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Impact of exercise training and supplemental oxygen on submaximal exercise performance in patients with COPD

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Abstract

Functional impairment caused by chronic obstructive pulmonary disease (COPD) impacts on activities of daily living and quality of life. Indeed, patients' submaximal exercise capacity is of crucial importance. It was the aim of this study to investigate the effects of an exercise training intervention with and without supplemental oxygen on submaximal exercise performance. This is a secondary analysis of a randomized, controlled, double-blind, crossover trial. 29 COPD patients (63.5 ± 5.9 years; FEV_1 46.4 ± 8.6%) completed two consecutive 6-week periods of high-intensity interval cycling and strength training, which was performed three times/week with either supplemental oxygen or medical air (10 L/min). Submaximal exercise capacity as well as the cardiocirculatory, ventilatory, and metabolic response were evaluated at isotime (point of termination in the shortest cardiopulmonary exercise test), at physical work capacity at 110 bpm of heart rate (PWC 110), at the anaerobic threshold (AT), and at the lactate-2 mmol/L threshold. After 12 weeks of exercise training, patients improved in exercise tolerance, shown by decreased cardiocirculatory (heart rate, blood pressure) and metabolic (respiratory exchange ratio, lactate) effort at isotime; ventilatory response was not affected. Submaximal exercise capacity was improved at PWC 110, AT and the lactate-2 mmol/L threshold, respectively. Although supplemental oxygen seems to affect patients' work rate at AT and the lactate-2 mmol/L threshold, no other significant effects were found. The improved submaximal exercise capacity and tolerance might counteract patients' functional impairment. Although cardiovascular and metabolic training adaptations were shown, ventilatory efficiency remained essentially unchanged. The impact of supplemental oxygen seems less important on submaximal training effects.

KEYWORDS

cardiopulmonary exercise test, chronic obstructive pulmonary disease, exercise capacity, interval training, strength training

1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most common causes of morbidity and mortality, thus representing a global health burden.[1] Functional impairment and limitations in activities of daily living (ADL) are frequent in patients with COPD.[2] Moreover, disease-related symptoms and functional exercise capacity have a great influence on ADL also in these patients.[2] In this regard, submaximal exercise capacity is of major interest, since it reflects the functional performance during daily living. Assessing and improving functional capacity using patient-centered submaximal outcome measures might thus better reflect the impact of exercise capacity on patients' quality of life.[3] Furthermore, it is known that the level of independence to perform ADL can be increased by improving functional exercise capacity and reducing symptoms.[2,3] Indeed, physical exercise training is a cornerstone of COPD treatment and thus recommended in all international guidelines.[1,4-10] It was clearly shown that regular physical activity and exercise training improve the hallmark symptom dyspnea, as well as muscular strength, maximal and submaximal exercise capacity and thereby ADL.[1,6] What remains unsolved, however, is whether non-hypoxemic COPD patients should exercise with supplemental oxygen.[9,11] Several studies have applied oxygen during exercise training in patients with COPD, showing conflicting results.[12-25] However, we have previously shown that supplemental oxygen might improve the training effect on peak exercise capacity, when high oxygen flow rate, oxygen-specific exercise prescription and progressive adaptation of high-intensity interval training is provided.[20,26,27]

The aim of this study was thus to investigate whether high-intensity exercise training with and without supplemental oxygen has an impact on submaximal exercise performance, which reflects patients' functional status.

2 | METHODS

This is an analysis of secondary endpoints of submaximal exercise performance after a training intervention performed during the Salzburg COPD Exercise and Oxygen (SCOPE) study, a prospective, randomized, controlled, double-blind, crossover trial (RCT) in patients with stable non-hypoxemic COPD.[20,28] The ethics committee of Salzburg approved this study, which was registered on clinicaltrials.gov (NCT01150383). All participating patients provided written informed consent.

The study design is shown in Figure 1 and was described in detail previously.[20] Patients completed two consecutive exercise training periods of 6 weeks each. During the first 6 weeks of training, either 10 L/min of supplemental oxygen (O_2) or medical air (Air) were administered. The gas supply was changed at crossover for the second 6-weeks training period, respectively. For warm-up and cooldown, gas supply was reduced to 4 L/min. Blinding was achieved by locked away gas cylinders and a hidden gas distributing system that connected to junctions for nasal cannulas.

2.1 | Eligibility criteria

Patients aged ≥30 years with stable COPD, FEV_1 between 30%-60% of predicted and resting arterial $PaO_2 > 55$ mmHg and $PaCO_2 < 45$ mmHg were eligible. Patients with comorbidities known to impair physical exercise training, myocardial infarction within the previous six months, left ventricular ejection fraction < 40%, creatinine > 2 mg/dL, hemoglobin < 10 g/dL,

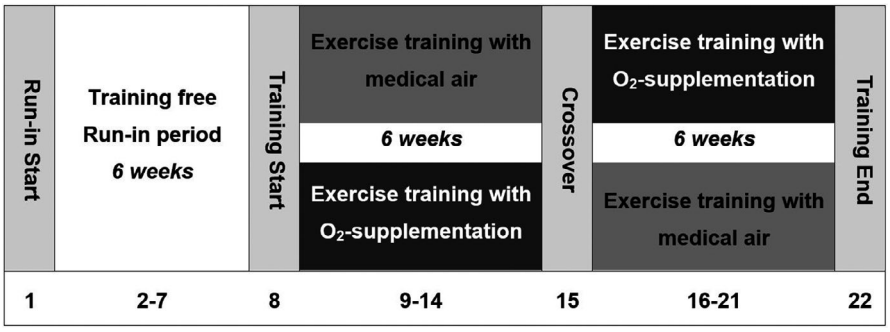

FIGURE 1 The study design. All included patients underwent a training-free run-in period lasting 6 weeks to optimize pharmacologic treatment according to international guidelines. Forty-four patients were randomized at training start to group "O_2 → Air" or group "Air → O_2" and performed two 6-week periods of exercise training; patients started the training program with supplemental oxygen followed by medical air or vice versa. Participants, caregivers, and those assessing outcomes were blinded for the provided gas supply. Study investigations, analyzing contemporarily all study outcomes, were performed at run-in start, training start, crossover, and training end. A timeline (weeks) is shown at the bottom of Figure 1

or expected non-compliance due to specific psychosocial conditions were not eligible for participation.

2.2 | Exercise testing

Exercise capacity was assessed by ECG-monitored, incremental cardiopulmonary exercise testing (CPET) using Jaeger Oxycon Pro Hardware and analyzed with the JLAB Software on a stationary cycle ergometer (Ergoline Ergoselect 200) without gas supply.[20] Testing started at 20 watts and increased by 10 watts/min in men and 5 watts/min in women until exhaustion (Borg-RPE: 18-20). Capillary blood samples for lactate measurements as well as patients' blood pressure were obtained every two minutes. Lactate measurements were analyzed with the EKF Biosen-C lactate analyzer. CPET parameters were registered breath by breath. Gas-specific peak work rate was additionally determined through exercise testing with the respective gas supply (10 L/min) at training start and crossover, to ensure accurate gas-specific exercise prescription. Tests were performed at least 48h apart. All presented data were obtained from normoxic CPET.

2.3 | Exercise training

Patients performed supervised, ECG-monitored endurance training on stationary bikes and strength training sessions three times a week. Each endurance training session lasted 31 minutes and consisted of seven one-minute high-intensity intervals starting at 70-80% of gas-specific peak work rate separated by two minutes of active recovery. These intermittent recovery periods as well as the five minutes warm-up and cooldown were performed at about 50% of peak work rate. Exercise intensity was adapted according to calculated training heart rates (HR) [HRrest+(HRmax–HRrest)x(0.7-0.8)].[29] Moreover, workload was progressively increased during the course of study whenever a patient's training heart rate decreased.

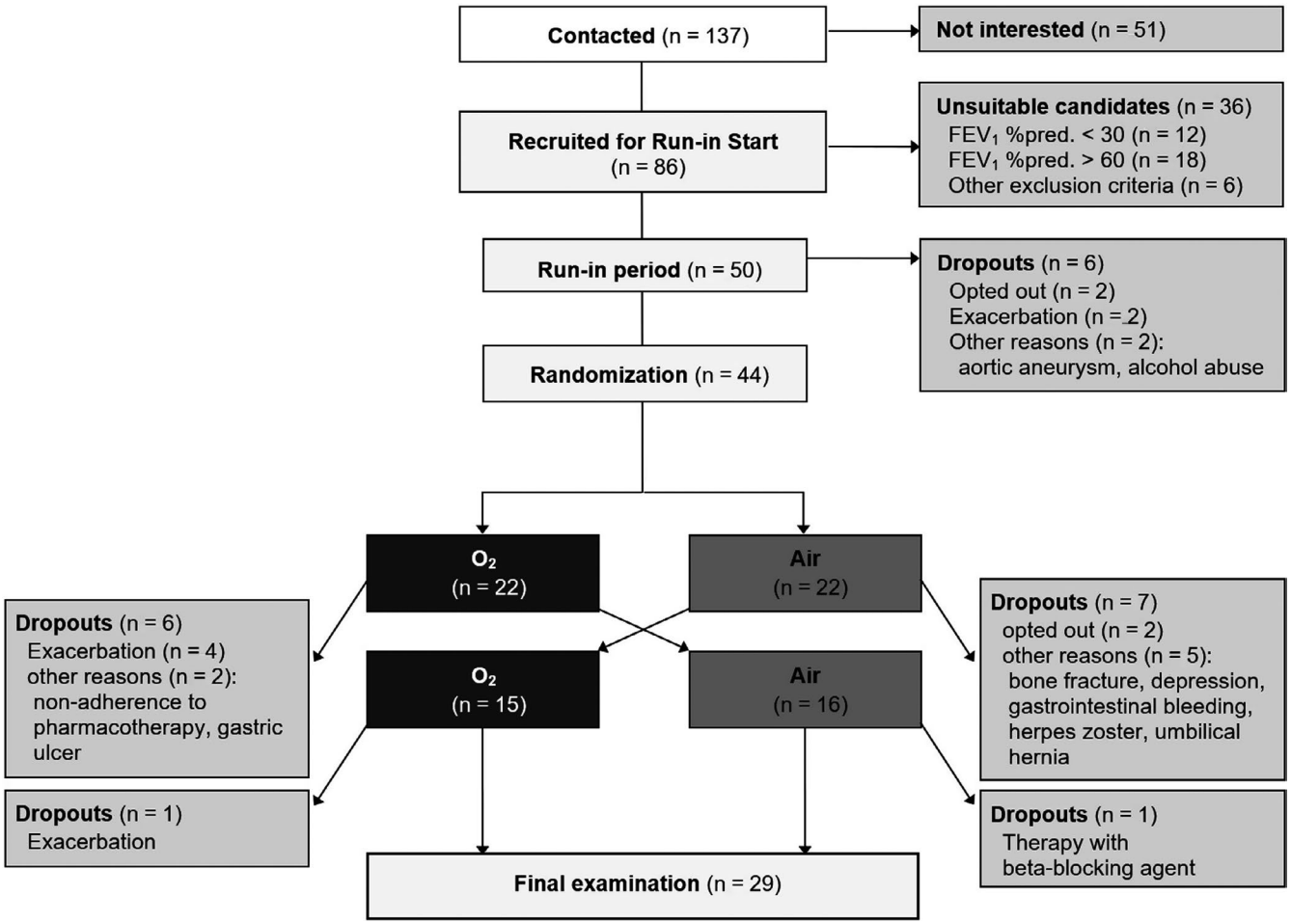

FIGURE 2 Flow diagram. Fifty of 137 contacted patients met eligibility criteria and entered the run-in phase. An external block randomization was carried out at training start to ensure a blinded and concealed allocation of a similar number of patients to the two study groups. Although during the training periods 15 patients dropped out, no differences in dropout rates were observed between groups. Furthermore, only two patients opted out during the training period, at a very early stage of the intervention. Other withdrawals were because of comorbidities and exacerbations during the cold winter months

Eight high-intensity strength training exercises were performed on weightlifting machines: latissimus pull-down, shoulder press, back extension, abdominal crunch, butterfly, butterfly reverse, leg extension, and leg flexion. Patients performed 1 set with 8 to 15 repetitions to failure. Whenever more than 15 repetitions were realized, weight was increased.

2.4 | Study endpoints

It was aimed to investigate submaximal exercise performance, evaluating the cardiocirculatory, ventilatory, and metabolic response. Moreover, patients' exercise capacity was assessed by work rate on a cycle ergometer (watt) and through oxygen consumption (VO_2). The submaximal response of the cardiocirculatory system to exercise was evaluated by HR, blood pressure (BP), and oxygen pulse (VO_2/HR). Furthermore, the ventilatory response during exercise was investigated by minute ventilation (VE), breathing frequency (BF), tidal volume (TV), and the ventilatory equivalent for oxygen (VE/VO_2). Finally, the respiratory exchange ratio (RER) and capillary blood lactate concentration provided data regarding patients' metabolic response during submaximal exercise intensities.

These test parameters were evaluated at different submaximal exercise thresholds. Moreover, the impact of exercise training and supplemental oxygen on submaximal exercise performance was analyzed at isotime (ie, the point of termination in the shortest CPET during study investigations for each individual),[27] at physical work capacity at 110 bpm of heart rate (PWC 110), at the anaerobic threshold (AT; determined by the V-slope-method),[30] and at the lactate-2 mmol/L threshold. The latter was determined via polynomic function based on measured lactate values per time unit and evaluates the predominantly aerobic performance before blood lactate accumulation.

Furthermore, cardiopulmonary efficiency was assessed via CPET slope parameters. Linear regression analysis determined the VO_2/Watt slope, the HR/VO_2 slope, and the slope of the ventilator equivalent for CO_2 (VE/VCO_2 slope) from incremental exercise test data. Furthermore, the oxygen uptake efficiency slope (OUES) is defined as the slope of linear regression of VO_2 (L/m) vs. log of VE (L/m), determined over the entire test protocol.[31-33]

2.5 | Statistical analysis

The analysis method for crossover trials was performed as previously described by Hills and Armitage, whereas carryover effects between study periods were analyzed as described by Schumacher and Schulgen.[34,35] Unpaired t tests were used for comparisons between study arms, and paired t tests within study arms. Statistical significance was defined as $P < .05$.

3 | RESULTS

Out of 137 contacted patients, 29 (21 males; 63.5 ± 5.9 years) were analyzed for the study outcomes. A flow chart of patients' recruitment is presented in Figure 2, while baseline characteristics are shown in Table 1.

3.1 | Study endpoints

The impact of 12 weeks of exercise training was statistically significant at isotime regarding cardiocirculatory (HR −3.94%, systolic BP −7.78%, diastolic BP −5.97%, VO_2/HR 4.44%; all $P < .05$) and metabolic adaptations (RER −1.85%, Lactate −14.54%; both $P < .05$). Patients' ventilation did not

TABLE 1 Patients' baseline characteristics at training start

a: At rest	
	Mean (±SD)
Age, y	63.5 (±5.9)
BMI, kg/m^2	27.3 (±5.4)
Systolic BP, mm Hg	119 (±14)
Diastolic BP, mm Hg	75 (±9)
FEV_1/FVC, %	59.7 (±11.3)
FEV_1, % pred.	46.4 (±8.6)
VC inspired, % pred.	80.2 (±15.6)
PaO_2, mmHg	69.2 (±8.6)
$PaCO_2$, mmHg	38.0 (±3.2)
Hemoglobin, g/ld.	16.7 (±1.5)
SaO_2, %	94.4 (±2.2)
b: At peak exercise	
	Mean (±SD)
Heart rate, bpm	128 (±18)
Work rate, Watt	85.7 (±31.2)
Peak VO_2, mL/min/kg	18.4 (±3.8)
Systolic BP, mmHg	170 (±34)
Diastolic BP, mmHg	77 (±13)
VE, L/min	53.0 (±11.4)
BF, breaths/min	33 (±5.4)
RER	1.0 (±0.1)
BORG, RPE (6-20)	18.9 (±1.1)
Lactate, mmol/L	3.8 (±1.1)
SaO_2, %	90.2 (±7.7)

Note: Table 1 shows the patients' baseline characteristics at rest (table 1.a) and at peak exercise (table 1.b) measured at training start (N = 29). Data are presented as mean ± standard deviation (SD). BMI: Body mass index, BP: Blood pressure, FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, VC: Vital capacity, PaO2: Arterial oxygen partial pressure, PaCO2: Arterial carbon dioxide partial pressure, SaO2: Oxygen saturation, peak VO2: Peak oxygen consumption, VE: Minute ventilation, BF: Breathing frequency, RER: Respiratory exchange ratio, RPE: Rating of perceived exertion scale.

TABLE 2 Impact of exercise training and supplemental oxygen on submaximal exercise performance

		Isotime N = 29	PWC 110 N = 22	AT N = 26	2 mmol·L^{-1} Lactate N = 28	Isotime N = 29	PWC 110 N = 22	AT N = 26	2 mmol·L^{-1} Lactate N = 28
Exercise capacity		**Work rate [Watt]**				**VO_2 [mL·min^{-1}·kg^{-1}]**			
Training Start	Mean ± SE	-	56.5† ± 5.3	46.2†±4.9	58.3 ± 4.6	17.4 ± 0.7	13.6 ± 0.8	11.9 ± 0.7	13.3 ± 0.7
Training End	Mean ± SE	-	68.3 ± 5.9	55.7 ± 5.6	68.6 ± 4.3	17.6 ± 0.7	14.9 ± 0.8	13.0 ± 0.6	14.9 ± 0.6
Training effect	[%]	-	20.92	20.77	17.67	0.84	9.46	8.53	11.66
Training effect	*P*	-	.032*	.048*	.005**	.366	.081	.099	.020*
Exercise Training with oxygen	Delta ± SE	-	3.41 ± 3.47	12.50 ± 5.50	7.50 ± 2.42	−0.02 ± 0.22	0.30 ± 0.61	1.14 ± 0.71	0.34 ± 0.39
Exercise Training with medical air	Delta ± SE	-	4.57 ± 2.57	−1.92 ± 4.43	1.43 ± 2.49	0.16 ± 0.34	0.68 ± 0.40	−0.15 ± 0.66	0.97 ± 0.45
Oxygen effect	*P*	-	.110	.070	.068	.429	.172	.119	.416
Cardiocirculatory response									
		HR [beats·min^{-1}]				**VO_2·HR^{-1}**			
Training Start	Mean ± SE	124 ± 3	-	102 ± 3	107 ± 3	11.0 ± 0.5	9.6 ± 0.5	9.2† ±0.5	9.7 ± 0.5
Training End	Mean ± SE	119 ± 3	-	103 ± 3	109 ± 2	11.5 ± 0.5	10.5 ± 0.6	9.9 ± 0.5	10.6 ± 0.5
Training effect	[%]	−3.94	-	0.64	1.44	4.44	9.48	8.07	9.46
Training effect	*P*	.007**	-	.292	.282	.041*	.131	.035*	.033*
Exercise Training with oxygen	Delta ± SE	−2.60 ± 1.31	-	2.96 ± 2.51	0.36 ± 2.02	0.14 ± 0.18	0.08 ± 0.45	0.63 ± 0.38	0.13 ± 0.289
Exercise Training with medical air	Delta ± SE	−2.28 ± 1.67	-	−1.54 ± 2.51	0.93 ± 1.90	0.35 ± 0.21	0.49 ± 0.29	0.12 ± 0.36	0.63 ± 0.35
Oxygen effect	*P*	.258	-	.065	.230	.161	.100	.234	.283
		Systolic BP [mm Hg]				**Diastolic BP [mm Hg]**			
Training Start	Mean ± SE	165 ± 6	143 ± 4	133 ± 4	143 ± 4	76 ± 2	76 ± 2	74 ± 2	74 ± 2
Training End	Mean ± SE	152 ± 5	1375	129 ± 5	137 ± 4	72 ± 2	69 ± 2	71 ± 2	71 ± 2
Training effect	[%]	−7.78	−4.19	−2.59	−3.9	−5.97	−9.80	−3.70	−4.86
Training effect	*P*	<.001***	.123	.215	.013*	.017*	<.001***	.083	.031*
Exercise Training with oxygen	Delta ± SE	−8.74 ± 2.88	−4.09 ± 3.96	1.15 ± 4.81	−1.75 ± 2.94	−4.14 ± 1.70	−4.32 ± 1.72	−1.73 ± 1.92	−0.89 ± 1.78
Exercise Training with medical air	Delta ± SE	−4.08 ± 4.39	0.00 ± 4.10	−4.62 ± 4.68	−4.64 ± 3.69	−0.40 ± 1.77	−1.52 ± 2.21	−1.15 ± 1.97	−2.50 ± 1.53
Oxygen effect	*P*	.091	.058	.453	.408	.193	.386	.363	.378
Ventilatory response									
		VE [L·min^{-1}]				**BF [breaths·min^{-1}]**			
Training Start	Mean ± SE	50.3 ± 2.0	37.0 ± 2.0	31.4 ± 1.8	36.4 ± 1.7	32.1 ± 1.0	24.5 ± 1.1	23.0 ± 1.0	25.6†±0.8
Training End	Mean ± SE	50.1 ± 2.1	41.2 ± 2.4	34.3 ± 2.3	40.5 ± 1.9	31.1 ± 1.2	26.8 ± 1.3	24.3 ± 1.3	26.2 ± 1.1
Training effect	[%]	−0.27	11.46	9.03	11.23	−2.94	9.26	5.62	2.32
Training effect	*P*	.457	.111	.118	.022*	.154	.020*	.177	.237

(Continues)

TABLE 2 (Continued)

Ventilatory response									
		VE [L·min^{-1}]				**BF [breaths·min^{-1}]**			
Exercise Training with oxygen	Delta ± SE	−1.18 ± 1.05	0.09 ± 1.86	2.96 ± 2.09	1.11 ± 1.14	−1.45 ± 0.88	1.26 ± 0.73	1.12 ± 1.14	0.46 ± 0.81
Exercise Training with medical air	Delta ± SE	1.05 ± 1.20	2.36 ± 1.31	0.08 ± 2.08	2.46 ± 1.19	0.51 ± 1.10	0.62 ± 0.85	0.12 ± 0.97	0.14 ± 0.70
Oxygen effect	*P*	.130	.206	.128	.274	.179	.227	.243	.158
		TV [L]				**VE·VO$_2$$^{-1}$**			
Training Start	Mean ± SE	1.6 ± 0.1	1.5†±0.1	1.4†±0.1	1.4 ± 0.1	36.6 ± 1.1	33.5 ± 0.9	32.2 ± 0.8	34.4 ± 1.0
Training End	Mean ± SE	1.7 ± 0.1	1.6 ± 0.1	1.4 ± 0.1	1.6 ± 0.1	35.9 ± 0.9	34.4 ± 1.0	31.7 ± 0.8	34.0 ± 1.1
Training effect	[%]	3.87	2.05	5.58	9.88	−1.80	2.59	−1.50	−1.35
Training effect	*P*	.123	.330	.075	.017*	.173	.216	.265	.270
Exercise Training with oxygen	Delta ± SE	0.05 ± 0.06	−0.06 ± 0.06	0.07 ± 0.06	0.00 ± 0.05	−0.79 ± 0.53	0.22 ± 0.74	−0.89 ± 0.67	−0.02 ± 0.56
Exercise Training with medical air	Delta ± SE	0.01 ± 0.05	0.06 ± 0.06	0.02 ± 0.06	0.12 ± 0.05	0.13 ± 0.58	0.22 ± 0.49	0.35 ± 0.60	−0.37 ± 0.61
Oxygen effect	*P*	.457	.154	.090	.192	.118	.232	.490	.275

Metabolic response									
		RER				**Lactate [mmol·L^{-1}] N = 23 N = 17**			
Training Start	Mean ± SE	0.97 ± 0.01	0.88† ± 0.02	0.83 ± 0.02	0.87 ± 0.01	3.7 ± 0.3	2.2†±0.3	1.6 ± 0.2	-
Training End	Mean ± SE	0.95 ± 0.01	0.89 ± 0.02	0.83 ± 0.02	0.89 ± 0.01	3.1 ± 0.2	2.2 ± 0.2	1.6 ± 0.2	-
Training effect	[%]	−1.85	1.15	0.23	1.65	−14.54	2.04	2.04	-
Training effect	*P*	.033*	.472	.434	.155	.010*	.443	.439	-
Exercise Training with oxygen	Delta ± SE	−0.004 ± 0.007	0.008 ± 0.015	0.014 ± 0.015	0.011 ± 0.011	−0.23 ± 0.17	−0.18 ± 0.24	0.22 ± 0.29	-
Exercise Training with medical air	Delta ± SE	−0.014 ± 0.007	−0.004 ± 0.011	−0.010 ± 0.017	0.001 ± 0.009	−0.28 ± 0.17	0.09 ± 0.18	−0.18 ± 0.26	-
Oxygen effect	*P*	.210	.467	.067	.179	.326	.280	.253	-

Note: Effects of exercise training and supplemental oxygen on main parameters of this study. For the presented study outcomes, significant carryover effects due to the crossover study design could be statistically excluded, except at PWC110 for Systolic BP and Lactate. Parameters that differed significantly between study groups at training start are indicated with a (†).

Abbreviations: BF, breathing frequency; BP, Blood pressure; HR, heart rate; RER, respiratory exchange ratio; SE, Standard error; TV, expiratory tidal volume; VE, ventilation; VE·VO$_2$$^{-1}$, ventilatory equivalent for oxygen; VO$_2$, oxygen consumption; VO$_2$·HR^{-1}, oxygen pulse.

*$P < .05$;

**$P < .01$:

***$P < .001$.

TABLE 3 Impact of exercise training and supplemental oxygen on cardiorespiratory efficiency

		VO_2·$Watt^{-1}$ slope N = 29	HR·VO_2^{-1} slope N = 29	OUES N = 29	VE·VCO_2^{-1} slope N = 29
Training Start	Mean	12.19	0.041	2000.1	0.035
	±SE	±0.54	±0.003	±102.0	±0.001
Training End	Mean	11.33	0.046	2086.6	0.036
	±SE	±0.37	±0.003	±87.0	±0.002
Training effect	[%]	−7.12	13.27	4.33	1.41
Training effect	*P*-value	.039*	.007**	.098	.260
Exercise Training with oxygen	Delta	−0.46	0.003	63.60	0.000
	±SE	±0.48	±0.002	±60.75	±0.001
Exercise Training with medical air	Delta	−0.41	0.002	22.95	0.001
	±SE	±0.25	±0.002	±42.93	±0.001
Oxygen effect	*P*-value	.363	.479	.142	0.488

Effects of exercise training and supplemental oxygen on cardiopulmonary slope parameters determined during incremental exercise testing. For the presented study outcomes significant carryover effects due to the crossover study design could be statistically excluded. Parameters that differed significantly between study groups at training start are indicated with a (†).

Abbreviations: HR, heart rate; OUES, oxygen uptake efficiency slope; SE, Standard error; VE.VCO_2^{-1}, ventilatory equivalent for CO_2; VO_2, oxygen consumption.

*$P < .05$;

**$P < .01$;

***$P < .001$.

change at isotime and no significant effect of supplemental oxygen was detected (Table 2).

Patients' exercise capacity at PWC 110 improved after the training intervention (watt 20.92%, $P = .032$; VO_2 9.46%, statistical trend with $P = .081$). Moreover, cardiocirculatory and ventilatory parameters were significantly affected (diastolic BP −9.80% and BF 9.26%, respectively; both $P < .05$), while the metabolic response was not. No significant impact was found for supplemental oxygen on these parameters determined at PWC 110 (Table 2).

During the training period exercise capacity and oxygen pulse significantly improved at the AT (watt 20.77%, VO_2/HR 8.07%; both $P < .05$). All other variables did not significantly change. The impact of supplemental oxygen on patients' exercise capacity at the AT was shown by an increase in work rate of 12.50 ± 5.50 watt when patients trained with oxygen, compared to −1.92 ± 4.43 watt after normoxic training (statistical trend with $P = .070$; Table 2).

At the lactate-2 mmol/L threshold, exercise capacity (watt 17.67%, VO_2 11.66%; both $P < .05$) and the cardiocirculatory response (systolic BP −3.90%, diastolic BP −4.86%, VO_2/HR 9.46%; all $P < .05$) improved. Moreover, an associated increased ventilatory response was seen (VE 11.23%, TV 9.88%; both $P < .05$). Furthermore, a statistical trend favoring exercise training with supplemental oxygen for increasing exercise capacity was found (watt, $P = .068$; Table 2).

With regard to patients' cardiopulmonary efficiency, the VO_2/watt slope decreased after exercise training (−7.12%, $P = .039$), while the HR/VO_2 slope significantly increased (13.27%, $P = .007$). However, slope parameters more closely associated with ventilatory efficiency remained unchanged (OUES, VE/VCO_2). No significant oxygen effect was determined (Table 3).

4 | DISCUSSION

Functional impairment and dyspnea have a main impact on the limitations of ADL in patients with COPD and thus on their quality of life.[2,7] The evaluation of submaximal exercise capacity is therefore of major interest, since it best reflects the functional performance during daily living.[3] The analysis of the assessed secondary SCOPE study endpoints clearly shows that high-intensity exercise training leads to a significant improvement of parameters related to submaximal exercise capacity/tolerance and functional performance (Figure 3).

4.1 | Training effects

Training adaptations on cardiocirculatory and metabolic parameters evaluated at isotime, demonstrate increased exercise tolerance. Indeed, after 12 weeks of exercise training, lower HR and BP were associated with decreased RER, and blood lactate concentration at comparable exercise intensity. This was reciprocally confirmed by a significantly improved exercise capacity at comparable submaximal cardiocirculatory and metabolic effort. Moreover, after the training intervention patients showed higher work rates at the thresholds PWC 110, AT and lactate-2 mmol/L, respectively (Figure 3).

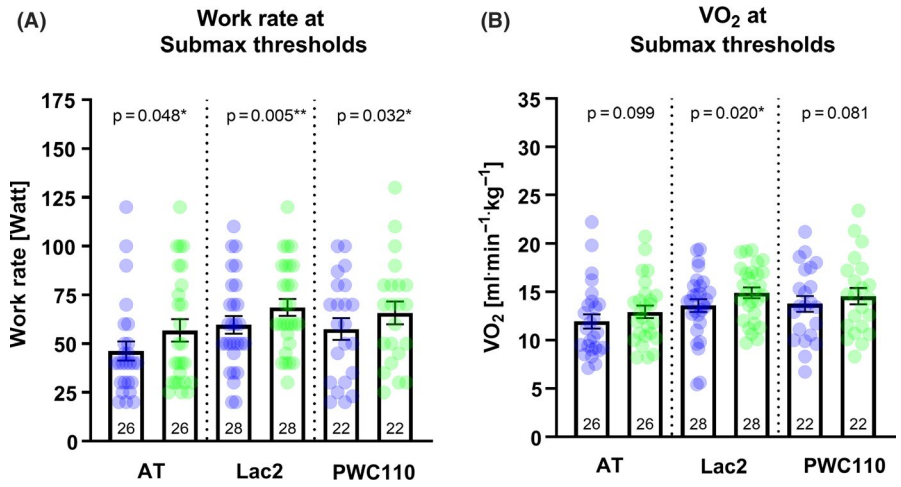

FIGURE 3 Submaximal thresholds of work rate and VO_2. Work rate (Watt) (A) and oxygen consumption (VO_2) (B) at the Anaerobic Threshold (AT), the lactate threshold at 2 mmol·L^{-1} (Lac2) and the Physical Work Capacity at 110 bpm of heart rate (PWC 110) at training start (blue dots) and training end (green dots). Column height representing mean values ± standard error as error bars; individual values are plotted as dots. A number of included patients are depicted at the base of each column. Statistically significant changes are marked with * $P < .05$, ** $P < .01$, *** $P < .001$

Similarly, a previous study by Porszasz et al has shown that exercise training in patients with COPD dramatically improves submaximal exercise endurance.[27]

The repeated assessments of the cardiocirculatory response to physical exercise during this training intervention study demonstrate that the cardiovascular system was less challenged over time at submaximal efforts. Furthermore, the increased oxygen pulse at different exercise intensities and HR/VO_2 slope might indicate a less restricted cardiocirculatory response to exercise. This could be due to cardiovascular and peripheral muscular adaptations as well as improved exercise tolerance, leading to less constraining pulmonary limitations, arising at higher exercise intensities.[7,27] Indeed, the cardiovascular and metabolic systems can be more exploited due to postponed ventilatory limitation to exercise.

Similarly, the metabolic adaptations during exercise were found positively affected by 12 weeks of high-intensity exercise training. Moreover, lower RER and blood lactate concentrations were found at isotime, while higher work rates were shown both at the AT and lactate-2 mmol/L threshold. This means that patients can indeed increasingly use the aerobic metabolism during higher exercise intensities. Moreover, the improved aerobic function of skeletal muscles and thus the increased metabolic efficiency will lead to decreased ventilatory demands and thus to potentially reduced dyspnea during ADL.[2,7]

Patients' ventilatory response to exercise was less influenced by the training intervention. Indeed, the main ventilatory parameters, that is, VE, BF, and TV remained essentially unchanged when evaluated at comparable work rates (isotime). However, increased BF and VE/TV were found at PWC 110 and the lactate-2 mmol/L threshold, respectively. This might be simply due to the increased exercise performance at these submaximal intensities and therefore higher ventilatory demands. Indeed, no parameters evaluating ventilatory efficiency during submaximal exercise were affected by exercise training. Moreover, although exercise and aerobic capacity improved at submaximal and maximal exercise intensities,[20] the OUES and ventilatory equivalents for oxygen/carbon dioxide (VE/VO_2, VE/VCO_2) have not significantly changed. These findings are in line with previous studies, showing that pulmonary function cannot be influenced by physical exercise training.[7,20] However, it has been previously described that decreased dynamic hyperinflation may, in part, mediate the improvement in exercise endurance by delaying the attainment of a critically high inspiratory lung volume.[27]

4.2 | Supplemental oxygen

Although some previous studies have shown a positive impact of supplemental oxygen during exercise training on patients' exercise capacity,[20,22] others did not confirm these results.[12-15,17,19,21,23] Indeed, study outcomes are heterogenous and evidence is still low for using oxygen during pulmonary rehabilitation.[11] Our data indicate no significant impact of supplemental oxygen on the cardiocirculatory, ventilatory, and metabolic response to submaximal exercise performance. However, an impact on patients' exercise capacity could be assumed due to the positive statistical trend of the oxygen effect shown on work rate both at the AT and lactate-2 mmol/L threshold (Figure S1). The oxygen effect was more pronounced at peak exercise intensities,[20,26] since it was aimed to reach highest training intensities during the study intervention by providing supplemental oxygen. Moreover, supplemental oxygen seems not only to act via increasing arterial oxygen content, but also through inhibition of carotid body stimulation, reduced respiratory drive, and pulmonary vasodilatation.[36,37]

This might increase cardiac output and muscle oxygen delivery, but decrease ventilation as well as dynamic hyperinflation during exercise.[36-39] Therefore, high oxygen flow rates should lead in certain patients to increased exercise tolerance and training intensities, which must be considered by oxygen-specific exercise prescription.[26] Moreover, patients' exercise capacity should thus be tested also with supplemental oxygen and in case of increased performance, high-flow oxygen could be prescribed for the training intervention. This individualized approach might lead to a significant oxygen effect during the training intervention on exercise capacity, particularly at high intensities, the main target of this study intervention.[20] However, it has been suggested that exercise training in room air might be superior in order to induce improvement of peripheral endothelial dysfunction. Indeed, oxygen supplementation demonstrated great importance in increasing peak exercise capacity, but the effects on inflammation and vascular dysfunction seem to mainly depend on the exercise training itself.[28]

5 | CONCLUSIONS

This prospective, randomized, controlled, double-blind crossover trial investigated the impact of high-intensity exercise training and supplemental oxygen on submaximal exercise performance and the associated cardiocirculatory, ventilatory, and metabolic response. The adaptations to training (irrespective of supplemental oxygen vs. medical air) led to improved submaximal exercise capacity and tolerance. Indeed, the cardiovascular and metabolic systems worked more efficiently after exercise training and provided improved responses during submaximal intensities. However, ventilatory efficiency was thereby not affected. The impact of supplemental oxygen during training appeared less important on these submaximal training adaptations but might have affected exercise capacity, particularly at higher intensities. This study highlights the role of exercise training as a cornerstone therapy for patients with COPD, showing a significant improvement of submaximal exercise tolerance and functional capacity, which directly affect patients' ADL and thus quality of life.

6 | PERSPECTIVES

Future research will be important to improve existing knowledge regarding the impact of different training modalities on biological adaptations in COPD. Furthermore, the limited statistical power for some secondary endpoints of the SCOPE study should motivate upcoming studies to further investigate how to best merge advantages from normoxic and hyperoxic exercise training in COPD. Indeed, supplemental oxygen might be specifically utilized during exercise training when peak exercise capacity should be quickly improved in patients with important functional impairment or when higher training intensities are needed to further stimulate training adaptations[20]; for other patients who do not increase exercise tolerance with supplemental oxygen or for those presenting endothelial dysfunction it might though not be needed.[28] Thus, the impact of supplemental oxygen during exercise training should be investigated in different subpopulations, identifying responder and non-responder as well as dose-response relationships, in order to better understand the currently heterogenous study outcomes.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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