ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original research article

Hyperoxia improves exercise capacity in cardiopulmonary disease A series of RCT's

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

Please cite this article as: Müller J, Lichtblau M, Saxer S, *et al*. Hyperoxia improves exercise capacity in cardiopulmonary disease A series of RCT's. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00563-2022).

Hyperoxia improves exercise capacity in cardiopulmonary disease

A series of RCT's

Author names

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

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

[2] University of Zurich, Zurich, Switzerland

Correspondence:

Prof. Dr. med. Silvia Ulrich

Department of Pulmonology, University Hospital Zurich

Rämistrasse 100

CH-8091 Zürich, Switzerland

E-mail: silvia.ulrich@usz.ch

Take home message: 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.

ABSTRACT

Background: To study the overall and differential effect of breathing hyperoxia (FiO_2 0.5) vs. placebo (ambient air, FiO_2 0.21) to enhance exercise performance in healthy people, patients with pulmonary vascular disease (PVD) with precapillary pulmonary hypertension (PH), chronic obstructive pulmonary disease (COPD), PH due to heart failure with preserved ejection fraction (HFpEF) and cyanotic congenital heart disease (CHD) using data of five RCTs performed with identical protocols.

Methods: 91 subjects (32 healthy, 22 PVD with pulmonary arterial or distal chronic thromboembolic PH, 20 with COPD, 10 with PH in HFpEF and 7 with CHD) performed 2 cycle incremental (IET) and 2 constant work-rate exercise tests (CWRET) at 75% of maximal load (W_{max}), each with ambient air and hyperoxia in single blinded, randomized-controlled cross-over trials. The main outcomes were differences in W_{max} (IET) respectively cycling time (CWRET) with hyperoxia vs ambient air.

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

Conclusion: This large collective of healthy and patients with various cardiopulmonary disease 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.

Approved by the institutional ethical committee (KEK 2012-0251), registered at ClinicalTrials.gov: NCT 03196089, NCT04157660, NCT01748474, NCT04076501

1. INTRODUCTION

In cardiopulmonary diseases, different pathophysiological mechanisms lead to limitation of exercise capacity and dyspnea, 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, uptake and diffusion of oxygen (O_2) into the arterial blood, as well as sufficient supply and utilization 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 (PiO_2), a product of the fractional air content of O_2 ($F_iO_2 \approx 0.21$) and the barometric pressure (P_b), (at sea level $Pb \approx 101$ kPa, $PiO_2 \sim 21$ kPa)[3]. By increasing F_iO_2 (normobaric hyperoxia), greater amounts of O_2 are bound to haemoglobin to improve arterial saturation (SaO_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 (PVD) characterized 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 specialized 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 programs.

We have previously shown in five randomized, placebo-controlled cross-over trials with identical protocols that hyperoxia improves cycling exercise in both, maximal ramp 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), chronic obstructive pulmonary disease (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.

2. MATERIALS AND METHODS

Study design: The current investigation is a post-hoc analysis of data from five randomized, placebo-controlled, single-blinded, cross-over trials using identical protocols to evaluate the effect of hyperoxia vs. placebo air on exercise performance in healthy[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: Healthy, non-smoking, adults over a wide range of age groups who use no medication on regular basis.

PVD: Adults with PAH/CTEPH diagnosed according to 2015-guidelines[12], stable on PH-targeted drug therapy, mean pulmonary artery pressure (mPAP) ≥25 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg assessed by right-heart catheterization.

COPD: Adults with stable COPD, GOLD1-4 (forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) <0.7) and resting pulseoximetric oxygen saturation (SpO_2) ≥90%.

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

CHD: Adult patients with cyanotic CHD (Eisenmenger syndrome, unrepaired congenital heart defects).

Patients with severe resting hypoxemia PaO_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 two cycle exercise tests at pedalling rates of 50-60 rpm to exhaustion, one with FiO_2 0.21, one with FiO_2 0.50 in randomized orders: On the first day, two IET with increments of 10-20 watts/min according to the patient's fitness, on the second day two CWRET at 75% of individual W_{max} achieved with ambient air. There was a recovery period of at least two hours 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 FiO_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. SpO_2 was recorded continuously[20-22].

Physiological variables were averaged over 30 sec intervals. Variables at end-exercise were defined as mean over the final 30 sec before termination of exercise defined as a drop in cycling rate <50 rpm. 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: Maximum work-rate[W] during IET and cycling time[sec] during CWRET.

Secondary outcomes: SpO_2, V'E, HR, $V'E/V'CO_2$, lactate, $PaCO_2$, PaO_2, SaO_2 and BorgCR10 dyspnea and leg-fatigue scores were defined as secondary outcomes of interest.

Randomization and blinding: On day1, patients were randomly allocated to the order of the two different conditions by software-based block-randomization. On day2, the same order was maintained. Participants were blinded to the FiO_2.

Data analysis: Physiological variables were averaged over the first 30sec during rest and the last 30sec for end-exercise respectively. Isotime compares physiological values of tests with- and without hyperoxia at identical timepoint of the longer test corresponding to end-exercise of the shorter test. Data were summarized as mean±standard deviation. 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 analyzed. 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.

3. 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 +12.4W (95CI: 9.1 to 15.6 W, p<0.001) during IET. At end-exercise, hyperoxia increased the mean SpO_2 by +4% (from 92% to 96%, 95CI: 3.2 to 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, 95CI: -4.6 to -2.0, p<0.001). Patient reported less dyspnea while breathing hyperoxia, BorgCR10 -0.6 (95CI: -0.2 to -0.9, p=0.001). BorgCR10 leg fatigue scale was unchanged (Table 2 and figure 1, 2).

There was no significant change in arterial lactate at end-exercise (aBGA available in 49 patients (54%)). $PaCO_2$, PaO_2 and SaO_2 were significantly higher with hyperoxia +0.5 kPa (95CI: 0.3 to 0.7 kPa), +21.3 kPa (95CI: 19.1 to 23.4 kPa) and +7.1% (95CI: 5.4 to 8.9%), respectively, all three p<0.001 (Table 2 and figure 3).

Isotime: In IET at isotime, hyperoxia increased the mean SpO_2 by +4% (from 93% to 97%, 95CI: 3.0 to 5.3%, p<0.001). V'E, HR and V'E/V'CO_2 were significantly reduced by -5.9 l/min (95CI: -8.8 to-3.1 l/min), by -4bpm (95CI: -6.3 to -1.6 bpm) and by -3.6 (95CI: -4.3 to -3), respectively, all three p<0.001 (Table 2, figure 4).

CWRET

End-exercise: 81 of 91 patients performed two CWRET, 10 patients did not perform CWRET as they could not come back 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 to 7:35 min, p<0.001) during CWRET. Breathing hyperoxia increased SpO_2 from 91% to 97%, mean change +6.0% (95CI: 4.3 to 6.9%, p<0.001). V'E and V'E/V'CO2 were both significantly lower in CWRET with hyperoxia, -5.0 l/min (66.0 to 61.0 l/min, 95CI: -2.0 to -8.0 l/min) and -3.0 (37.0 to 34.0, 95CI: -2.2 to -4.1), both p<0.001. HR was unchanged. Patients reported reduced dyspnea and leg fatigue with hyperoxia, BorgCR10 for dyspnea -0.9 (95CI: -0.5 to -1.3, p=0.001) and BorgCR10 for leg fatigue -0.4 (95CI: -0.1 to -0.8, p=0.029). (Table 2 and figure 1, 2).

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 (6.2 to 4.7 mmol/l, 95CI: -2.2 to -0.8 mmol/l, p<0.001). $PaCO_2$, PaO_2 and SaO_2 were significantly higher in hyperoxia +0.3 kPa (95CI: 0.2 to 0.5 kPa), +18.2 kPa (95CI: 15 to 21.5 kPa) and +10% (95CI: 7.3 to 12.0%), respectively, all three p<0.001.

Isotime: In CWRET at isotime, hyperoxia increased mean SpO_2 by+5% (from 92% to 97%, 95CI: 3.4 to 5.8%, p<0.001). V'E, HR and V'E/V'CO_2 were significantly reduced by -8.3 l/min (95CI: -11.2 to -5.4 l/min), by -6.0 bpm (95CI: -7.2 to -3.9 bpm) and by -4.9 (95CI: -5.8 to -4.1) all three p<0.001 (Table 2, figure 4).

CHANGES IN DIFFERENT DISEASES

The differential changes with hyperoxia vs. 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 increase their cycling performance.

When comparing the different groups, patients with PVD showed the highest improvments with hyperoxia in both protocols (IET/CWRET): +12.4 W/+6:54 min (95CI: 4.7 to 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 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 figure 2,3. As expected, SpO_2 is higher in both protocols at end-exercise under hyperoxia. Overall, in healthy, PVD and COPD, V'E and HR at end-exercise were unchanged or increased with hyperoxia, whereas 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 SaO_2, PaO_2 and $PaCO_2$ and in the CWRET lower blood lactate with hyperoxia.

Table 4 and figure 4 show the changes of physiological secondary outcomes at isotime. Breathing hyperoxia significantly increases SpO_2 and decreases V'E, HR and V'E/V'CO_2 with mostly consistent results across all disease groups.

4. DISCUSSION

In the present analysis on the effects of hyperoxia on exercise performance in healthy and different cardiopulmonary diseases performing identical protocols with FiO_2 0.21 and 0.5, we have shown that breathing hyperoxia vs. 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, 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 whilst 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 (SpO_2: IET +4%, CWRET +6%; SaO_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 PCO_2 as evidenced by a higher end-tidal PCO_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 in CWRET. Therefore, in IET as well as in CWRET, $V'E/V'CO_2$ were significantly reduced in a similar range while HR was unchanged. As opposed to hypoxic pulmonary vasoconstriction aiming to optimize 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 whilst ventilatory efficiency and as well dyspnea 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 all presumably have been a contributory factor in patients reaching their cardiopulmonary exhaustion later. Comparing V'E at isotime with end-exercise (-8.3 vs. -5 l/min) whilst 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 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 dyspnea at end-exercise with hyperoxia in IET and CWRET. Less sensation of dyspnea 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/l 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 utilization and/or more rapid lactate clearance[29, 30]. Other studies on this topic found reduced levels of epinephrine and norepinephrine whilst 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 SpO_2 on hyperoxia vs. ambient air and improvements in exercise performance (figures 1-3). Especially in CWRET we observed the highest differences of SpO_2 in PVD (SpO_2: 9%, SaO_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 randomized-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. (2007) which identified five studies for inclusion. The authors concluded that there is little evidence that supports hyperoxia but called for more and larger studies[32]. Some studies investigated the effect of hyperoxia during exercise interventions during training periods in rehabilitation programs, some revealed benefits, others not[33, 34]. Alison et al. (2018) investigated 111 patients with COPD and exposed them to exercise three times weekly for eight weeks. 52 patients received additional oxygen via nasal prongs and showed no significant improvements compared with placebo[35].

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 in the alveolae is inconstant.

In line with our results, a recent review[24] reported the physiological mechanisms underlying the beneficial ergogenic effect of FiO_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, whilst cardiac and breathing reserves were higher during isotime in hyperoxia compared to normoxia leading to lower symptoms[24].

In PVD, besides our paper there is one other RCT with a comparable study design. Boutou et al. (2021) investigated the effect of FiO_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[36].

Thus, overall, the current analysis shows that supplemental oxygen vs. placebo air improved exercise performance in healthy and all investigated cardiopulmonary disease groups. Our findings are of potential clinical relevance as they are well above the minimal clinical important difference of 5 W in IET in patients with COPD, as described by Puhan et al. (2011) of 1:45 min in CWRET according to Casaburi et al. (2005) with our studies revealing an increase in +12.4 W in IET and +6:13 min in CWRET[37, 38].

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], leading to the improved ventilatory efficiency as indicated by the shift of the V'E/V'CO_2 vs. endtidal CO_2 parabola according to the re-arranged alveolar gas equation to the favourable lower right corner, illustrated in[14] and in regard of the unchanged death space ventilation, these improvements could be mainly attributed to the reduced respiratory drive with higher values of alveolar and end-tidal PCO_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 randomized-controlled trials showed that nocturnal or domiciliary oxygen-therapy improves daytime performance on ambient air in patients with nocturnal hypoxemia and exercise-induced desaturation[41, 42]. Current guidelines recommend supplemental oxygen in severely hypoxic patients (PaO_2<8 KPa) with symptomatic benefits and improved SpO_2 during exercise with hyperoxia[12]. Consistently, patients in the present PVD cohort had nearly normal PaO_2 at rest.

CONCLUSION

This post-hoc analysis from five randomized controlled cross-over trials using identical protocols and including a large collective of 91 patients with different cardiopulmonary diseases and healthy controls demonstrated that hyperoxia consistently enhances exercise capacity vs. 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 dyspnea perception, our data support to further investigate the use and application method of supplemental oxygen during daily exercise and training in patients with various cardiopulmonary diseases and especially in patients PVD with the purpose to improve exercise performance and potentially enhance training effects.

TABLES

Table 1 Baseline characteristics

Healthy[N]	32
Female; male	12;20
Age [years]	43 ± 15
Body mass index [kg/m^2]	23 ± 2.6
SpO_2 at rest [%]	99 ±1
Pulmonary vascular disease[N]	22
Chronic thromboembolic pulmonary hypertension[N]	11
Pulmonary arterial hypertension [N]	11
Female; male	8;14
Age [years]	61 ± 14
Body mass index [kg/m^2]	27.1 ± 6
SpO_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
Chronic obstructive pulmonary disease [N]	20
Female; male	11;9
Age [years]	65 ± 6
Body mass index [kg/m^2]	27.1 ± 6
SpO_2 at rest [%]	95 ±2
GOLD grade 1/2/3/4	4/11/4/1
FEV_1[%pred]	64 ±18
FCV[%pred]	107 ± 17
FEV_1/FVC	0.5 ± 0.1
Heart failure with preserved ejection fraction [N]	10
Female; male	5;5
Age [years]	60 ± 9
Body mass index [kg/m^2]	28 ± 6
SpO_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 [N]	7
Female; male	4;3
Age [years]	36 ± 9
Body mass index [kg/m^2]	23 ± 2
SpO_2 at rest [%]	87 ± 6
Corrective heart surgery in childhood [N]	3

Data are presented as means ± standard deviations or absolute numbers. SpO_2, oxygen saturation by pulse oximetry; GOLD, Global Initiative for chronic obstructive lung disease; FEV_1, forced expiratory volume in 1 second, FVC, forced vital capacity, LVEF, left ventricular ejection fraction

Table 2: Overall results ambient air vs hyperoxia – end-exercise and isotime

	Ambient air	***Hyperoxia***			
	end-exercise	**end-exercise**		**isotime**	
	mean	***mean***	***difference(95CI)***	***mean***	***difference(95%CI)***
IET Overall					
Work-rate [W]	155.4	167.8	12.4 (9.1/15.6)***	NA	NA
SpO_2 [%]	92.0	96.0	4.0 (3.2/5.4)***	97.0	4.0 (3.4/5.6)***
V'E [l/min]	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]	5.0	5.14	0.14 (-0.5/0.2)	NA	NA
$PaCO_2$ [kPa]	5.0	5.5	0.5 (0.3/0.7)***	NA	NA
PaO_2 [kPa]	9.6	30.9	21.3 (19.1/23.4)***	NA	NA
SaO_2 [%]	92.3	99.4	7.1 (5.4/8.9)***	NA	NA
Borg CR10 dysp. 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 [min:sec]	10:43	16:56	6.13(4:59/7:35)***	NA	NA
SpO_2 [%]	91.0	97.0	6.0 (4.3/6.9)***	96.0	5.0 (3.4/5.8)***
V'E [l/min]	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]	6.2	4.7	-1.5 (-2.2/-0.8)***	NA	NA
$PaCO_2$ [kPa]	5.0	5.3	0.3 (0.2/0.5)***	NA	NA
PaO_2 [kPa]	13.9	32.1	18.2 (15/21.5)***	NA	NA
SaO_2 [%]	90.1	99.7	9.6 (7.3/12)***	NA	NA
Borg CR10 dysp. 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 limb/upper limb). ***, p<0.001; **, p=0.01; *, p=0.05. NA, not available. SpO_2, oxygenation by pulse oximetry; V'E, minute ventilation; $V'E/V'CO_2$, ventilatory equvalent for CO_2, $PaCO_2$, PaO_2, arterial partial pressure for CO_2 and O_2, SaO_2, arterial oxygen saturation.

Table 3: Changes with ambient air vs hyperoxia for all disease groups are shown at end-exercise

End-Exercise	*mean differences (95CI) 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)
SpO_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]	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]	NA	0.5 (-0.1/1.2)	0.2 (-0.6/0.6)	-0.5 (-1.2/0.3)	NA
$PaCO_2$ [kPa]	NA	0.7 (0.4/1)***	0.5 (0.2/0.7)**	0.3 (-0.3/0.8)	NA
PaO_2 [kPa]	NA	23.3(20.1/26.5)***	22.1 (20.6/23.6)***	15.7(8.6/22.8)***	NA
SaO_2 [%]	NA	9.0 (5.9/13.2)***	6.6(5.1/8)***	3.3 (0.9/5.7)*	NA
Borg CR10 dysp. 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)
SpO_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]	-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]	NA	-1.8 (-3.5/0.04)	-1.5 (-2.2/-0.9)***	-0.7 (-1.8/0.4)	NA
$PaCO_2$ [kPa]	NA	0.7 (-0.03/0.9)	0.5 (0.3/0.7)***	0.25 (-0.1/0.6)	NA
PaO_2 [kPa]	NA	22.0 (16.6/27.6)***	23.1 (21.5/24.7)***	23.4 (19.2/27.6)**	NA
SaO_2 [%]	NA	11.7 (8.3/15)***	9.7 (5.6/13.8)***	6.1 (3/9.2)**	NA
Borg CR10 dysp. 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. ***, p<0.001; **, p=0.01; *, p=0.05. 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. SpO_2, oxygenation by

pulse oximetry; V'E, minute ventilation; V'E/V'CO_2, ventilatory equivalent for CO_2, $PaCO_2$, PaO_2, arterial partial pressure for CO_2 and O_2, SaO_2, arterial oxygen saturation.

Table 4:

Changes with ambient air vs hyperoxia for all disease groups are shown at isotime

Isotime	*mean differences (95CI) with hyperoxia*				
	Healthy	***PVD***	***COPD***	***HFpEF***	***CHD***
IET					
SpO_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]	-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					
SpO_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]	-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. ***, p<0.001; **, p=0.01; *, p=0.05. 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. SpO_2, oxygenation by pulse oximetry; V'E, minute ventilation; V'E/V'CO_2, ventilatory equivalent for CO_2, $PaCO_2$, PaO_2, arterial partial pressure for CO_2 and O_2, SaO_2, arterial oxygen saturation.

REFERENCES

1. Amann, M. and J.A. Calbet, *Convective oxygen transport and fatigue.* J Appl Physiol (1985), 2008. **104**(3): p. 861-70.
2. Noakes, T.D., J.E. Peltonen, and H.K. Rusko, *Evidence that a central governor regulates exercise performance during acute hypoxia and hyperoxia.* J Exp Biol, 2001. **204**(Pt 18): p. 3225-34.
3. Sperlich, B., et al., *The Impact of Hyperoxia on Human Performance and Recovery.* Sports Med, 2017. **47**(3): p. 429-438.
4. Yan, Z. and H.R. Spaulding, *Extracellular superoxide dismutase, a molecular transducer of health benefits of exercise.* Redox Biol, 2020. **32**: p. 101508.
5. Prieur, F., et al., *Effects of moderate hyperoxia on oxygen consumption during submaximal and maximal exercise.* Eur J Appl Physiol, 2002. **88**(3): p. 235-42.
6. Amann, M., et al., *Arterial oxygenation influences central motor output and exercise performance via effects on peripheral locomotor muscle fatigue in humans.* J Physiol, 2006. **575**(Pt 3): p. 937-52.
7. Oussaidene, K., et al., *Cerebral oxygenation during hyperoxia-induced increase in exercise tolerance for untrained men.* Eur J Appl Physiol, 2013. **113**(8): p. 2047-56.
8. Wilkerson, D.P., N.J. Berger, and A.M. Jones, *Influence of hyperoxia on pulmonary O2 uptake kinetics following the onset of exercise in humans.* Respir Physiol Neurobiol, 2006. **153**(1): p. 92-106.
9. Safdar, B. and A.A. Mangi, *Survival of the Fittest: Impact of Cardiorespiratory Fitness on Outcomes in Men and Women with Cardiovascular Disease.* Clin Ther, 2020. **42**(3): p. 385-392.
10. Kaminsky, L.A., et al., *Cardiorespiratory fitness and cardiovascular disease - The past, present, and future.* Prog Cardiovasc Dis, 2019. **62**(2): p. 86-93.
11. Grunig, E., 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**(23): p. 2284-2295.
12. Galie, N., 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**(1): p. 67-119.
13. Hasler, E.D., 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**(3): p. 213-224.
14. Ulrich, 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**(15): p. 1159-1168.
15. Ulrich, S., et al., *Mechanisms of Improved Exercise Performance under Hyperoxia.* Respiration, 2017. **93**(2): p. 90-98.
16. Muller, J., 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**: p. 692029.
17. Saxer, S., et al., *Effect of oxygen therapy on exercise performance in patients with cyanotic congenital heart disease: Randomized-controlled trial.* Int J Cardiol, 2022. **348**: p. 65-72.
18. Ponikowski, P., et al., *2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.* Rev Esp Cardiol (Engl Ed), 2016. **69**(12): p. 1167.
19. Ulrich, S., S.R. Schneider, and K.E. Bloch, *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**(6): p. 1657-1670.

20. Subudhi, A.W., A.C. Dimmen, and R.C. Roach, *Effects of acute hypoxia on cerebral and muscle oxygenation during incremental exercise.* J Appl Physiol (1985), 2007. **103**(1): p. 177-83.
21. Ulrich, S., et al., *Cerebral Oxygenation in Patients With OSA: Effects of Hypoxia at Altitude and Impact of Acetazolamide.* Chest, 2014. **146**(2): p. 299-308.
22. Muller-Mottet, S., et al., *Effects of Exercise and Vasodilators on Cerebral Tissue Oxygenation in Pulmonary Hypertension.* Lung, 2014.
23. Ferreira, E.V., et al., *Optimizing the evaluation of excess exercise ventilation for prognosis assessment in pulmonary arterial hypertension.* Eur J Prev Cardiol, 2014. **21**(11): p. 1409-19.
24. Megaritis, D., P.D. Wagner, and I. Vogiatzis, *Ergogenic value of oxygen supplementation in chronic obstructive pulmonary disease.* Intern Emerg Med, 2022. **17**(5): p. 1277-1286.
25. Li, Y., et al., *Hyperoxia affects the regional pulmonary ventilation/perfusion ratio: an electrical impedance tomography study.* Acta Anaesthesiol Scand, 2014. **58**(6): p. 716-25.
26. Carta, A.F., et al., *The Impact of Breathing Hypoxic Gas and Oxygen on Pulmonary Hemodynamics in Patients With Pulmonary Hypertension.* Front Med (Lausanne), 2022. **9**: p. 791423.
27. Wunderlich, T., et al., *Influence of hyperoxia on diastolic myocardial and arterial endothelial function.* Undersea Hyperb Med, 2017. **44**(6): p. 521-533.
28. Wensel, R., et al., *Impaired cardiac autonomic control relates to disease severity in pulmonary hypertension.* Eur Respir J, 2009. **34**(4): p. 895-901.
29. Cardinale, D.A. and B. Ekblom, *Hyperoxia for performance and training.* J Sports Sci, 2018. **36**(13): p. 1515-1522.
30. Kane, D.A., *Lactate oxidation at the mitochondria: a lactate-malate-aspartate shuttle at work.* Front Neurosci, 2014. **8**: p. 366.
31. Stellingwerff, T., et al., *Hyperoxia decreases muscle glycogenolysis, lactate production, and lactate efflux during steady-state exercise.* Am J Physiol Endocrinol Metab, 2006. **290**(6): p. E1180-90.
32. Nonoyama, M., et al., *Oxygen therapy during exercise training in chronic obstructive pulmonary disease.* Cochrane Database of Systematic Reviews, 2007(2).
33. Fujimoto, K., et al., *Benefits of oxygen on exercise performance and pulmonary hemodynamics in patients with COPD with mild hypoxemia.* Chest, 2002. **122**(2): p. 457-63.
34. Liu, Y. and F. Gong, *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**(5): p. 4081-4089.
35. Alison, J.A., et al., *Oxygen compared to air during exercise training in COPD with exercise-induced desaturation.* Eur Respir J, 2019. **53**(5).
36. Boutou, A.K., 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**: p. 103677.
37. Puhan, M.A., et al., *The minimal important difference of exercise tests in severe COPD.* Eur Respir J, 2011. **37**(4): p. 784-90.
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**(1): p. 131-6.
39. Mallette, M.M., D.G. Stewart, and S.S. Cheung, *The Effects of Hyperoxia on Sea-Level Exercise Performance, Training, and Recovery: A Meta-Analysis.* Sports Med, 2018. **48**(1): p. 153-175.
40. Mereles, D., et al., *Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension.* Circulation, 2006. **114**(14): p. 1482-9.
41. Ulrich, S., 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**(10): p. 615-23.

42. Ulrich, S., 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**(2).

FIGURE LEGENDS

Figure 1: Changes with ambient air vs hyperoxia in the cycling incremental ramp (a) exercise and constant work-rate (b) exercise test are shown

Improvements of incremental exercise tests (a, blue boxes) and constant work-rate exercise tests (b, red circles) 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*

Figure 2. Changes of the secondary outcomes at end-exercise with hyperoxia

Improvements of incremental exercise tests (blue boxes) and constant work-rate exercise tests (red circles) 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. SpO2, arterial oxygenation by pulse oximetry; VE, ventilation; HR, heart rate; VE/VCO2, ventilatory equivalent for carbon dioxide.*

Figure 3. Changes of arterial blood gas analysis at end-exercise with hyperoxia

Improvements of incremental exercise tests (blue boxes) and constant work-rate exercise tests (red circles) in tests with hyperoxia at end-exercise by subgroups (not available for healthy and CHD). 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 aBGA 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. SaO_2, arterial oxygen saturation; PaCO2, partial pressure of oxygen; PaO2, partial pressure of carbon dioxide.*

Figure 4. Changes of the secondary outcomes at isotime with hyperoxia

Improvements of incremental exercise tests (blue boxes) and constant work-rate exercise tests (red circles) in tests 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. SpO2, arterial oxygenation by pulse oximetry; VE, ventilation; HR, heart rate; VE/VCO2, ventilatory equivalent for carbon dioxide.*

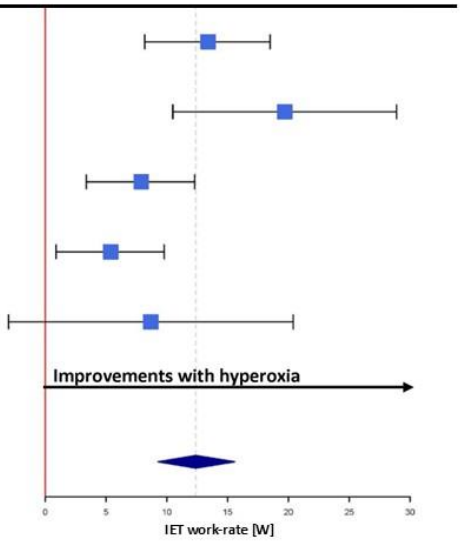
ACKNOWLEDGEMENTS:

Authors' contribution: SU, ML, SS, EDH, EIS, KEB contributed to the conception and design. JM, ML, EDH, KEB, PA, MB, SRS, EIS and SU contributed to acquisition, analysis, or interpretation of data. JM, ML and SU 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.

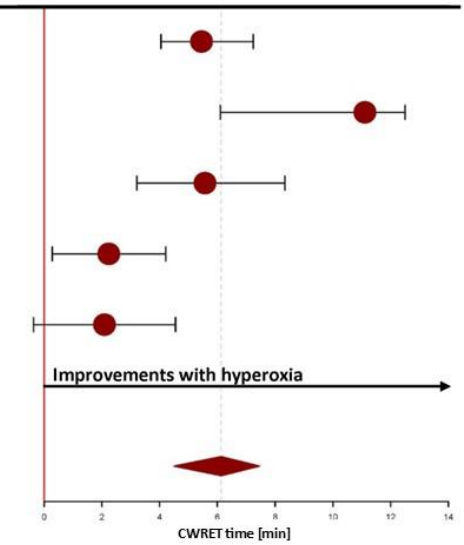
a. Incremental exercise test [watts]

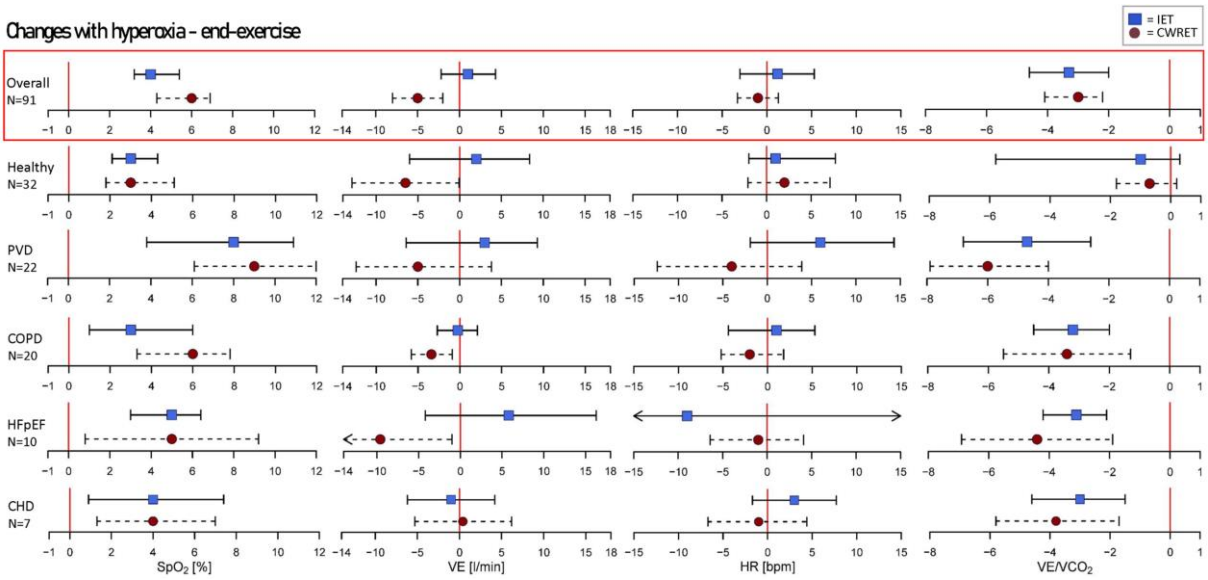
Group	Hyperoxia	Ambient-air	Mean Difference
Healthy (N=32)	270.3	256.9	13.4
PVD (N=22)	132.3	112.6	19.7
COPD (N=20)	103.6	95.7	7.9
HFpEF (N=10)	98.9	93.5	5.4
CHD (N=7)	94	85.3	8.7
Overall (N=91)			**12.4 W**

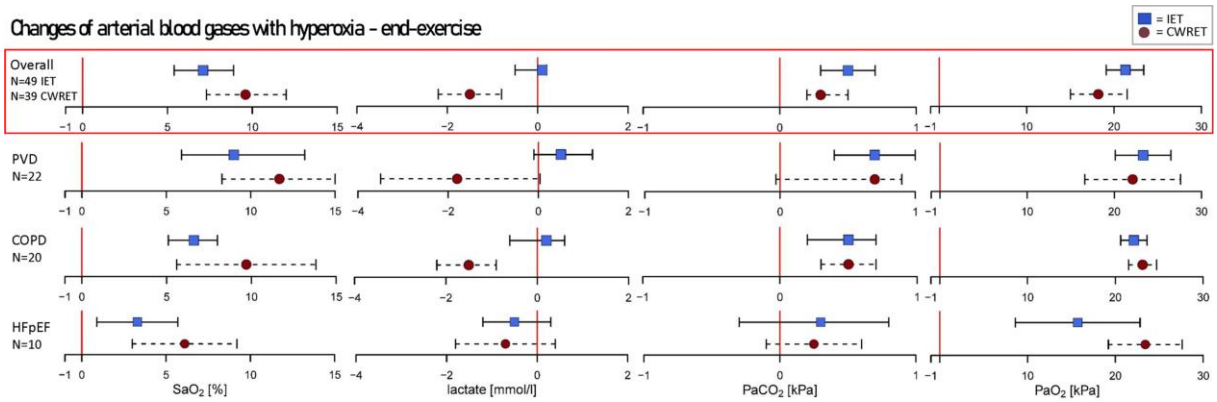


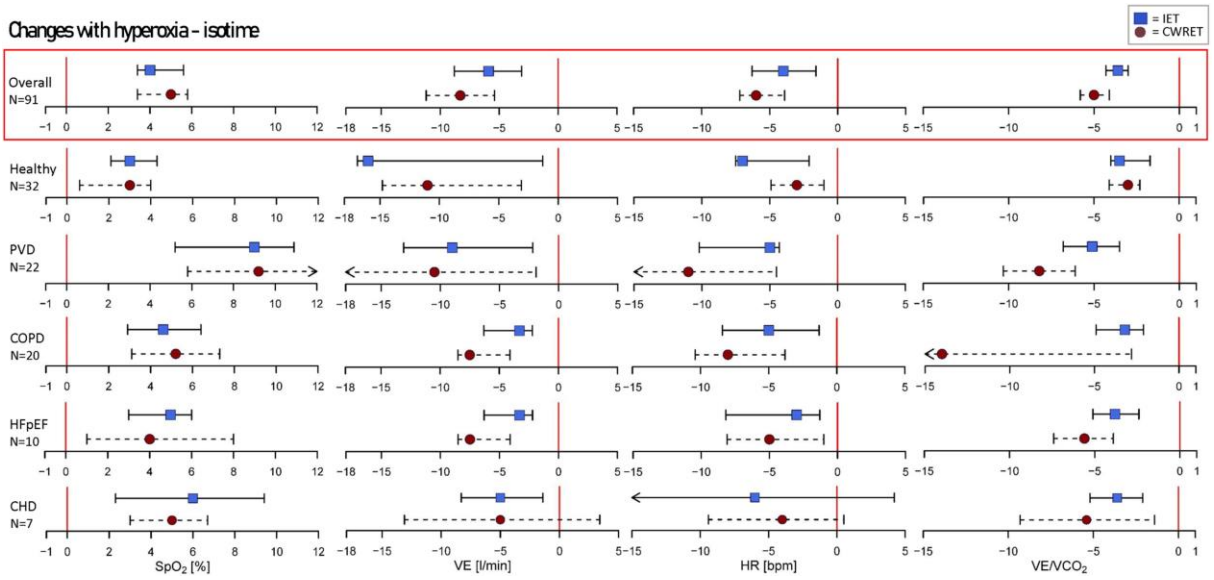
b. Constant work rate exercise test [minutes]

Group	Hyperoxia	Ambient-air	Mean Difference
Healthy (N=32)	18:48	13:04	5:45
PVD (N=22)	20:42	9:31	11:11
COPD (N=20)	16:03	10:05	5:57
HFpEF (N=10)	11:22	7:58	2:24
CHD (N=7)	10:46	8:37	2:09
Overall (N=91)			**6:13 min**




Changes with hyperoxia - end-exercise
= IET
= CWRET
Overall
N=91
Healthy
N=32
PVD
N=22
COPD
N=20
HFpEF
N=10
CHD
N=7
SpO2 [%]
VE [l/min]
HR [bpm]
VE/VCO2


Changes of arterial blood gases with hyperoxia - end-exercise
= IET
= CWRET
Overall
N=49 IET
N=39 CWRET
PVD
N=22
COPD
N=20
HFpEF
N=10
−1 0 5 10 15
−4 −2 0 2
−1 0 1
−1 10 20 30
SaO2 [%]
lactate [mmol/l]
PaCO2 [kPa]
PaO2 [kPa]


Changes with hyperoxia - isotime
= IET
= CWRET
Overall
N=91
Healthy
N=32
PVD
N=22
COPD
N=20
HFpEF
N=10
CHD
N=7
SpO2 [%]
VE [l/min]
HR [bpm]
VE/VCO2