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Early View

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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

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Effect of domiciliary oxygen therapy on exercise capacity and quality of life in patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension: a randomized, placebo-controlled trial

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Take home message

Domiciliary oxygen therapy improves the 6-minute walk distance and quality of life in patients with precapillary pulmonary hypertension who desaturate during exercise and should thus be considered as adjunct to medical therapy.

Abstract

The question addressed by the study: We investigated whether domiciliary oxygen therapy (DOXT) increases exercise capacity and quality of life in patients with pulmonary arterial or distal chronic thromboembolic pulmonary hypertension (PAH/CTEPH) presenting with mild resting hypoxemia and exercise-induced oxygen desaturation.

Materials and Methods: 30 patients with PAH/CTEPH, mean age (±SD) 60±15y, pulmonary artery pressure 39±11mmHg, resting pulse oximetry (SpO_2) ≥90%, SpO_2 drop during a 6MWD ≥4%, on PH-targeted medication, were randomized in a double-blind cross-over protocol to DOXT and placebo (ambient air) treatment, each during 5 weeks, at 3 liters/min via nasal cannula during nights and daytime when resting. Treatment periods were separated by 2 weeks wash-out. Co-primary outcomes were changes in 6-min walk distance (6MWD, breathing ambient air) and physical functioning scale (PF) of the short form medical outcome questionnaire (SF-36) during treatment periods.

Results: DOXT increased the 6MWD from baseline 478±113m by a mean (95%CI) of 19m (6 to 32), and PF from 52±29 by 4 points (0 to 8). Corresponding changes with placebo were 1m (-11 to 13) in 6MWD and -2 points (-6 to 2) in PF. Between-treatment differences in changes were 6MWD 18m (1 to 35, P=0.042) and PF 6 points (1 to 11, P=0.029). DOXT significantly improved the NYHA functional class vs. placebo.

Answer to the question: This first randomized trial in PAH/CTEPH patients with exercise-induced hypoxemia demonstrates that DOXT improves exercise capacity, quality of life and functional class. The results support large long-term randomized-trial of DOXT in PAH/CTPEH.

Trial registration: clinicaltrials.gov NCT01884012.

Keywords: Pulmonary hypertension, oxygen therapy, exercise, precapillary pulmonary hypertension

Introduction

In the absence of relevant lung disease, the major forms of precapillary pulmonary hypertension (PH) are pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH). The main symptoms of PAH/CTEPH are exertional dyspnea, impaired exercise performance and reduced quality of life.[1-3] Several pathophysiologic mechanisms may account for the symptoms of PH. Typically, there is an excessive ventilatory drive leading to inefficient ventilation with high ventilatory equivalents for oxygen uptake and carbon dioxide output.[4] Impairments in cardiac output, ventilation-perfusion mismatch, right-left shunt along with a reduced pulmonary diffusing capacity result in arterial and mixed venous hypoxemia that worsens PH even further by pulmonary vasoconstriction.[5] The already elevated ventilatory drive is additionally stimulated by progressive arterial hypoxemia during exercise.[4, 6] As a consequence, oxygen delivery to the muscles, the brain and other organs is reduced and exercise capacity is limited.[4, 7, 8]

We have recently shown that breathing oxygen-enriched air during cycle ergometry significantly increases maximal exercise capacity and almost doubles submaximal endurance time in patients with PAH/CTEPH and exercise-induced hypoxemia.[4] This was related to a higher arterial oxygen content promoting oxygen availability in the brain and muscle tissue and reducing the excessive ventilatory response to exercise, thus enhancing ventilatory efficiency.[4] In a further randomized, placebo controlled, double blind trial in patients with PAH/CTEPH with nocturnal hypoxemia and sleep related breathing disturbances we found that nocturnal oxygen therapy over the course of one week improved the 6 minute walk distance (6MWD) compared to placebo (ambient air).[9]

The treatment of precapillary PH includes targeted medication, supportive measures such as diuretics and exercise training, pulmonary endarterectomy or balloon-angioplasty in selected patients with CTEPH,[10] and lung transplantation.[1] However, according to current

guidelines, the role of supplemental oxygen therapy is not clearly established. Recommendations are based on studies in patients with chronic obstructive pulmonary disease (COPD)[11] and expert opinion suggesting that long-term oxygen therapy should be prescribed in patients with PH if the arterial partial pressure of oxygen (PaO_2) at rest is <8 kPa or if there is exercise-induced hypoxemia with amelioration of symptoms by oxygen therapy during exercise.[1] In a systematic review of the literature we have identified only the two above mentioned randomized-controlled trials[4, 9] evaluating the efficacy of oxygen therapy in PAH/CTEPH.[12] Therefore, the current randomized, placebo-controlled trial tested the hypothesis that domiciliary oxygen therapy (DOXT) used for as many hours/day as possible over the course of five weeks improves the exercise performance and quality of life in patients with PAH/CTEPH who have exercise-induced hypoxemia.

Materials and Methods

Study subjects

Patients with PAH/CTEPH diagnosed according to current guidelines,[1] 18 to 85 y old, both sexes, were recruited among outpatients of the Pulmonary Hypertension Clinic, University Hospital Zurich. Study participants had to be in stable condition on therapy for >4 weeks. Patients with CTEPH had distal disease not suitable for endarterectomy or persistent PH after endarterectomy. Participants had to have a resting pulse oximetry (SpO_2) ≥90% and exercise-induced hypoxemia, i.e., a drop in SpO_2 by ≥4% to ≤92% during a 6MWD test breathing ambient air. Patients with severe hypoxemia (SpO_2 <90% or PaO_2 <7.3 kPa at rest that would require long-term oxygen therapy according to current standards), with other forms of PH, unstable condition, inability to follow study procedures, relevant comorbidities, obstructive sleep apnea syndrome or pregnancy were excluded. The study was carried out from January 2014 to January 2017. Participants provided written informed consent. The protocol was approved by the Cantonal Ethics Committee Zurich (2012-0538) and registered at www.clinicaltrials.gov NCT01884012.

Study design

This randomized, placebo-controlled, double-blind, cross-over trial in patients with PAH or distal CTEPH receiving advanced PH-targeted therapy evaluated the effect of DOXT at the patient's home over the course of 5 weeks on exercise performance and quality of life.

Minimal important differences (and SD) for the co-primary outcomes were assumed as 35 m (SD 50) for the 6MWD[9] and 10 points (SD 10) for the SF-36 physical functioning scale.[13] To achieve a power of 80%, alpha 0.05, a minimal number of 26 participants was required. Accounting for possible drop-outs, the goal was to include 30 participants.

Participants were randomized to a treatment sequence in balanced blocks of 4 using a computer-generated list. The study staff and participants were unaware of the type of

administered treatment (double blinded design). Unblinding was performed only after completion of data analysis.

Methods

Interventions

Patients received DOXT by an oxygen concentrator (EverFlow, Respironics, Zofingen, Switzerland) or ambient air (in the following termed placebo) by an identically looking, modified device at a rate of 3 l/min via a nasal cannula during nights and during daytime at home using a long tube for oxygen delivery. The flow rate of 3 l/min was selected because it was effective in our previous trial[9] and in order to achieve the highest possible effect and compliance while avoiding nasal discomfort and mucosal dryness. Patients were instructed to use each treatment for as long as possible but at least 16 h/24 h over treatment periods. At the end of the first treatment period, a study nurse blinded to the type of treatment collected the first concentrator and, after a 2-week washout period, delivered the second concentrator for the subsequent 5-week period. Operating hours of concentrators were recorded by a built-in counter.

Assessments

Medical history, physical examination and the New York heart Association (NYHA) functional class were evaluated. A 6MWD test was performed while participants were breathing ambient air.[14] Quality of life was assessed by the 1-week-recall form of the short form of the medical outcome questionnaire (SF-36) and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[3, 15] Arterial blood gas analysis of a radial artery blood sample (ABL 90FlTex-blood gas analyzer, Radiometer, Switzerland) and lung function tests were performed.

Echocardiography (Philips iE33; Philips, Zofingen, Switzerland) was performed at the end of the 5-week treatment periods to measure the right atrial (RA) and right ventricular

(RV) areas, fractional area change (RVFAC) and tricuspid annular plain systolic excursion (TAPSE).[16] The maximal systolic velocity of the tricuspid regurgitation jet determined by Doppler ultrasound was used to determine the tricuspid pressure gradient (TPG). RA pressure was estimated from the dimension and respiratory variability of the inferior cava vein.

Arterial blood gas analyses were obtained while patients were at rest and breathing ambient air (ABL Blood Gas Analyzer, Radiometer, Switzerland).

Respiratory sleep studies including pulse oximetry and nasal pressure swings (ApneaLink, ResMed, Basel, Switzerland) were performed in the last night of each 5-week treatment period at the patients' home. Mean nocturnal SpO_2, the oxygen desaturation index (ODI, number of SpO_2 dips $\geq$ 4% lasting $\geq$10 s per h), the pulse rate and the apnea/hypopnea index (AHI, number of apneas+hypopneas per h with reduction of breathing amplitude <50% of baseline lasting $\geq$10 s and associated with a SpO_2 dip $\geq$ 4%) were determined.[17] Cognitive performance was tested with the Stroop test.[18]

Over the course of the last week of each treatment period, physical activity was recorded by an accelerometer worn at the upper non-dominant arm (Sensewear, BodyMedia, Inc, Pittsburgh, Pennsylvania).[19]

Outcomes

Co-primary outcomes were the changes in the 6MWD and in the SF-36 physical functioning scale from the beginning to the end of the 5-weeks treatment periods with oxygen and placebo, respectively. Secondary outcomes assessed at the end of each 5-weeks treatment period included the NYHA functional class, results of questionnaire evaluations, echocardiography, sleep studies and actimetry. All outcomes measured during daytime were assessed while patients were breathing ambient air.

Analysis

Data are summarised as means ±SD and frequency (percentages). Analysis of co-primary outcomes was performed in the intention-to-treat population with missing values replaced by multiple imputations using chained equations.[20] Treatment effects were assessed by computing linear mixed effects regression models with fixed effects of treatment (oxygen, placebo) and random effects of patients. This provided unadjusted differences of variables with 95% confidence intervals (95% CI) between oxygen and placebo treatment periods; adjusted treatment effects were computed by including treatment, age, sex and treatment order as independent variables into the models. Effect sizes were computed as mean change in a variable divided by the SD of baseline; values of 0.2 were considered small and 0.5 moderate.[21]Analyses of secondary outcomes was performed in the per-protocol population with all available data. For the NYHA class, treatment effects were estimated by random-effects ordered logistic regression and expressed as odds ratio with 95% CI. A probability of $P<0.05$ was assumed as statistically significant.

Results

Patients

The patient flow is illustrated in figure 1. Patient characteristics are shown in table 1. Thirty patients with PAH/CTEPH were randomised and represented the intention-to-treat population. One patient withdrew consent after randomisation for personal reasons, another after completing the first treatment period due to newly detected breast cancer and pending treatment. For the intention-to-treat analysis, the missing data of these 2 patients were replaced by multiple imputation. The per-protocol analysis included 28 patients who completed the entire protocol.

Main outcomes

Table 2 presents the main outcomes. Over the course of the 5 weeks DOXT, the 6MWD increased by a mean of 19 m (95% confidence interval [CI], 6 to 32), while the corresponding change with placebo was -1 m (-11 to 13). The mean between-treatment difference (treatment effect) was 18 m (95% CI 1 to 35, P = 0.042) in favor of DOXT; the effect size was 0.40 (95% CI 0.01 to 0.79). The per-protocol analysis and the analysis with adjustment for baseline 6MWD, age, sex and treatment order (figure 2, supplementary table 1) revealed consistent results. The heart rate at the end of the 6MWD increased to a higher value over the course of 5 weeks DOXT period compared to placebo and patients rated their dyspnea at the end of the 6MWD slightly higher with DOXT than with placebo. The SF-36 physical functioning scale revealed an increase over the course of the 5 weeks DOXT while there was no significant change with placebo resulting in a between-treatment difference of 6 points (95% CI 1 to 11, P = 0.029) in favor of DOXT; the effect size was 0.50 (95% CI 0.05 to 0.95). Results were similar in the intention-to-treat and the per-protocol analysis, and after adjustment for baseline scores, age, sex and treatment order (figure 2, supplementary table 2). The PH class (PAH and CTEPH) was not a significant predictor of the main outcomes (supplementary tables 4 and 4).

On average, treatment adherence with DOXT was 13.2 h/day which was less than the recommended use of >16 h/day. Nevertheless, adherence with DOXT was significantly greater than that with placebo by a mean of 2.8 h/day (95% CI 0.3 to 5.3, P = 0.026).

Secondary outcomes

Over the course of 5 weeks DOXT, the proportion of patients in NYHA functional classes 1 and 2 increased while the proportion of patients in classes 3 and 4 decreased (table 3). With placebo, there was an increase in the proportion of patients in classes 1 and 4 and a decrease in classes 2 and 3. Correspondingly, logistic regression analysis indicated a

beneficial effect of DOXT on the NYHA class as reflected in a low odds ratio for an increase by one class over the 5 weeks DOXT of 0.13 (95% CI 0.03 to 0.61, P = 0.010) compared to placebo (table 3). The SF-36 physical and mental component summary scores and the CAMPHOR quality of life symptoms and activity domains were similar at the end of the treatment periods with DOXT and placebo.

Echocardiography at the end of treatment periods did not reveal differences between DOXT and placebo in terms of the elevated tricuspid pressure gradient, the estimated right atrial pressure and the indices of right ventricular function (RVFAC, TAPSE) (table 3). However, there was a significant decrease in the RV systolic and diastolic area at the end of the DOXT compared to the placebo period (table 3).

Arterial blood gas analyses whilst breathing ambient air did not show any significant changes in PaO_2 and $PaCO_2$ with treatment (table 3).

The sleep studies revealed mild hypoxemia at baseline and an ODI and AHI within the normal range (table 3). At the end of the 5 weeks treatment periods (performed while using the corresponding treatment) the mean nocturnal SpO_2 was increased with DOXT and unchanged with placebo. In addition, there was a slight decrease in the ODI with DOXT compared to placebo (P = 0.011) and a trend for a decrease in mean nocturnal heart rate with DOXT (P=0.058).

Cognitive testing revealed an increased speed in Stroop 1 assessed at the end of the DOXT compared to the placebo period (table 3).

Activity recordings over the course of week 5 of the treatment periods did not show any difference in the estimated number of steps/day (table 3).

No serious adverse event occurred. Episodes of mild epistaxis were reported by 7/30 patients during the DOXT period and by 6/30 patients during the placebo period.

Discussion

The current randomized, placebo-controlled, double-blind, cross-over trial is the first to evaluate the effect of DOXT in patients suffering from PAH/CTEPH with mild resting hypoxemia and oxygen desaturation during exercise. The results demonstrate that 5 weeks of DOXT during nights and rest at home leads to a significant increase in the 6MWD and in the SF-36 PF quality of life scale compared to placebo treatment. Moreover, DOXT improved the NYHA functional class, aspects of cognitive performance and it increased and stabilized the nocturnal SpO_2. The current trial provides important new evidence supporting the use of DOXT as a valuable adjunct to medical therapy in selected patients with PAH/CTEPH. It corroborates and extends our two previous randomized, placebo-controlled trials in patients with PAH/CTEPH demonstrating an improvement in cycling endurance with oxygen administration and in the 6MWD after 1 week of nocturnal oxygen therapy in those with sleep disordered breathing.[4, 9, 22]

Until recently, there has been a lack of evidence supporting a benefit of DOXT in patients with PH. Acknowledging this limitation, the authors of the 2015 ESC/ERS guidelines[1] have suggested to use data from studies in patients with COPD performed more than 30 years ago[11, 23, 24] as a guidance to prescribe DOXT to patients with PH "when PaO_2 is consistently <8.0 kPa" and to consider ambulatory oxygen "when there is evidence of symptomatic benefit and correctable desaturation during exercise". Considering the fundamentally different pathophysiology of COPD and PAH/CTEPH the urgent need for robust evidence evaluating the role of oxygen therapy in PAH/CTEPH is obvious. The current randomized, placebo-controlled trial address this gap in knowledge by demonstrating a beneficial effect of DOXT in a specific setting, i.e., in patients with PAH/CTEPH who have mild hypoxemia at rest that exacerbates during physical activity.

The symptoms and limitations of exercise performance in PH and its distinct characteristic, exercise-induced hypoxemia, can be attributed to several pathophysiological mechanisms: impaired pulmonary gas exchange due to ventilation-perfusion mismatch,[4, 7] limitation of pulmonary vasculature recruitment, excessive rise in PVR hindering an adequate increase in cardiac output by the already stressed right ventricle,[25] increased respiratory drive leading to hypocapnia with inefficient ventilation, and worsening of PVR due to hypoxic pulmonary vasoconstriction with progressive arterial and mixed-venous hypoxemia during exercise.

In healthy individuals[26] and patients with PAH/CTEPH,[4] we showed that breathing oxygen-enriched air during cycling exercise substantially increased performance by acting on the cited pathophysiologic mechanisms. In particular, breathing oxygen-enriched air reduced the ventilatory response to exercise that is typically excessive in PH, thereby reduced the ventilatory equivalents for CO_2 output and improved the arterial oxygenation along with a greater availability of oxygen in muscles and in the brain.[4],[26] In the current study, even though oxygen therapy was not provided during assessment of the 6MWD at the end of the 5 weeks DOXT, the performance was improved compared to placebo. Presumably, alleviation of hypoxemia by DOXT reflected in the higher nocturnal SpO_2 with DOXT (table 3) may have contributed to a reduction of the ventilatory drive with enhanced ventilatory efficiency and a stabilizing effect on ventilation as suggested by the reduced ODI (table 3). Moreover, the trend for a reduction in nocturnal pulse rate during DOXT is consistent with a reduction in sympathetic tone. Together, these effects of DOXT may have promoted a reduction in the PVR that was sustained even during temporary discontinuation of oxygen administration during daytime and the 6MWD tests. The reduction in the RV dimensions documented by echocardiography (table 3) is consistent with RV unloading by DOXT.

Physical activity is of paramount importance for living a normal life, and inability of participating in daily physical activities is associated with a reduced quality of life.[27] Thus, the improvements in the NYHA functional class and in the PF scale of SF-36 quality of life by DOXT are important, patient-centred outcomes of our study (table 3). The QoL domains assessed with the PH-specific CAMPHOR questionnaire did not significantly change during the study. Consistent with the current results, our earlier trial in patients with PAH/CTEPH and sleep related breathing disturbances revealed improvements in the 6MWD after 1 week of nocturnal oxygen therapy in association with an increase in the SF-36 PF scale. However, physical activity assessed during the last week of DOXT or placebo by an accelerometer showed no difference between the two treatment periods. Apparently, the daily activity was not adapted to the greater performance ability with DOXT or actimetry was not sensitive enough to capture subtle changes.

We have previously shown that cerebral tissue oxygenation is correlated to cognitive performance in PAH/CTEPH patients,[8] and that a lower cerebral tissue oxygenation during exercise is prevented with oxygen therapy.[4, 18] Thus, by improving systemic and possibly cerebral oxygenation DOXT may have enhanced cerebral functions (table 3).

DOXT was well tolerated by the patients and, apart from occasional minor nasal bleeding, did not have any relevant undesirable effects. Nevertheless, the inconvenience of wearing a nasal cannula during the night and daytime may have prevented a positive effect of DOXT in certain quality of life domains other than PF. Interestingly, patients used DOXT for more hours per day (+2.8 h/day on average, table 1) than placebo, raising the possibility that the lack of a perceived beneficial effect of placebo might have negatively influenced adherence.

Although oxygen therapy was applied in the current trial over a much longer time period (5 weeks) than in previous randomized studies (up to one week)[9] we cannot exclude

that an even more prolonged treatment over several months or years and a greater adherence to DOXT than the observed mean use of 13.2 h/day would have improved pulmonary hemodynamics and important outcomes such as time to clinical worsening. Therefore, the current results may serve as a valuable basis for designing larger trials evaluating long-term DOXT in patients with PH. The effect size achieved with DOXT was small to moderate but still considerable, taking into account that patients were already on PH-targeted drugs. Moreover, we cannot exclude that the estimated treatment effect of DOXT was diluted to some degree by the cross-over design of our trial even though our analysis did not indicate any carry-over or order effect (supplementary tables 1 and 2).

In conclusion, our randomised, placebo-controlled trial demonstrates that 5 weeks of DOXT improves exercise performance, quality of life and the NYHA functional class in patients with PAH/CTEPH who have exercise induced hypoxemia. Therefore, in addition to its beneficial effects in PAH/CTEPH with sleep related breathing disorders,[9] DOXT has the potential to serve as a valuable adjunct to PH-targeted drug treatment in patients with PAH/CTEPH who show mild hypoxemia at rest that is exacerbated during exercise.

Author contributions

SU and KEB contributed to the conception and design. SS, EDH, EIS, SRS, MF, PRB, ML, KEB and SU contributed to acquisition, analysis, or interpretation of data. SU and SS drafted the manuscript. All revised it critically for important intellectual content. SU is the guarantor of the study.

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Data sharing

Individual de-identified patient data will be shared with non-commercial entities upon a personalized request to the author.

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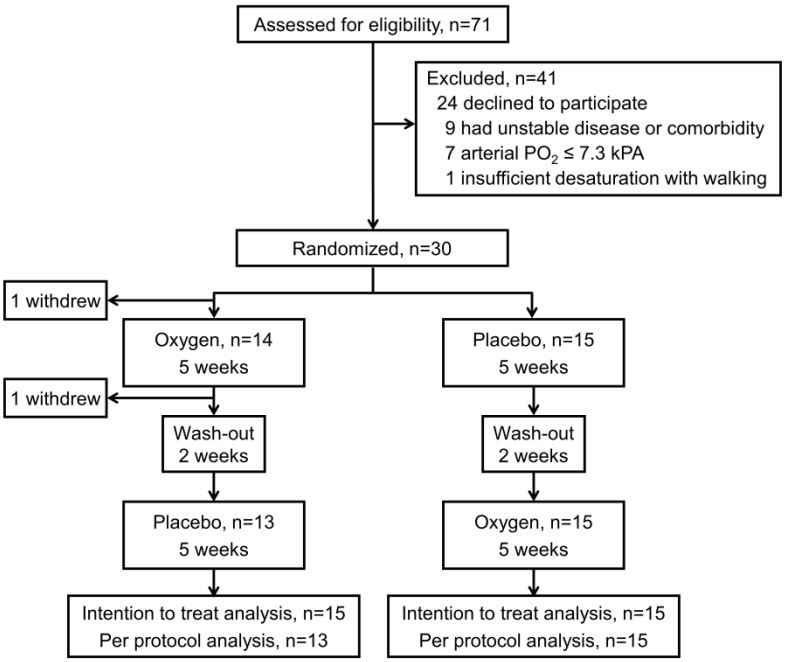
Figure legends

Figure 1: Patient flow chart.

Figure 2: Effect of domiciliary oxygen therapy for 5 weeks on the 6-minute walk distance (upper panels) and the physical functioning scale of quality of life (lower panels). The pink and red bars with whiskers represent mean (SE) adjusted values at the beginning and end of the 5-weeks treatment period with oxygen, the blue columns and whiskers represent corresponding values of the physical functioning scale of the short form 36 of the medical outcome questionnaire (SF-36). The right panels show the treatment effect of oxygen compared to placebo calculated as adjusted mean difference (with 95% confidence intervals) of changes during oxygen therapy minus corresponding vales during placebo therapy (regression models are shown in supplementary tables 1 and 2).


Assessed for eligibility, n=71
Excluded, n=41
24 declined to participate
9 had unstable disease or comorbidity
7 arterial PO_2 ≤ 7.3 kPA
1 insufficient desaturation with walking
Randomized, n=30
1 withdrew
Oxygen, n=14
5 weeks
Placebo, n=15
5 weeks
1 withdrew
Wash-out
2 weeks
Wash-out
2 weeks
Placebo, n=13
5 weeks
Oxygen, n=15
5 weeks
Intention to treat analysis, n=15
Per protocol analysis, n=13
Intention to treat analysis, n=15
Per protocol analysis, n=15

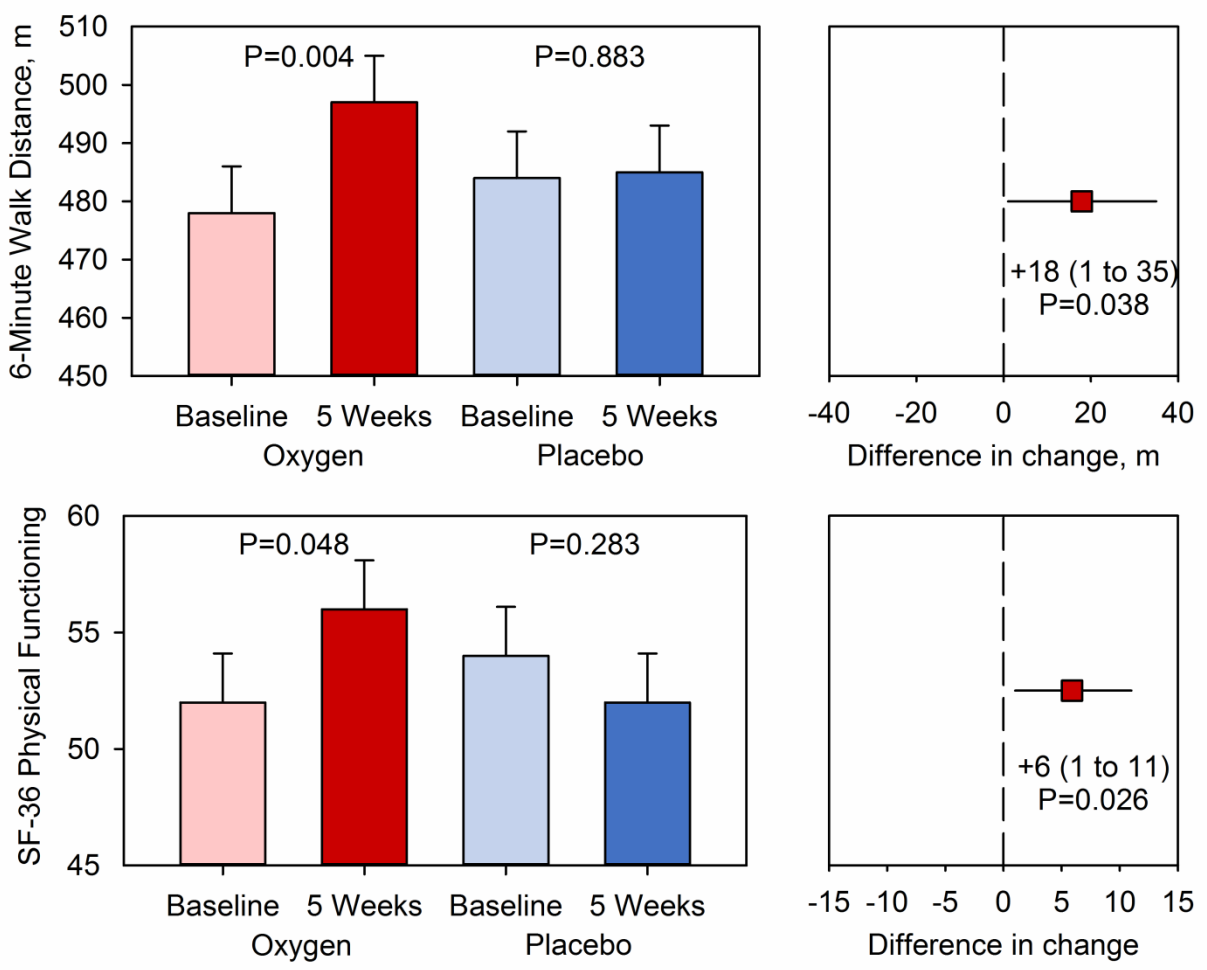

6-Minute Walk Distance, m
510
500
490
480
470
460
450
P=0.004
P=0.883
Baseline
5 Weeks
Baseline
5 Weeks
Oxygen
Placebo
+18 (1 to 35)
P=0.038
-40
-20
0
20
40
Difference in change, m
SF-36 Physical Functioning
60
55
50
45
P=0.048
P=0.283
Baseline
5 Weeks
Baseline
5 Weeks
Oxygen
Placebo
+6 (1 to 11)
P=0.026
-15
-10
-5
0
5
10
15
Difference in change

Table 1. Patient characteristics

Number of participants (female)	30 (20)
Age, years	60 ± 15
Pulmonary hypertension classification	
Pulmonary arterial hypertension	14 (47%)
- Idiopathic	12 (40%)
- Connective tissue disease related	2 (7%)
Chronic thromboembolic pulmonary hypertension	16 (53%)
Right heart catheter data and systemic blood pressure	
Mean pulmonary artery pressure, mmHg	39 ± 11
Pulmonary artery wedge pressure, mmHg	11 ± 3
Right atrial pressure, mmHg	8 ± 4
Cardiac index, l/min/m^{-2}	3.0 ± 0.8
Pulmonary vascular resistance, Wood units	5.8 ± 3.0
Mixed venous oxygen saturation, %	67 ± 8
Heart rate, bpm	70 ± 12
Systemic blood pressure, systolic, mmHg	126 ± 18
Systemic blood pressure, diastolic, mmHg	75 ± 13
Arterial blood gas analysis	
pH	7.42 ± 0.04
PaO_2, kPa	10.0 ± 1.7
$PaCO_2$, kPa	4.5 ± 0.5
Lung function	
Forced expiratory volume in 1 sec (FEV1), % predicted	88 ± 22
Forced vital capacity (FVC), % predicted	93 ± 22
FEV1/FVC, %	77 ± 8
Diffusing capacity for carbon monoxide, % predicted	69 ± 15
Pulmonary Hypertension treatment	
Endothelin receptor antagonist	19 (63%)
Phosphodiesterase-5-Inhibtor	14 (47%)
Soluble guanylate cyclase stimulator	8 (28%)
Prostanoids	3 (10%)
Combination therapy	11 (37%)

means ±SD, number (%).

Table 2. Main outcomes

		Placebo (ambient air)			Domiciliary oxygen therapy			Treatment effect	
		Beginning of treatment period	**End of 5 weeks treatment period**	**Mean change (95% CI)**	**Beginning of treatment period**	**End of 5 weeks treatment period**	**Mean change (95% CI)**	**Mean difference of change (95% CI)**	**P value**
6-minute walk test (breathing ambient air)									
6-min walk distance, m	ITT	484±113	485±113	1 (-11 to 13)	478±113	497±114	19 (6 to 32)	18 (1 to 35)	0.042
	PP	484±113	484±107	0 (-12 to 11)	477±107	495±101	18 (6 to 30)	19 (2 to 35)	0.028
Heart rate at rest, 1/min		84±15	79±14	-5 (-10 to 0)	84±14	76±13	-8 (-12 to -3)	-3 (-10 to 4)	0.427
Heart rate at end exercise, 1/min		122±19	114±19	-7 (-13 to -1)	114±19	120±18	6 (-1 to 12)	13 (4 to 22)	0.003
SpO_2 at rest, %		95±3	95±3	0 (-1 to 2)	95±3	94±3	-1 (-2 to 0)	-1 (-3 to 0)	0.136
SpO_2 at end exercise, %		88±5	89±5	1 (-1 to 3)	89±5	88±5	-1 (-3 to 1)	-2 (-5 to 1)	0.119
SpO_2 desaturation with walk		-7±4	-7±5	1 (-1 to 3)	-6±5	-6±5	0 (-2 to 2)	-1 (-4 to 2)	0.604
Dyspnea, Borg CR10 score		5.2±2.7	5.1±2.6	-0.2 (-1.0 to 0.7)	4.3±2.6	5.5±2.5	1.1 (0.2 to 2.0)	1.3 (0.1 to 2.5)	0.036
Quality of life									
SF-36 physical functioning scale, %									
	ITT	54±29	52±29	-2 (-6 to 2)	52±29	56±29	4 (0 to 8)	6 (1 to 11)	0.029
	PP	56±27	54±26	-2 (-6 to 2)	53±26	57±26	4 (0 to 8)	6 (1 to 12)	0.022
Treatment adherence									
Mean concentrator use, h/night		-	10.4±6.7	-	-	13.2±6.9	-	2.8 (0.3 to 5.3)	0.026

Means ±SD. Treatment effects were computed as mean difference in change (with 95% confidence intervals) during 5 weeks oxygen minus corresponding change during 5 weeks placebo. ITT = intention-to-treat analysis; PP = per-protocol analysis; SF-36 = short form of the medical outcome questionnaire

Table 3. Secondary outcomes

	Baseline	End of 5 weeks placebo treatment (ambient air)	End of 5 weeks domiciliary oxygen therapy	Treatment effect (mean difference, 95%CI)	P-value
Functional class and quality of lif					
NYHA class (I, II, III, IV), % patients	(7/30/53/10)	(14/28/45/14)	(21/32/43/4)	0.13 (0.03 to 0.61)*	0.010
Physical component score SF-36, %	38±11	39±11	39±11	0 (-2 to 3)	0.819
Mental component score SF-36, %	49±11	50±11	51±11	0 (-2 to 3)	0.904
CAMPHOR, symptoms	8.0±6.3	7.2±6.3	6.5±5.4	-0.8 (-2.3 to 0.8)	0.333
CAMPHOR, activity	7.3±5.9	7.4±5.9	6.7±5.9	-0.7 (-2.1 to 0.7)	0.316
CAMPHOR, quality of life	4.0±5.3	4.7±5.4	3.7±5.4	-1.0 (-2.2 to 0.3)	0.120
MLHF, general	30.4±22.8	29.6±22.9	27.9±23.0	-1.7 (-6.3 to 2.8)	0.457
MLHF, physical	14.1±10.1	14.5±10.2	13.5±10.2	-1.0 (-3.1 to 1.0)	0.329
MLHF, emotional	7.4±7.0	6.9±7.0	6.7±7.0	-0.3 (-1.7 to 1.2)	0.713
Echocardiography					
Tricuspid pressure gradient, mmHg	NA	46±22	47±22	1 (-6to 8)	0.822
Right atrial pressure, mmHg	NA	5.3±2.1	5.3±2.2	-0.1 (-0.9 to 0.8)	0.918
Tricuspid annular plane systolic excursion, cm	NA	1.9±2.8	2.6±2.9	0.7 (-0.7 to 2.2)	0.305
Right ventricular fractional area change,, %	NA	33±11	38±11	5 (-2 to 11)	0.158
Right ventricular area, systolic, cm^2	NA	17.3±7.7	14.0±7.7	-3.2 (-5.3 to -1.2)	0.002
Right ventricular area, diastolic, cm^2	NA	25.1±9.1	21.6±9.0	-3.4 (-5.8 to -1.1)	0.005
NT-pro brain natriuretic peptide (ng/l)	495±993	555±986	586±990	32 (-142 to 206)	0.722
Arterial blood gas analysis					
PaO_2, kPa	10.0±1.6	9.3±1.6	9.4±1.6	0.1 (-0.4 to 0.6)	0.627
$PaCO_2$, kPa	4.5±0.7	4.8±0.7	4.6±0.7	-0.2 (-0.5 to 0.0)	0.099
Sleep studies					
Mean nocturnal SpO_2, %	89±4	89±4	91±4	1 (0 to 2)	0.006
Oxygen desaturation index, events/h	8.7±8.9	9.2±9.0	6.2±9.1	-3.0 (-5.4 to -0.7)	0.011
Apnea/hypopnea index, events/h	10.7±14.6	10.5±14.6	8.6±14.8	-1.9 (-5.4 to 1.5)	0.279
Mean nocturnal pulse rate, ppm	65±9	66±9	64±8	-2 (-5 to 0)	0.058

Cognitive performance					
Stroop 1 time, s	15±3	14±3	13±3	-1 (-2 to 0)	0.033
Stroop 2 time, s	19±4	17±4	17±4	0 (-1 to 1)	0.868
Stroop 3 time, s	29±10	28±10	26±10	-2 (-5 to 1)	0.270
Activity recordings					
Steps/day	5654±3274	5055±3279	5222±3290	167 (-407 to 742)	0.568

Means ±SD. Treatment effects are the mean difference (with 95% confidence intervals) between outcomes at the end of 5 weeks oxygen treatment period minus corresponding values at the end of the 5 weeks placebo treatment period. * For the New York heart association (NYHA) class, treatment effects were computed by logistic regression and expressed as odds ratio of reducing the NYHA class by 1 class with DOXT vs. placebo. CAMPHOR = Cambridge pulmonary hypertension outcome review; MLHF: Minnesota living with heart failure questionnaire; PaO2 = arterial partial pressure of oxygen; PaCO2 arterial partial pressure of carbon dioxide. NA=echocardiography not available at baseline.

Supplementary data to

Effect of domiciliary oxygen therapy on exercise capacity and quality of life in patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension: a randomized, placebo-controlled trial

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Supplementary table 1. Multivariable linear regression analysis of predictors of the 6-minute walk distance

Dependent variable 6-minute walk distance				
Predictors	Coefficient	SE	95% CI	P value
Effect of treatment period				
Reference: baseline of room air treatment period, m	-	-	-	-
End of 5 weeks room air treatment period, m	-3	8	-20 to 13	0.679
Baseline of oxygen treatment period, m	0	9	-18 to 17	0.963
End of 5 weeks oxygen treatment period, m	18	10	-1 to 38	0.066
Effect of treatment order				
Reference: room air treatment first, m	-	-	-	
Oxygen treatment first, m	-28	38	-103 to 47	0.459
Interaction effect treatment period * treatment order				
Reference: room air treatment first, baseline of room air treatment period, m	-	-	-	-
Room air treatment first, end of 5 weeks room air treatment period, m	9	12	-14 to 31	0.459
Oxygen treatment first, baseline of oxygen treatment period, m	-10	12	-33 to 14	0.413
Oxygen treatment first, end of 5 weeks oxygen treatment period, m	-9	13	-34 to 16	0.458
Age, years	-3	1	-5 to 0	0.026
Sex, female vs. male	-4	40	-83 to 74	0.913
Intercept	668	84	504 to 832	<0.001

Intention-to-treat analysis, missing data replaced by multiple imputation. n=30 participants, 120 observations. The regression model was used to compute the adjusted treatment effect, figure 2.

Supplementary table 2. Multivariable linear regression analysis of predictors of the physical functioning scale, short form medical outcome questionnaire (SF-36)

Dependent variable physical functioning scale				
Predictors	Coefficient	SE	95% CI	P value
Effect of treatment period				
Reference: baseline of room air treatment period, m	-	-	-	-
End of 5 weeks room air treatment period, m	-1	3	-6 to 4	0.700
Baseline of oxygen treatment period, m	1	3	-5 to 6	0.779
End of 5 weeks oxygen treatment period, m	3	3	-2 to 8	0.258
Effect of treatment order				
Reference: room air treatment first, m	-	-	-	
Oxygen treatment first, m	-17	10	-36 to 2	0.088
Interaction effect treatment period * treatment order				
Reference: room air treatment first, baseline of room air treatment period, m	-	-	-	-
Room air treatment first, end of 5 weeks room air treatment period, m	-2	4	-10 to 6	0.593
Oxygen treatment first, baseline of oxygen treatment period, m	-6	4	-14 to 1	0.109
Oxygen treatment first, end of 5 weeks oxygen treatment period, m	-3	4	-11 to 4	0.408
Age, years	0	0	0 to 1	0.724
Sex, female vs. male	10	10	-10 to 29	0.339
Intercept	50	21	9 to 90	0.018

Intention-to-treat analysis, missing data replaced by multiple imputation. n=30 participants, 120 observations. The regression model was used to compute the adjusted treatment effect, figure 2.

Supplementary table 3. Multivariable linear regression analysis of predictors of the 6-minute walk distance including classification of pulmonary hypertension

Dependent variable 6-minute walk distance				
Predictors	Coefficient	SE	95% CI	P value
Effect of treatment period				
Reference: baseline of room air treatment period, m	-	-	-	-
End of 5 weeks room air treatment period, m	1	6	-11 to 13	0.885
Baseline of oxygen treatment period, m	-5	6	-17 to 7	0.384
End of 5 weeks oxygen treatment period, m	13	7	1 to 26	0.041
Effect of classification of pulmonary hypertension				
Reference: Pulmonary arterial hypertension (Group I)	-	-	-	
Chronic thromboembolic pulmonary hypertension (Group IV)	-1	3	-7 to 5	0.770
Age, years	0	0	-1 to 1	0.797
Sex, female vs. male	-3	8	-20 to 13	0.703
Baseline 6MWD	1	0	1 to 1	<0.001
Intercept	32	30	-26 to 89	0.284

Intention-to-treat analysis, missing data replaced by multiple imputation. n=30 participants, 120 observations.

Supplementary table 4. Multivariable linear regression analysis of predictors of the physical functioning scale, short form medical outcome questionnaire (SF-36) including classification of pulmonary hypertension

Dependent variable 6-minute walk distance				
Predictors	Coefficient	SE	95% CI	P value
Effect of treatment period				
Reference: baseline of room air treatment period, m	-	-	-	-
End of 5 weeks room air treatment period, m	-2	2	-6 to 2	0.292
Baseline of oxygen treatment period, m	-2	2	-6 to 1	0.219
End of 5 weeks oxygen treatment period, m	1	2	-2 to 5	0.450
Effect of classification of pulmonary hypertension				
Reference: Pulmonary arterial hypertension (Group I)	-	-	-	
Chronic thromboembolic pulmonary hypertension (Group IV)	1	1	-1 to 2	0.419
Age, years	0	0	0 to 0	0.531
Sex, female vs. male	4	2	0 to 9	0.043
Baseline score	1	0	1 to 1	<0.001
Intercept	3	5	-6 to 12	0.452

Intention-to-treat analysis, missing data replaced by multiple imputation. n=30 participants, 120 observations.