Effect of oxygen therapy on exercise performance in patients with cyanotic congenital heart disease: Randomized-controlled trial

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Abstract: Background: Patients with unrepaired cyanotic congenital heart disease (CHD) suffer from aggravated hypoxemia during exercise. We tested the hypothesis that supplemental oxygen improves exercise performance in these patients. Methods: In this randomized, sham-controlled, single-blind, cross-over trial cyanotic CHD-patients underwent four cycle exercise tests to exhaustion, while breathing either oxygen-enriched (FiO2 0.50, oxygen) or ambient air (FiO2 0.21, air) using incremental (IET) or constant work-rate (CWRET) exercise test protocols (75% of maximal work rate achieved under FiO2 0.21). Pulmonary gas-exchange, electrocardiogram, arterial blood gases, oxygen saturation (SpO2), cerebral and quadriceps muscle tissue oxygenation (CTO and QMTO) by near-infrared spectroscopy were measured. Results: We included seven patients with cyanotic CHD (4 Eisenmenger syndrome, 3 unrepaired cyanotic defects, 4 women) median (quartiles) age 36 (32;50) years, BMI 23 (20;26) kg/m2 and SpO2 at rest 87 (83;89) %. When comparing supplemental oxygen with air during exercise, maximal work-rate in IET increased from 76 (58;114) Watts to 83 (67;136) Watts, median difference 9 (0;22) W (p = 0.046) and CWRET-time increased from 412 s (325;490) to 468 s (415;553), median increase 56 (39;126) s (p = 0.018). In both IET and CWRET SpO2 was significantly higher and ventilatory equivalent for carbon dioxide significantly lower at end-exercise with oxygen compared to air, whereas CTO and QMTO did not significantly differ. Conclusions: Patients with cyanotic CHD significantly improved their exercise performance, in terms of maximal work-rate and endurance time along with an improved arterial oxygenation and ventilatory efficiency with supplemental oxygen compared to air. Keywords: Cyanotic congenital heart disease; Eisenmenger; Exercise performance; Oxygen; Oxygen therapy; Pulmonary hypertension.

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Effect of oxygen therapy on exercise performance in patients with cyanotic congenital heart disease: Randomized-controlled trial

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\textbf{ABSTRACT}

\textbf{Background:} Patients with unrepaired cyanotic congenital heart disease (CHD) suffer from aggravated hypoxemia during exercise. We tested the hypothesis that supplemental oxygen improves exercise performance in these patients.

\textbf{Methods:} In this randomized, sham-controlled, single-blind, cross-over trial cyanotic CHD-patients underwent four cycle exercise tests to exhaustion, while breathing either oxygen-enriched (FiO\textsubscript{2} 0.50, oxygen) or ambient air (FiO\textsubscript{2} 0.21, air) using incremental (IET) or constant work-rate (CWRET) exercise test protocols (75\% of maximal work rate achieved under FiO\textsubscript{2} 0.21). Pulmonary gas-exchange, electrocardiogram, arterial blood gases, oxygen saturation (SpO\textsubscript{2}), cerebral and quadriceps muscle tissue oxygenation (CTO and QMTO) by near-infrared spectroscopy were measured.

\textbf{Results:} We included seven patients with cyanotic CHD (4 Eisenmenger syndrome, 3 unrepaired cyanotic defects, 4 women) median (quartiles) age 36 (32;50) years, BMI 23 (20;26) kg/m\textsuperscript{2} and SpO\textsubscript{2} at rest 87 (83;89) \%. When comparing supplemental oxygen with air during exercise, maximal work-rate in IET increased from 76 (58;114) Watts to 83 (67;136) Watts, median difference 9 (0;22) W (p = 0.046) and CWRET-time increased from 412 s (325;490) to 468 s (415;553), median increase 56 (39;126) s (p = 0.018). In both IET and CWRET SpO\textsubscript{2} was significantly higher and ventilatory equivalent for carbon dioxide significantly lower at end-exercise with oxygen compared to air, whereas CTO and QMTO did not significantly differ.

\textbf{Conclusions:} Patients with cyanotic CHD significantly improved their exercise performance, in terms of maximal work-rate and endurance time along with an improved arterial oxygenation and ventilatory efficiency with supplemental oxygen compared to air.

1. Introduction

Congenital heart disease (CHD) is the most common congenital disease, with a prevalence of eight per 1000 live births \cite{1}. Most patients affected by complex defects are cyanotic at birth. Without intervention, most of these patients die in early childhood and only few survive to adulthood \cite{2}. In contemporary cohorts, adult survivors with cyanotic heart disease thus comprise a small proportion (<5\%) of all adults with CHD \cite{3}. This includes patients with cyanotic heart defects without or with incomplete cardiac repair and patients with Eisenmenger syndrome as late sequelae of an unoperated shunt lesions. These patients have the highest morbidity and risk for early mortality as young adults and experience most severe limitations of exercise capacity among all CHD-patients \cite{4–6}.

Beneficial effects of regular exercise in patients with acquired heart disease, such as coronary artery disease, valvular or hypertensive heart
disease, are well established [7]. Regular physical exercise is thus recommended in the current guidelines [8]. Patients with cyanotic CHD show lowest exercise performance compared to healthy controls along with lower peak oxygen uptake (V′O2) among all patients with CHD [6,9]. Oxygen desaturation is known to be a major determinant of exercise intolerance in adults with CHD. Whether supplemental oxygen may improve exercise capacity in this patient group is unknown.

Due to the insufficient understanding of exercise limitation in complex heart abnormalities and the presence of very few studies, the current guidelines do not recommend special rehabilitation programs for cyanotic CHD with or without PAH [10,11]. Nevertheless, exercise therapy has been shown to be an effective adjunct to pharmacological therapies in patients with PAH-CHD, in terms of improved exercise capacity and quality of life [11].

One of the most common forms of cyanotic CHD in adult patient is the Eisenmenger syndrome defined as irreversible pulmonary arterial hypertension with shunt reversal and progressive cyanosis as a late sequelae of congenital shunt lesions. The current guidelines for the management in adults with cyanotic CHD support oxygen supplementation for symptom improvement, but not to target higher SpO2 or enhance exercise performance [12]. There are no recommendations for oxygen supplementation during exercise [12]. In a small, underpowered pilot trial in 23 patients with Eisenmenger syndrome, nocturnal oxygen therapy given for 8 h/night during a mean period of 19.8 months revealed no difference in survival, symptoms or six-minute walking distance [13].

Despite the right-left shunt in cyanotic CHD, arterial oxygen saturation increases from 81 to 88% as shown in 29 patients receiving oxygen (FiO2 0.4) for a duration of ten minutes at rest, which indicates the potential of oxygen therapy to increase systemic arterial oxygenation also in cyanotic CHD [14]. Whether oxygen therapy given during exercise would increase exercise performance in patients with PAH associated with cyanotic CHD or un repaired cyanotic defects without PAH is not known so far.

Therefore, the aim of the current study is to test whether short-term oxygen therapy has an effect on exercise performance in patients with cyanotic CHD (with and without PAH).

2. Methods

2.1. Design

This randomized, sham-controlled, single-blinded, cross-over trial compares two consecutive test sequences to evaluate effect of short-term oxygen therapy on exercise performance in patients with PAH-CHD or un repaired cyanotic defects without PAH. The study was approved by the cantonal Ethics Board of Zurich (KEK 2012–2051) and registered at clinicaltrials.gov (NCT04076501). All included patients provided written informed consent to participate in the trial.

2.2. Patients

Adults (>18 years) with cyanotic CHD with or without PAH, followed by a multi-disciplinary team for adults with CHD at the University Hospital of Zurich (Switzerland) where approached by their treating physician for participation in the study. Patients were eligible, when they had a stable health status with stable medications in the last four weeks prior to the study. Pregnant women, patients with new medication or unstable condition during the last 4 weeks or patients with clinically relevant comorbidities were excluded.

2.3. Interventions

The participants were instructed to avoid heavy physical activity, heavy meals and caffeinated drinks four hours before the testing. Patients performed four cardiopulmonary exercise tests (CPET) on a cycle ergometer in randomized sequences, which took place on two different days as previously described [15–17]. The first two tests were incremental exercise tests (IET) with a ramp protocol to exhaustion performed sequentially under oxygen enriched air (oxygen, FiO2 0.5) or ambient air (air, FiO2 0.21) according to randomization. After the first test participants had a two-hour break before the second test (Fig. 1). They breathed through a mask, connected to the flow sensor of a metabolic unit (Ergostick, Geratherm Medical, Gschwend, Germany) and a two-way valve (Hans Rudolph, Shawnee, USA). The inlet of the valve was connected to a gas-mixing device set to provide air or oxygen-enriched air (Altitrainer, Nyon, Switzerland). After a two-minute phase of unloaded pedalling, the load was increased by 10 or 15 watts/min to achieve a maximum test duration of 8–12 min [18]. Participants were required to maintain a cadence of 60 rpm . The test was stopped if the patient was not able to pedal with >55 rpm, the blood pressure was over 220/120 mm Hg, the patient felt uncomfortable or the physician in attendance noticed other signs requiring discontinuation of exercise (e. g. on ECG). At the end of the test, subjects evaluated their subjective exhaustion using the Borg-CR10 scale for dyspnoea and leg discomfort. On the second visit day, the study participants performed two constant work-rate exercise test (CWRET) at 75% of individual maximal work rate achieved under air during IET sequentially under oxygen-enriched resp. air according to randomization. Both CWRET were completed under the same test conditions and up to maximum exhaustion. For the safety of the patient, a physician was present at each test.

2.4. Assessments

Assessments used in this study were identical with those in previous studies [15,17,19] including medical history, clinical examinations, functional capacity assessed by the New York Heart Association functional class (NYHA), spirometry and arterial blood gas analysis at rest and peak exercise.

During CPET, breath-by-breath values for minute ventilation (V′E), breath rate, tidal volume, carbon dioxide output (V′CO2), oxygen uptake (V′O2) were recorded. Oxygen uptake was not analyzed, as the accuracy of the O2-Sensor outside of the calibration range could not be verified [15]. Heart rate was derived from a 12-lead ECG, blood pressure (BP) by automated arm-cuff measurements and finger pulse oximetry as well as regional brain tissue (CTO) and quadriceps muscle oxygenation (MTO) were monitored by near-infrared spectroscopy (NIRS, Hamamatsu, NIRO-200NX, Shizuoka, Japan).

2.5. Outcomes

Primary outcomes were the changes in maximal exercise capacity during IET (Wmax) and the changes in maximal exercise duration in CWERT (Tmax) induced by oxygen-enriched vs air. Secondary outcomes are changes in symptoms, oxygen saturation (SpO2), CTO and MTO, heart rate, breath reserve (BR), tidal volume (VT), breathing frequency (BF), VE, V′CO2 output and arterial blood gases.

2.6. Sample size

According to the current literature on patients with respiratory disorders, the minimal clinical important difference of Wmax is 4 ± 1 W [20,21]. Sample size estimation for cross-over with above assumptions and a desired power of 0.8 and 0.05% significance level revealed that seven subjects will be needed, to account also for dropouts. The minimum relevant difference for the CWERT is 1.75 min [22], which would also result in a required number of six subjects.

2.7. Randomisation and blinding

A computer-simulated block randomization was performed. Subjects were blinded to whether they were tested under air or oxygen. After the tests, subjects were asked to whether they believed to have performed
the test under oxygen or air.

2.8. Data analysis and statistics

Data is presented as median and quartiles. Differences at end-exercise and isotime between oxygen and air are presented as median differences and 95% confidence interval. As data was skewed in the included population, Wilcoxon test for nonparametric data was used for comparison of test with and without supplemental oxygen. All patients underwent all tests and therefore we had no missing data of the primary endpoints and the intention-to-treat and per protocol analysis is the same. Data from IET during both incremental tests were compared by calculating mean over successive fractions of maximal exercise time during air, i.e. over the periods from 1 to 10%, 11-20%, etc., up to 91-100% exercise time under air, and over identical time periods in tests with oxygen. Resting and exercise values were averaged over 30s. Data from CWRET in oxygen and air were compared at end-exercise and at isotime. Isotime refers to the time under oxygen that corresponds to the time of end-exercise under air. A significance level of \( p < 0.05 \) is assumed. SPSS was used for statistical analysis (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

3. Results

3.1. Patients

Seven patients with PAH-CHD were included in the study and participated between October 2019 and February 2020. Patients had a median age of 36 (32; 50) years, all had cyanotic CHD, 4/7 had pulmonary arterial hypertension, body mass index was 23 (21; 26) kg/m\(^2\), FEV\(_1\) 68 (56; 74) % predicted, tricuspid regurgitation pressure gradient 91 (72;111) mm Hg and resting SpO\(_2\) was 87 (83;89) %. Two patients were in NYHA functional class I, three in NYHA II and two in NYHA III. The patient flow is shown in Fig. 1 and patient characteristics are shown in Table 1. All patients completed all tests according to protocol.
### Table 1
Patient characteristics.

| Characteristic                                      | Value |
|-----------------------------------------------------|-------|
| Number of participants (female)                     | 7 (4) |
| Age, years                                          | 36 (32; 50) |
| Diagnosis, n (%)                                     | 4 (57) |
| Ventricular septal defect                           | 4 (57) |
| Atrial septal defect                                 | 3 (43) |
| Aortopulmonary window                               | 1 (14) |
| Patent ductus arteriosial                            | 1 (14) |
| Complex                                             | 4 (57) |
| Correction surgery in childhood                      | 3 (43) |
| Pulmonary arterial hypertension in congenital heart disease | 4 (57) |
| NYHA functional class I/II/III/IV                    | 2/3/2/0 |
| Body mass index, kg/m²                               | 23 (21; 26) |
| 6-min walking distance, m (n = 4)                   | 602 (530; 647) |
| Oxygen saturation at rest, %                         | 87 (82; 99) |
| Oxygen saturation at end of 6-min walk test, %       | 69 (65; 77) |
| NT-proBNP, ng/L                                     | 530 (217; 815) |
| Hemoglobin concentration, g/L                       | 181 (165; 222) |
| Ferritin, μg/L                                      | 145 (65; 164) |
| Echocardiography                                    |       |
| Tricuspid regurgitation pressure gradient*, mm Hg    | 91 (72; 111) |
| Right ventricular fractional area change, %         | 36 (30; 39) |
| Tricuspid annular plane systolic excursion, mm       | 15 (13; 17) |
| Tissue Doppler right ventricular wall systolic, cm/s | 9 (8; 11) |
| Left ventricular ejection fraction, %               | 66 (58; 76) |
| Left ventricular dilation, %                        | 69 (42; 69) |
| Left ventricular end-diastolic dimension, %         | 68 (37; 68) |
| Lung function                                        |       |
| FEV₁, %predicted                                    | 68 (56; 74) |
| FVC, % predicted                                    | 70 (57; 77) |
| FEV₁/FVC                                            | 91(87; 101) |
| Medication, n (%)                                    |       |
| Anticoagulants                                      | 5 (71) |
| Diuretics                                           | 5 (41) |
| PAH-targeted therapy                                 |       |
| Endothelin receptor antagonists                      | 3 (43) |
| PDE-5 inhibitors                                    | 4 (57) |
| Combination therapy                                  | 3 (43) |
| Ramp watt increase per min, n                        |       |
| 10/15 W/min                                         | 4 (57) / 3 (43) |

Data are presented as median (IQR) or number (%). NYHA, New York Heart Association functional class; *, only measurable in three patients; FEV₁, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; NT-proBNP, N-terminal pro-brain natriuretic peptide; PaO₂, arterial partial pressure of oxygen; PaCO₂ partial pressure of carbon dioxide.

### Table 2
Incremental exercise test ambient air vs oxygen.

|                      | Ambient air (FiO₂ 0.21) at end-exercise | Oxygen (FiO₂ 0.5) |
|----------------------|----------------------------------------|------------------|
|                      | Isotonic to end-exercise | p-Value (change vs. ambient air) | End-exercise | p-Value (change vs. ambient air) |
| Maximal Work rate, W | 76 (58; 114) | 76 (58; 114) | − | 83 (67; 136) | 0.046* |
| Heart rate, bpm      | 152 (106; 162) | 131 (92; 167) | 0.917 | 152 (90; 169) | 0.249 |
| Heart rate reserve, bpm | 27 (20; 76) | 45 (13; 77) | 0.612 | 18 (8; 91) | 0.310 |
| Minute ventilation (VE), L/min | 44 (34; 53) | 37 (26; 50) | 0.310 | 40 (25; 62) | 0.735 |
| Breathing reserve, % MVV | 42 (28; 52) | 42 (25; 64) | 0.237 | 41 (24; 64) | 0.612 |
| Tidal volume, L.      | 1.4 (1.1; 2.1) | 1.2 (1.1; 1.7) | 0.128 | 1.3 (1.1; 1.7) | 0.237 |
| Breathing frequency, 1/min | 32 (19; 42) | 29 (17; 38) | 0.398 | 33 (16; 40) | 0.398 |
| Carbon dioxide output (V′CO₂) L/min | 0.9 (0.8; 1.1) | 0.8 (0.7;1.3) | 0.612 | 0.9 (0.7; 1.4) | 0.310 |
| V′E/V′CO₂ | 40 (38; 47) | 37 (34; 45) | 0.018* | 38 (34; 45) | 0.018* |
| V′E/V′CO₂ slope | 44.2 (39.4; 48.0) | NA | NA | 38.2 (32.7; 48.0) | 0.128 |
| PetCO₂, mm Hg         | 27 (23; 30) | 29 (24; 31) | 0.018* | 29 (24; 31) | 0.018* |
| Oxygen saturation by pulseoximetry, %               | 76 (72; 82) | 86 (76; 88) | 0.018* | 85 (76; 87) | 0.018* |
| Cerebral tissue oxygenation, %                        | 62 (58; 67) | 65 (62; 68) | 0.310 | 67 (61; 67) | 0.237 |
| Quadriceps muscle tissue oxygenation, %              | 59 (54; 72) | 61 (56; 70) | 0.237 | 60 (53; 70) | 0.499 |
| Borg CR10 dyspnea | 8 (7; 9) | NA | − | 8 (7; 9) | 0.581 |
| Borg CR10 fatigue | 7 (6; 8) | NA | − | 6 (5; 7) | 0.037* |

Data are presented as median (quartiles), p-values were calculated with Wilcoxon-Test for non-parametrical data. V′E/V′CO₂, ventilatory equivalent for carbon dioxide; PetCO₂, end-tidal carbon dioxide; PaO₂, Arterial partial pressure of O₂; PaCO₂, partial pressure of CO₂.
4. Discussion

This first randomized, placebo-controlled, single-blind, cross-over trial performed in patients with cyanotic CHD showed that oxygen-enriched air significantly improved cycle exercise performance in terms of $W_{\text{max}}$ in IET and endurance time in a CWRET protocol compared to air. The improvements whilst breathing oxygen-enriched air were associated with a higher $\text{SpO}_2$, an improved ventilatory efficiency and less perceived leg fatigue compared to exercise under air.

The improved exercise capacity in patients with cyanotic CHD whilst breathing oxygen-enriched air vs. air found in our study during IET are not only novel, but with an increase of $+9$ W also clinically relevant, as a difference of $4 \pm 1$ W was defined as minimal important difference [20,21]. The current cyanotic CHD-patients had a lower $W_{\text{max}}$ (air 76 (58;114)W; oxygen: 83(67;136)W, compared to a previous study where adults with different CHD (coarctation of the aorta, tetralogy of Fallot, dextro-transposition of the great arteries and patients with uni-ventricular heart) performed 142-235 W. However, our collective was older and all had cyanotic CHD [9].

The improvements in CWRET cycling time was also significant, but with 56 s (39;126) a bit lower than the minimal important difference suggested for patients with COPD 75 s (range 46–105 s) [23], however, the clinically relevant difference for CHD is not known. In line with the present study, we also found improved exercise performance with oxygen-enriched vs. air in patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension (PAH/CTEPH, summarized as PH), in whom improvements were even more pronounced [15]. The presently investigated patients with cyanotic CHD revealed a higher $\text{SpO}_2$ over the entire duration of IET ($\text{SpO}_2$) and CWRET with oxygen vs. air. Although $\text{PaO}_2$, $\text{SaO}_2$ were higher at end-exercise with oxygen, the difference to air was not statistically significant, most likely related to the small sample size as an arterial blood sample could not be obtained in all participants at end-exercise.

Oxygen was not associated with significant changes in heart rate neither at isotime nor at end-exercise compared to air in the presently investigated patients with PAH-CHD. However, participants were able to increase their exercise performance with the same maximal heart rate consistent with an enhanced oxygen delivery promoted by oxygen supplementation.

The improvement in exercise performance was not associated with a significantly reduced respiratory rate or minute ventilation, but with a lower $\text{VE}/\text{VCO}_2$ at isotime and end-exercise during both IET and

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**Fig. 2.** Changes in physiological variables during incremental ramp exercise from rest (represented by “0”) to end-exercise (“$\text{max}$”). The circles (black = ambient air, white = oxygen-enriched air) represent medians over successive 10% fractions of maximal exercise duration individually achieved with ambient air and over identical time periods in tests with oxygen, i.e., 1–10% (“5”), 11–20% (“15”), etc., up to 91–100% (“95”) of total exercise duration with ambient air. The last values (“$\text{max}$”) represent medians over the final 30 s at end-exercise. $\text{SpO}_2$: oxygen saturation; MTO: muscle tissue oxygenation; VE: minute ventilation; CTO: cerebral tissue oxygenation; $\text{VE}/\text{VCO}_2$: ventilatory equivalent for carbon dioxide. * $p < 0.05$ for oxygen-enriched versus ambient air.
Table 3
Constant work rate exercise test with ambient air vs. oxygen.

|                           | Ambient air (FiO₂ 0.21) at end-exercise | Oxygen (FiO₂ 0.5) | p-Value (difference to ambient air) | End-exercise | p-Value (difference to ambient air) |
|---------------------------|----------------------------------------|------------------|-------------------------------------|--------------|-------------------------------------|
| Exercise duration, s      | 412 (325; 490)                         | 412 (325; 490)   | NA                                  | 468 (415; 553) | 0.018*                             |
| Work rate, watts          | 58 (45; 85)                            | 58 (45; 85)      | NA                                  | 58 (45; 85)  | NA                                 |
| Heart rate, bpm           | 153 (113; 168)                         | 115 (90; 158)    | 0.075                               | 155 (113; 160) | 0.600                             |
| Heart rate reserve, bpm   | 51 (8; 77)                             | 50 (18; 79)      | 0.141                               | 37 (16; 71)  | 0.917                             |
| Minute Ventilation (VE), L/min | 34 (19; 62) | 34 (20; 52) | 0.235                               | 35 (25; 54)  | 0.588                             |
| Breathing reserve, % MVV  | 65 (46; 84)                            | 75 (51; 80)      | 0.249                               | 71 (49; 78)  | 0.686                             |
| Tidal volume, L           | 1.1 (0.7; 1.8)                         | 1.4 (0.7; 1.9)   | 0.612                               | 1.3 (0.8; 1.8) | 0.753                             |
| Breathing frequency, 1/min| 32 (19; 47)                            | 28 (20; 33)      | 0.088                               | 29 (19; 47)  | 0.066                             |
| Carbon dioxide output (VCO₂, L/min) | 0.8 (0.3; 1.3) | 0.9 (0.5; 1.2) | 0.725                               | 0.9 (0.6; 1.3) | 0.463                             |
| V′E/V′CO₂                 | 46 (41; 51)                            | 38 (37; 50)      | 0.018*                              | 39 (37; 50)  | 0.018*                             |
| PetCO₂, mm Hg             | 25 (21; 27)                            | 28 (24; 32)      | 0.016*                              | 27 (24; 32)  | 0.017*                             |
| Oxygen saturation by pulse oximetry, % | 78 (66; 91) | 83 (76; 91) | 0.018*                              | 82 (71; 95)  | 0.027*                             |
| Cerebral tissue oxygenation, % | 62 (56; 63) | 62 (56; 63) | 0.028*                              | 62 (56; 63)  | 0.753                             |
| Quadriceps muscle tissue oxygenation, % | 56 (54; 68) | 63 (61; 74) | 0.499                               | 60 (56; 63)  | 0.249                             |
| Borg CR10 dyspnea         | 7 (5; 8)                              | NA               | –                                   | 8 (7; 9)     | 0.129                             |
| Borg CR10 fatigue         | 9 (7; 9)                              | NA               | –                                   | 8 (5; 9)     | 0.336                             |

Data are presented as median (quartiles), p-values were calculated with Wilcoxon-Test for non-parametrical data, *p < 0.05. V′E/V′CO₂, ventilatory equivalent for carbon dioxide; PetCO₂, end-tidal carbon dioxide.
CWRET, indicating a more efficient ventilation. These findings are in line with the result in patients with PH and COPD [15,16] and may indicate a reduced chemosensitivity to CO2 in the carotid bodies or a reduced dead space ventilation. The V'E/V'CO2 slope has been shown to be a good predictor of survival in patients with repaired tetralogy of Fallot [24]. The mechanisms of an increased V'E/V'CO2 in CHD-patients is still incompletely understood and the increase of the V'E/V'CO2 slope is even more pronounced in cyanotic CHD-patients with or without PH compared to those with mere CHD [25,26]. In the study of Dimopoulos et al. adult CHD patients had a lower V'E/V'CO2 slope (36.3 ± 15.3) compared to the current study (44.2(39.4; 48.0) [25]), however, the subgroup of cyanotic patients in their study revealed a much higher slope 56.9 ± 23.2 compared to non-cyanotic CHD 32.8 ± 9.9 [25], similarly also to the study of Gläser et al. [27]. In the current study the slope was significantly different in the IET with oxygen compared to air, however there was also trend for a steeper slope with air compared to oxygen.

Despite the significantly increased SpO2 with oxygen vs. air, MTO and CTO at end-exercise were similar in the IET and CWRET but with a longer exercise duration, which may indicate that the cerebral and muscular deoxygenation contributed to maintain exercise longer under longer exercise duration, which may indicate that the cerebral and muscular deoxygenation contributed to maintain exercise longer under oxygen vs. air. At isotime in CWRET, CTO was significantly higher with oxygen compared to air consistent with the notion that an improved blood- and tissue oxygenation with oxygen- enriched air breathing enhanced the exercise endurance. This is in line with previous study in PH, where we also found a difference in CTO at isotime in the CWRET [15].

At end-exercise, we found the same level of subjective exhaustion by the Borg dyspnoea scale with oxygen vs. air in IET and CWRET, despite a longer exercise duration with oxygen. Leg fatigue was significantly reduced with oxygen vs. air in the IET suggesting that exercise limitation was mainly due to dyspnea rather then due to leg discomfort.

5. Limitations and outlook

The sample size of our study was relatively small, however, the chosen randomized-cross over design allows to reduce the sample size in a usually heterogeneous patient collective and due to the large effect size of oxygen on the primary outcomes of Wmax and endurance time, the differences were statistically significant. The study might have been underpowered to reveal significant differences in exploratory secondary outcomes. Cyanotic CHD occurs in different underlying abnormalities of the heart, which may have influenced the effect size and our study does not allow to compare efficacy of oxygen in different types of CHD. Furthermore, only stable patients have been included and therefore the results cannot be extrapolated to a more severe patient collective. Finally, a selection bias towards the fitter patients cannot be excluded. We acknowledge, that further studies on longer-term oxygen during daily activity, exercise training or sleep are needed to study long-term effects of oxygen on exercise performance, daily activities, haematological parameters and quality of life. Oxygen therapy is comparably easy to implement during stationary exercise training, such as cycling, however, to study the effect of oxygen therapy during everyday activities may be challenging, but favourable effects of oxygen therapy in longer-term studies would be needed before this therapy can be recommended to be used during daily activity.

6. Conclusion

This first randomized, placebo-controlled, single-blinded study shows that patients with cyanotic CHD significantly improve their cycling exercise performance whilst breathing oxygen-enriched air compared to air by increasing both the maximal work rate during IET and endurance time during CWRET. The improvements were associated with a significantly higher SpO2 during exercise, associated with an improved ventilatory efficiency for CO2 output. The results of our pilot study encourage further exploration of the impact of supplemental oxygen therapy during exercise training or daily activity in cyanotic CHD in longer-term, sufficiently powered studies, in order to unravel the question of whether oxygen therapy applied during everyday activities and training would result in persistently improved exercise performance and potentially quality of life in this subgroup of CHD patients with the most severe exercise limitations.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jncardio.2021.11.066.

Declaration of Competing Interest

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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References

[1] H. Dolk, M. Loane, E. Garne, European Surveillance of Congenital Anomalies Working G, Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005, Circulation 123 (8) (2011) 841-849.
[2] C.A. Warnes, R. Librithson, G.K. Danielson, A. Dore, L. Harris, J.I. Hoffman, J. Somerville, R.G. Williams, G.D. Webb, Task force 1: the changing profile of congenital heart disease in adult life, J. Am. Coll. Cardiol. 37 (5) (2001) 1170-1175.
[3] M. Patruitt, J. Bracher, F. Bonanis, B. Santos, C. Gruner, S.F. Stampfl, T. Wolber, O. Kreutzkarch, A. Osenius, G. DePasquale, T. Seeliger, T.F. Luscher, C. Attenhofer Jost, M. Greutmann, Impact of growing cohorts of adults with congenital heart disease on clinical workload: a 20-year experience at a tertiary care Centre, Swiss Med. Wkly. 147 (2017), w14443.
[4] G.P. Diller, A. Kempny, R. Alonso-Gonzalez, L. Swan, A. Uebing, W. Li, S. Babu-Narayan, S.J. Wört, K. Dimopoulos, M.A. Gatzoulis, Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre, Circulation 132 (22) (2015) 2118-2125.
[5] M. Greutmann, D. Tobler, A.H. Kovacs, M. Greutmann-Yantiri, S.R. Haile, H. Dolk, M. Loane, E. Garne, European Surveillance of Congenital Anomalies Working G, Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005, Circulation 123 (8) (2011) 841-849.
[6] C.A. Warnes, R. Librithson, G.K. Danielson, A. Dore, L. Harris, J.I. Hoffman, J. Somerville, R.G. Williams, G.D. Webb, Task force 1: the changing profile of congenital heart disease in adult life, J. Am. Coll. Cardiol. 37 (5) (2001) 1170-1175.
[7] M. Patruitt, J. Bracher, F. Bonanis, B. Santos, C. Gruner, S.F. Stampfl, T. Wolber, O. Kreutzkarch, A. Osenius, G. DePasquale, T. Seeliger, T.F. Luscher, C. Attenhofer Jost, M. Greutmann, Impact of growing cohorts of adults with congenital heart disease on clinical workload: a 20-year experience at a tertiary care Centre, Swiss Med. Wkly. 147 (2017), w14443.
[8] G.P. Diller, A. Kempny, R. Alonso-Gonzalez, L. Swan, A. Uebing, W. Li, S. Babu-Narayan, S.J. Wört, K. Dimopoulos, M.A. Gatzoulis, Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre, Circulation 132 (22) (2015) 2118-2125.
[9] M. Greutmann, D. Tobler, A.H. Kovacs, M. Greutmann-Yantiri, S.R. Haile, H. Dolk, M. Loane, E. Garne, European Surveillance of Congenital Anomalies Working G, Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005, Circulation 123 (8) (2011) 841-849.
[10] C.A. Warnes, R. Librithson, G.K. Danielson, A. Dore, L. Harris, J.I. Hoffman, J. Somerville, R.G. Williams, G.D. Webb, Task force 1: the changing profile of congenital heart disease in adult life, J. Am. Coll. Cardiol. 37 (5) (2001) 1170-1175.
[11] M. Patruitt, J. Bracher, F. Bonanis, B. Santos, C. Gruner, S.F. Stampfl, T. Wolber, O. Kreutzkarch, A. Osenius, G. DePasquale, T. Seeliger, T.F. Luscher, C. Attenhofer Jost, M. Greutmann, Impact of growing cohorts of adults with congenital heart disease on clinical workload: a 20-year experience at a tertiary care Centre, Swiss Med. Wkly. 147 (2017), w14443.
[12] G.P. Diller, A. Kempny, R. Alonso-Gonzalez, L. Swan, A. Uebing, W. Li, S. Babu-Narayan, S.J. Wört, K. Dimopoulos, M.A. Gatzoulis, Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre, Circulation 132 (22) (2015) 2118-2125.
[13] M. Greutmann, D. Tobler, A.H. Kovacs, M. Greutmann-Yantiri, S.R. Haile, H. Dolk, M. Loane, E. Garne, European Surveillance of Congenital Anomalies Working G, Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005, Circulation 123 (8) (2011) 841-849.
[14] C.A. Warnes, R. Librithson, G.K. Danielson, A. Dore, L. Harris, J.I. Hoffman, J. Somerville, R.G. Williams, G.D. Webb, Task force 1: the changing profile of congenital heart disease in adult life, J. Am. Coll. Cardiol. 37 (5) (2001) 1170-1175.
[15] M. Patruitt, J. Bracher, F. Bonanis, B. Santos, C. Gruner, S.F. Stampfl, T. Wolber, O. Kreutzkarch, A. Osenius, G. DePasquale, T. Seeliger, T.F. Luscher, C. Attenhofer Jost, M. Greutmann, Impact of growing cohorts of adults with congenital heart disease on clinical workload: a 20-year experience at a tertiary care Centre, Swiss Med. Wkly. 147 (2017), w14443.
A.M. Valente, G.F. Van Hare, 2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines, Circulation 139 (14) (2019) e637–e697.

J. Sandoval, J.S. Aguirre, T. Pulido, M.L. Martinez-Guerra, E. Santos, P. Alvarado, M. Rosas, E. Bautista, Nocturnal oxygen therapy in patients with the Eisenmenger syndrome, Am. J. Respir. Crit. Care Med. 164 (9) (2001) 1682–1687.

F. Walker, M.J. Mullen, S.J. Woods, G.D. Webb, Acute effects of 40% oxygen supplementation in adults with cyanotic congenital heart disease, Heart 90 (9) (2004) 1073–1074.

S. Ulrich, E.D. Hasler, S. Saxer, M. Furian, S. Muller-Mottet, S. Keusch, K.E. Bloch, Effect of breathing oxygen-enriched air on exercise performance in patients with pre-capillary pulmonary hypertension: randomized, sham-controlled cross-over trial, Eur. Heart J. 38 (15) (2017) 1159–1168.

E.D. Hasler, S. Saxer, S.R. Schneider, M. Furian, M. Lichtblau, E.I. Schwarz, K. E. Bloch, S. Ulrich, Effect of breathing oxygen-enriched air on exercise performance in patients with chronic obstructive pulmonary disease: randomized, placebo-controlled, cross-over trial, Respiration (2020) 1–12.

S. Ulrich, E.D. Hasler, S. Muller-Mottet, S. Keusch, M. Furian, T.D. Lanhag, S. Schneider, S. Saxer, K.E. Bloch, Mechanisms of improved exercise performance under hyperoxia, Respiration 93 (2) (2017) 90–96.

T. Radtke, S. Crook, G. Kalsakas, Z. Louvaris, D. Berton, D.S. Urquhart, A. Kampouras, R.A. Rabinovich, S. Verge, D. Kontopidis, J. Boyd, T. Tonia, D. Langer, J. De Brandt, Goertz YMJ, C. Burtin, M.A. Spruit, Braeken DCW, S. Dacha, Franssen FME, P. Laveneziana, E. Eber, T. Troosters, J.A. Neder, M. A. Puhan, R. Casaburi, P. Calverley, P.S. Burge, P.M. Calverley, B.R. Celli, P.W. Jones, D.A. Mahler, B. Make, M. Miravitlles, C.P. Fage, P. Palange, D. Paer, M. Pistolesi, S.I. Rennard, M.P. Rutten-von Molken, B. Stockley, S.D. Sullivan, J.A. Wedzicha, E.F. Wouters, American Thoracic S, European Respiratory Society task force on outcomes of C, Outcomes for COPD pharmacological trials: from lung function to biomarkers, Eur. Respir. J. 31 (2) (2008) 416–469.

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