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Early View

Review

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Diagnostic, prognostic and differential-diagnostic relevance of pulmonary hemodynamics during exercise – a systematic review

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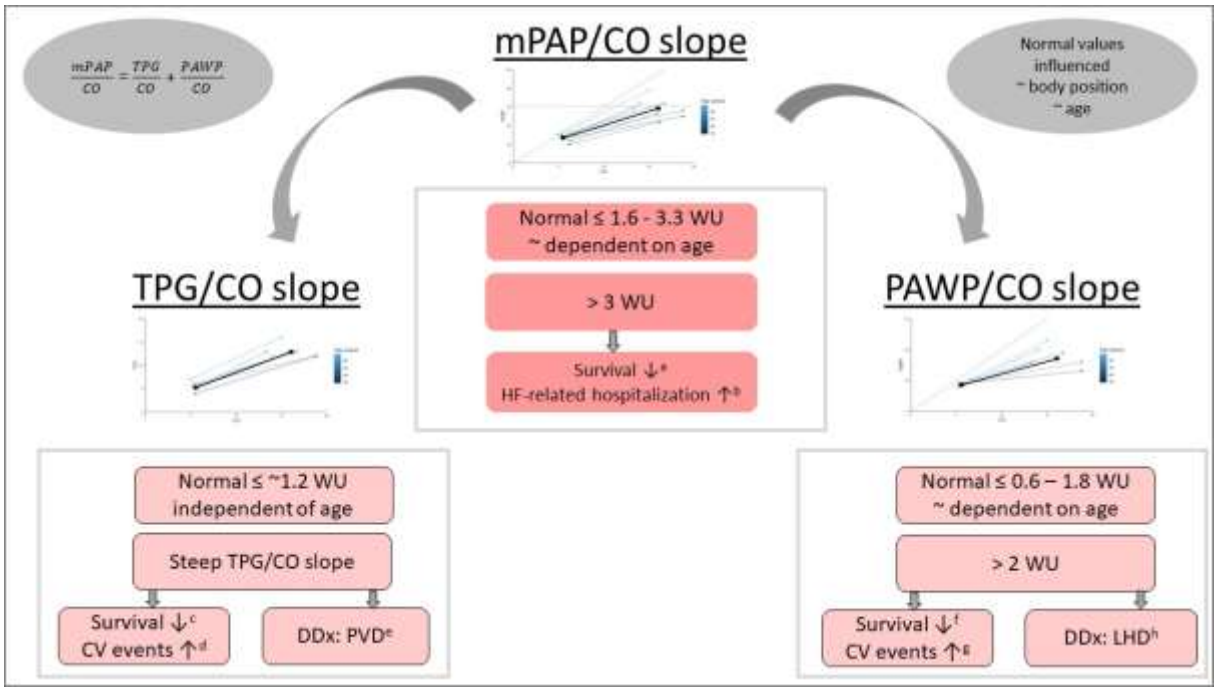
Central illustration: mPAP/CO, PAWP/CO and TPG/CO slopes for the characterization of pulmonary hemodynamics during exercise



Abnormal pulmonary hemodynamics during exercise may be defined by an increased mean pulmonary arterial pressure (mPAP)/cardiac output (CO) slope. The mPAP/CO slope is strongly age-dependent and its upper limit of normal (ULN, mean + 2 SD) ranges from 1.6 (in ~30-year-old healthy subjects) to 3.3 (in ~70-year-old healthy subjects) Wood Units (WU) in the supine position (see also Table 2). Of note, the ULN based on the weighted mean and SD of all healthy subjects included in this analysis was 2.7 WU in the supine position. An increased mPAP/CO slope with a cut-off above 3 WU is independently associated with poor survival and heart failure (HF)-related hospitalizations.

The mPAP/CO slope corresponds to the sum of the trans-pulmonary gradient (TPG)/CO slope and the pulmonary arterial wedge pressure (PAWP)/CO slope. Like the mPAP/CO slope, the PAWP/CO slope is also strongly age-dependent and its ULN ranges from 0.6 to 1.8 WU. An increased PAWP/CO slope with a cut-off above 2 WU is associated with impaired survival and increased cardio-vascular (CV) events and may be diagnostic for a post-capillary cause of PAP elevation during exercise. The ULN for TPG/CO slope is 1.2 WU and age-independent. An increased TPG/CO slope is also associated with impaired survival and may be suggestive of pulmonary vascular disease (PVD).

mPAP = mean pulmonary arterial pressure, CO = cardiac output, PAWP = pulmonary arterial wedge pressure, TPG = trans-pulmonary gradient, DDx = diagnosis, LHD = left heart disease.

Studies reporting on the prognostic relevance of the mPAP/CO, TPG/CO and PAWP/CO slopes: a) Ho et al 2020 (validating mPAP/CO > 3 WU cut-off); Hasler 2016 et al; Stamm 2016 et al; Blumberg 2013 et al; Lewis 2011 et al; Zeder et al 2021; b) Ho et al 2020 (validating mPAP/CO > 3 WU cut-off); c) Ho et al 2020; Zeder et al 2021; d) Ho et al 2020; e) Hager 2013, Saggar 2010, Nagel 2019; Gorter, Keusch 2014; f) Eisman et al 2018 (validating PAWP/CO > 2 WU cut-off); Ho et al 2020; Dorfs 2014 et al ; g) Eisman 2018 et al (validating PAWP/CO > 2 WU cut-off); Ho et al 2020; h) Eisman 2018 et al (validating PAWP/CO > 2 WU cut-off); Borlaug 2010 et al.

Abstract (248 words)

The cardiopulmonary hemodynamic profile observed during exercise may identify patients with early stage pulmonary vascular and primary cardiac diseases, and is used clinically to inform prognosis. However, a standardized approach to interpreting hemodynamics is lacking.

We performed a systematic literature search according to PRISMA guidelines to identify parameters that may be diagnostic for an abnormal hemodynamic response to exercise and offer optimal prognostic and differential-diagnostic value. We performed random-effects-meta-analyses of the normal values and reported effect sizes as weighted means and standard deviations (SD). Results of diagnostic and prognostic studies are reported descriptively.

We identified n=45 eligible studies with n=5598 subjects. The mean pulmonary arterial pressure (mPAP)/cardiac output (CO) slope, pulmonary arterial wedge pressure (PAWP)/CO slope and peak cardiac index (or CO) provided the most consistent prognostic hemodynamic parameters during exercise. The best cut-offs for survival and cardiovascular events were mPAP/CO slope > 3 Wood units (WU) and PAWP/CO slope > 2 WU. A PAWP/CO slope cut-off > 2 WU best differentiated pre- from post-capillary causes of PAP elevation during exercise. Upper limits of normal (defined as mean + 2SD) for the mPAP/CO and PAWP/CO slopes were strongly age-dependent and ranged in 30-to 70-year old healthy subjects from 1.6 to 3.3 WU and 0.6 to 1.8 WU, respectively.

Increased mPAP/CO slope during exercise is associated with impaired survival and an independent, prognostically relevant cut-off >3WU has been validated. A PAWP/CO slope >2WU may be suitable for the differentiation between pre- and post-capillary causes of PAP increase during exercise.

Introduction

Cardiopulmonary hemodynamics during exercise have been investigated since the introduction of right heart catheterization (RHC) into clinical practice (1). The relevance of exercise hemodynamics *per se* to diagnosing pulmonary circulatory disorders, which include a constellation of highly morbid pulmonary hypertension subtypes encountered commonly in cardiovascular medicine practice, was considered by the World Health Organization (WHO) meeting on *cor pulmonale* in 1960 (2) and at the first WHO Pulmonary Hypertension congress in 1973 (3). The first expert consensus definition of exercise pulmonary hypertension (exercise PH) focused on mean pulmonary artery pressure (mPAP) >30 mmHg at peak physical activity (4). This definition was also used by the National Institutes of Health (NIH) registry in the USA to collect data on patients diagnosed as having primary pulmonary hypertension (5). However, this approach did not consider the effect of age and work load on global hemodynamic response to exercise, and therefore, did not distinguish normal from clinically relevant patient profiles. This has been pointed out by a systematic literature review, analyzing the hemodynamic data of almost 1200 healthy subjects at rest and during exercise (1). As a

consequence, the term exercise PH has been abandoned from the hemodynamic definition of PH in the latest PH guidelines (6-8). Indeed, a standardized definition of exercise PH remains lacking, despite accumulating data indicating that exercise cardiopulmonary hemodynamics offers a critical opportunity for timely PH diagnosis, optimized risk stratification, and appropriate management strategies.

To address these issues, a European Respiratory Society (ERS) Task Force (9) and a consecutive Clinical Research Collaboration (10) (PEX-NET) have been assembled. In addition to this large collaborative effort, a significant number of studies have been initiated in the last ten years by individual centers investigating exercise hemodynamics in healthy subjects and various patient populations. Novel hemodynamic variables addressing the pressure-flow relationship during exercise, such as the mPAP/cardiac output (CO), the pulmonary arterial wedge pressure (PAWP)/CO and the trans-pulmonary gradient (TPG)/CO slopes have been introduced in order to appropriately define exercise PH (11). Two potential hemodynamic definitions for exercise PH have been suggested (12-16), each acknowledging that pulmonary pressure is strongly dependent on changes in pulmonary blood flow provoked by exercise. According to the ERS Task Force, the preliminary definition of exercise PH is mPAP > 30 mmHg and total pulmonary resistance (TPR) > 3 WU at peak exercise (9,15), while an alternative definition suggested to consider exercise PH by using a mPAP/CO slope > 3 WU threshold (13,16). With minor differences, both definitions implicate that in patients with exercise PH mPAP increases steeply in relation to pulmonary blood flow during exercise.

Based on the above considerations, we had three aims in this systematic literature review and meta-analysis: 1) to assess the thresholds of normal exercise hemodynamics based on RHC investigations in healthy individuals, focusing mainly on the pressure-flow relationship during exercise 2) to assess the prognostic value of cardiopulmonary hemodynamics during exercise; and 3) to assess the differential-diagnostic value of exercise hemodynamics for the distinction between pre-and post-capillary causes of PAP increase.

Methods

To address these questions, we performed three independent systematic literature analyses: one for normal (i.e. to diagnose an abnormal hemodynamic reaction to exercise), one for prognostic and one for differential-diagnostic values of cardiopulmonary hemodynamics during exercise. We searched for English-language, peer-reviewed original publications (we only included original manuscripts with original data) that assessed cardiopulmonary hemodynamics during exercise by using RHC. Two independent researchers (K.Z. and G.K.) evaluated study eligibility and quality independently. The

same researchers performed data extraction by using standardized data collection sheets. Disagreements were resolved by consensus.

Of note, we included studies after 1945 for the prognostic and differential-diagnostic questions, as these questions have not been addressed systematically. For the normal values we included studies after 2003, because this question has been addressed in a previous systematic review, which included studies between 1947 and 2003 (1). An additional reason was that more recent studies used modern diagnostic tools to exclude any relevant comorbidities in the included healthy volunteers.

For normal values, studies were included if pulmonary hemodynamics during exercise were assessed by RHC, with at least one valid measurement at rest as well as during exercise, if they provided at least mPAP and CO at rest and during exercise and if they included at least one group of subjects that was described as being healthy. Here, we identified studies that included healthy volunteers ("healthy subjects") and studies that included subjects presenting with mild to moderate dyspnea on effort and undergoing RHC due to clinical reasons who were claimed to be healthy by the authors ("healthy patients"). These patients had normal resting hemodynamics and clinical work-up did not provide explanation for their symptoms. In the main analysis, we only included the data of symptom-free healthy volunteers.

In the final analysis of normal values, hemodynamic parameters were estimated separately for studies in the supine and upright positions both for healthy subjects and healthy patients. Upper limits of normal (ULN) were calculated as mean + 2SD. Slopes (mPAP/CO slope = (mPAP max – mPAP rest) / (CO max – CO rest); PAWP/CO slope = (PAWP max – PAWP rest) / (CO max – CO rest); TPG/CO slope = (TPG max – TPG rest) / (CO max – CO rest) were only calculated when measurements at rest and during exercise were performed in the same body position. The meta-analysis was computed with a random-effects model, thus assuming a degree of between-study heterogeneity. We further conducted three separate moderator analyses: 1) we compared estimates of hemodynamic parameters at rest vs. during exercise; 2) we compared estimates of hemodynamic parameters in healthy subjects vs. healthy patients; and 3) we tested whether age had an effect on the hemodynamic parameters. Moderator analyses 1) and 2) were conducted with categorical moderator variables, while age was included as a continuous covariate in the meta-regression. Given the limited number of studies in each condition, we decided to follow a conservative strategy for the estimation of the parameters by applying the Knapp-Hartung correction (17-19) to the meta-analysis with and without moderators. This correction returns the meta-analytic findings with robust standard errors and broader confidence intervals, which in turn enable a more conservative interpretation of results. To illustrate how age influenced mPAP/CO and PAWP/CO slopes, we provided age-adjusted estimates for the minimum, mean and maximum mean age values in the

group of included studies under consideration. We calculated values for mPAP/CO slope with the equation: estimate = -0.2719 + 0.0386*age, R^2 (amount of heterogeneity accounted for) = 0.93, and estimate = -0.5805 + 0.0293*age, R^2 = 1.00 for the PAWP/CO slope. The results of prognostic and differential-diagnostic studies were summarized with descriptive statistics.

Detailed additional description of data sources, search strategy, study selection, data preparation and stratification of the data are available in the online Supplement.

Results

Normal pulmonary hemodynamics and the diagnosis of abnormal hemodynamic response to exercise

We identified n=11 studies that included 250 symptom-free volunteers in whom major comorbidities had been excluded with state-of-the-art methods. In n=6/11 studies (119 subjects), RHC was performed in the supine position and in n=5/11 (131 subjects) in the upright position. A detailed overview of the studies is provided in Supplement Table 1a and 1b.

In the supine position, resting weighted mean values for mPAP, PAWP, and pulmonary vascular resistance (PVR) were 13.5 ± 2.0 mmHg, 8.6 ± 0.6 mmHg, and 1.0 ± 0.2 WU (Table 1a), respectively. Of all reported parameters, only systolic systemic arterial pressure and PVR were significantly influenced by age at rest. The upper limit of normal resting PVR ranged between 1.3 and 1.8 WU among 30-70-year-old healthy subjects. Corresponding values in the upright position are provided in Table 1b. During exercise, mPAP and PAWP increased significantly in both positions ($p < 0.001$). PVR showed a slight decrease, which, however, was not significant (supine: $p = 0.114$; upright: $p = 0.05$).

During supine exercise, older age was associated with a higher systolic systemic arterial pressure, mPAP, PAWP, TPR and right atrial pressure as well as with a higher mPAP/CO-slope and PAWP/CO-slope (see Table 1a and Figure 1). The mPAP/CO slope was 0.8 ± 0.4 WU (ULN 1.6 WU) in subjects ~30 years (reflecting the minimum of reported mean age across the included studies), 1.6 ± 0.2 WU (ULN 2.1 WU) in subjects ~50 years (reflecting the mean of reported mean age across the included studies) and 2.4 ± 0.5 WU (ULN 3.3 WU) in subjects ~70 years (reflecting the maximum of reported mean age across the included studies). The PAWP/CO slope ranged from 0.3 ± 0.2 WU (ULN 0.6 WU) in ~30-year-old subjects to 1.4 ± 0.2 WU (ULN 1.8 WU) in ~70-year-old subjects (Table 2). The TPG/CO slope was 0.8 ± 0.2 WU (ULN 1.2 WU) and was not significantly affected by age. In the upright position, the influence of age on hemodynamics was less pronounced (Table 1b). Multipoint mPAP/CO

measurements during exercise were only available from a small number of studies (n=4) and were therefore not further analyzed.

Patients with mild to moderate dyspnea on exercise

In addition to the described n=11 studies of healthy individuals, we identified n=9 studies with 303 subjects (n=194 subjects from n=6 studies in the supine and n=109 subjects from n=3 studies in the upright position) presenting with mild to moderate dyspnea on exercise who were claimed to be "healthy" by the authors ("healthy patients"). This was based on normal resting hemodynamics and the fact that clinical work-up had excluded obvious cardiovascular factors as explanation of symptoms. When these subjects were compared to our healthy symptom-free volunteers, there were only slight hemodynamic differences at rest and exercise, and no significant differences in the mPAP/CO (1.7 ± 0.8 (healthy patients) vs. 1.6 ± 0.6 WU (healthy subjects)), PAWP/CO (0.8 ± 0.4 (healthy patients) vs. 0.9±0.5 WU (healthy subjects)) and TPG/CO (0.8 ± 0.3 (healthy patients) vs. 0.8 ± 0.2 WU (healthy subjects)) slopes either in the supine (data provided) or in the upright position. Of note, similar to healthy subjects, the mPAP/CO and PAWP/CO slopes of "healthy patients" were age-dependent in the supine position (Supplement Table 1b and 2).

Prognostic relevance of pulmonary hemodynamics during exercise

We identified 18 studies with 3981 patients, focusing on the prognostic relevance of cardiopulmonary hemodynamics during exercise as assessed by RHC. In most of these studies, all-cause mortality alone or combined with heart failure related hospitalization were defined as prognostic end-points. The studies were heterogeneous in size, the number of subjects ranging from 27 to 1772 (median 71). Most studies (n=8) investigated patients with left heart disease (heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), valvular heart disease or coronary artery disease), or pre-capillary PH (n=5). The remaining studies included patients with unexplained dyspnea (n=2), COPD (n=2) and systemic sclerosis (n=1).

The following cardiopulmonary exercise parameters were most frequently reported to be significantly associated with prognosis in the identified studies: mPAP/CO slope, PAWP/CO slope, peak CI (or CO), peak PVR, peak PAWP, and the change in CI, sPAP, and heart rate from rest to peak exercise (Table 3).

The mPAP/CO slope, a hemodynamic parameter that was suggested as key parameter for the diagnosis of exercise PH (16), presented as a general prognostic marker across different conditions and was independently associated with survival in patients with exercise dyspnea, pre-capillary PH,

left heart disease and systemic sclerosis. In patients with exercise dyspnea, the cut-off for increased mortality was 3 WU (20) and in systemic sclerosis it was 3.5 WU (21). An elevated PAWP/CO slope was strongly associated with prognosis in subjects with exercise dyspnea (20) and the best cut-off > 2 WU was found in subjects with suspected or overt left heart disease (22). Peak CI (and CO) was also strongly associated with prognosis in several cohorts of patients with pre-capillary PH and left heart disease (Table 3).

Recognition of left heart or pulmonary vascular disease based on exercise hemodynamics

N=16 studies with 1367 patients investigated the cause of pulmonary pressure increase during exercise, mainly aiming to recognize left heart or pulmonary vascular disease and to distinguish between pre- and post-capillary causes of dyspnea in patients with normal resting PAWP.

Hemodynamic parameters that identified left heart disease as cause of dyspnea or exercise limitation included peak PAWP with predefined cut-offs by the authors at 20 or 25mmHg, and the PAWP/CO slope with a cut-off >2 WU. In contrast, an elevated TPG/CO slope or peak PVR may be suggestive for pulmonary vascular disease in patients with exercise dyspnea and systemic sclerosis (Table 4).

Discussion

Normal pulmonary hemodynamics and the diagnosis of abnormal hemodynamic response to exercise

Cardiopulmonary hemodynamics at rest and during exercise

The weighted means of resting hemodynamic variables (Table 1a and 1b) corresponded well to previously described normal values from systematic literature analyses and meta-analyses (1,23,24). Of note, based on the provided values (means and standard deviations), it is likely that some individuals in the included studies had mPAP > 20 mmHg, which is considered to be abnormal. In line with previous studies (1,23), mPAP and PAWP increased significantly during exercise both in the supine and upright positions while PVR showed a trend for a moderate decrease during exercise. The mPAP/CO slope emerged as simple and consistent variable characterizing pulmonary hemodynamic changes during exercise.

We did not perform a direct comparison of data derived from the supine and upright position due to the limited number of comparable studies and because the data in different positions were not available from the same subjects and the same studies. The effect of posture on cardiopulmonary

hemodynamics during exercise has been described previously (1,23) considering only studies that tested the same subjects in both positions.

Of note, in this study, the variability of resting hemodynamic parameters (i.e. standard deviations) was smaller than in previous systematic reviews. This may be explained by the relative homogeneity of the subjects included in this analysis and the applied methodology (healthy volunteers without dyspnea, relevant cardiopulmonary comorbidities excluded by modern diagnostic methods, more homogenous zero levels) as compared to previous systematic reviews.

The present review is solely based on studies providing hemodynamic data based on RHC. This decision was made to ensure highest data quality to define thresholds for normal hemodynamics during exercise, as well as prognostic and differential-diagnostic cut-offs. Non-invasive assessment of exercise hemodynamics with echocardiography is of increasing clinical value, however, it is still considered to lack precision as compared to invasive hemodynamic measurements (9).

Age-dependency of normal mPAP/CO slope

Based on the identified studies, the weighted mean of mPAP/CO slope was influenced by age and the ULN for 30- to 70-year old subjects ranged from 1.6 to 3.3 WU. The age-dependency of the mPAP/CO slope was mainly driven by the age-dependency of the PAWP/CO slope while the TPG/CO slope was not significantly age-dependent. This might indicate the decline of the left ventricle´s filling compliance during exercise as part of a physiologic aging process (25), whereas the distensibility of the pulmonary vessels may remain largely unaffected by age. As shown in Figure 2a, studies in healthy subjects with mean age > 60 yrs were under-represented in the current meta-analysis, which was also the case in earlier physiologic studies (1,23). Therefore, the hemodynamic values provided for elderly subjects may be less reliable.

Due to the limited number of studies including multi-point mPAP/CO slopes and PAWP/CO slopes, it was not possible to analyze the curvilinearity of the slopes in healthy individuals within the framework of the present study. Previous investigations suggested an almost linear mPAP/CO slope, eventually with a gradual flattening at high levels of exercise (13,23,25-27). This supports the use of the mPAP/CO slope as key parameter of cardiopulmonary exercise hemodynamics.

Prognostic relevance of pulmonary hemodynamics during exercise

Prognostic relevant cut-offs in exercise dyspnea: mPAP/CO > 3 WU, PAWP/CO > 2 WU

Two large studies aimed to provide prognostic relevant hemodynamic thresholds during exercise for a general population with dyspnea on effort. Ho and colleagues included n=714 subjects and analysed the association between exercise PH and a combined endpoint defined as all-cause mortality or cardiovascular hospitalization (20). The authors defined exercise PH as mPAP/CO slope > 3 WU. The presence of exercise PH was associated with a 2-fold increased risk of an event. In addition, besides the mPAP/CO slope, both TPG/CO and PAWP/CO slopes were independently associated with prognosis (20).

In a second large study, Eisman and colleagues 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. In patients with dyspnea, a PAWP/CO slope >2 WU was found in about 40% of subjects and this was associated with adverse clinical outcomes, defined as cardiovascular death, hospitalization due to heart failure, or abnormal resting PAWP in a future RHC (22). As a consequence, a PAWP/CO slope >2 WU may be considered as a prognostically relevant marker in HFpEF subjects with normal resting PAWP and ejection fraction.

Prognostically relevant hemodynamic parameters in cardiopulmonary diseases

The prognostic relevance of cardiopulmonary hemodynamics during exercise has also been assessed in patients with pre-capillary PH, left heart diseases and COPD. In pre-capillary PH, two hemodynamic variables appeared to have the strongest prognostic relevance. First, cardiac index (CI) at peak exercise or its change from rest to exercise was found to be of prognostic relevance in most of the studies (28-32). Of note, an increase in cardiac index by >50% of its resting value (28) or $\geq$0.55 L/min/m^2 (32) was associated with a better prognosis. Second, similar to patients with exercise dyspnea, also in pre-capillary PH, an elevated mPAP/CO slope was associated with a poor survival (29,32). However, in patients with PH at rest, the range of the slopes was much higher: even in patients with better survival the mPAP/CO-slope was frequently > 10 WU (32).

In patients with suspected or confirmed left heart disease, a steep increase of PAWP during exercise appeared as the single most important prognostic hemodynamic parameter. In patients with dyspnea and suspected HFpEF, a steep increase in PAWP during exercise was strongly associated with mortality, even if hemodynamics at rest were normal (34). The best cut-off for a poor survival

was >25.5 mmHg/W/kg, e.g. in a subject with 75 kg body weight, PAWP would increase above 25 mmHg at 75W work load. Of note, pulmonary blood flow during exercise is dependent on workload, but with large individual variability (16). Nevertheless, these results support the data of Eisman et al. and the prognostic relevance of the PAWP/CO-slope in patients with dyspnea and at risk for HFpEF (22). Also in patients with established left heart disease, the mPAP/CO (or mPAP/workload) slope appears to be of prognostic relevance. A steep initial increase of mPAP (0.41±0.16 mmHg/watt) followed by a plateau was associated with severely impaired survival in patients with HFrEF as compared to subjects with a moderate, linear mPAP increase during exercise (0.28±0.12 mmHg/watt) (12).

Two studies investigated the prognostic relevance of cardiopulmonary hemodynamics during exercise in COPD. An increase in mPAP and PVR during exercise was associated with clinical deterioration (36), while a low peak CI during exercise predicted poor results of lung surgery, defined as death or prolonged ventilation (37).

As systemic sclerosis (SSc) represents a significant risk for pulmonary arterial hypertension, changes in cardiopulmonary hemodynamics during exercise may reveal early signs of pulmonary vascular disease with potential clinical relevance. A recent study stratified SSc patients into subjects with PH at rest, with exercise PH, and normal hemodynamics. Survival was superior in patients with normal hemodynamics as compared to the other groups, but it was not significantly different between resting and exercise PH. Hemodynamic variables including mPAP at peak exercise, mPAP increase during exercise and the mPAP/workload slope were predictors of transplant-free survival, while hemodynamics at rest were not (38). A further study revealed that both PVR and CO at peak exercise and the mPAP/CO slope were predictors of long-term survival in SSc patients with no or mildly increased PAP, whereas resting hemodynamics were not (21). Of note, the best mPAP/CO cut-off to predict survival was 3.5 WU, which is very similar to the prognostic threshold in patients with exercise dyspnea (3 WU).

Taken together, in patients with exercise dyspnea or different cardiopulmonary conditions, the mPAP/CO slope, the PAWP/CO slope and peak CI (or CO) appear to be the most robust prognostically relevant hemodynamic parameters during exercise.

Recognition of left heart or pulmonary vascular disease based on exercise hemodynamics

PAWP/CO > 2 WU identifies a post-capillary cause of elevated PAP during exercise

According to the identified studies, an increased PAWP/CO slope with a cut-off > 2 WU may be the most important indicator of a post-capillary cause for abnormal cardiopulmonary hemodynamics

during exercise. Nearly all patients with overt HFpEF and elevated resting PAWP (PAWP > 15 mmHg) had a PAWP/CO slope far above this threshold (22), whereas in subjects with normal resting PAWP, a PAWP/CO slope > 2.0 WU was associated with adverse cardiac outcomes (22).

In patients with normal resting PAWP, higher PAWP values during exercise were associated with increased left atrial area and volumes (39), highlighting the role of exercise hemodynamics in uncovering latent left heart disease. Of note, peak PAWP ≥ 25 mmHg during exercise has been suggested to identify HFpEF in patients with exertional dyspnea, normal ejection fraction and resting PAWP ≤ 15 mmHg (40). This suggestion was also adopted in the current ESC diagnostic algorithm for HFpEF (41).

As compared to peak PAWP values, the PAWP/CO slope incorporates the level of increasing flow during exercise and may therefore be more suitable to describe an abnormal hemodynamic response to exercise than peak PAWP alone.

Hemodynamic patterns suggesting pulmonary vascular disease

Some studies aimed to describe hemodynamic patterns during exercise that may be characteristic for pre-capillary pulmonary vascular involvement, despite normal or near normal resting hemodynamics. The relevance of the mPAP/CO slope and pulmonary arterial compliance during exercise as potential markers of pulmonary vascular disease was highlighted in a study comparing untreated CTEPH patients, CTEPH patients with normalized hemodynamics after pulmonary endarterectomy (PEA) and healthy controls. In post-PEA patients as compared to healthy controls, the mPAP/CO slope was steeper, while pulmonary arterial compliance was similar to patients with untreated CTEPH, suggesting that such changes may indicate pulmonary vascular disease (42).

In addition, increased PVR or TPG during exercise have been considered as suggestive for early pulmonary vascular disease in patients with systemic sclerosis (43-45). However, currently no large prospective studies are available that could confirm that a certain hemodynamic pattern is significantly associated with the development of pulmonary arterial hypertension.

Potential definition of exercise PH

A flow-corrected, simple, reliable hemodynamic parameter with a single, prognostic relevant cut-off at the ULN would represent an optimal definition for exercise PH. However, mainly due to the strong age-dependency of most cardiopulmonary hemodynamic parameters during exercise and the limited number of available datasets in healthy older subjects, no parameter and cut-off appears to fulfil all

these criteria. Hemodynamic parameters incorporating CO, such as the mPAP/CO slope appropriately account for the impact of blood flow on mPAP as compared to the absolute value of maximal mPAP, which was previously used to define exercise PH. In addition, the mPAP/CO slope is a consistent variable to describe abnormalities of the pulmonary circulation during exercise and is independently associated with prognosis in patients with exercise dyspnea and in several cardiovascular conditions. Based on these considerations, the mPAP/CO slope may be suitable to define exercise PH.

Limitations

We acknowledge several limitations of our study. We cannot exclude that some relevant studies were missed by our systematic search strategy. In addition, we included a limited number of studies per condition for the meta-regression models and therefore generalization to a broader population of values may not be accurate. Our decision to consider only studies after 2003 for the analysis of normal values contributed to the limited number of included studies for this question. However, this approach was used to ensure the best possible quality of data and the inclusion of 250 healthy subjects complying with state-of-the-art work-up for exclusion of co-morbidities, examined by RHC, allowed for robust general conclusions. Referral bias may have influenced the available data, because invasive studies may not have been offered at all clinics. The estimation of age-dependency of ULN for slopes in healthy elderly controls should be interpreted with caution because the number of these subjects in the dataset was small. Nevertheless, the results were consistent with a similar dataset of symptomatic patients with no pathological findings, suggesting robustness of the data. Age was included in the moderator analysis as an aggregated variable, underestimating the true variability of this parameter within each individual study. Some methodological details such as the zero reference point or the exact method for assessment of pulmonary pressures during exercise (end-expiratory vs. averaging over several respiratory cycles) were not provided in all studies. However, it can be assumed that recent discussions and recommendations have reduced the heterogeneity as compared to previous studies. Further, study results were reported heterogeneously and therefore some statistical approximations and calculations had to be performed, as outlined in the Supplement. These calculations may have introduced a degree of uncertainty in our data. It is unlikely, though, that they significantly influenced the major results of our analysis. Comparisons for sex and race have not been performed due to the limited number of studies that would have allowed such an analysis. Finally, beyond their description, a true direct comparison between hemodynamic indices for their prognostic or differential-diagnostic relevance is not possible based on the currently available data. We expect that this question may be addressed within the next years in a large, well-powered multi-center clinical registry study (46).

Conclusions

In conclusion, the mPAP/CO and PAWP/CO slopes appear to be the most valuable parameters to characterize the pulmonary circulation during exercise. In contrast to the absolute values of mPAP, the mPAP/CO slope is largely unaffected by work load, but it is strongly age-dependent, its upper limit of normal ranging from 1.6 WU to 3.3 WU. An increased mPAP/CO slope is associated with impaired survival in different cardiopulmonary conditions and an independent prognostic cut-off with mPAP/CO > 3 WU has been validated in dyspnea patients (see central illustration).

The PAWP/CO slope is strongly age-dependent and its upper limit of normal ranges between 0.6 WU to 1.8 WU. The PAWP/CO slope > 2 WU is associated with adverse cardiovascular events and differentiates between pre- and post-capillary causes of exercise PH. These findings may contribute to the identification of early pulmonary vascular and early left ventricular disease and provide a basis for future therapeutic studies.

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Figure legend:

Central illustration:

Abnormal pulmonary hemodynamics during exercise may be defined by an increased mean pulmonary arterial pressure (mPAP)/cardiac output (CO) slope. The upper limit of normal (ULN, mean + 2 SD) for mPAP/CO slope is strongly age-dependent and ranges from 1.6 (in ~30-year-old healthy subjects) to 3.3 (in ~70-year-old healthy subjects) Wood Units (WU) in the supine position (see also Table 2). Of note, the ULN based on the weighted mean and SD of all healthy subjects included in this analysis was 2.7 WU in the supine position. An increased mPAP/CO slope with a cut-off above 3 WU is independently associated with poor survival and heart failure (HF)-related hospitalizations.

The mPAP/CO slope corresponds to the sum of the trans-pulmonary gradient (TPG)/CO slope and the pulmonary arterial wedge pressure (PAWP)/CO slope. Like the mPAP/CO slope, the ULN for PAWP/CO slope is also strongly age-dependent and ranges from 0.6 to 1.8 WU. An increased PAWP/CO slope with a cut-off above 2 WU is associated with impaired survival and increased cardio-vascular (CV) events and may be diagnostic for a post-capillary cause of PAP elevation during exercise. The ULN for TPG/CO slope is 1.2 WU and age-independent. An increased TPG/CO slope is also associated with impaired survival and may be suggestive of pulmonary vascular disease (PVD). DDx = diagnosis, LHD = left heart disease.

Figure 1:

Figure 1 shows a) mPAP/CO slope (in mmHg/L/min; WU) and b) PAWP/CO slope (in mmHg/L/min; WU) by age groups in the supine position. Each line represents an individual study group or a subgroup according to stratification to age in one study (see Figure 2 for details). Older subjects (blue line) have a steeper mPAP/CO- and PAWP/CO slope and tend to have higher mPAP at rest. During exercise, older subjects reach higher mPAP and PAWP at lower CO values as compared to younger individuals. The solid black lines show the age-adjusted mean slopes (estimated by mean age across the included studies). Exercise values in healthy subjects did not exceed mPAP > 30 mmHg in combination with exercise TPR > 3 WU (dashed line in Figure 1a).

Figure 2:

Forrest plots of the identified studies in heathy subjects in the supine position for a) mean age b) mPAP/CO slope and c) PAWP/CO slope. The study of Wolsk et al and Andersen et al assessed different age groups that are seperately displayed in the Forrest plot, showing the influence of age on cardiopulmonary hemodynamics during exercsie. Wolsk2017_1 was the youngest (age <40yrs) whereas Wolsk2017_3 and Andersen2019_3 the oldest subjects (age >60 yrs).

Table 1: Resting and exercise cardiopulmonary hemodynamics in healthy subjects in the a) supine position, b) upright position.

a)

Condition	Parameter (unit)	k	Estimate	SD
Rest	mPAP (mmHg)	8	13.5[§]	2.0
Rest	PAWP (mmHg)	6	8.6[§]	0.6
Rest	PVR (WU)	6	1.0*[#]	0.2
Rest	CO (L/min)	8	5.6[§]	0.5
Rest	CI (L/min/m^2)	8	2.9[§]	0.2
Rest	RAP (mmHg)	5	6.1	1.5
Rest	HR (bpm)	8	63[§]	3
Rest	dSAP (mmHg)	5	74[§]	6
Rest	sSAP (mmHg)	5	129*[§]	10
Rest	TPR (WU)	8	2.4[§]	0.5
Exercise	mPAP (mmHg)	8	29.2*	5.3
Exercise	PAWP (mmHg)	6	17.8*	3.7
Exercise	PVR (WU)	6	0.8	0.2
Exercise	CO (L/min)	8	16.0*	2.0
Exercise	CI (L/min/m^2)	8	8.4*	1.0
Exercise	RAP (mmHg)	4	8.6*	2.0
Exercise	HR (bpm)	8	131	13
Exercise	dSAP (mmHg)	5	88	5
Exercise	sSAP (mmHg)	5	178*	13
Exercise	TPR (WU)	8	1.8*	0.5
	mPAP/CO slope (WU)	8	1.5*	0.6
	PAWP/CO slope (WU)	6	0.9*	0.5
	TPG/CO slope (WU)	6	0.8	0.2

b)

Condition	Parameter (unit)	k	Estimate	SD
Rest	mPAP (mmHg)	4	17.3[§]	0.6
Rest	PAWP (mmHg)	4	10.5*[§]	1.7
Rest	PVR (WU)	4	1.4	0.2
Rest	CO (L/min)	4	4.7[§]	0.3
Rest	CI (L/min/m^2)	4	2.6[§]	0.2
Rest	RAP (mmHg)	4	6.0	0.9
Rest	HR (bpm)	4	68[§]	10
Rest	dSAP (mmHg)	3	80	2
Rest	sSAP (mmHg)	3	129[§]	1
Rest	TPR (WU)	4	3.6[§]	0.3
Exercise	mPAP (mmHg)	8	27.6	4.3
Exercise	PAWP (mmHg)	7	16.5	3.4

Exercise	PVR (WU)	7	0.9	0.2
Exercise	CO (L/min)	8	14.7	3.6
Exercise	CI (L/min/m^2)	8	7.9	1.8
Exercise	RAP (mmHg)	7	8.4	2.0
Exercise	HR (bpm)	8	140*	22
Exercise	dSAP (mmHg)	3	80	1
Exercise	sSAP (mmHg)	3	169	5
Exercise	TPR (WU)	8	2.0*	0.5
	mPAP/CO slope (mmHg)	4	1.3	0.2
	PAWP/CO slope (mmHg)	4	0.7*	0.2
	TPG/CO slope (mmHg)	4	0.6	0.1

* significant influence of age (or age-dependency) ($p<0.05$)

§ significant difference between rest and exercise conditions ($p<0.05$)

Upper limits of normal (ULN) of PVR at rest in the supine position are 0.7 ± 0.3 WU (ULN 1.3 WU) for ~30-year-old subjects, 1.0 ± 0.2 WU (ULN 1.3 WU) for ~50-year-old subjects and 1.3 ± 0.3 WU (ULN 1.8 WU) for ~70-year-old subjects

Data are presented as weighted mean ± SD. HR: heart rate; dSAP: diastolic systemic arterial pressure; sSAP: systolic systemic arterial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; RAP: right atrial pressure; TPR: total pulmonary resistance; TPG: trans-pulmonary gradient; WU: Wood units; bpm: beats per minute

Slopes were only calculated when rest and exercise measurements were performed in the same position, therefore, n=2 studies were excluded for the calculation in the upright position.

References: supine: (42,47-51); upright (52-56).
A more detailed description of all identified studies is provided in Online Supplement Table 1a

Table 2

Effect of age on exercise cardiopulmonary hemodynamics and upper limits of normal for mPAP/CO slope and PAWP/CO slope in healthy subjects in the supine position.

Slope	Age (yrs)	Nr. of groups included	Predicted value (mean and 95% CI)	Standard deviation	Upper limit of normal
mPAP/CO slope	29	8	0.8 (0.5-1.27) WU	0.4 WU	**1.6 WU**
	39	8	1.2 (1.0-1.5) WU	0.3 WU	**1.7 WU**
	49	8	1.6 (1.4-1.8) WU	0.2 WU	**2.1 WU**
	59	8	2.0 (1.7-2.3) WU	0.3 WU	**2.7 WU**
	69	8	2.4 (2.0-2.8) WU	0.5 WU	**3.3 WU**
PAWP/CO slope	29	6	0.3 (0.1-0.4) WU	0.2 WU	**0.6 WU**
	39	6	0.6 (0.4-0.7) WU	0.1 WU	**0.8 WU**
	49	6	0.8 (0.7-1.0) WU	0.1 WU	**1.0 WU**
	59	6	1.1 (1.0-1.3) WU	0.1 WU	**1.4 WU**
	69	6	1.4 (1.2-1.7) WU	0.2 WU	**1.8 WU**

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output

Table 3: Overview of the identified studies for prognostic value and their main characteristics based on their underlying condition

Publication	N	Age ± SD (IQR), years	Sex (M:F)	Main inclusion criteria	Endpoint	Exercise parameters predicting events
Exercise dyspnea						
Ho 2020 (20)	714	57 ± 16	292:422	exercise dyspnea; LVEF≥50%	all-cause mortality, HF related hospitalization	mPAP/CO slope > 3 WU, elevated TPG/CO slope and PAWP/CO slope
Eisman 2018 (22)	175	57 ± 17	65:110	exercise dyspnea; LVEF>50%, PAWP<15mmHg	HF related hospitalization, HF related mortality, elevation of resting PAWP in follow-up RHC>15mmHg	PAWP/CO slope > 2 WU
Dorfs 2014 (34)	355	61 ± 11	120:235	exercise dyspnea and suspected HFpEF	all-cause mortality	steep PAWP increase (>25.5 mmHg/W/kg) *
Left heart disease						
Dobarro 2020 (57)	33	74 ± 8	30:3	Moderate to severe aortic stenosis, <85yrs	all-cause mortality, surgical aortic valve replacement, TAVI or planned intervention for AST	PaO_2 at peak exercise
Huang 2018 (58)	104	61 ± 12	39:65	HFpEF (normal LVEF, no valvular heart disease)	all-cause mortality, HF related hospitalization	PVR > 1 WU at peak exercise
Rieth 2017 (59)	167	65 ± 12	125:42	HFrEF (LVEF≤45%)	all-cause mortality, LuTX and/or HTX, heart assist device	change in CO < 1.154 L/min and change in sPAP < 17.5 mmHg
Lewis 2011 (12)	60	60 ± 12	47:13	HFrEF (LVEF<40%, NYHA II-IV)	all-cause mortality	mPAP/Watt slope > median (0.25 mmHg/Watt), steep increase in mPAP followed by a plateau pattern
Griffin 1991 (35)	49	63 ± 11	39:10	congestive heart failure (symptoms > 1 year)	HF related mortality	PAWP at rest and exercise, peak stroke work index
Szlachicic 1985 (60)	27	56	27:0	congestive heart failure (clinically stable)	all-cause mortality	Peak CI
Gohlke 1983 (61)	1772	50 ± 6	1595:177	coronary artery disease and normal or mildly impaired left ventricular function	all-cause mortality	Peak CO
Pulmonary arterial hypertension						
Faure 2020 (31)	49	53 ± 16	16:33	PAH	all-cause mortality	Change in HR and sPAP
Tang 2018 (30)	140	33 ± 11	39:101	IPAH	LuTX and/or HTX, HF related mortality	change in HR, peak work rate, PVR and CI
Hasler 2016 (32)	70	65 (50-73)	27:43	PAH+CTEPH	all-cause mortality, LuTX and/or HTX	maximal workload, peak and change in CI and mPAP/CO
Chaouat 2014 (28)	55	54 ± 16	25:30	IPAH, heritable or anorexigen-associated PAH	all-cause mortality, LuTX and/or HTX	peak CI, change in sPAP, change in CI
Blumberg 2013 (29)	36	54 ± 15	15:21	PAH+CTEPH (NYHA II-III)	all-cause mortality, LuTX and/or HTX	mPAP/CO slope, peak CI *
Systemic sclerosis						
Stamm 2016 (38)	72	Range: 42-74	10:62	SSc with exercise dyspnea ± reduced DLCO or FVC/DLCO >1.6	all-cause mortality, LuTX and/or HTX	Peak mPAP, mPAP increase, mPAP/Watt increase *
COPD						
Olsen 1989 (37)	29	64 ± 5	29:0	Lung resection due to airflow obstruction and lung mass	postoperative death within 60days or prolonged ventilation (>30days)	Peak CI
Finlay 1983 (36)	74	59	60:14	clinically stable COPD, symptoms > 3yrs	all-cause mortality	increase in mPAP + PVR during exercise

SD: standard deviation; M: Male; F: Female; LVEF: left ventricular ejection fraction; HF: heart failure; mPAP: mean pulmonary arterial pressure; TPG: trans-pulmonary pressure gradient; PAWP: pulmonaty arterial wedge pressure; CO: cardiac output; RHC: right heart catheterization; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LuTX: lung transplantation; HTX: heart

transplantation; sPAP: systolic pulmonary arterial pressure; PaO2: partial pressure of oxygen; PVR: pulmonary vascular resistance; CI: cardiac index; HR: heart rateExercise protocol was ergometry for all studies. * in these studies only exercise and not resting pulmonary hemodynamics predicted the endpoint.

Table 4: Overview of the identified studies for diagnostic and differential-diagnostic value and their most relevant findings

Publication	N	Age ± SD, years	Sex (M:F)	Patient cohort	Most relevant finding
Recognizing left heart disease					
Goda 2019 (62)	71	67 ± 11	15:56	CTEPH	Patients with ***peak PAWP*** >20 mmHg (predefined) had larger left atrial volume index (40 vs. 34 ml/m^2) as compared to patients with peak PAWP ≤ 20 mmHg, suggesting left heart disease.
Eisman 2018 (22)	175	57 ± 17	65:110	HFpEF + Dyspnea + Controls	***PAWP/CO slope*** = 2 WU was the ULN in controls and > 2 WU was characteristic of HFpEF, related to lower exercise capacity, and may also identify HFpEF in patients with normal PAWP at rest.
Maor 2015 # (39)	63	60 ± 20	18:45	Dyspnea	Patients with resting PAWP 12-15mmHg were 4.5 times more likely to present with a ***steep PAWP increase*** during exercise as compared to patients with resting PAWP < 12 mmHg.
Andersen 2015 (63)	26	70 ± 9	9:15	HFpEF + Controls	94% of patients with left ventricular diastolic dysfunction in Echo but 0% of controls had ***peak PAWP*** > 25 mmHg during exercise. Steep PAWP increase may uncover left heart disease.
van Empel 2014 (64)	28	62 ± 1	-	HFpEF + Controls	HFpEF patients had higher ***PAWP at peak exercise*** than controls (32 vs. 16 mmHg).
Borlaug 2010 (40)	55	56 ± 15	17:38	Dyspnea	Exercise PAWP was used to classify patients with resting PAWP < 15 mmHg as having HFpEF (***PAWP at exercise*** ≥ 25 mmHg) or non-cardiac dyspnea (PAWP at exercise < 25 mmHg). PAWP and sPAP were strongly correlated during exercise.
Yoshida 1985 (65)	40	Range 26-71	38:2	Coronary artery disease + Controls	***dPAP/CO slope*** is steeper in patients with coronary artery disease and angina than in those without angina or in controls.
Recognizing pulmonary vascular disease					
Nagel 2019 (44)	112	58 ± 13	24:88	SSc	SSc patients with resting mPAP 21-24 mmHg had higher ***peak PVR*** (2.7 vs. 1.8 WU), and lower 6-minute walking distance and peak cardiac index as compared to patients with resting mPAP ≤ 20 mmHg, which may indicate early pulmonary vascular disease.
Gorter 2018 (66)	161	67 ± 11	59:102	HFpEF	Among HFpEF patients (resting PAWP ≥ 15 mmHg), cpcPH was associated with higher ***peak PVR*** (4.5 vs. 1.9 WU) and lower peak pulmonary arterial compliance (1.4 vs. 2.3 ml/mmHg) as compared to ipcPH suggesting the presence of pulmonary vascular disease.
Claessen 2015 (42)	36	62 ± 12	27:9	CTEPH + Controls	***mPAP/CO slope*** was steeper in CTEPH patients after pulmonary endarterectomy than in controls and similar to those with not operated CTEPH suggesting the presence of residual pulmonary vascular disease.
Taylor 2015 (67)	39	57 ± 9	32:7	Heart Failure	At a given cardiac output (~4.5 L/min) during exercise, ***mPAP*** was greater in patients with heart failure and combined pre- and post-capillary PH, than in patients without PH and, to a lesser extent, than in patients with isolated post-capillary PH (~55 vs. ~32 vs. ~45 mmHg, respectively).
Tolle 2008 (68)	109	55 ± 15	40:69	PAH + Controls	Exercise patterns differ between PAH patients and controls. PAH present with a ***strong initial increase of mPAP*** followed by a plateau, whereas a continuous moderate mPAP increase was characteristic in controls.
Recognizing left heart and pulmonary vascular disease					
Bentley 2020* (69)	121	55 (range 50-60)	61:60	Dyspnea + Controls	***Pulse pressure/PAWP slope*** > 2.5 (ULN in controls) uncovers a subgroup among subjects with a normal mPAP/CO slope (ULN in controls = 3.2 WU) that is suggestive of an exaggerated pulmonary vascular to PAWP response and might indicate an abnormal PAP response, which is not driven by LHD. The ULN of the ***PAWP/CO slope*** in controls was 2.0 WU.
Keusch 2014* (70)	101	61 (range 52-68)	31:70	Dyspnea	Out of patients with exercise dyspnea and resting PAP 20-24 mmHg, about the same number had either a ***steep PAWP or PVR increase***, suggesting either post- or pre-capillary cause of mPAP elevation during exercise.
Hager 2013*# (45)	173	53 ± 13	20:153	SSc + Controls	Exercise may distinguish between pre-capillary (i.e. pulmonary vascular disease, characterized by an ***increase in TPG and PVR during exercise***) and post-capillary (i.e. mainly HFpEF, characterized by a ***steep PAWP/CO slope*** and no significant change in TPG during exercise) cause of exercise PH in SSc.
Saggar 2010* (43)	57	50 ± 13	12:45	SSc	According to predefined criteria by the authors, SSc patients may reveal pre- or post-capillary causes of exercise PH. The main characteristics of post-capillary exercise PH may be the relevant ***increase of PAWP at peak exercise***, while the main characteristics of pre-capillary exercise PH may be an ***increased PVR and TPG at peak exercise***.

*these studies provide data both for the recognition of left heart disease and pulmonary vascular disease based on parameters of exercise hemodynamics; #in these studies the exercise protocol was arm lifting with weights, in all other studies patients performed cycle-ergometry. mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; CO: cardiac output; CI: cardiac

index; yrs: years; WU: wood units; L: liter; min: minute; SSc: systemic sclerosis; HFpEF: heart failure with preserved ejection fraction; CTEPH: chronic thromboembolic pulmonary hypertension, LDH: left heart disease, PH: pulmonary hypertension; TPG: trans-pulmonary gradient; PAH: pulmonary arterial hypertension; sPAP: systolic pulmonary arterial pressure; dPAP: diastolic pulmonary arterial pressure.

Figure 1: mPAP/CO slope and PAWP/CO slope in the supine position.

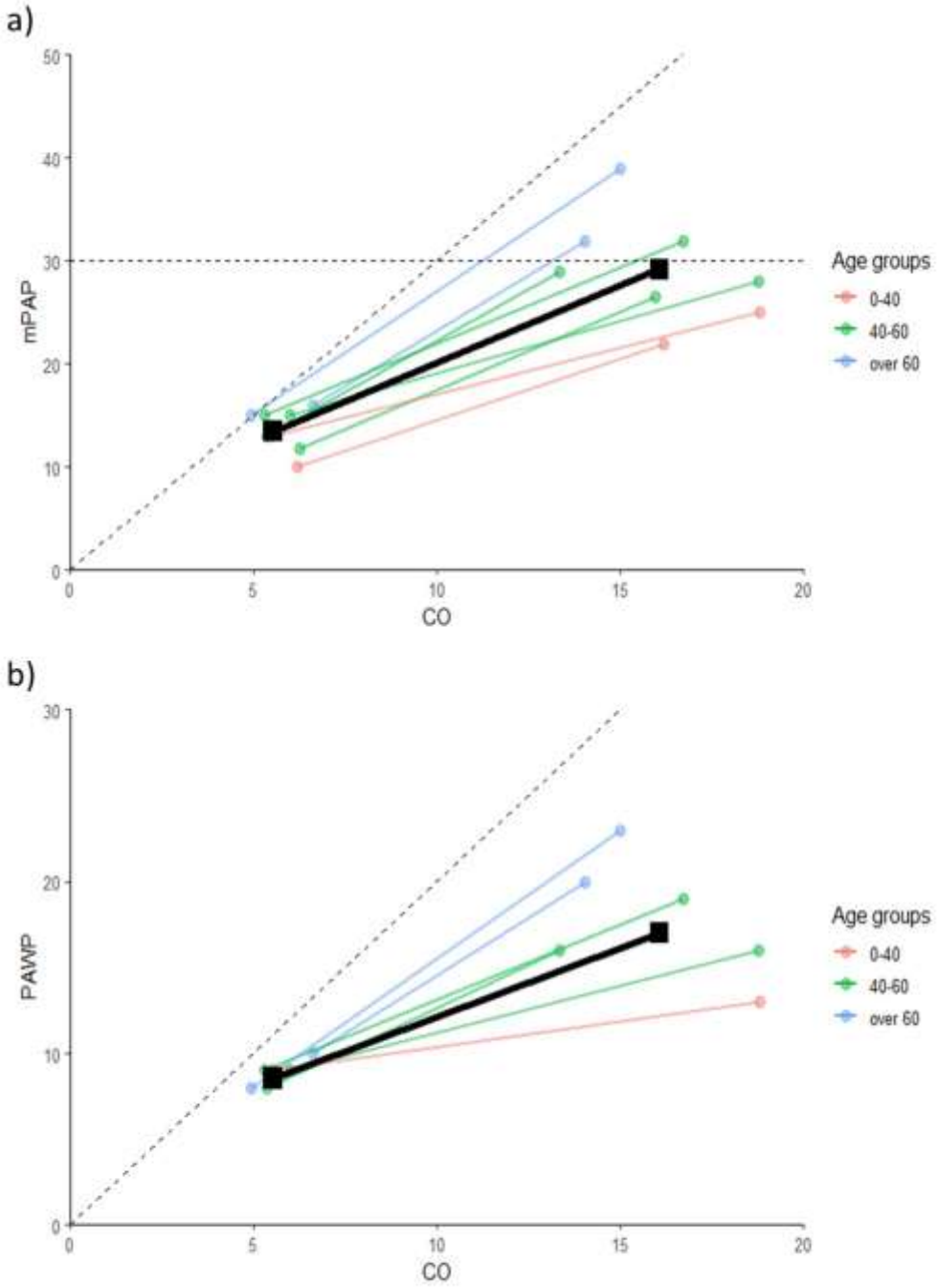


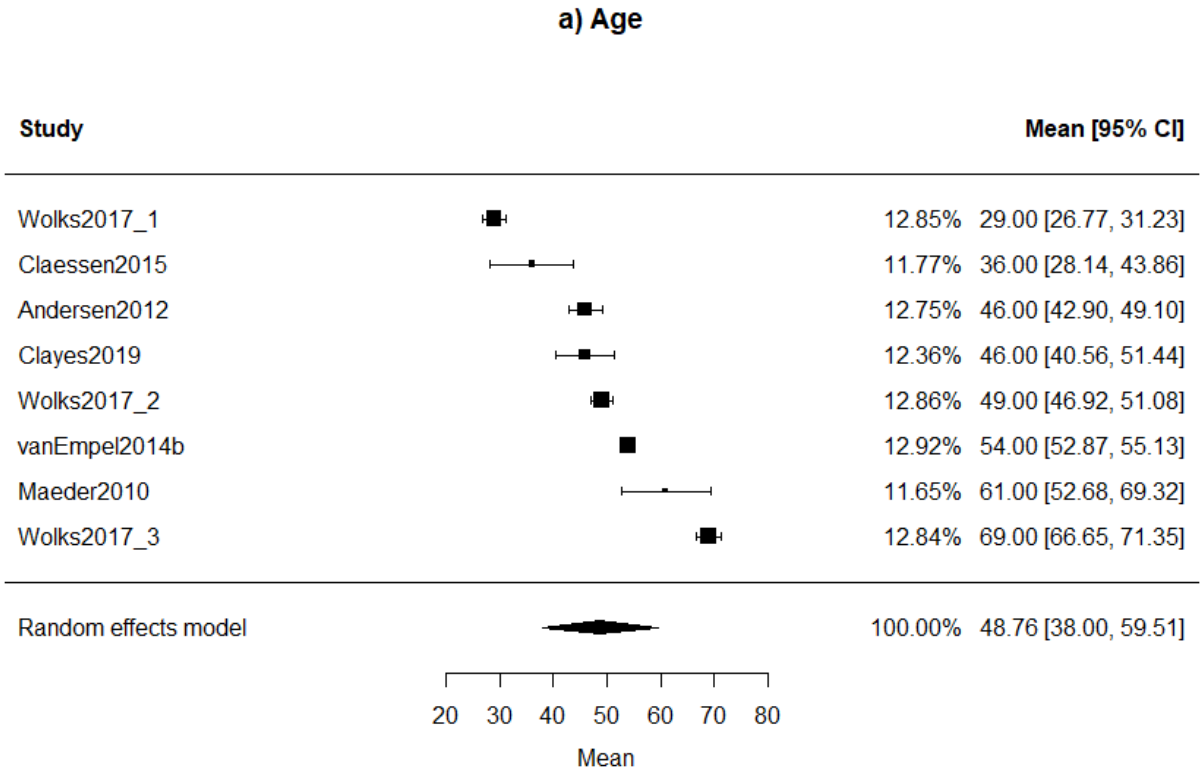
Figure 1 shows a) mPAP/CO slope (in mmHg/L/min; WU) and b) PAWP/CO slope (in mmHg/L/min; WU) by age groups in the supine position. Each line represents an individual study group or a subgroup according to stratification to age in one study (see Figure 2 for details). Older subjects (blue line) have a steeper mPAP/CO- and PAWP/CO slope and tend to have higher mPAP at rest. During exercise, older subjects reach higher mPAP and PAWP at lower CO values as compared to younger individuals. The solid black lines show the age-adjusted mean slopes (estimated by mean age across the included studies). Exercise values in healthy subjects did not exceed mPAP > 30 mmHg in combination with exercise TPR > 3 WU (dashed line in Figure 1a).

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; yrs: years; TPR: total pulmonary resistance

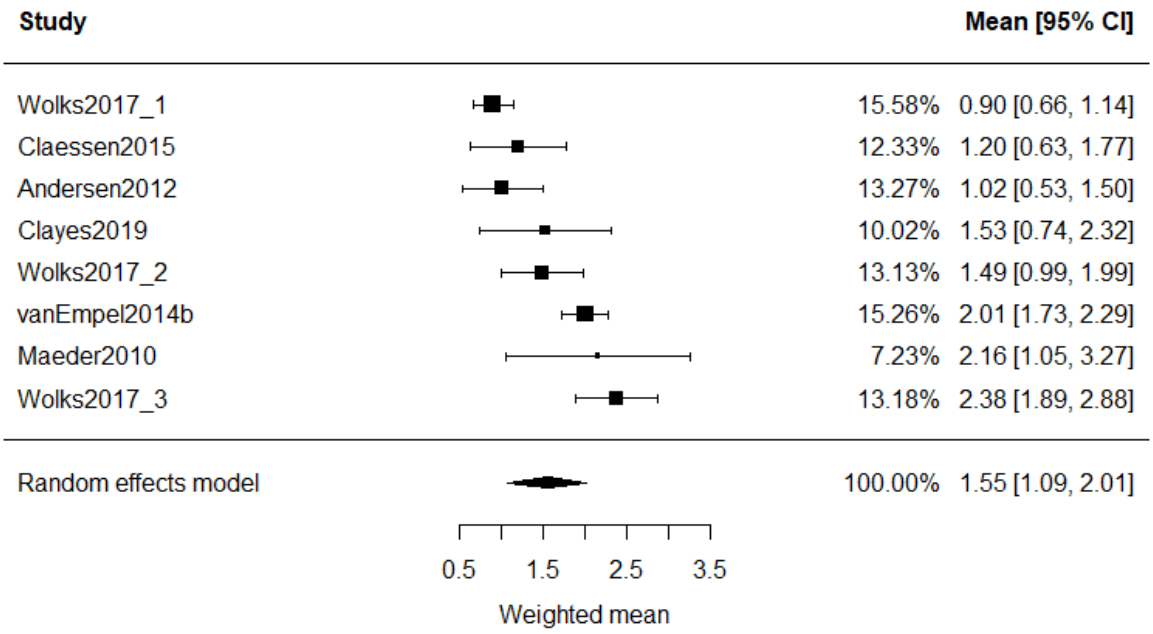
Figure 2

Forrest plots of the identified studies in heathy subjects in the supine position for a) mean age (yrs) b) mPAP/CO slope (WU) and c) PAWP/CO slope (WU). Estimates were computed using the Knapp-Hartung correction due to the low number of available studies. The study of Wolks et al. assessed different age groups that are seperately displayed in the Forrest plot, showing the influence of age on cardiopulmonary hemodynamics during exercsie. Wolks 2017_1 provided the youngest (age <40yrs) and Wolks 2017_3 the oldest subjects (age >60 yrs).

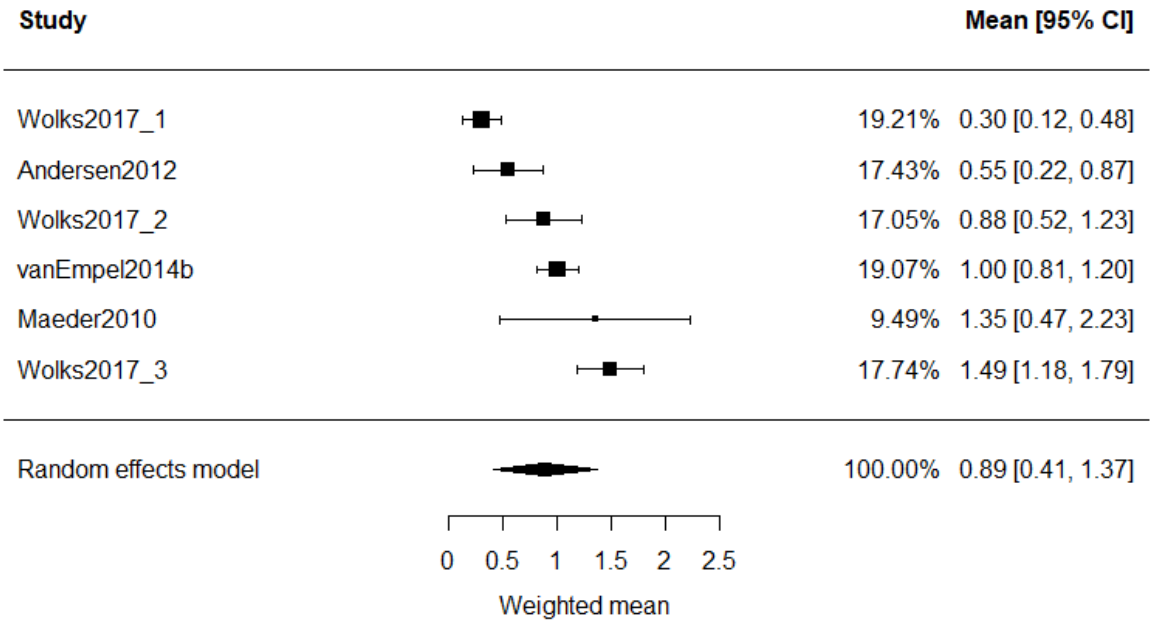
mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; yrs: years



b) mPAP/CO slope



c) PAWP/CO slope



Online Supplement: Methodology of systematic literature analysis and meta-analysis

Normal values of exercise pulmonary hemodynamics

Data sources and search strategy

We searched Pubmed (MEDLINE), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials from 01.01.2003 - 01.11.2020. We performed separate searches for mPAP, PAWP and PVR. The following Medical Subject Headings (MESH) were used: "healthy", "health*", "normal", "normative", "athletes" AND "exercise". For the analysis of mPAP we used the following additional MESH: „mean pulmonary arterial pressure (MESH)", „Pulmonary Arterial Pressure", „mPAP", „meanPAP", „mean pulmonary arterial pressure", „mean pulmonary artery pressure", „PAPm", „Pulmonary Artery Pressure", "Pulmonary Hypertension (MESH)", „Pulmonary Artery Hypertension", „Pulmonary Arterial Hypertension". For the PAWP analysis we used: „pulmonary arterial wedge pressure (MESH)", „pulmonary wedge pressure", „pulmonary artery wedge pressure", „PAWP", „Pulmonary Capillary Wedge Pressure", „pulmonary capillary pressure", „pulmonary artery occlusion pressure", „PAOP", „PCWP", „pulmonary arterial occlusion pressure", „pulmonary venous wedge pressure", „PVWP", „pulmonary venous pressure", „lung venous pressure" AND "Pulmonary Hypertension (MESH)", "Pulmonary Artery Hypertension", "Pulmonary Arterial Hypertension". For PVR analysis we used: „pulmonary vascular resistance (MESH)", „total pulmonary resistance", „PVR", „TPR", „total pulmonary vascular resistance" AND "Pulmonary Hypertension (MESH)", "Pulmonary Artery Hypertension", "Pulmonary Arterial Hypertension".

Study Selection

In total n=1069 studies were identified through database screening. N=547 remained after removing all duplicates and were screened. In n=62 studies, full text was assessed for eligibility. We only included original manuscripts with original data. N=51 studies were excluded due to several reasons (n=22 no exercise RHC; n=8 no baseline RHC; n=1 no original data; n=9 same subjects used; n=9 not healthy). In addition, we excluded studies that did not provide numerical data of pulmonary hemodynamics (eg: only graphical data)(n=1; [1]) and studies that measured CO by echocardiography and not by RHC (n=1; [2]). In total, n=11 studies were included in the qualitative and quantitative synthesis (see Supplement Figure 1: Flow-Chart). Of note, the zero reference level was provided only in a small number of studies (n=5). An overview of the included studies is provided in Supplement Table 1.

Excluded studies

Exclusion reason	Study
No exercise RHC in healthy	[1,3-23]
No baseline RHC values available	[24-31]
No original data	[32]
Same subjects used	[7,33-38] [160]
Claimed healthy but dyspnea patients	[39-47]
CO measured by Doppler	[48]
No mPAP	[49]

Outcomes

The primary outcome of interest was pulmonary hemodynamics in healthy subjects.

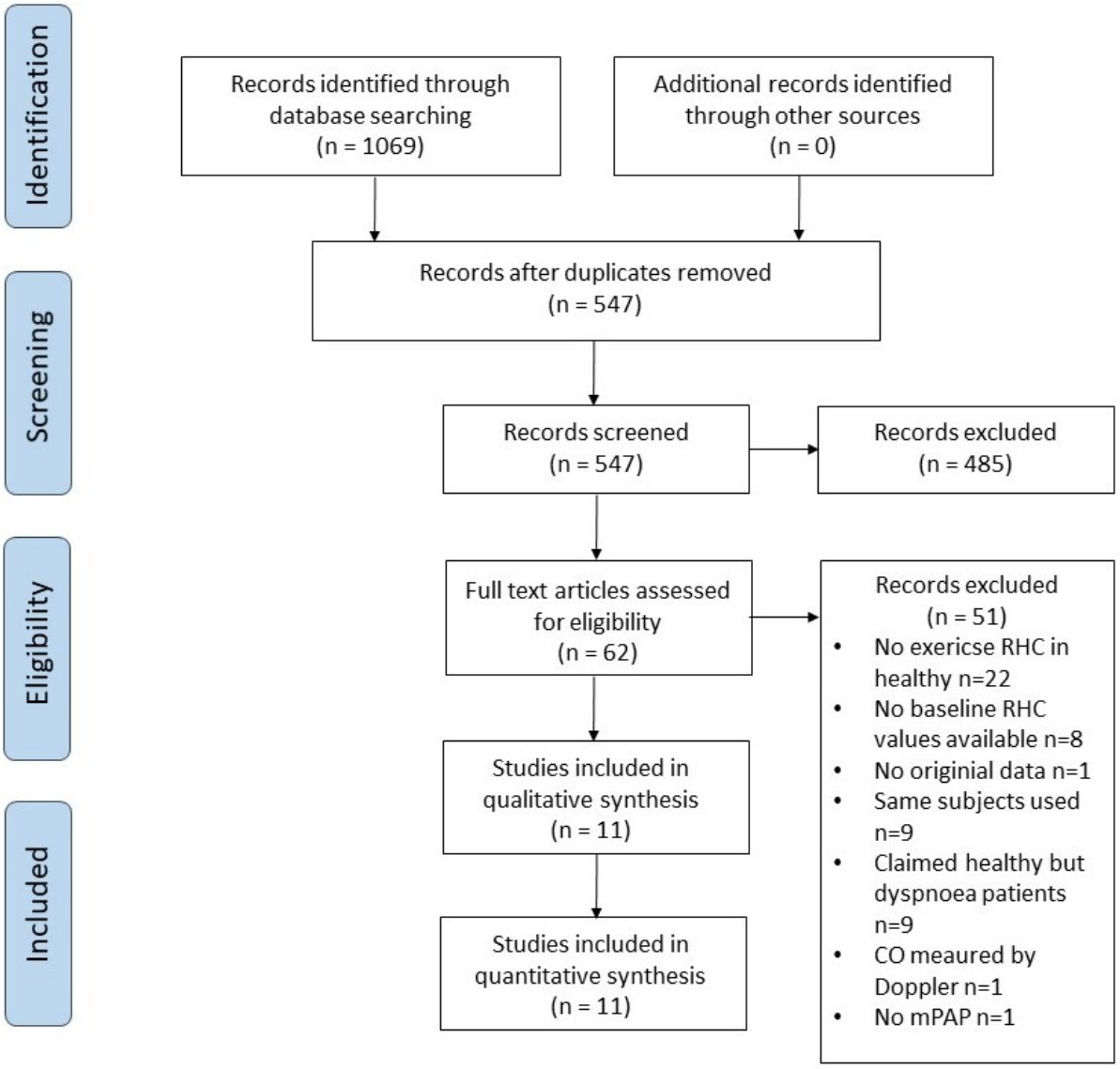
Data preparation

In the identified studies, data was reported differently. Some authors gave the mean values and the standard deviation of parameters for the whole group, others median and IQR, Q1, Q3 or 95% CI. Mean and SD were calculated from median and IQR with the formula described by Wan et al 2014 [50]. SD were also calculated from 95% CI. If only median and IQR were available, Q1 and Q3 were calculated as Q1 = median – (IQR/2) and Q3 = median + (IQR/2). In one study (Lewis et al. 2011), the SD of the RAP value at rest was reported as 0 probably due to approximation. To enable the estimation of the weighted means moderated by age, this value was replaced by 0.1. Furthermore, mean values of a number of parameters were not reported in some studies and had to be calculated using the following formulas: Height(m) = Square-root(Weight/BMI); BSA=Square-root(Height(cm)*Weight(Kg)/3600), this corresponds to the Mosteller Formula. Note that, if mean height and weight were not available, mean BSA was calculated by interpolating the mean values reported for normal weight and overweight in Verbraecken et al. [51]; CO = CI * BSA; CI = CO/BSA; PVR = (mPAP – PAWP)/CO; PVR = PVRI/BSA; TPG = mPAP – PAWP; TPR = mPAP/CO; PAC = (CO*1000/HR) / (sPAP-dPAP); Slope mPAP/CO = (mPAP max – mPAP rest) / (CO max – CO rest); Slope PAWP/CO = (PAWP max – PAWP rest) / (CO max – CO rest); Slope TPG/CO = (TPG max – TPG rest) / (CO max – CO rest). Slopes were only calculated when measurements at rest and during exercise were performed in the same body position. Please note that only mean values were calculated using the above-listed formulas. Standard deviations of the calculated variables (representing the “uncertainty” of the measure) depend upon the uncertainties of the variables used in the formula. The standard deviation of the output variables was therefore calculated with derivatives, using the R package “errors” and following the error propagation method

described by Ucar, Pebesma, & Azcorra [52].” In the case of BSA values obtained by interpolation, the corresponding SDs were computed from the mean of the available SDs.

Measurements in the supine position were grouped as supine. Measurements in the semi-supine or semi-upright position were grouped as upright.

Supplement Figure 1: Flow-Chart for normal value



Prognostic value of exercise pulmonary hemodynamics

Data sources and search strategy

We searched Pubmed (MEDLINE), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials from 1945 through 01.11.2020 for English-language, peer-reviewed publications. For mPAP, PAWP and PVR we performed independent systematic literature analyses. The following Medical Subject Headings (MESH) were used: „prognosis“, „outcome“, „death“, „prognos*“, „survival“, as well as „Pulmonary Hypertension (MESH)“, „Pulmonary Artery Hypertension“, „Pulmonary Arterial Hypertension“, AND “exercise” (MESH). For the analysis of mPAP we used the following additional MESH: „mean pulmonary arterial pressure (MESH)“, „Pulmonary Arterial Pressure“, „mPAP“, „meanPAP“, „mean pulmonary arterial pressure“, „mean pulmonary artery pressure“, „PAPm“, „Pulmonary Artery Pressure“, “Pulmonary Hypertension (MESH)“, „Pulmonary Artery Hypertension“, „Pulmonary Arterial Hypertension“. For the PAWP analysis we used: „pulmonary arterial wedge pressure (MESH)“, „pulmonary wedge pressure“, „pulmonary artery wedge pressure“, „PAWP“, „Pulmonary Capillary Wedge Pressure“, „pulmonary capillary pressure“, „pulmonary artery occlusion pressure“, „PAOP“, „PCWP“, „pulmonary arterial occlusion pressure“, „pulmonary venous wedge pressure“, „PVWP“, „pulmonary venous pressure“, „lung venous pressure“ AND “Pulmonary Hypertension (MESH)”, “Pulmonary Artery Hypertension”, “Pulmonary Arterial Hypertension”. For PVR analysis we used: „pulmonary vascular resistance (MESH)“, „total pulmonary resistance“, „PVR“, „TPR“, „total pulmonary vascular resistance“ AND “Pulmonary Hypertension (MESH)”, “Pulmonary Artery Hypertension”, “Pulmonary Arterial Hypertension”.

Excluded studies

Exclusion reason	**Study**
Endpoint other than mortality	[14,23,56-90]
No original data	[91-98]
No exercise RHC	[99-127]
Editorial/Abstract	[128-137]

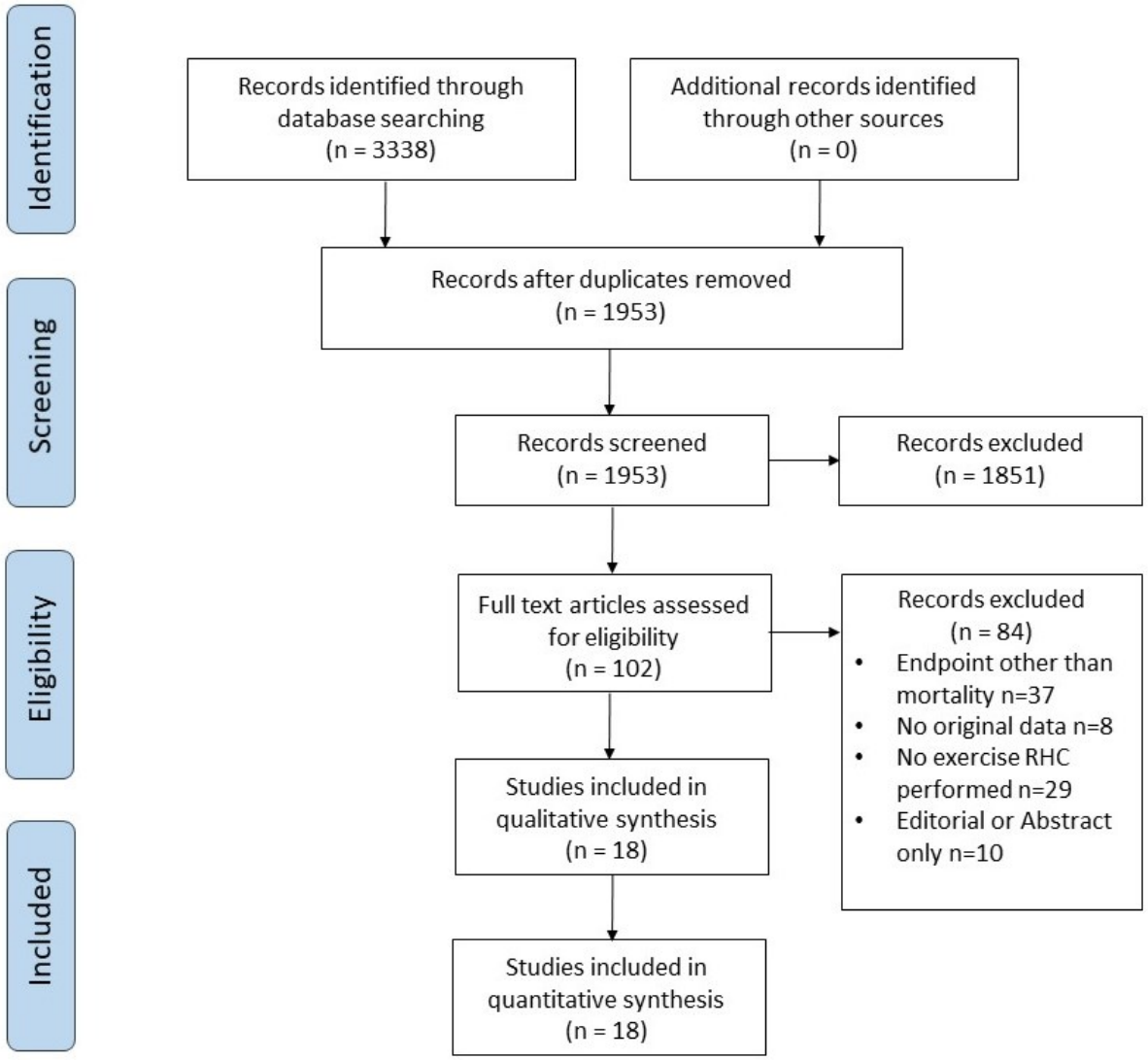
Outcomes

The primary outcome was all-cause mortality.

Statistical analysis

Prognostic studies are provided descriptively in the main document.

Supplement Figure 2: Flow-Chart for prognostic studies



Diagnostic value of exercise pulmonary hemodynamics

Data sources and search strategy

We searched Pubmed (MEDLINE), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials from 1945 through 01.11.2020 for English-language, peer-reviewed publications. For mPAP, PAWP and PVR we performed independent systematic literature analyses. The following Medical Subject Headings (MESH) were used: "Differential diagnos*", "Phenotype", "Clinical diagnos*" AND "right heart catheterization (MESH)", "pulmonary catheter", "pulmonar* arter* cathet*", "right heart catheter", "right heart catheter*", "right cardiac* cathet*", "Cardiac* cathet*" AND "exercise" (MESH). For the analysis of mPAP we used the following additional MESH: „mean pulmonary arterial pressure (MESH)", „Pulmonary Arterial Pressure", „mPAP", „meanPAP", „mean pulmonary arterial pressure", „mean pulmonary artery pressure", „PAPm", „Pulmonary Artery Pressure", "Pulmonary Hypertension (MESH)", „Pulmonary Artery Hypertension", „Pulmonary Arterial Hypertension". For the PAWP analysis we used: „pulmonary arterial wedge pressure (MESH)", „pulmonary wedge pressure", „pulmonary artery wedge pressure", „PAWP", „Pulmonary Capillary Wedge Pressure", „pulmonary capillary pressure", „pulmonary artery occlusion pressure", „PAOP", „PCWP", „pulmonary arterial occlusion pressure", „pulmonary venous wedge pressure", „PVWP", „pulmonary venous pressure", „lung venous pressure" AND "Pulmonary Hypertension (MESH)", "Pulmonary Artery Hypertension", "Pulmonary Arterial Hypertension". For PVR analysis we used: „pulmonary vascular resistance (MESH)", „total pulmonary resistance", „PVR", „TPR", „total pulmonary vascular resistance" AND "Pulmonary Hypertension (MESH)", "Pulmonary Artery Hypertension", "Pulmonary Arterial Hypertension".

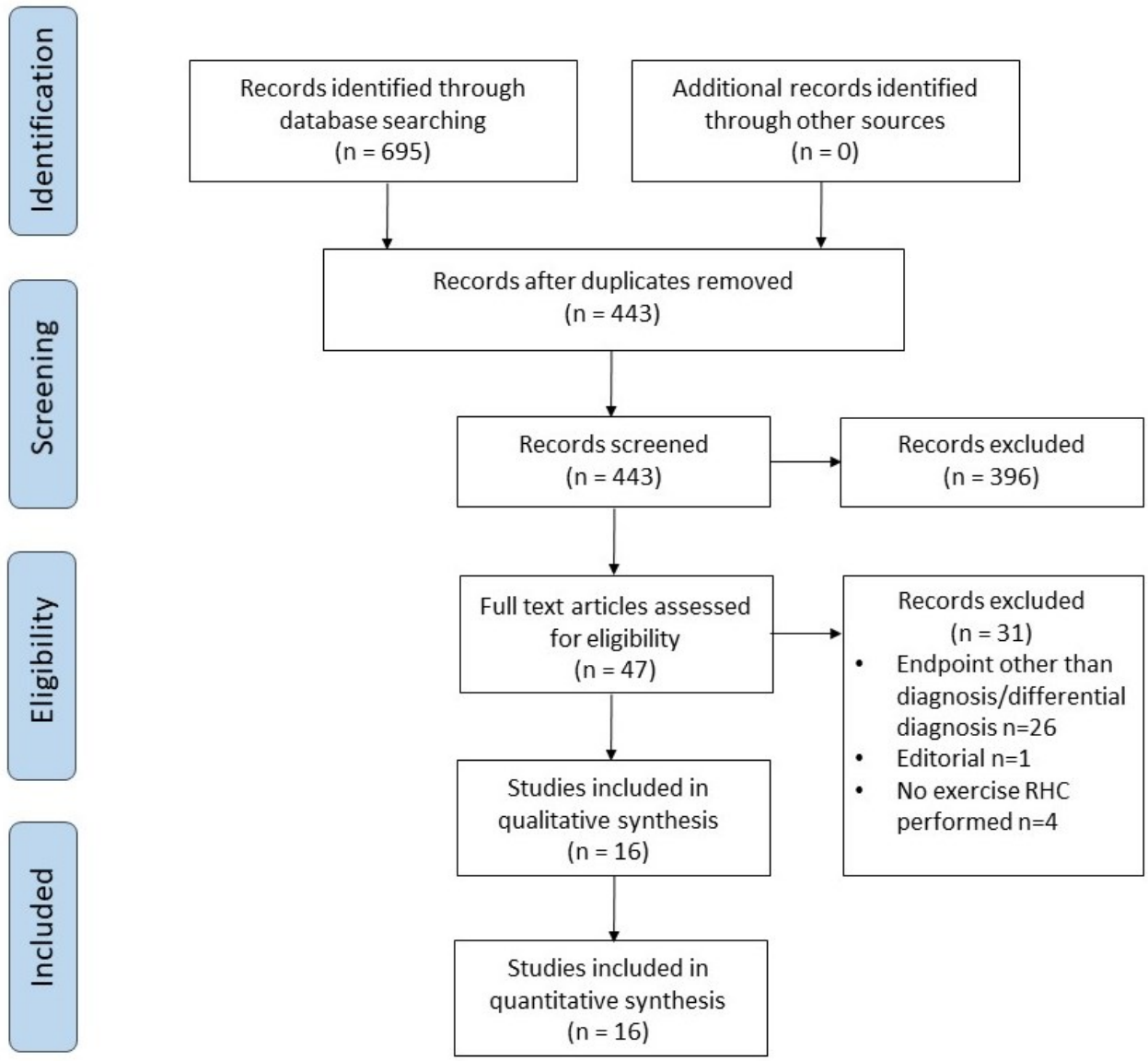
Excluded studies

Exclusion reason	**Study**
Endpoint other than diagnosis/differential diagnosis	[14,57,58,60,61,64,65,73,75,82,84,85,99,100,129,138-148]
Editorial	[59]
No exercise RHC performed	[56,127,149,150]

Statistical analysis

Diagnostic studies are provided descriptively in the main document.

Supplement Figure 3: Flow-Chart for diagnostic studies



Supplement Table 1a: Overview of the included studies for normal data and main characteristics in healthy subjects.

	Publication	N	Age ± SD (range; yrs)	Body position during exercise	Exercise level	Resting mPAP (mmHg)	Exercise mPAP (mmHg)	Restig PAWP (mmHg)	Exercise PAWP (mmHg)	Resting PVR/PVRI (WU)	Exercise PVR/PVRI (WU)	Resting CO (L/min)	Exercise CO (L/min)	Resting CI (L/min/m^2)	Exercise CI (L/min/m^2)	Resting heart rate (bpm)	Exercise heart rate (bpm)	Watt
1	Andersen et al 2019	16	31 (18-40)	Semi-SUP**	Individual peak	12±3	23±5	8±2	13±4	0.7±0.3	0.6±0.1	5.5±1.1	18.8±1.7	2.9±0.4	10±0.8	62±13	145±17	-
	Andersen et al 2019	15	49 (40-59)	Semi-SUP**	Individual peak	14±3	31±12	9±3	19±10	0.9±0.3	0.7±0.4	5.1±0.9	17.1±2.6	2.7±0.3	9.1±1.3	66±9	138±14	-
	Andersen et al 2019	19	69 (60-80)	Semi-SUP**	Individual peak	14±3	36±7	8±3	23±5	1.3±0.5	0.9±0.3	5±1	14.7±2.8	2.6±0.4	7.9±1.3	63±8	129±16	-
2	Claeys et al 2019	13	46±10	SUP	Individual peak	11.8±2.9	26.6±10.2	-	-	-	-	-	-	3.3±0.9	8.4±2.8	67±12	145±15	-
3	Esfandiari et al 2017	18	58±6	semi-UP	Moderate and light exercise levels	18±2	26±6	12±2	15±5	1.49±0.61	1.2±0.3	4.6±0.6	10.3±1.5	2.5±0.4	5.4±1.8	64±8	122±3	-
	Esfandiari et al 2017	18	54±7	semi-UP	Moderate and light exercise levels	17±3	25±6	11±3	15±5	1.3±0.4	1.14±0.4	5.1±0.9	12.3±3.2	2.8±0.6	6.6±1.9	62±7	121±2	-
4	Wolsk et al 2017	20	29 (20-39)	SUP	Individual peak,moderate and light exercise	13 (95%CI 12-14)	25 (95%CI22-28)	9 (95%CI 8-9)	13 (95%CI10-15)	0.8 (IQR 0.7-1)	0.7 (95%CI 0.6-0.8)	-	-	2.9 (95%CI 2.6-3.1)	9.9 (95%CI 9.6-10.4)	63 (95%CI 57-69)	141 (95%CI 132-151)	174 (95%CI 155-192)
	Wolsk et al 2017	22	49 (40-59)	SUP	Individual peak, moderate and light exercise	15 (95%CI 13-16)	32 (95%CI27-38)	9 (95%CI 8-10)	19 (95%CI15-23)	1 (IQR 0.8-1.2)	0.8 (95%CI 0.8-1)	-	-	2.8 (95%CI 2.6-2.9)	8.8 (95%CI 8.4-9.3)	64 (95%CI 60-69)	126 (95%CI 117-135)	144 (95%CI 129-159)
	Wolsk et al 2017	20	69 (60-80)	SUP	Peak, moderate and light exercise level	15 (95%CI 14-16)	39 (95%CI36-43)	8 (95%CI 7-9)	23 (95%CI21-25)	1.5 (IQR 1.2-1.7)	1.1 (95%CI 0.9-1.4)	-	-	2.6 (95%CI 2.4-2.8)	7.9 (95%CI 7.2-8.6)	62 (95%CI 58-66)	128 (95%CI 121-136)	130 (95%CI 113-147)
5	Wright et al 2016	28	55±6	semi-UP	Moderate and light exercise levels	17±3	25±6	11±3	15±5	1.28±0.39	0.96±0.38	4.8±0.8	11.1±2.8	-	6.8±1.5	63±8	122±2	-
6	Claessen et al 2015	14	36±15	SUP	Individual peak	10±3	22±8	-	-	-	-	6.2±1.9	16.2±5.3	3.3±0.8	8.5±2.3	66±7	149±11	-
7	van Empel et al 2014	12	54±2	SUP	Individual peak	13±1	29±2	8±1	16±2	-	-	-	-	2.9±0.2	7.2±0.3	60±3	118±5	114±12
8	Andersen et al 2012	10	46±5	SUP	Individual peak	15±4	28±8	9±2	16±6	PVRI 2.01±1.2	PVRI: 1.3±0.3	-	-	3±0.3	9.4±1.6	64±8	129±23	-
9	Maeder et al 2010	8	61±12	SUP	Individual peak	16±4	32±8	10±4	20±7	PVRI 1.9±0.8	PVRI: 1.5±0.7	-	-	3.5±1	7.4±1.4	72±25	112±20	-
10	Regenstein er et al 2009	10	39±6	UP	Individual peak	16.6±3	30.3±6.7	8±2.2	16.7±3.7	-	-	-	13.5±2.1	2.4±0.3	7.6±1.1	84±11	166±15	123±27.5
11	Lonsdorfer-Wolf et al 2003	7	38±5	UP**	Peak, moderate and light exercise level	13.5±2	26.5±5.6	-	-	-	-	5.4±1.5	20±3.3	-	-	79±10	178±8	276±50

Data is presented as mean ± standard deviation (SD) or median (IQR), unless otherwise stated. 95%CI: 95% confidence interval; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; CO: cardiac output; CI: cardiac index; HR: heart rate; yrs: years; WU: wood units; L: liter; min: minute; bpm: beats per minute; UP: upright; SUP: supine; semi-UP: semi-upright; semi-SUP: semi-supine. Exercise protocol was ergometry for all studies. ** body position is different at rest

Supplement Table 1b: Overview of the included studies for normal data and main characteristics in healthy patients (subjects claimed to be healthy by the authors presenting with dyspnea on effort but having normal pulmonary hemodynamics and normal clinical work-up).

	Publication	N	Age ± SD (yrs)	Body position during exercise	Exercise level	Resting mPAP (mmHg)	Exercise mPAP (mmHg)	Restig PAWP (mmHg)	Exercise PAWP (mmHg)	Resting PVR/PVRI (WU)	Exercise PVR/PVRI (WU)	Resting CO (L/min)	Exercise CO (L/min)	Resting CI (L/min/m^2)	Exercise CI (L/min/m^2)	Resting heart rate (bpm)	Exercise heart rate (bpm)	Watt
1	Singh et al 2020 [151]	24	50±14	UP**	Individual peak	14±3	27±5	6±2	12±5	1.7±0.6	1.36±0.61	5.1±2.1	12.9±5.3	-	-	82±15	144±33	142±81
2	Jain et al 2019 [152]	23	50.7±18	SUP	Moderate exercise level	15.6±4.2	21.8±7.8	7.7±2.8	10.8±4.7	1.4±0.6	1.02±0.44		-	3.3±0.6	5.8±1.2	-	-	-
3	Watts et al 2018 [153]	39	32±6	SUP	Light exercise level	13.8±2.8	20.1±4.4	7.9±2.4	9.4±3	0.9±0.5	0.83±0.31	-	-	3.5±0.7	-	69±12	109±14	-
4	Oliveira et al 2016 [154]	41	61 (>50)	UP	Individual peak	12±3	23±5	4±3	9±4	1.68±0.57	1.2±0.45	5 (IQR 3.8-5.8)	12.1 (IQR 9.4-14.2)	2.6 (IQR 2.2-3.1)	6.6 (IQR 5.9-7.9)	-	143±19	103 (IQR 87-140)
	Oliveira et al 2016	25	44 (<50)	UP	Individual peak	12±4	22±4	4±3	9±5	1.31±0.53	0.82±0.26	5.9 (IQR 4.6-7.8)	16.2 (IQR 13.8-19.2)	3.2 (IQR 2.7-3.7)	8.6 (IQR 8-10.3)	-	163±18	148 (IQR 133-173)
5	Held et al 2016 [155]	41	63±13	SUP	Individual peak	15 (IQR 2)	28 (IQR 16.3)	7 (IQR 3.5)	11 (IQR 9.5)	1.65 (IQR 1.5125)	-	5.2 (IQR 1.5)	9.3 (IQR 4.5)	2.6 (IQR 0.7)	4.9 (IQR 1.9)	-	-	100
6	Lau et al 2016 [156]	26	51±13	SUP	Individual peak	14±4	25±5	7±3	12±5	1.1±0.6	1±0.4	6.4±2.1	12.8±2.6	-	-	72±14	112±21	58±24
7	van Empel et al 2014 [157]	20	67±8	SUP	Individual peak	15.6±4.1	30.7±6.9	8.7±3	18.1±6.4	1.3±0.6	1.2±0.3	-	-	3.1±0.6	6±1.3	64±11	116±19	-
	van Empel et al 2014	35	40±9	SUP	Individual peak	15.5±3.1	24.4±6.5	9.2±2.6	14±4.4	1.1±0.8	0.9±0.4	-	-	3.3±0.8	6.8±1.1	79±16	132±18	-
8	Lewis et al 2011 [158]	19	60±12	UP	Individual peak	15±1	29±1	6±1	17±1	2.01±0.19	0.8±0.08	5±0.3	15.5±0.8	-	-	72±3	137±4	142±11
9	Bonderman et al 2011 [159]	10	50±10	SUP	Light exercise level	19±6	25±7	11±6	15±7	1.3±0.6	0.89±0.53	7.3±2.7	10.8±4.4	-	-	78±16	104±28	-

Data is presented as mean ± standard deviation (SD) or median (IQR), unless otherwise stated. IQR: interquartile range; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; CO: cardiac output; CI: cardiac index; HR: heart rate; yrs: years; WU: wood units; L: liter; min: minute; bpm: beats per minute; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; CO: cardiac output; CI: cardiac index; HR: heart rate. UP: upright; SUP: supine.

Exercise protocol was ergometry for all studies. ** body position is different at rest

Supplement Table 2
Resting and exercise cardiopulmonary hemodynamics in healthy patients in the a) supine and b) upright positions.

a)

Condition	Parameter (unit)	k	Estimate	SD
Rest	mPAP (mmHg)	7	15.0[b]	1.1
Rest	PAWP (mmHg)	7	8.0 [b]	1.1
Rest	PVR (WU)	7	1.2 [a]	0.2
Rest	CO (L/min)	7	6.2[b]	0.6
Rest	CI (L/min/m^2)	7	3.2 [b]	0.4
Rest	RAP (mmHg)	3	4.6	0.4
Rest	HR (bpm)	5	72[b,c]	6
Rest	TPR (WU)	7	2.4 [a]	0.3
Exercise	mPAP (mmHg)	7	24.8 [a]	3.6
Exercise	PAWP (mmHg)	7	12.7 [c]	3.0
Exercise	PVR (WU)	7	1.0 [a]	0.3
Exercise	CO (L/min)	7	11.8[c]	1.6
Exercise	CI (L/min/m^2)	7	6.2[c]	0.8
Exercise	RAP (mmHg)	1	4.5	0.4
Exercise	HR (bpm)	5	116 [c]	11
Exercise	TPR (WU)	7	2.1 [a]	0.5
	mPAP/CO slope (WU)	7	1.7 [a]	0.8
	PAWP/CO slope (WU)	7	0.8 [a]	0.4
	TPG/CO slope (WU)	7	0.8	0.3

b)

Condition	Parameter (unit)	k	Estimate	SD
Rest	mPAP (mmHg)	3	13.1 [b,c]	1.8
Rest	PAWP (mmHg)	3	4.7[c]	1.2
Rest	PVR (WU)	3	1.7 [b]	0.4
Rest	CO (L/min)	3	5.0 [b]	0.2
Rest	CI (L/min/m^2)	3	2.8 [b]	0.4
Rest	RAP (mmHg)	3	2.4 [b,c]	0.6
Rest	HR (bpm)	1	72 [b]	1
Rest	TPR (WU)	3	2.5 [c]	0.5
Exercise	mPAP (mmHg)	4	25.3	3.3
Exercise	PAWP (mmHg)	4	11.8	3.8
Exercise	PVR (WU)	4	1.0	0.3
Exercise	CO (L/min)	4	14.2	2.1
Exercise	CI (L/min/m^2)	4	7.5	1.1
Exercise	RAP (mmHg)	4	6.8	2.1
Exercise	HR (bpm)	4	147	12

Exercise	TPR (WU)	4	1.8	0.3
	mPAP/CO slope (WU)	3	1.3	0.3
	PAWP/CO slope (WU)	3	0.8	0.3
	TPG/CO slope (WU)	3	0.5	0.3

Note. [a]significant influence of age (or age-dependency); [b] significant difference between rest and exercise conditions; [c]significant difference as compared to healthy participants (Table 1a and 1b); dSAP and sSAP not reported because there was max 1 study per condition

Data are presented as weighted mean ± SD. HR: heart rate; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; RAP: right atrial pressure; TPG: trans-pulmonary gradient; bpm: beats per minute; WU: wood units;

Slopes were only calculated when rest and exercise measurements were performed in the same position.

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