > 3 mmHg/L/min) and a combined endpoint defined as all-cause mortality or cardiovascular hospitalization[15]. The presence of exercise PH was associated with a two-fold increased risk of an event after adjustment for potential clinical confounders including age, sex, hypertension, prior heart failure, chronic obstructive pulmonary disease (COPD), interstitial lung disease and smoking status. The results remained significant even after further adjustment for the presence of resting PH (defined as resting mPAP > 20 mmHg). When comparing their prognosis, patients with resting PH had the worst overall survival, followed by those with exercise PH and patients without resting or exercise PH, who had the best prognosis (Fig. 2). In this study, in addition to the mPAP/CO slope, both the TPG/CO and PAWP/CO slopes were independently associated with prognosis[15].

In a second large study, Eisman and colleagues[24] included n = 110 patients with dyspnea on exercise but normal PAWP and ejection fraction at rest. The authors defined the upper limit of normal PAWP/CO slope at 2 WU (1.2 ± 0.4 WU), based on the hemodynamic values of a control group. A PAWP/CO slope > 2 WU was found in ~40% of subjects and was associated with poor clinical outcomes, defined as cardiovascular death, hospitalization due to heart failure, or abnormal resting PAWP in a future RHC.

Recently, the prognostic relevance of pulmonary hemodynamics during exercise was demonstrated in patients with SSc. n = 80 patients with resting mPAP < 25 mmHg have been investigated with exercise RHC and followed up for more than 10 years. The authors found that exercise pulmonary resistances (PVR and TPR), as well as the mPAP/CO and TPG/CO slopes, but none of the resting hemodynamic variables was able to predict ten-year mortality (Fig. 3). Of note, the best mPAP/CO

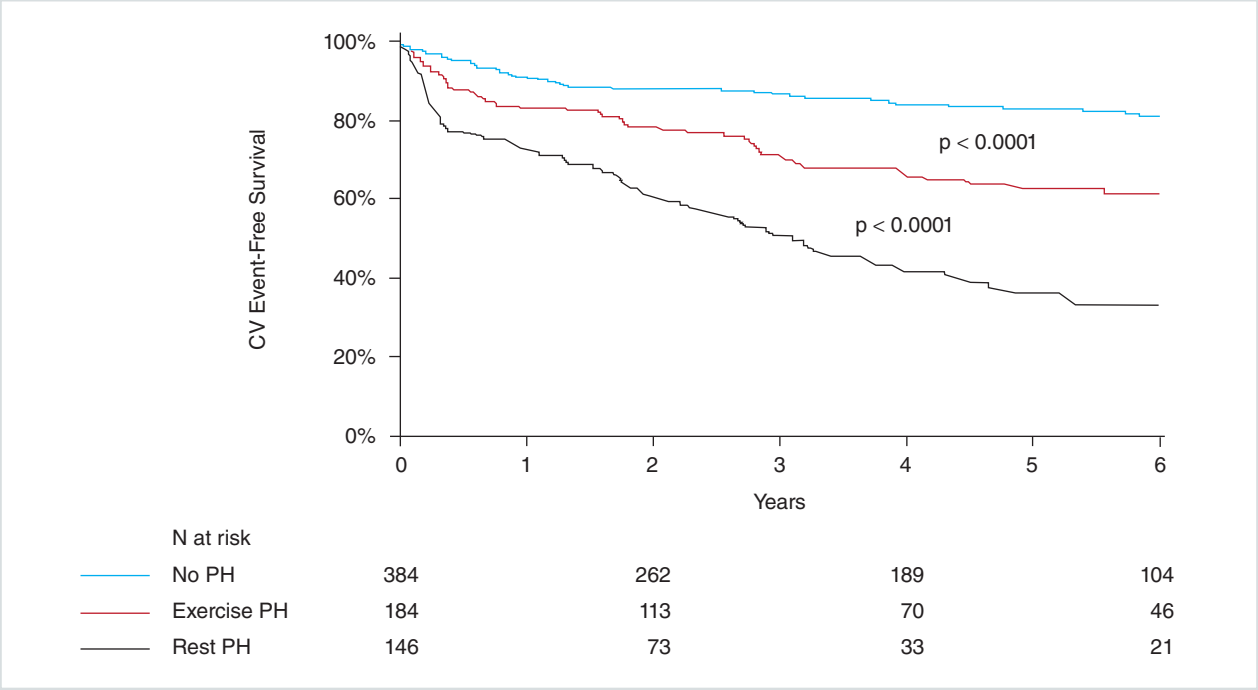

Figure 2. Central illustration. Cardiovascular event-free survival among individuals with dyspnea by pulmonary hypertension status. Colors designate those without PH (blue), rest PH (black, defined as rest PAP > 20 mm Hg), and exercise PH (red, defined as rest PAP ≤ 20 mm Hg and PAP/CO slope > 3 mm Hg/l/min) *(reproduced with the authors' authorization [Ho et al. 2020])*[15].
CO: cardiac output; CV: cardiovascular; PAP: pulmonary arterial pressure; PH: pulmonary hypertension.

slope to identify long-term mortality was 3.5 WU, and none of the participating patients below this cut-off died or developed PH within the study[28].

IMPORTANT DETAILS FOR THE CORRECT INTERPRETATION OF EXERCISE HEMODYNAMICS

The gold standard for assessing pulmonary hemodynamics during exercise is the direct invasive measurement by means of RHC. In the research setting, exercise echocardiography is an emerging novel, non-invasive tool. A major limitation of the method is the relatively low precision, precluding reliable decision-making for the individual patient in clinical practice. Collaborate research efforts may provide evidence for the future clinical role of exercise echocardiography[30].

In order to characterize pulmonary hemodynamics during exercise by RHC, the assessment of at least mPAP, PAWP and CO is suggested at each exercise level. These parameters allow the calculation of total pulmonary resistance (TPR = mPAP/CO) and PVR = (mPAP–PAWP)/CO)[9]. Some details regarding reading and interpretation of the data deserve special attention.

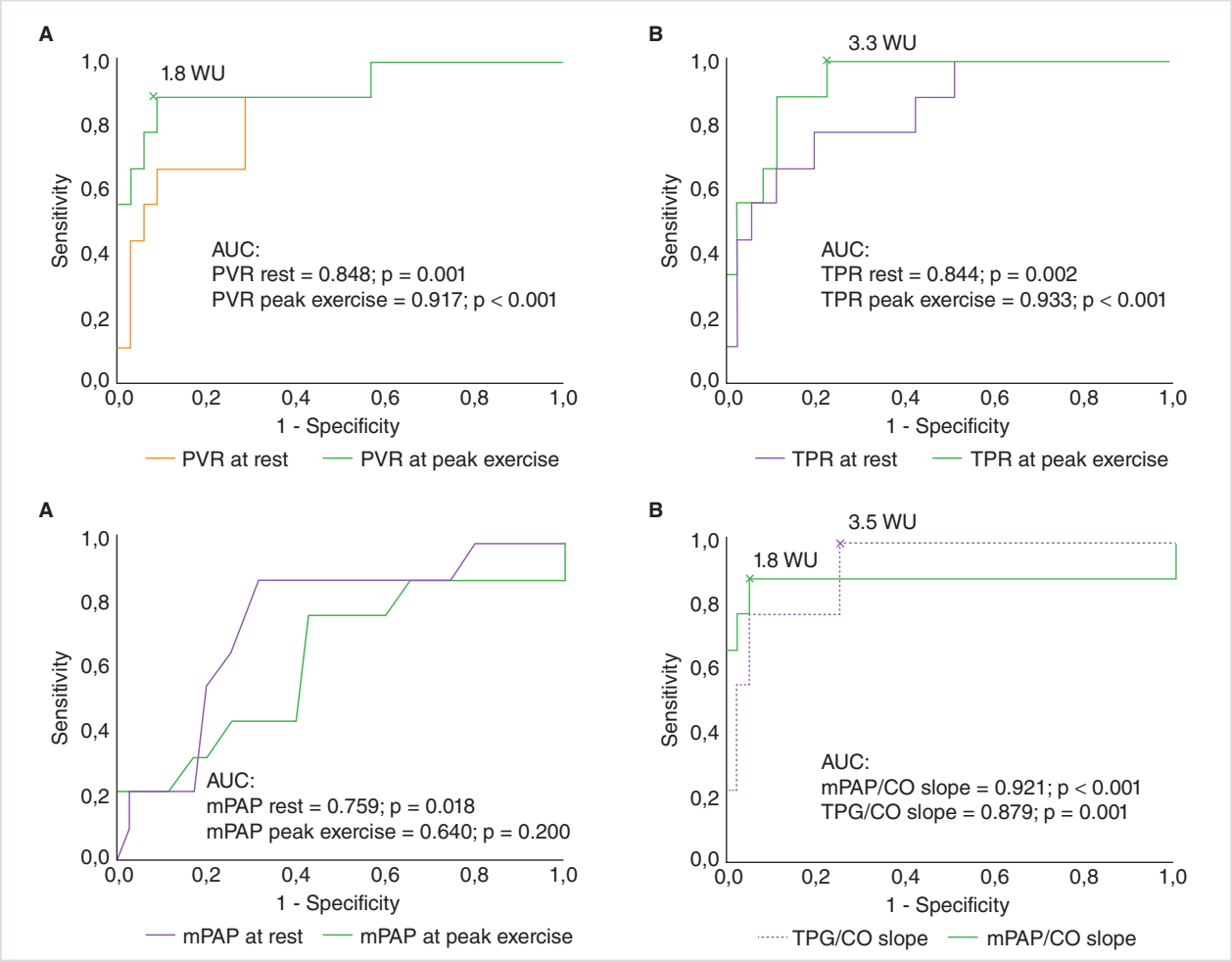

Figure 3. **A:** AUCs for predicting 10-year mortality (n = 44). **A:** mPAP, **B:** mPAP/CO slope and TPG/CO slope. Resting hemodynamic parameters are presented in blue and exervise hemodynamic parameters are presented in red. **B:** AUCs for predicting 10-year mortality (n = 44). **A:** A, PVR, B, TPR. Resting hemodynamic parameters are presented in blue and exercise hemodynamic parameters are presented in red.
AUC: area under the receiving operating characteristic curve; CO: cardiac output; mPAP: mean pulmonary arterial pressure; TPG: transpulmonary gradient; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance; WU: Wood unit.

Age and sex dependency

Pulmonary hemodynamics are dependent on age. In the supine position, in subjects aged < 50 years, an 85% increase in CO is associated with a ~40% increase in mPAP, a 25% decrease in TPR and a 12% decrease in PVR. However, subjects aged > 50 years show a completely different response pattern. An initial increase in CO by ~70% is associated with a ~65% increase in mPAP, while TPR remains unchanged and PVR decreases by ~20%[6]. These age-related hemodynamic changes result in a steeper mPAP/CO slope in elderly subjects, as compared to younger subjects[1,6,30-33]. The main driver for this difference appears to be

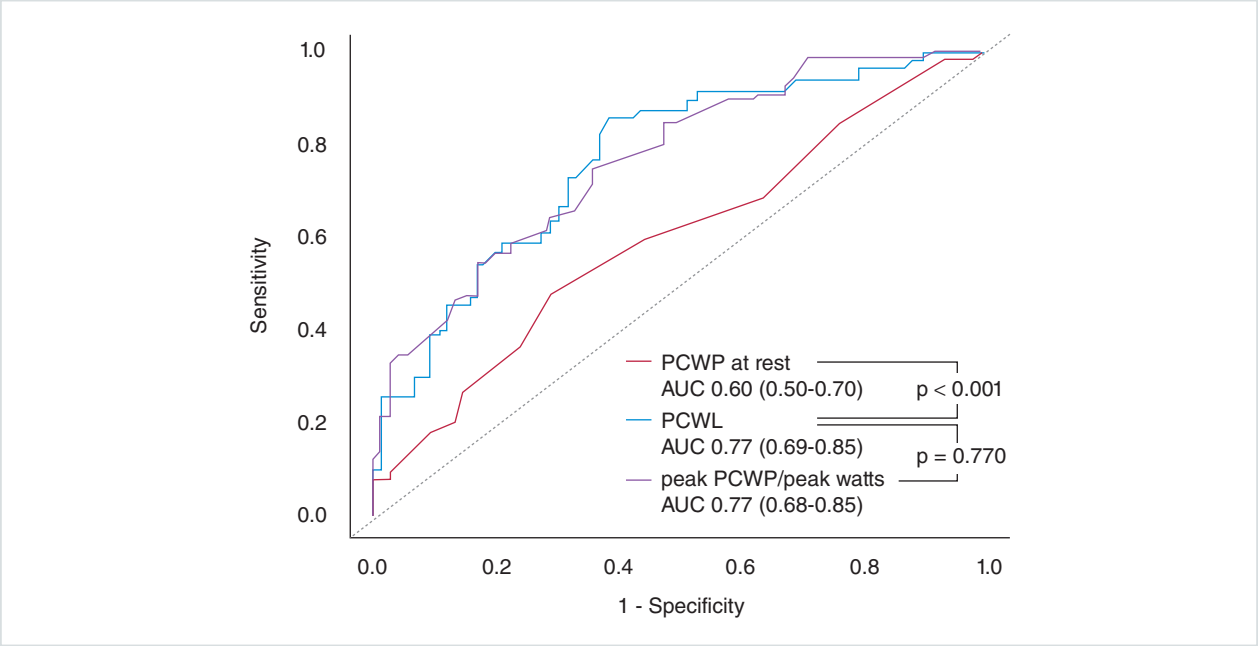

Figure 4. Receiver-operating characteristic analysis of pulmonary capillary wedge pressure at rest (red), PCWL (blue), and peak watts (purple) for the prediction of mortality through 14 years *(reproduced with permission of the ©ERS 2022. European Respiratory Journal. 2014;44:3103-12. DOI: 10.1093/eurheartj/ehu315).*
AUC: area under the receiving operating characteristic curve; PCWP: pulmonary capillary wedge pressure; PCWL: ratio of PCWP at peak exercise to workload normalized to body weight.

the behaviour of PAWP during mild levels of exercise: in younger subjects, a typically moderate increase of PAWP is observed (PAWP usually remains < 15 mmHg and rarely reaches 20 mmHg) and the PAWP/CO relationship representing the "left ventricular filling resistance", decreases significantly. In contrast, in older subjects, PAWP frequently exceeds 20 mmHg and the PAWP/CO relationship does not decrease and may even increase[1,6].

The available data do not suggest significant differences in pulmonary hemodynamics during exercise between healthy men and women[9]. Of note, in a recent study, PAWP during exercise indexed to work rate and body size was significantly elevated in healthy women as compared to healthy men, although the PAWP/CO slope was within the normal range in all subjects[34]. Further investigations are needed to answer the question if this finding suggests that women may be more susceptible to HFpEF than men.

Body position dependency

Pulmonary hemodynamics are dependent on body position. Resting mPAP, PAWP and CO are lower in the upright position as compared to the supine position. In contrast, heart rate, TPR and PVR are increased[9]. In the supine position, TPR but not so much

PVR shows an initial decrease during exercise, which is more prominent in the upright position. These kinds of subtle differences vanish during later stages of exercise when different body positions are compared[6]. Due to these differences, it is of great importance that the assessment of hemodynamics should take place in the same body position both at rest and during exercise and, importantly, the calculation of the mPAP/CO and PAWP/CO slopes should only be done based on hemodynamic values assessed in the same body position.

Respiratory swings

Respiratory pressure swings correspond to the changes in the sum of transmural vascular pressure and intrathoracic pressure during the respiratory cycle. The latter is a more variable value that is influenced by alveolar pressure, lung volume, lung compliance, respiratory phase, body position and age. At rest, respiratory swings in healthy subjects and most patients are small, and therefore end-expiratory or averaged pressure values over three-four respiratory cycles may both be used in clinical practice. However, in patients with obstructive airway diseases, respiratory pressure swings may significantly influence pulmonary pressures already at rest and therefore need to be averaged[9]. The same is true for exercise, when both tidal volume and breathing frequency increase and respiratory swings become larger. Therefore, the only reliable way to assess intrathoracic pressure values during exercise is to average them over three-four respiratory cycles[9]. Of note, the absolute value of the intrathoracic pressure, as estimated by the pleural pressure, is largely dependent on the presence of an airway- or parenchymal lung disease such as COPD (mean intrathoracic pressure is increased) or idiopathic pulmonary fibrosis (mean intrathoracic pressure is decreased)[35].

Zero reference level

The importance of a correctly set zero reference level has been extensively discussed[35,36]. In the ERS consensus statement on exercise pulmonary hemodynamics it was emphasized that in the supine position, the zero-reference level should be set at the mid-thoracic level both at rest and during exercise, which corresponds to the level of the left atrium[36]. In the upright position, a standardized zero reference point may be the intersection of the frontal plane at the mid-thoracic level, the transverse plane at the level of fourth anterior intercostal space and the mid-sagittal plane. In many centers, exercise RHC is performed in a different position than at rest (e.g., supine measurement at rest and exercise measurement in the upright position). In such cases it is of utmost importance to adequately set the zero-reference level after assuming a new body position[9].

Exercise duration/protocols

There is a wide variability of exercise protocols, which are currently in use in different expert centers. Most available studies use incremental work with step or ramp protocols. Less data is available for constant submaximal exercise or isometric exercise. If using a step protocol, it may take around 3-5 minutes to

reach "steady state" and to perform all measurements at each exercise level. These "longer" steps may, however, lead to exhaustion at a submaximal level and therefore, shorter time intervals of about two minutes per step have been frequently used in the literature[9]. An obvious advantage of step protocols is that all measurements are performed at the same exercise level. Most centers combine exercise RHC with cardiopulmonary exercise testing (CPET), thus maximizing the available information for each workload.

PAWP and CO measurement

The correct assessment of PAWP is essential because the absolute value of PAWP during exercise and the PAWP/CO slope may be used to distinguish between pre- and post-capillary patients. However, PAWP measurements are sometimes challenging even at rest and more so during exercise. An incompletely wedged or an "over-wedged" balloon are the most frequent problems, both leading to an overestimation of PAWP. Similar to other intrathoracic pressures, we suggest that PAWP values are averaged over three-four respiratory cycles during exercise[9].

The gold standard for measuring CO during RHC is the direct Fick method. This necessitates, however, the simultaneous measurement of oxygen consumption. An alternative is the thermodilution technique, which is also accepted as sufficiently reliable both at rest and during exercise[9]. Other methods like the indirect Fick method, which uses estimated values of oxygen uptake, or the inert gas method, lack reliability (either accuracy or precision) and are not recommended[8].

Safety

In experienced centers, complications during invasive assessment of pulmonary hemodynamics during exercise are rare. Apparently, there is no significant additional risk of exercise as compared to resting RHC. However, there is no larger study that has investigated this issue. Exercise RHC should not be performed without thorough resting work-up and the risk/benefit ratio seems unfavourable in patients with unstable disease or decompensated right heart failure[9].

The major considerations concerning the methodological aspects of exercise RHC are presented in Table 1.

EXERCISE PH - OUTLOOK

Currently, exercise PH is not part of the overall PH definition. However, as data on the normal ranges of hemodynamic variables, as well as on the prognostic and diagnostic relevance of pulmonary hemodynamics during exercise accumulate, the clinical value of exercise PH is emerging. In addition to the currently available studies, a large international collaborative effort (The pulmonary haemodynamics during exercise – research network [PEX-NET])[37] is being conducted and will reveal data based on a large number of patients.

CONCLUSION

Exercise pulmonary hemodynamics appear to be prognostically relevant in several cardiopulmonary conditions, although their assessment may be demanding. Exercise hemodynamics

Table 1. Methodological details for the correct interpretation of pulmonary hemodynamics during exercise

Most important hemodynamic measurements and calculations	mPAP, PAWP, CO, PVR, TPR, mPAP/CO slope
Age dependency	Pulmonary hemodynamics are strongly age dependent. Older subjects have steeper slopes.
Sex dependency	Gender differences have not been sufficiently explored
Body position dependency	Pulmonary hemodynamics are dependent on body position. mPAP, PAWP and CO being lower in upright versus supine position
Respiratory swings	Averaging over 3-4 respiratory cycles is most reliable at rest and exercis
Zero reference level	At the level of left atrium for both resting and exercise readings
Exercise protocols	Ramp versus Step protocol. Step protocols provide all measurements at the same exercise level
CO measurement	Gold standard: direct Fick. Reliable alternative: thermodilution
Safety	Exercise RHC should not be performed without thorough resting work-up or in a decompensated disease state

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CO: cardiac output; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; RHC: right heart catheterization; TPR: total pulmonary resistance.

have an added value to resting hemodynamics concerning mortality assessment and classification of patients into early left heart versus early pulmonary vascular disease. Novel hemodynamic parameters such as the mPAP/CO and the PAWP/CO slopes are of increasing interest for the characterization of the hemodynamic patterns.

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CONFLICTS OF INTEREST

There are no conflicts of interest regarding this article.

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