# Hyperoxia improves exercise capacity in cardiopulmonary disease: a series of randomised controlled trials

Julian Müller [1,2], Mona Lichtblau [1,2], Stéphanie Saxer [1], Simon R. Schneider [1,2], Paula Appenzeller[1], Meret Bauer[1], Elisabeth D. Hasler[1], Esther I. Schwarz[1,2], Konrad E. Bloch[1,2] and Silvia Ulrich [1,2]

[1]Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland. [2]University of Zurich, Zurich, Switzerland.

Corresponding author: Silvia Ulrich (silvia.ulrich@usz.ch)



Shareable abstract (@ERSpublications)
**Supplemental oxygen during exercise significantly improves exercise performance in cardiopulmonary disease in terms of maximal work rate as well as endurance time. Largest improvements were found in patients with pulmonary vascular disease.** https://bit.ly/3W1i6Ti

Cite this article as: Müller J, Lichtblau M, Saxer S, *et al*. Hyperoxia improves exercise capacity in cardiopulmonary disease: a series of randomised controlled trials. *ERJ Open Res* 2023; 9: 00563-2022 [DOI: 10.1183/23120541.00563-2022].



Received: 24 Oct 2022
Accepted: 6 Dec 2022

## Abstract

***Background*** The aim of this study was to investigate the overall and differential effect of breathing hyperoxia (inspiratory oxygen fraction ($F_{IO_2}$) 0.5) *versus* placebo (ambient air, $F_{IO_2}$ 0.21) to enhance exercise performance in healthy people, patients with pulmonary vascular disease (PVD) with precapillary pulmonary hypertension (PH), COPD, PH due to heart failure with preserved ejection fraction (HFpEF) and cyanotic congenital heart disease (CHD) using data from five randomised controlled trials performed with identical protocols.

***Methods*** 91 subjects (32 healthy, 22 with PVD with pulmonary arterial or distal chronic thromboembolic PH, 20 with COPD, 10 with PH in HFpEF and seven with CHD) performed two cycle incremental (IET) and two constant work-rate exercise tests (CWRET) at 75% of maximal load ($W_{max}$), each with ambient air and hyperoxia in single-blinded, randomised, controlled, crossover trials. The main outcomes were differences in $W_{max}$ (IET) and cycling time (CWRET) with hyperoxia *versus* ambient air.

***Results*** Overall, hyperoxia increased $W_{max}$ by +12 W (95% CI: 9–16, p<0.001) and cycling time by +6:13 min (4:50–7:35, p<0.001), with improvements being highest in patients with PVD ($W_{max}$/min: +18%/+118% *versus* COPD: +8%/+60%, healthy: +5%/+44%, HFpEF: +6%/+28%, CHD: +9%/+14%).

***Conclusion*** This large sample of healthy subjects and patients with various cardiopulmonary diseases confirms that hyperoxia significantly prolongs cycling exercise with improvements being highest in endurance CWRET and patients with PVD. These results call for studies investigating optimal oxygen levels to prolong exercise time and effects on training.

## Introduction

In cardiopulmonary diseases, different pathophysiological mechanisms lead to limitation of exercise capacity and dyspnoea, but the final result is, among others, limited oxygen delivery to the tissue. Exercise performance in humans is codetermined by alveolar ventilation, match of ventilation and perfusion, and uptake and diffusion of oxygen ($O_2$) into the arterial blood, as well as sufficient supply and utilisation of $O_2$ by working muscles, vital organs and the neural system [1, 2]. This process is substantially influenced by the inspiratory partial pressure of $O_2$ ($P_{IO_2}$), a product of the fractional air content of $O_2$ (inspiratory oxygen fraction ($F_{IO_2}$) ≈0.21) and the barometric pressure ($P_b$) (at sea level $P_b$≈101 kPa, $P_{IO_2}$ ~21 kPa) [3]. By increasing $F_{IO_2}$ (normobaric hyperoxia), greater amounts of $O_2$ are bound to haemoglobin to improve arterial oxygen saturation ($S_{aO_2}$) and are physically dissolved in the arterial blood plasma resulting in increased blood oxygen content [3]. It is presumed that breathing oxygen-enriched air (hyperoxia, $F_{IO_2}$ >0.21) during exercise triggers different cellular, molecular, neural, hormonal and enzymatic responses that lead to improved exercise performance in both maximal and submaximal workloads [2–5]. In previous studies in healthy volunteers, breathing hyperoxia during exercise was associated with an increase of up to 30% maximal work rate ($W_{max}$) and up to 130% endurance time compared with ambient air [5–8].

The multiple benefits in terms of quality of life and survival by increased cardiorespiratory fitness in cardiopulmonary diseases are well known [9, 10]. Even in patients with pulmonary vascular diseases (PVDs) characterised by pulmonary hypertension (PH) to whom physicians were reluctant to recommend training in fear of right-heart failure, supervised exercise training is nowadays widely practiced in specialised centres and recommended by the European Respiratory Society in addition to drug therapy [11, 12]. If the exercise-enhancing effects of hyperoxia enables patients with limitations due to cardiopulmonary disease to train on higher exercise intensities and therefore to gain higher fitness levels, this could increase the benefit of rehabilitation programmes.

We have previously shown in five randomised, placebo-controlled, crossover trials with identical protocols that hyperoxia improves cycling exercise in both maximal incremental ramp exercise test (IET) and constant work-rate exercise (CWRET) protocols in healthy patients with PVD due to precapillary PH (pulmonary arterial or chronic thromboembolic PH), COPD, postcapillary PH due to heart failure with preserved ejection fraction (HFpEF) and cyanotic congenital heart disease (CHD) [13–17]. The aim of the current analysis was to evaluate the overall effect of hyperoxia to enhance exercise performance and to study the different effects in healthy patients with PVD, COPD, HFpEF and CHD.

## Materials and methods

### Study design

The current investigation is a *post hoc* analysis of data from five randomised, placebo-controlled, single-blinded, crossover trials using identical protocols to evaluate the effect of hyperoxia *versus* placebo air on exercise performance in healthy subjects [15] and patients with PVD [14], COPD [13], HFpEF [16] and CHD [17]. The results of the individual trials were reported and published previously.

### Participants

#### Healthy

The healthy participants were healthy, non-smoking adults over a wide range of age groups who did not use medication on a regular basis.

#### PVD

PVD patients were adults with pulmonary arterial hypertension (PAH)/chronic thromboembolic pulmonary hypertension (CTEPH) diagnosed according to 2015 guidelines [12], stable on PH-targeted drug therapy, with mean pulmonary artery pressure (mPAP) ⩾25 mmHg and pulmonary artery wedge pressure (PAWP) ⩽15 mmHg assessed by right-heart catheterisation.

#### COPD

COPD patients were adults with stable COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD)1–4 (forced expiratory volume in 1 s/forced vital capacity ($FEV_1$/FVC) <0.7) and resting pulse oximetric oxygen saturation ($S_{pO_2}$) ⩾90%.

#### HFpEF

HFpEF patients had postcapillary PH, mPAP ⩾25 mmHg, PAWP ⩾15 mmHg, pulmonary vascular resistance (PVR) <3 WU and left ventricular ejection fraction >50% [18].

#### CHD

CHD patients were adults with cyanotic CHD (Eisenmenger syndrome, unrepaired congenital heart defects). Patients with severe resting hypoxaemia arterial oxygen tension ($P_{aO_2}$) <7.3 kPa, an unstable condition, age <18 or >80 years or contraindication for ergometry were excluded.

### Interventions

On two separate days, patients performed each of two cycle exercise tests at pedalling rates of 50–60 *xg* to exhaustion, one with $F_{IO_2}$ 0.21 and one with $F_{IO_2}$ 0.50 in randomised order: on the first day, two IETs with increments of 10–20 watts·min$^{-1}$ according to the patient's fitness; on the second day two CWRETs at 75% of individual $W_{max}$ achieved with ambient air. There was a recovery period of at least 2 h between the tests. Subjects were connected to the flow sensor of a metabolic unit *via* a mouthpiece and a low resistance two-way valve. The nose was occluded with a nose-clip. The inlet of the valve was connected to a gas-mixing device to provide different levels of $F_{IO_2}$. At rest and at end-exercise, arterial blood gas (aBGA) samples from a radial artery were taken in PVD, COPD and HFpEF.

### Assessments

Clinical and diagnostic assessments were performed as described previously [13–17, 19].

Breathing rate, minute ventilation ($V'_E$), carbon dioxide output ($V'_{CO_2}$) and derived variables were recorded breath-by-breath. Heart rate (HR) was derived from a 12-lead electrocardiogram. $S_{pO_2}$ was recorded continuously [20–22].

Physiological variables were averaged over 30-s intervals. Variables at end-exercise were defined as mean over the final 30 s before termination of exercise defined as a drop in cycling rate <50 *xg*. The ventilatory equivalents for $V'_{CO_2}$ were calculated as $V'_E/V'_{CO_2}$ at end-exercise and $V'_E/V'_{CO_2}$ as slope over the entire duration of ramp exercise [23].

### *Primary outcomes*

Primary outcomes were maximum work rate (W) during IET and cycling time (s) during CWRET.

### *Secondary outcomes*

$S_{pO_2}$, $V'_E$, HR, $V'_E/V'_{CO_2}$, lactate, arterial carbon dioxide tension ($P_{aCO_2}$), $P_{aO_2}$, $S_{aO_2}$ and BorgCR10 dyspnoea and leg fatigue scores were defined as secondary outcomes of interest.

### *Randomisation and blinding*

On day 1, patients were randomly allocated to the order of the two different conditions by software-based block-randomisation. On day 2, the same order was maintained. Participants were blinded to the $F_{IO_2}$.

### *Data analysis*

Physiological variables were averaged over the first 30 s during rest and the last 30 s for end-exercise respectively. Isotime compares physiological values of tests with and without hyperoxia at an identical timepoint of the longer test corresponding to end-exercise of the shorter test. Data were summarised as mean±SD. To compare the main outcomes of exercise tests between ambient air and hyperoxia and between disease groups, data were pooled and a linear mixed model was fitted to the data with treatment, period and treatment–period interaction as fixed effects and subject as random intercept, thus controlling for carry-over (treatment–period interaction) and period effects. We tested if treatment–period interaction could be removed from the model, otherwise only the data from the first period would be analysed. Model assumptions were tested by visual inspection of the homogeneity and normality of the residuals and the random effects.

The analysis of the secondary outcomes followed the same procedure as above but included baseline characteristics in addition.

In all analyses, a 95% confidence interval that excluded the null effect was considered evidence of statistical significance.

## Results

Data of 91 participants (32 heathy, patients: 22 PVD, 20 COPD, 10 HFpEF, 7 CHD) were included (table 1) [13–17]. The visual inspection of the model assumptions allowed to assume homogeneity and normality of the residuals and the random effects. No carry-over and no period-effect was found with the model. All of the following results were corrected for patient group.

### *Changes overall*

#### *IET*

##### End-exercise

In 91 patients (40 women, age 54±16 years, BMI 24.9±4.7 kg·m$^{-2}$) breathing hyperoxia compared with ambient air increased $W_{max}$ from 155.4 W to 167.8 W, corresponding to a mean change of +12.4 W (95% CI: 9.1–15.6 W, p<0.001) during IET. At end-exercise, hyperoxia increased the mean $S_{pO_2}$ by +4% (from 92% to 96%, 95% CI: 3.2–5.4%, p<0.001) whereas $V'_E$ and HR were unchanged. Breathing hyperoxia significantly reduced $V'_E/V'_{CO_2}$ by −3.3 (from 35.9 to 32.6, 95% CI: −4.6– −2.0, p<0.001). Patients reported less dyspnoea while breathing hyperoxia (BorgCR10 −0.6; 95 % CI: −0.2– −0.9, p=0.001). BorgCR10 leg fatigue scale was unchanged (table 2 and figures 1 and 2).

There was no significant change in arterial lactate at end-exercise (aBGA available in 49 patients (54%)). $P_{aCO_2}$, $P_{aO_2}$ and $S_{aO_2}$ were significantly higher with hyperoxia +0.5 kPa (95% CI: 0.3–0.7 kPa), +21.3 kPa (95% CI: 19.1–23.4 kPa) and +7.1% (95% CI: 5.4–8.9%), respectively, all three p<0.001 (table 2 and figure 3).

**TABLE 1** Baseline characteristics

| | |
|---|---|
| **Healthy** | 32 |
| Female/male | 12/20 |
| Age years | 43±15 |
| Body mass index kg·m$^{-2}$ | 23±2.6 |
| $S_{pO_2}$ at rest % | 99±1 |
| **Pulmonary vascular disease** | 22 |
| Chronic thromboembolic pulmonary hypertension | 11 |
| Pulmonary arterial hypertension | 11 |
| Female/male | 8/14 |
| Age years | 61±14 |
| Body mass index kg·m$^{-2}$ | 27.1±6 |
| $S_{pO_2}$ at rest % | 95±3 |
| Mean pulmonary arterial pressure mmHg | 35±9 |
| Pulmonary arterial wedge pressure mmHg | 11±3 |
| Pulmonary vascular resistance WU | 4.7±2.5 |
| **COPD** | 20 |
| Female/male | 11/9 |
| Age years | 65±6 |
| Body mass index kg·m$^{-2}$ | 27.1±6 |
| $S_{pO_2}$ at rest % | 95±2 |
| GOLD grade 1/2/3/4 | 4/11/4/1 |
| $FEV_1$ % pred | 64±18 |
| FVC % pred | 107±17 |
| $FEV_1$/FVC | 0.5±0.1 |
| **Heart failure with preserved ejection fraction** | 10 |
| Female/male | 5/5 |
| Age years | 60±9 |
| Body mass index kg·m$^{-2}$ | 28±6 |
| $S_{pO_2}$ at rest % | 98±2 |
| Mean pulmonary arterial pressure mmHg | 37±14 |
| Pulmonary arterial wedge pressure mmHg | 18±2 |
| LVEF % | 63±5 |
| **Cyanotic congenital heart disease** | 7 |
| Female/male | 4/3 |
| Age years | 36±9 |
| Body mass index kg·m$^{-2}$ | 23±2 |
| $S_{pO_2}$ at rest % | 87±6 |
| Corrective heart surgery in childhood | 3 |

Data are presented as mean±SD or absolute numbers. $S_{pO_2}$: oxygen saturation by pulse oximetry; GOLD: Global Initiative for Chronic Obstructive Lung Disease; $FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; LVEF: left ventricular ejection fraction.

### Isotime

In IET at isotime, hyperoxia increased the mean $S_{pO_2}$ by +4% (from 93% to 97%, 95% CI: 3.0–5.3%, p<0.001). $V'_E$, HR and $V'_E/V'_{CO_2}$ were significantly reduced by −5.9 L·min$^{-1}$ (95% CI: −8.8– −3.1 L·min$^{-1}$), by −4 bpm (95% CI: −6.3– −1.6 bpm) and by −3.6 (95% CI: −4.3– −3), respectively, all three p<0.001 (table 2, figure 4).

## *CWRET*

### End-exercise

81 of 91 patients performed two CWRETs, 10 patients did not perform a CWRET as they could not come back on the 2nd scheduled exercise day for logistical reasons. Overall, breathing hyperoxia increased endurance time from 10:43 min to 16:56 min corresponding to a mean change of +6:13 min (95% CI: 4:59–7:35 min, p<0.001) during CWRETs. Breathing hyperoxia increased $S_{pO_2}$ from 91% to 97%, mean change +6.0% (95% CI: 4.3–6.9%, p<0.001). $V'_E$ and $V'_E/V'_{CO_2}$ were both significantly lower in CWRET with hyperoxia, −5.0 L·min$^{-1}$ (66.0 to 61.0 L·min$^{-1}$, 95% CI: −2.0– −8.0 L·min$^{-1}$) and −3.0 (37.0 to 34.0, 95% CI: −2.2– −4.1), both p<0.001. HR was unchanged. Patients reported reduced dyspnoea and leg fatigue with hyperoxia, BorgCR10 for dyspnoea −0.9 (95% CI: −0.5– −1.3, p=0.001) and BorgCR10 for leg fatigue −0.4 (95% CI: −0.1– −0.8, p=0.029) (table 2 and figures 1 and 2).

**TABLE 2** Overall results for ambient air *versus* hyperoxia – end-exercise and isotime

| | Ambient air end-exercise mean | Hyperoxia | | | |
|---|---|---|---|---|---|
| | | End-exercise | | Isotime | |
| | | Mean | Difference (95% CI) | Mean | Difference (95% CI) |
| **IET overall** | | | | | |
| Work rate W | 155.4 | 167.8 | 12.4 (9.1–15.6)*** | NA | NA |
| $S_{pO_2}$ % | 92.0 | 96.0 | 4.0 (3.2–5.4)*** | 97.0 | 4.0 (3.4–5.6)*** |
| $V'_E$ L·min$^{-1}$ | 70.7 | 71.7 | 1.0 (−2.2–4.3) | 39.2 | −5.9 (−8.8– −3.1)*** |
| Heart rate bpm | 141.0 | 142.0 | 1.2 (−3.0–5.3) | 118.0 | −4 (−6.3– −1.6)*** |
| $V'_E/V'_{CO_2}$ | 35.9 | 32.6 | −3.3 (−4.6– −2.0)*** | 33.9 | −3.6 (−4.3– −3.0)*** |
| Arterial lactate mmol·L$^{-1}$ | 5.0 | 5.14 | 0.14 (−0.5–0.2) | NA | NA |
| $P_{aCO_2}$ kPa | 5.0 | 5.5 | 0.5 (0.3–0.7)*** | NA | NA |
| $P_{aO_2}$ kPa | 9.6 | 30.9 | 21.3 (19.1–23.4)*** | NA | NA |
| $S_{aO_2}$ % | 92.3 | 99.4 | 7.1 (5.4–8.9)*** | NA | NA |
| Borg CR10 dyspnoea score | 6.0 | 5.4 | −0.6 (−0.2– −0.9)*** | NA | NA |
| Borg CR10 leg score | 5.4 | 5.7 | 0.3 (−0.7–0.2) | NA | NA |
| **CWRET overall** | | | | | |
| Endurance time minutes:seconds | 10:43 | 16:56 | 6.13 (4:59–7:35)*** | NA | NA |
| $S_{pO_2}$ % | 91.0 | 97.0 | 6.0 (4.3–6.9)*** | 96.0 | 5.0 (3.4–5.8)*** |
| $V'_E$ L·min$^{-1}$ | 66.0 | 61.0 | −5.0 (−2.0– −8.0)*** | 54.7 | −8.3 (−11.2– −5.4)*** |
| Heart rate bpm | 145.0 | 144.0 | −1.0 (−3.3–1.3) | 135.0 | −6.0 (−7.2– −3.9)*** |
| $V'_E/V'_{CO_2}$ | 37.0 | 34.0 | −3.0 (−2.2– −4.1) | 31.9 | −4.9 (−5.8– −4.1)*** |
| Arterial lactate mmol·L$^{-1}$ | 6.2 | 4.7 | −1.5 (−2.2– −0.8)*** | NA | NA |
| $P_{aCO_2}$ kPa | 5.0 | 5.3 | 0.3 (0.2–0.5)*** | NA | NA |
| $P_{aO_2}$ kPa | 13.9 | 32.1 | 18.2 (15–21.5)*** | NA | NA |
| $S_{aO_2}$ % | 90.1 | 99.7 | 9.6 (7.3–12)*** | NA | NA |
| Borg CR10 dyspnoea score | 6.0 | 5.1 | −0.9 (−0.5– −1.3)*** | NA | NA |
| Borg CR10 leg score | 5.5 | 5.1 | −0.4 (−0.8– −0.1)* | NA | NA |

Data are presented as mean and mean differences with 95% confidence intervals (lower limit–upper limit). IET: incremental exercise test; CWRET: constant work-rate exercise test; NA: not available; $S_{pO_2}$: oxygenation by pulse oximetry; $V'_E$ : minute ventilation; bpm: beats per min; $V'_E/V'_{CO_2}$: ventilatory equivalent for $CO_2$: $P_{aCO_2}$, $P_{aO_2}$: arterial tension for $CO_2$ and $O_2$; $S_{aO_2}$: arterial oxygen saturation. *: p=0.05; ***: p<0.001.

In aBGA (available in 39 patients (43%)) at end-exercise of CWRET arterial lactate levels were significantly lower under hyperoxia. Lactate −1.5 mmol·L$^{-1}$ (6.2 to 4.7 mmol·L$^{-1}$, 95% CI: −2.2– −0.8 mmol·L$^{-1}$, p<0.001). $P_{aCO_2}$, $P_{aO_2}$ and $S_{aO_2}$ were significantly higher in hyperoxia +0.3 kPa (95% CI: 0.2–0.5 kPa), +18.2 kPa (95% CI: 15–21.5 kPa) and +10% (95% CI: 7.3–12.0%), respectively, all three p<0.001.

### Isotime

In CWRET at isotime, hyperoxia increased mean $S_{pO_2}$ by +5% (from 92% to 97%, 95% CI: 3.4–5.8%, p<0.001). $V'_E$, HR and $V'_E/V'_{CO_2}$ were significantly reduced by −8.3 L·min$^{-1}$ (95% CI: −11.2– −5.4 L·min$^{-1}$), by −6.0 bpm (95% CI: −7.2– −3.9 bpm) and by −4.9 (95% CI: −5.8– −4.1), all three p<0.001 (table 2 and figure 4).

### *Changes in different diseases*

The differential changes with hyperoxia *versus* ambient air in IET and CWRET are shown in table 3 and illustrated in figure 1 for the main outcomes. It is shown that all disease groups significantly increased their cycling performance.

When comparing the different groups, patients with PVD showed the highest improvements with hyperoxia in both protocols (IET/CWRET): +12.4 W/+6:54 min (95% CI: 4.7–20.0 W, p<0.003/3:13 to 10:35 min, p=0.001). Patents with PVD had significantly higher increases in exercise capacity compared to those with COPD (+11.8 W/+5:14 min, p=0.010/0.007), HFpEF (+14.3 W/+8:47 min, p=0.012/0.001), CHD (+11.0 W/+9:02 min, p=0.086/0.001). The different changes of the physiological secondary outcomes and aBGA at end-exercise in different patient groups are shown in table 3 and figures 2 and 3. As expected, $S_{pO_2}$ is higher in both protocols at end-exercise under hyperoxia. Overall, in healthy, PVD and COPD subjects, $V'_E$ and HR at end-exercise were unchanged or increased with hyperoxia, whereas

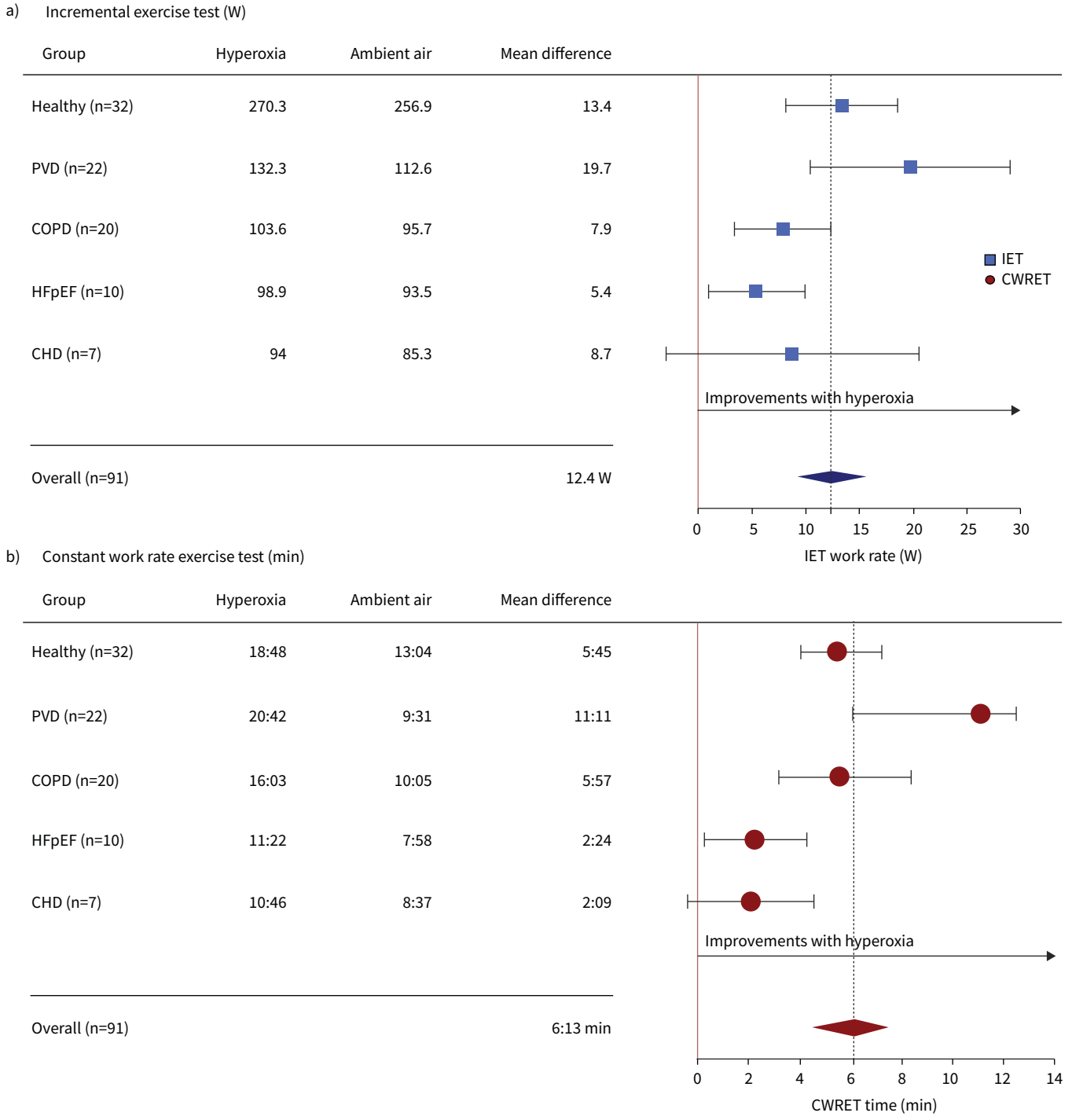


**FIGURE 1** Changes with ambient air *versus* hyperoxia in the a) cycling incremental ramp exercise test (IET) and b) constant work-rate exercise test (CWRET) are shown. Improvements of incremental exercise tests and constant work-rate exercise tests in tests with hyperoxia at end-exercise are shown overall and by subgroups of the different diseases. Data were presented as means and mean differences with 95% confidence intervals (horizontal lines). The zero line represents unity. Overall represents the treatment effect for all 91 patients (blue/red diamond). COPD: chronic obstructive pulmonary disease; healthy: healthy controls; PVD: precapillary pulmonary hypertension due to pulmonary vascular disease; HFpEF: heart failure with preserved ejection fraction; CHD: congenital heart disease.

they decreased in CWRET. $V'_E/V'_{CO_2}$ decreased under hyperoxia overall and in all subgroups, with largest improvements seen in PVD. aBGA showed higher $S_{aO_2}$, $P_{aO_2}$ and $P_{aCO_2}$ and in the CWRET lower blood lactate with hyperoxia.

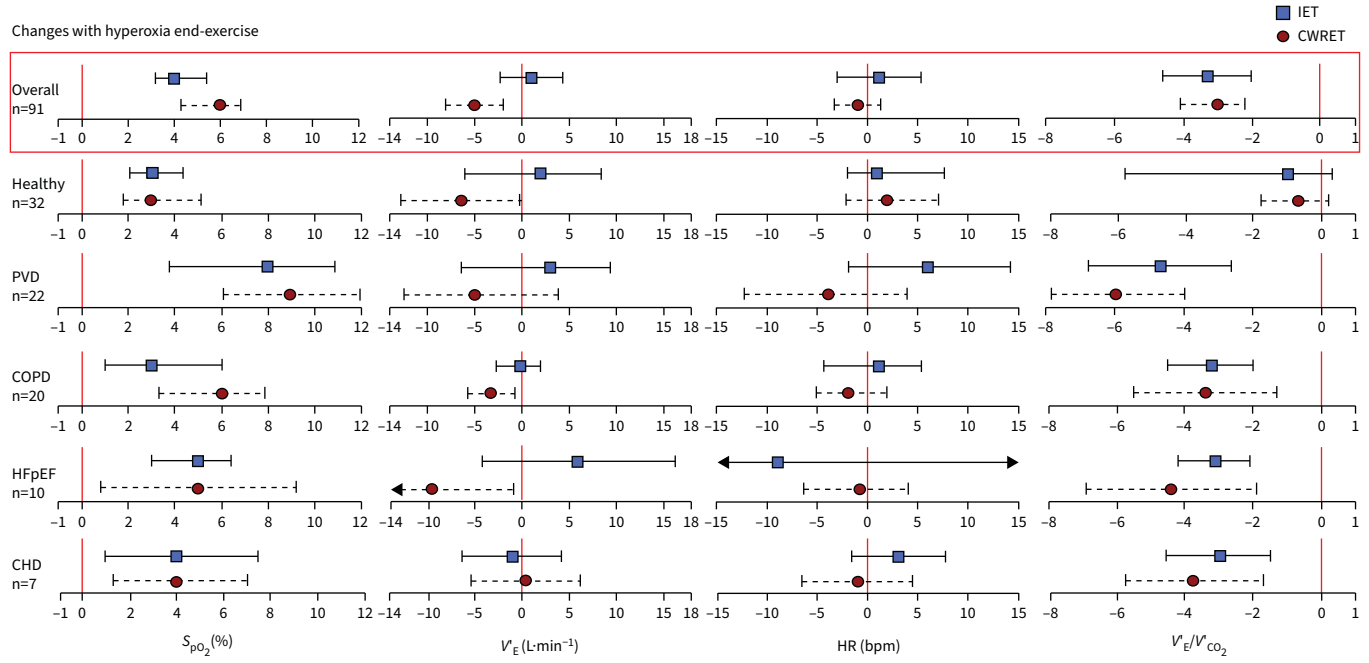


**FIGURE 2** Changes of the secondary outcomes at end-exercise with hyperoxia. Improvements of incremental exercise tests (IETs) and constant work-rate exercise tests (CWRETs) in tests with hyperoxia at end-exercise by subgroups. Data were presented as mean differences with 95% confidence intervals (horizontal lines). The zero line represents unity. Overall represents the treatment effect for all 91 patients. COPD: chronic obstructive pulmonary disease; healthy: healthy controls; PVD: precapillary pulmonary hypertension due to pulmonary vascular disease; HFpEF: heart failure with preserved ejection fraction; CHD: congenital heart disease; $S_{pO_2}$: arterial oxygenation by pulse oximetry; $V'_E$: minute ventilation; HR: heart rate; bpm: beats per min; $V'_E/V'_{CO_2}$: ventilatory equivalent for carbon dioxide.

Table 4 and figure 4 show the changes of physiological secondary outcomes at isotime. Breathing hyperoxia significantly increases $S_{pO_2}$ and decreases $V'_E$, HR and $V'_E/V'_{CO_2}$ with mostly consistent results across all disease groups.

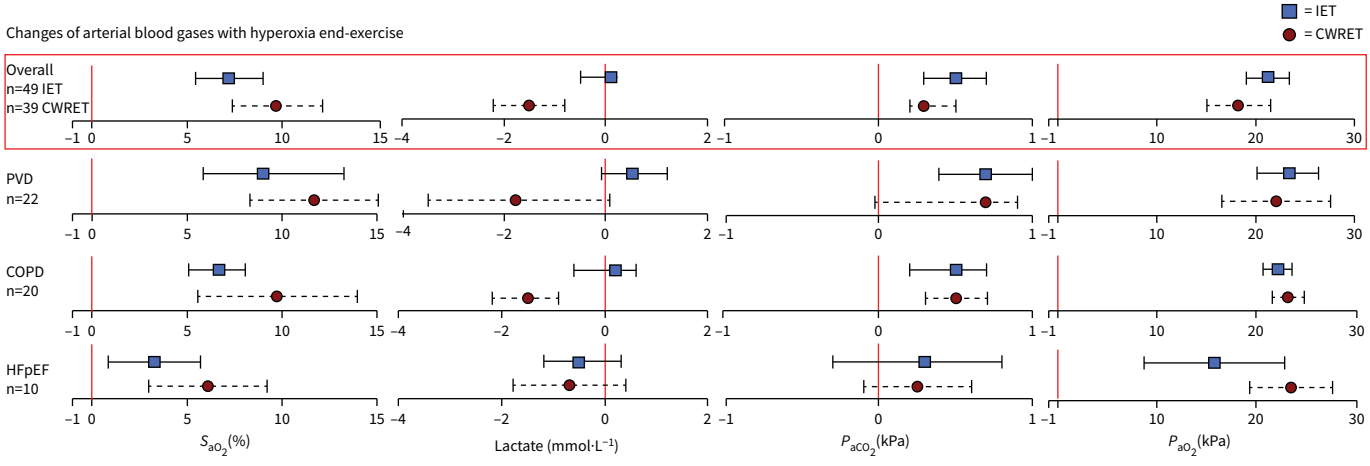


**FIGURE 3** Changes of arterial blood gas analysis at end-exercise with hyperoxia. Improvements of incremental exercise tests (IETs) and constant work-rate exercise tests (CWRETs) in tests with hyperoxia at end-exercise by subgroups (not available for healthy and congenital heart disease). Data were presented as mean differences with 95% confidence intervals (horizontal lines). The zero line represents unity. Overall represents the treatment effect for all patients where arterial blood gas was available. COPD: chronic obstructive pulmonary disease; healthy: healthy controls; PVD: precapillary pulmonary hypertension due to pulmonary vascular disease; HFpEF: heart failure with preserved ejection fraction; $S_{aO_2}$: arterial oxygen saturation; $P_{aO_2}$: arterial oxygen tension; $P_{aCO_2}$: arterial carbon dioxide tension.

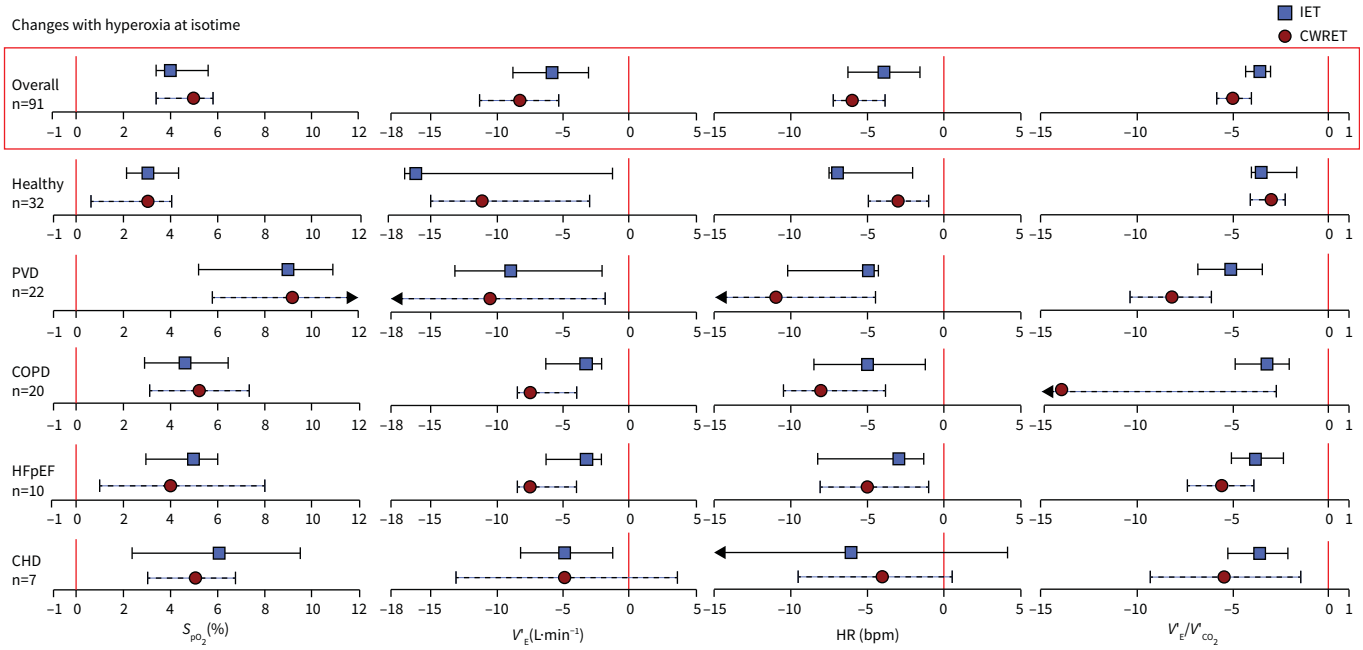


FIGURE 4 Changes of the secondary outcomes at isotime with hyperoxia. Improvements of incremental exercise tests (IETs) and constant work-rate exercise tests in tests (CWRETs) with hyperoxia at isotime by subgroups. Data were presented as mean differences with 95% confidence intervals (horizontal lines). The zero line represents unity. Overall represents the treatment effect for all 91 patients. COPD: chronic obstructive pulmonary disease; healthy: healthy controls; PVD: precapillary pulmonary hypertension due to pulmonary vascular disease; HFpEF: heart failure with preserved ejection fraction; CHD: congenital heart disease; $S_{pO_2}$: arterial oxygenation by pulse oximetry; $V'_E$: minute ventilation; HR: heart rate; $V'_E/V'_{CO_2}$: ventilatory equivalent for carbon dioxide.

## Discussion

In the present analysis on the effects of hyperoxia on exercise performance in healthy subjects and different cardiopulmonary diseases performing identical protocols with $F_{IO_2}$ 0.21 and 0.5, we have shown that breathing hyperoxia *versus* air increases $W_{max}$ in IET by 8% and CWRET endurance time even by 58%. Improvements in exercise performance in IET and CWRET were found in all investigated groups, but improvements were significantly higher in patients with PVD. Besides an increased blood oxygenation, hyperoxia was associated with a decreased HR and $V'_E$ and improvement in ventilatory efficiency as expressed by the lower $V'_E/V'_{CO_2}$ at isotime.

A possible explanation for the improvements with hyperoxia could be a change of energy metabolism while breathing supplemental oxygen, shifting the anaerobic threshold to more sustained aerobic metabolism with longer aerobic steady-state periods in CWRET [3]. We found significantly reduced levels of blood lactate in CWRET at end-exercise which are in line with another study that observed similar findings at end-exercise and isotimes in patients with COPD [24]. The higher blood oxygenation at end-exercise ($S_{pO_2}$: IET +4%, CWRET +6%; $S_{aO_2}$: IET +7%, CWRET +9.6%) could additionally lead to an inhibition of hypoxia-stimulated chemoreceptors which decrease $V'_E$ and HR, resulting in more efficient breathing patterns. This was related to an increase in alveolar carbon dioxide tension ($P_{CO_2}$) as evidenced by a higher end-tidal $P_{CO_2}$, along with a lower breathing rate and tidal volume while the dead space fraction remained unchanged [14]. At end-exercise with hyperoxia we found unchanged $V'_E$ despite greater $V'_{CO_2}$ in IET and a reduction of $V'_E$ by $-5$ L·min$^{-1}$ in CWRET. Therefore, in IET as well as in CWRET, $V'_E/V'_{CO_2}$ was significantly reduced in a similar range while HR was unchanged. As opposed to hypoxic pulmonary vasoconstriction aiming to optimise ventilation/perfusion ratio, there is evidence that hyperoxia causes pulmonary vasodilatation, which reduces PVR [25, 26]. The fact that $V'_E$ and HR are found unaltered at end-exercise during hyperoxia, despite significantly higher loads/endurance times (IET: +12.4 W; CWRET: +6:13 min) means that circulatory and breathing efforts remained unchanged, while ventilatory efficiency and also dyspnoea improved. To understand underlying mechanisms of improved exercise capacity, it is important to study physiological parameters at isotime in tests with hyperoxia. At isotime we found strong evidence that hyperoxia significantly reduced $V'_E$ and HR (IET and CWRET) along with a significant improvement in ventilatory efficiency as expressed by the lower $V'_E/V'_{CO_2}$, which

**TABLE 3** Changes with ambient air *versus* hyperoxia for all disease groups are shown at end-exercise

| End-exercise | Mean differences (95% CI) with hyperoxia | | | | |
|---|---|---|---|---|---|
| | Healthy | PVD | COPD | HFpEF | CHD |
| **IET** | | | | | |
| Work rate W | 13.0 (8.0–19.0)*** | 19.7 (10.5–28.9)*** | 7.9 (3.4–12.3)*** | 5.4 (0.9–9.8)* | 7.0 (−1.3–18.7) |
| $S_{pO_2}$ % | 3.0 (2.1–4.3)*** | 8.0 (3.8–10.9)*** | 3.0 (1.0–6.0)** | 5.0 (3.0–6.4)*** | 4.0 (0.9–7.4)* |
| $V'_E$ L·min$^{-1}$ | 2.0 (−6.0–8.4) | 3.0 (−6.4–9.3) | −0.25 (−2.7–2.1) | 5.8 (−4.2–16.3) | −1.0 (−6.2–4.2) |
| Heart rate bpm | 1.0 (−2–7.7) | 6.0 (−1.9–14.3) | 1.0 (−4.4–5.3) | −9.0 (−36.0–19.2) | 3.0 (−1.7–7.7) |
| $V'_E/V'_{CO_2}$ | −1.0 (−5.8–0.3) | −4.7 (−6.8– −2.6)*** | −3.2 (−4.5– −2.0)*** | −3.1 (−4.2– −2.1)*** | −3.0 (−4.6– −1.5)** |
| Arterial lactate mmol·L$^{-1}$ | NA | 0.5 (−0.1–1.2) | 0.2 (−0.6–0.6) | −0.5 (−1.2–0.3) | NA |
| $P_{aCO_2}$ kPa | NA | 0.7 (0.4–1)*** | 0.5 (0.2–0.7)** | 0.3 (−0.3–0.8) | NA |
| $P_{aO_2}$ kPa | NA | 23.3 (20.1–26.5)*** | 22.1 (20.6–23.6)*** | 15.7 (8.6–22.8)*** | NA |
| $S_{aO_2}$ % | NA | 9.0 (5.9–13.2)*** | 6.6 (5.1–8)*** | 3.3 (0.9–5.7)* | NA |
| Borg CR10 dyspnoea score | −0.9 (−1.5– −0.2)* | −0.6 (−1.2–0.1)*** | 0.0 (−0.7–0.7) | −0.8 (−1.5– −0.1)* | NA |
| Borg CR10 leg score | 0.1 (−0.6–0.9) | 0.5 (−0.8–1.7)*** | 0.4 (−0.4–1.2) | 0.1 (−0.5–0.7) | NA |
| **CWRET** | | | | | |
| Endurance time min | 5:45 (4:08–7:20)*** | 11:11 (6:45–15:36)*** | 5:57 (3:27–8:27)*** | 2:24 (0:39–4:10)* | 0:56 (−0:13–4:31) |
| $S_{pO_2}$ % | 3.0 (1.8–5.1)*** | 9.0 (6.1–12.5)*** | 6.0 (3.3–7.8)*** | 5.0 (0.8–9.2)* | 4.0 (1.3–7.0)* |
| $V'_E$ L·min$^{-1}$ | −6.5 (−12.9–0.05) | −5.0 (−12.4–3.8) | −3.4 (−5.8– −0.9)* | −9.6 (−18.3– −0.8) | 0.4 (−5.3–6.2) |
| Heart rate bpm | 2.0 (−2.1–7.1) | −4.0 (−12.4–3.9) | −2.0 (−5.2–1.8) | −1.0 (−6.4–4.1) | −1.0 (−6.7–4.4) |
| $V'_E/V'_{CO_2}$ | −0.7 (−1.8–0.2) | −6.0 (−7.9– −4.1)*** | −3.4 (−5.5– −1.3)** | −4.4 (−6.9– −1.9)* | −3.8 (−5.8– −1.7)** |
| Arterial lactate mmol·L$^{-1}$ | NA | −1.8 (−3.5–0.04) | −1.5 (−2.2– −0.9)*** | −0.7 (−1.8–0.4) | NA |
| $P_{aCO_2}$ kPa | NA | 0.7 (−0.03–0.9) | 0.5 (0.3–0.7)*** | 0.25 (−0.1–0.6) | NA |
| $P_{aO_2}$ kPa | NA | 22.0 (16.6–27.6)*** | 23.1 (21.5–24.7)*** | 23.4 (19.2–27.6)** | NA |
| $S_{aO_2}$ % | NA | 11.7 (8.3–15)*** | 9.7 (5.6–13.8)*** | 6.1 (3–9.2)** | NA |
| Borg CR10 dyspnoea score | −0.3 (−1.2–0.5) | −1.4 (−2.5–0.4)* | −0.9 (−1.5– −0.3)** | −1.3 (−2.1– −0.6)** | NA |
| Borg CR10 leg score | −0.1 (−0.7–0.5) | −0.6 (−1.5–0.3) | −0.5 (−1.2–0.3) | −0.8 (−1.7– −0.1) | NA |

Data are presented as mean differences with 95% confidence intervals. For more details on statistical analyses see the original publications [13–17]. PVD: pulmonary vascular disease with precapillary pulmonary hypertension; COPD: chronic obstructive pulmonary disease; HFpEF: heart failure with preserved ejection fraction with postcapillary pulmonary hypertension; CHD: cyanotic congenital heart disease; IET: incremental exercise test; CWRET: constant work-rate exercise test; NA: not available; $S_{pO_2}$: oxygenation by pulse oximetry; $V'_E$: minute ventilation; bpm: beats per min; $V'_E/V'_{CO_2}$: ventilatory equivalent for $CO_2$; $P_{aCO_2}$, $P_{aO_2}$: arterial tension for $CO_2$ and $O_2$; $S_{aO_2}$: arterial oxygen saturation. *: p=0.05; **: p=0.01; ***: p<0.001.

all presumably have been a contributory factor in patients reaching their cardiopulmonary exhaustion later. Comparing $V'_E$ at isotime with end-exercise (−8.3 *versus* −5 L·min$^{-1}$) while breathing hyperoxia during CWRET suggests that patients still have ventilatory reserves when stopping the test. Simultaneously, HR was lower at isotime (−6 bpm) but unchanged at end-exercise on hyperoxia. This could be interpreted as

**TABLE 4** Changes with ambient air *versus* hyperoxia for all disease groups are shown at isotime

| Isotime | Mean differences (95% CI) with hyperoxia | | | | |
|---|---|---|---|---|---|
| | Healthy | PVD | COPD | HFpEF | CHD |
| **IET** | | | | | |
| $S_{pO_2}$ % | 3.0 (2.1–4.3)*** | 9.0 (5.2–10.9)*** | 4.6 (2.9–6.4)*** | 5.0 (3–6)** | 6.0 (2.3–9.4)* |
| $V'_E$ L·min$^{-1}$ | −16.0 (−16.9– −1.3)* | −9.0 (−13.1– −2.2)* | −3.3 (−6.3– −2.2)*** | 2.0 (−9.9–13.9) | −4.9 (−8.3– −1.4)* |
| Heart rate bpm | −7.0 (−7.4– −2.1)** | −5.0 (−10.2– −4.3)*** | −5.0 (−8.4– −1.3)* | −3.0 (−8.2–1.3) | −6.0 (−15.3–4.2) |
| $V'_E/V'_{CO_2}$ | −3.5 (−3.6– −1.7)*** | −5.1 (−6.8– −3.5)*** | −3.2 (−4.9– −2.1)*** | −3.8 (−5.1– −2.4)** | −3.6 (−5.2– −2.1)** |
| **CWRET** | | | | | |
| $S_{pO_2}$ % | 3.0 (0.6–4)*** | 9.2 (5.8–12.6)*** | 5.2 (3.1–7.3)*** | 4.0 (1.0–8.0)* | 5.0 (3.0–6.7)** |
| $V'_E$ L·min$^{-1}$ | −11.0 (−14.8– −3.1)*** | −10.5 (−18.5– −1.9)* | −7.5 (−8.5– −4.1)*** | −8.5 (−10– −7.1)*** | −4.9 (−13.1–3.4) |
| Heart rate bpm | −3.0 (−4.9– −0.8)** | −11.0 (−15.2– −4.5)** | −8.0 (−10.4– −3.8)*** | −5.0 (−8.1– −0.9)* | −4.0 (−9.4–0.5) |
| $V'_E/V'_{CO_2}$ | −3.0 (−4.1– −2.3)*** | −8.2 (−10.3– −6.1)*** | −14.0 (−16.4– −2.8)*** | −5.6 (−7.4– −3.9)*** | −5.4 (−9.3– −1.4)* |

Data are presented as mean differences with 95% confidence intervals. For more details on statistical analyses see the original publications [13–17]. PVD: pulmonary vascular disease with precapillary pulmonary hypertension; COPD: chronic obstructive pulmonary disease; HFpEF: heart failure with preserved ejection fraction with postcapillary pulmonary hypertension; CHD: cyanotic congenital heart disease; IET: incremental exercise test; CWRET: constant work-rate exercise test; $S_{pO_2}$: oxygenation by pulse oximetry; $V'_E$: minute ventilation; $V'_E/V'_{CO_2}$: ventilatory equivalent for $CO_2$. *: p=0.05; **: p=0.01; ***: p<0.001.

an indicator of longer endurance with cardiac reserves. These findings are supported by another study which observed a reduction of cardiac output by 10% at isotime while breathing hyperoxia during exercise in patients with COPD [24]. Reduction of HR could also be attributed to the oxygen-induced peripheral vasoconstriction activating arterial baroreceptor reflex, resulting in vagal activation and sympathetic depression [27]. Especially in PH, right-heart strain is associated with adverse changes of cardiac autonomic control caused by an increase of sympathetic tone [28]. Besides the reduction of PVR, hyperoxia also decreases mPAP, which relieves right-heart strain and may increase stroke volume and thus contribute to higher exercise performance in patients with cardiopulmonary diseases [26].

Patients reported significantly less dyspnoea at end-exercise with hyperoxia in IET and CWRET. Less sensation of dyspnoea is an important outcome for cardiopulmonary patients and is contributing to the ergogenic effect of hyperoxia. Besides peripheral chemoreceptors, hyperoxia could influence the central nervous system by keeping α-motor units activated during exercise resulting in a reduction of central fatigue and neurotransmitter release affecting hormonal release [2].

Arterial blood lactate concentrations were >4 $mmol \cdot L^{-1}$ in all tests and show that patients reached the maximum-load criteria. The reduction of lactate concentrations in CWRET with hyperoxia could be a result of oxygen-induced reduction of muscle glycogen utilisation and/or more rapid lactate clearance [29, 30]. Other studies on this topic found reduced levels of epinephrine and norepinephrine while breathing hyperoxia and attributed those results to reduced glycogenolysis [31].

In patients with cardiopulmonary diseases, visual inspection revealed a correlation between the extent of differences in $S_{pO_2}$ on hyperoxia *versus* ambient air and improvements in exercise performance (figures 1–3). Especially in CWRET we observed the highest differences of $S_{pO_2}$ in PVD ($S_{pO_2}$: 9%, $S_{aO_2}$ 11.7%) followed by COPD (6%, 9.7%), HFpEF (5%, 6.1%) and CHD (4%, NA), while the extent of exercise improvements followed the same order. A cardinal finding in patients with PVD was the exertional oxygen desaturation, thus, beneficial exercise improvements might be enhanced in diseases with pronounced exercise-induced hypoxaemia, such as PVD.

The literature on hyperoxia to improve exercise performance in cardiopulmonary diseases, especially randomised-trials, are scarce and almost exclusively available in patients with COPD. The effect of hyperoxia in a single exercise test in COPD was assessed in a Cochrane systematic review by Nonoyama *et al*. [32], which identified five studies for inclusion. The authors concluded that there is little evidence that supports hyperoxia but called for more and larger studies. Some studies investigated the effect of hyperoxia during exercise interventions during training periods in rehabilitation programmes, and some revealed benefits, others not [33, 34]. Alison *et al*. [35] investigated 111 patients with COPD and exposed them to exercise three times weekly for 8 weeks. 52 patients received additional oxygen *via* nasal prongs and showed no significant improvements compared with placebo.

However, these studies are only comparable to ours to a limited extent. First, these are studies investigating the effect of supplemental oxygen during repetitive training sessions over a defined rehabilitation time of several weeks, with the outcome of rehabilitation measured by tests which are then mostly performed on ambient air. Second, in the mentioned training studies, oxygen is mainly applied *via* nasal prongs, which may not be effective in exercise settings, when most people breathe through the mouth, and the $F_{IO_2}$ in the alveolae is inconstant.

In line with our results, a recent review [24] reported the physiological mechanisms underlying the beneficial ergogenic effect of $F_{IO_2}$ 1.0 compared to ambient air on CWRET at the end-exercise and at isotime in patients with COPD. Authors synthesised data from two different trials undertaken by their group. Additionally, the study reports changes in locomotor and respiratory muscle and cerebral frontal cortex blood flow and oxygen delivery. Authors concluded that several factors contribute to the improved exercise tolerance during hyperoxia including greater oxygen delivery to the locomotor and respiratory muscles, while cardiac and breathing reserves were higher during isotime in hyperoxia compared to normoxia leading to decreased symptoms [24].

In PVD, besides our paper there is one other RCT with a comparable study design. Boutou *et al*. [36] investigated the effect of $F_{IO_2}$ 0.40 on exercise performance in nine patients with PVD, and in line with our study, they reported an increase in exercise performance, cardiac output and brain oxygenation with hyperoxia.

Thus, overall, the current analysis shows that supplemental oxygen *versus* placebo air improved exercise performance in healthy and all investigated cardiopulmonary disease groups. Our findings are of potential clinical relevance as they are above the minimal clinically important difference of 5 W in IET in patients with COPD, as described by Puhan *et al.* [37] and of 1:45 min in CWRET according to Casaburi *et al.* [38] with our studies revealing an increase in +12.4 W in IET and +6:13 min in CWRET.

Nevertheless, improvements in exercise performance varies depending on exercise types and underlying disease and follows different response patterns to hyperoxia [39].

### *Largest improvements in PVD*

We found the largest improvements in exercise performance with hyperoxia in patients with PVD, within-group (+18% in IET and +118% in CWRET) as well as between-group compared with the other cardiopulmonary diseases. This can probably be attributed to the oxygen-induced pulmonary vasodilatation reducing PVR, mPAP and ventilation-perfusion mismatch combined with peripheral vasoconstriction leading to vagal activation and HR reduction [26, 27], and leading to the improved ventilatory efficiency as indicated by the shift of $V'_E/V'_{CO_2}$ *versus* end-tidal $CO_2$ parabola according to the re-arranged alveolar gas equation to the favourable lower right corner, as illustrated in Ulrich *et al*. [14]. With regard to the unchanged death space ventilation, these improvements could be mainly attributed to the reduced respiratory drive with higher values of alveolar and end-tidal $P_{CO_2}$ values.

Supervised exercise rehabilitation showed promising beneficial effects in PAH in addition to medical treatment [40]. However, oxygen supplementation during exercise in PVD during rehabilitation has not been studied so far. Two randomised, controlled trials showed that nocturnal or domiciliary oxygen therapy improves daytime performance on ambient air in patients with nocturnal hypoxaemia and exercise-induced desaturation [41, 42]. Current guidelines recommend supplemental oxygen in severely hypoxic patients ($P_{aO_2}$ <8 kPa) with symptomatic benefits and improved $S_{pO_2}$ during exercise with hyperoxia [12]. Consistently, patients in the present PVD cohort had nearly normal $P_{aO_2}$ at rest.

### *Conclusion*

This *post hoc* analysis from five randomised, controlled, crossover trials using identical protocols and including a large sample of 91 patients with different cardiopulmonary diseases and healthy controls demonstrated that hyperoxia consistently enhances exercise capacity *versus* placebo air with greatest effect in in CWRET and in patients with PVD.

As exercise time was highly significantly increased, especially in CWRET, along with decreased dyspnoea perception, our data support the further investigation of the use and application method of supplemental oxygen during daily exercise and training in patients with various cardiopulmonary diseases and especially in patients with PVD with the purpose of improving exercise performance and potentially enhancing training effects.

Provenance: Submitted article, peer reviewed.

This study is registered at www.clinicaltrials.gov with identifier numbers NCT03196089, NCT04157660, NCT01748474 and NCT04076501. Individual participant data will be made available, as well as study protocols, informed consent forms and the statistical analysis plan, after publication, in our university's data storage.

Author contributions: S. Ulrich, M. Lichtblau, S. Saxer, E.D. Hasler, E.I. Schwarz and K.E. Bloch contributed to the conception and design. J. Müller, M. Lichtblau, E.D. Hasler, K.E. Bloch, P. Appenzeller, M. Bauer, S.R. Schneider, E.I. Schwarz and S. Ulrich contributed to acquisition, analysis or interpretation of data. J. Müller, M. Lichtblau and S. Ulrich drafted the manuscript. All authors revised the manuscript critically for important intellectual content and gave their final approval of the version to be published.

Conflict of interest: None of the authors has any financial or nonfinancial disclosures in context to this manuscript.

## References

1 Amann M, Calbet JA. Convective oxygen transport and fatigue. *J Appl Physiol (1985)* 2008; 104: 861–870.
2 Noakes TD, Peltonen JE, Rusko HK. Evidence that a central governor regulates exercise performance during acute hypoxia and hyperoxia. *J Exp Biol* 2001; 204: 3225–3234.
3 Sperlich B, Zinner C, Hauser A, *et al.* The impact of hyperoxia on human performance and recovery. *Sports Med* 2017; 47: 429–438.

4 Yan Z, Spaulding HR. Extracellular superoxide dismutase, a molecular transducer of health benefits of exercise. *Redox Biol* 2020; 32: 101508.
5 Prieur F, Benoit H, Busso T, *et al.* Effects of moderate hyperoxia on oxygen consumption during submaximal and maximal exercise. *Eur J Appl Physiol* 2002; 88: 235–242.
6 Amann M, Eldridge MW, Lovering AT, *et al.* Arterial oxygenation influences central motor output and exercise performance via effects on peripheral locomotor muscle fatigue in humans. *J Physiol* 2006; 575: 937–952.
7 Oussaidene K, Prieur F, Bougault V, *et al.* Cerebral oxygenation during hyperoxia-induced increase in exercise tolerance for untrained men. *Eur J Appl Physiol* 2013; 113: 2047–2056.
8 Wilkerson DP, Berger NJ, Jones AM. Influence of hyperoxia on pulmonary O2 uptake kinetics following the onset of exercise in humans. *Respir Physiol Neurobiol* 2006; 153: 92–106.
9 Safdar B, Mangi AA. Survival of the fittest: impact of cardiorespiratory fitness on outcomes in men and women with cardiovascular disease. *Clin Ther* 2020; 42: 385–392.
10 Kaminsky LA, Arena R, Ellingsen Ø, *et al.* Cardiorespiratory fitness and cardiovascular disease: the past, present, and future. *Prog Cardiovasc Dis* 2019; 62: 86–93.
11 Grunig E, MacKenzie A, Peacock AJ, *et al.* Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial. *Eur Heart J* 2021; 42: 2284–2295.
12 Galie N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37: 67–119.
13 Hasler ED, Saxer S, Schneider SR, *et al.* Effect of breathing oxygen-enriched air on exercise performance in patients with chronic obstructive pulmonary disease: randomized, placebo-controlled, cross-over trial. *Respiration* 2020; 99: 213–224.
14 Ulrich S, Hasler ED, Saxer S, *et al.* Effect of breathing oxygen-enriched air on exercise performance in patients with precapillary pulmonary hypertension: randomized, sham-controlled cross-over trial. *Eur Heart J* 2017; 38: 1159–1168.
15 Ulrich S, Hasler ED, Müller-Mottet S, *et al.* Mechanisms of improved exercise performance under hyperoxia. *Respiration* 2017; 93: 90–98.
16 Muller J, Lichtblau M, Saxer S, *et al.* Effect of breathing oxygen-enriched air on exercise performance in patients with pulmonary hypertension due to heart failure with preserved ejection fraction: a randomized, placebo-controlled, crossover trial. *Front Med (Lausanne)* 2021; 8: 692029.
17 Saxer S, Calendo LR, Lichtblau M, *et al.* Effect of oxygen therapy on exercise performance in patients with cyanotic congenital heart disease: randomized-controlled trial. *Int J Cardiol* 2022; 348: 65–72.
18 Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Rev Esp Cardiol (Engl Ed)* 2016; 69: 1167.
19 Ulrich S, Schneider SR, Bloch KE. Effect of hypoxia and hyperoxia on exercise performance in healthy individuals and in patients with pulmonary hypertension: a systematic review. *J Appl Physiol (1985)* 2017; 123: 1657–1670.
20 Subudhi AW, Dimmen AC, Roach RC. Effects of acute hypoxia on cerebral and muscle oxygenation during incremental exercise. *J Appl Physiol (1985)* 2007; 103: 177–183.
21 Ulrich S, Nussbaumer-Ochsner Y, Vasic I, *et al.* Cerebral oxygenation in patients with OSA: effects of hypoxia at altitude and impact of acetazolamide. *Chest* 2014; 146: 299–308.
22 Muller-Mottet S, Hildenbrand FF, Keusch S, *et al.* Effects of exercise and vasodilators on cerebral tissue oxygenation in pulmonary hypertension. *Lung* 2014; 193: 113–120.
23 Ferreira EV, Ota-Arakaki JS, Ramos RP, *et al.* Optimizing the evaluation of excess exercise ventilation for prognosis assessment in pulmonary arterial hypertension. *Eur J Prev Cardiol* 2014; 21: 1409–1419.
24 Megaritis D, Wagner PD, Vogiatzis I. Ergogenic value of oxygen supplementation in chronic obstructive pulmonary disease. *Intern Emerg Med* 2022; 17: 1277–1286.
25 Li Y, Tesselaar E, Borges JB, *et al.* Hyperoxia affects the regional pulmonary ventilation/perfusion ratio: an electrical impedance tomography study. *Acta Anaesthesiol Scand* 2014; 58: 716–725.
26 Carta AF, Lichtblau M, Berlier C, *et al.* The impact of breathing hypoxic gas and oxygen on pulmonary hemodynamics in patients with pulmonary hypertension. *Front Med (Lausanne)* 2022; 9: 791423.
27 Wunderlich T, Frey N, Kähler W, *et al.* Influence of hyperoxia on diastolic myocardial and arterial endothelial function. *Undersea Hyperb Med* 2017; 44: 521–533.
28 Wensel R, Jilek C, Dörr M, *et al.* Impaired cardiac autonomic control relates to disease severity in pulmonary hypertension. *Eur Respir J* 2009; 34: 895–901.
29 Cardinale DA, Ekblom B. Hyperoxia for performance and training. *J Sports Sci* 2018; 36: 1515–1522.
30 Kane DA. Lactate oxidation at the mitochondria: a lactate-malate-aspartate shuttle at work. *Front Neurosci* 2014; 8: 366.

31 Stellingwerff T, Leblanc PJ, Hollidge MG, *et al.* Hyperoxia decreases muscle glycogenolysis, lactate production, and lactate efflux during steady-state exercise. *Am J Physiol Endocrinol Metab* 2006; 290: E1180–E1190.

32 Nonoyama M, Brooks D, Lacasse Y, *et al.* Oxygen therapy during exercise training in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007; 2007: CD005372.

33 Fujimoto K, Matsuzawa Y, Yamaguchi S, *et al.* Benefits of oxygen on exercise performance and pulmonary hemodynamics in patients with COPD with mild hypoxemia. *Chest* 2002; 122: 457–463.

34 Liu Y, Gong F. Determination of whether supplemental oxygen therapy is beneficial during exercise training in patients with COPD: a systematic review and meta-analysis. *Exp Ther Med* 2019; 18: 4081–4089.

35 Alison JA, McKeough ZJ, Leung RWM, *et al.* Oxygen compared to air during exercise training in COPD with exercise-induced desaturation. *Eur Respir J* 2019; 53: 1802429.

36 Boutou AK, Dipla K, Zafeiridis A, *et al.* A randomized placebo-control trial of the acute effects of oxygen supplementation on exercise hemodynamics, autonomic modulation, and brain oxygenation in patients with pulmonary hypertension. *Respir Physiol Neurobiol* 2021; 290: 103677.

37 Puhan MA, Chandra D, Mosenifar Z, *et al.* The minimal important difference of exercise tests in severe COPD. *Eur Respir J* 2011; 37: 784–790.

38 Casaburi R. Factors determining constant work rate exercise tolerance in COPD and their role in dictating the minimal clinically important difference in response to interventions. *COPD* 2005; 2: 131–136.

39 Mallette MM, Stewart DG, Cheung SS. The effects of hyperoxia on sea-level exercise performance, training, and recovery: a meta-analysis. *Sports Med* 2018; 48: 153–175.

40 Mereles D, Ehlken N, Kreuscher S, *et al.* Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation* 2006; 114: 1482–1489.

41 Ulrich S, Keusch S, Hildenbrand FF, *et al.* Effect of nocturnal oxygen and acetazolamide on exercise performance in patients with pre-capillary pulmonary hypertension and sleep-disturbed breathing: randomized, double-blind, cross-over trial. *Eur Heart J* 2015; 36: 615–623.

42 Ulrich S, Saxer S, Hasler ED, *et al.* Effect of domiciliary oxygen therapy on exercise capacity and quality of life in patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension: a randomised, placebo-controlled trial. *Eur Respir J* 2019; 54: 1900276.