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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Domiciliary oxygen therapy improves 6-min walk distance and quality of life in patients with precapillary pulmonary hypertension who desaturate during exercise, and should thus be considered as an adjunct to medical therapy http://bit.ly/2M8H4iq

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ABSTRACT

Study question: 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 hypoxaemia and exercise-induced oxygen desaturation.

Materials and methods: 30 patients with PAH/CTEPH, mean±SD age 60±15 years, pulmonary artery pressure 39±11 mmHg, resting arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) ⩾90%, S_{pO_2} drop during a 6-min walk test ⩾4%, on pulmonary hypertension-targeted medication, were randomised in a double-blind crossover protocol to DOXT and placebo (ambient air) treatment, each over 5 weeks, at 3 L·min^{-1} *via* nasal cannula overnight and when resting during the day. Treatment periods were separated by 2 weeks of washout. Co-primary outcomes were changes in 6-min walk distance (6MWD, breathing ambient air) and physical functioning scale of the 36-item short-form medical outcome questionnaire during treatment periods.

Results: DOXT increased the 6MWD from baseline 478±113 m by a mean (95% CI) of 19 (6–32) m, and physical functioning from 52±29 by 4 (0–8) points. Corresponding changes with placebo were 1 (−11–13) m in 6MWD and −2 (−6–2) points in physical functioning. Between-treatment differences in changes were 6MWD 18 (1–35) m (p=0.042) and physical functioning 6 (1–11) points (p=0.029). DOXT significantly improved the New York Heart Association functional class *versus* placebo.

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

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 dyspnoea, impaired exercise performance and reduced quality of life [1–3]. Several pathophysiological 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 and right–left shunt along with a reduced pulmonary diffusing capacity result in arterial and mixed venous hypoxaemia that worsens PH even further by pulmonary vasoconstriction [5]. The already elevated ventilatory drive is additionally stimulated by progressive arterial hypoxaemia 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 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 hypoxaemia [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 randomised placebo-controlled double-blind trial in patients with PAH/CTEPH with nocturnal hypoxaemia and sleep-related breathing disturbances we found that nocturnal oxygen therapy over the course of 1 week improved the 6-min 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 oxygen tension (P_{aO_2}) at rest is <8 kPa or if there is exercise-induced hypoxaemia with amelioration of symptoms by oxygen therapy during exercise [1]. In a systematic review of the literature we have identified only the two aforementioned randomised controlled trials [4, 9] evaluating the efficacy of oxygen therapy in PAH/CTEPH [12]. Therefore, the current randomised placebo-controlled trial tested the hypothesis that domiciliary oxygen therapy (DOXT) used for as many hours per day as possible over the course of 5 weeks improves the exercise performance and quality of life in patients with PAH/CTEPH who have exercise-induced hypoxaemia.

Materials and methods

Study subjects

Patients with PAH/CTEPH diagnosed according to current guidelines [1], aged 18–85 years, of 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 arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) ⩾90% and exercise-induced hypoxaemia, *i.e.* a drop in S_{pO_2} by ⩾4% to ⩽92% during a 6-min walk test (6MWT) breathing ambient air. Patients with severe hypoxaemia (S_{pO_2} <90% or P_{aO_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 apnoea syndrome or pregnancy were excluded. The study lasted 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 randomised placebo-controlled double-blind crossover trial in patients with PAH or distal CTEPH receiving advanced PH-targeted therapy evaluated the effect of DOXT on exercise performance and quality of life at the patient's home over the course of 5 weeks.

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This study is registered at clinicaltrials.gov (NCT01884012). Individual de-identified patient data will be shared with non-commercial entities upon a personalised request to the author.

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

Participants were randomised to a treatment sequence in balanced blocks of four 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.

Interventions

Patients received DOXT *via* an oxygen concentrator (EverFlow; Respironics, Zofingen, Switzerland) or ambient air (termed placebo in the following) *via* a modified device identical in appearance at a rate of 3 L·min^{-1} *via* a nasal cannula overnight and *via* a long tube for oxygen delivery at home during the day. The flow rate of 3 L·min^{-1} 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 for $\geqslant$16 h·day^{-1} 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 New York Heart Association (NYHA) functional class were evaluated. A 6MWT was performed while participants were breathing ambient air [14]. Quality of life was assessed using the SF-36 1-week recall form and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [3, 15]. Arterial blood gas analysis of a radial artery blood samples (ABL90 FLEX blood gas analyser; 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 and right ventricular areas, right ventricular 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). Right atrial 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 analyser).

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 patient's home. Mean nocturnal S_{pO_2}, oxygen desaturation index (ODI: number of S_{pO_2} dips $\geqslant$4% lasting $\geqslant$10 s·h^{-1}), pulse rate and apnoea–hypopnoea index (AHI: number of apnoeas + hypopnoeas per hour with reduction of breathing amplitude <50% of baseline lasting $\geqslant$10 s and associated with a S_{pO_2} dip $\geqslant$4%) were determined [17]. Cognitive performance was tested using the Stroop test [18].

Over the course of the last week of each treatment period, physical activity was recorded using an accelerometer worn at the upper nondominant arm (SenseWear; BodyMedia, Pittsburgh, PA, USA) [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-week treatment periods with oxygen and placebo. Secondary outcomes assessed at the end of each 5-week treatment period included 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 mean±SD and n (%). 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 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 standard deviation of baseline; values of 0.2 were considered small and 0.5 moderate [21]. Analyses

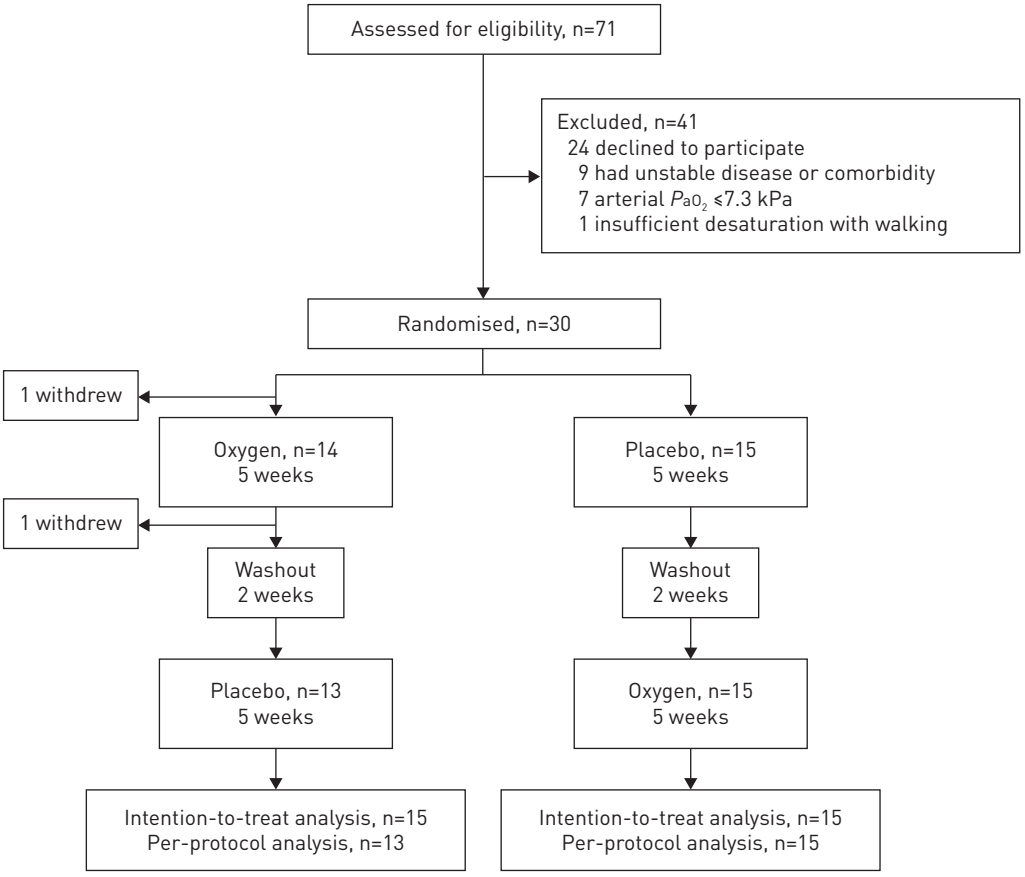

FIGURE 1 Patient flow chart. P_{aO_2}: arterial oxygen tension.

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 (95% CI). A probability of $p<0.05$ was assumed as statistically significant.

Results

Patients

The patient flow chart is illustrated in figure 1. Patient characteristics are shown in table 1. 30 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 two 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 (95% CI) of 19 (6–32) m, while the corresponding change with placebo was −1 (−11–13) m. The mean between-treatment difference (treatment effect) was 18 (1–35) m (p=0.042) in favour of DOXT; the effect size was 0.40 (0.01–0.79). The per-protocol analysis and the analysis with adjustment for baseline 6MWD, age, sex and treatment order (figure 2, supplementary table S1) revealed consistent results. The heart rate at the end of the 6MWT increased to a higher value over the course of 5 weeks DOXT period compared to placebo and patients rated their dyspnoea at the end of the 6MWT 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 (1–11) points (p=0.029) in favour of DOXT; the effect size was 0.50 (0.05–0.95). Results were similar in the intention-to-treat and the per-protocol analyses, and after adjustment for baseline scores, age, sex and treatment order (figure 2, supplementary table S2). The PH class (PAH and CTEPH) was not a significant predictor of the main outcomes (supplementary table S4).

TABLE 1 Patient characteristics

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)
CTEPH	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 $L \cdot min^{-1} \cdot m^{-2}$	3.0±0.8
Pulmonary vascular resistance Wood units	5.8±3.0
Mixed venous oxygen saturation %	67±8
Heart rate $beats \cdot min^{-1}$	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
P_{aO_2} kPa	10.0±1.7
P_{aCO_2} kPa	4.5±0.5
Lung function	
FEV_1 % pred	88±22
FVC % pred	93±22
FEV1/FVC %	77±8
D_{LCO} % pred	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)

Data are presented as n, mean±SD or n (%). CTEPH: chronic thromboembolic pulmonary hypertension; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

On average, treatment adherence with DOXT was 13.2 $h \cdot day^{-1}$ which was less than the recommended use of >16 $h \cdot day^{-1}$. Nevertheless, adherence with DOXT was significantly greater than that with placebo by a mean of 2.8 $h \cdot day^{-1}$ (95% CI 0.3 to 5.3, p=0.026).

Secondary outcomes

Over the course of 5 weeks of 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 of DOXT of 0.13 (95% CI 0.03–0.61, 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 TPG, the estimated right atrial pressure and the indices of right ventricular function (RVFAC, TAPSE) (table 3). However, there was a significant decrease in the right ventricular systolic and diastolic area at the end of the DOXT compared to the placebo period (table 3).

Arterial blood gas analyses while breathing ambient air did not show any significant changes in P_{aO_2} and arterial carbon dioxide tension with treatment (table 3).

The sleep studies revealed mild hypoxaemia at baseline and an ODI and AHI within the normal range (table 3). At the end of the 5-week treatment periods (performed while using the corresponding treatment) the mean nocturnal S_{pO_2} was increased with DOXT and unchanged with placebo. In addition,

TABLE 2 Main outcomes

	Placebo (ambient air)			Domiciliary oxygen therapy			Treatment effect[#]	
	Beginning of treatment period	End of 5-week treatment period	Mean change (95% CI)	Beginning of treatment period	End of 5-week treatment period	Mean change (95% CI)	Mean difference of change (95% CI)	p-value
6MWT (breathing ambient air)								
6MWD m								
ITT	484±113	485±113	1 (−11–13)	478±113	497±114	19 (6–32)	18 (1–35)	0.042
Per-protocol	484±113	484±107	0 (−12–11)	477±107	495±101	18 (6–30)	19 (2–35)	0.028
Heart rate at rest L·min^{-1}	84±15	79±14	−5 (−10–0)	84±14	76±13	−8 (−12–−3)	−3 (−10–4)	0.427
Heart rate at end exercise L·min^{-1}	122±19	114±19	−7 (−13–−1)	114±19	120±18	6 (−1–12)	13 (4–22)	0.003
S_{pO_2} at rest %	95±3	95±3	0 (−1–2)	95±3	94±3	−1 (−2–0)	−1 (−3–0)	0.136
S_{pO_2} at end exercise %	88±5	89±5	1 (−1–3)	89±5	88±5	−1 (−3–1)	−2 (−5–1)	0.119
S_{pO_2} desaturation with walk	−7±4	−7±5	1 (−1–3)	−6±5	−6±5	0 (−2–2)	−1 (−4–2)	0.604
Dyspnoea Borg CR10 score	5.2±2.7	5.1±2.6	−0.2 (−1.0–0.7)	4.3±2.6	5.5±2.5	1.1 (0.2–2.0)	1.3 (0.1–2.5)	0.036
Quality of life								
SF-36 physical functioning scale %								
ITT	54±29	52±29	−2 (−6–2)	52±29	56±29	4 (0–8)	6 (1–11)	0.029
Per-protocol	56±27	54±26	−2 (−6–2)	53±26	57±26	4 (0–8)	6 (1–12)	0.022
Treatment adherence								
Mean concentrator use h·night^{-1}		10.4±6.7			13.2±6.9		2.8 (0.3–5.3)	0.026

Data are presented as mean±SD, unless otherwise stated. 6MWT: 6-min walk test; 6MWD: 6-min walk distance; ITT: intention-to-treat analysis; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; SF-36: 36-item short-form medical outcome questionnaire. [#]: mean difference in change (95% CI) between outcomes during 5 weeks of oxygen minus corresponding change during 5 weeks of placebo.

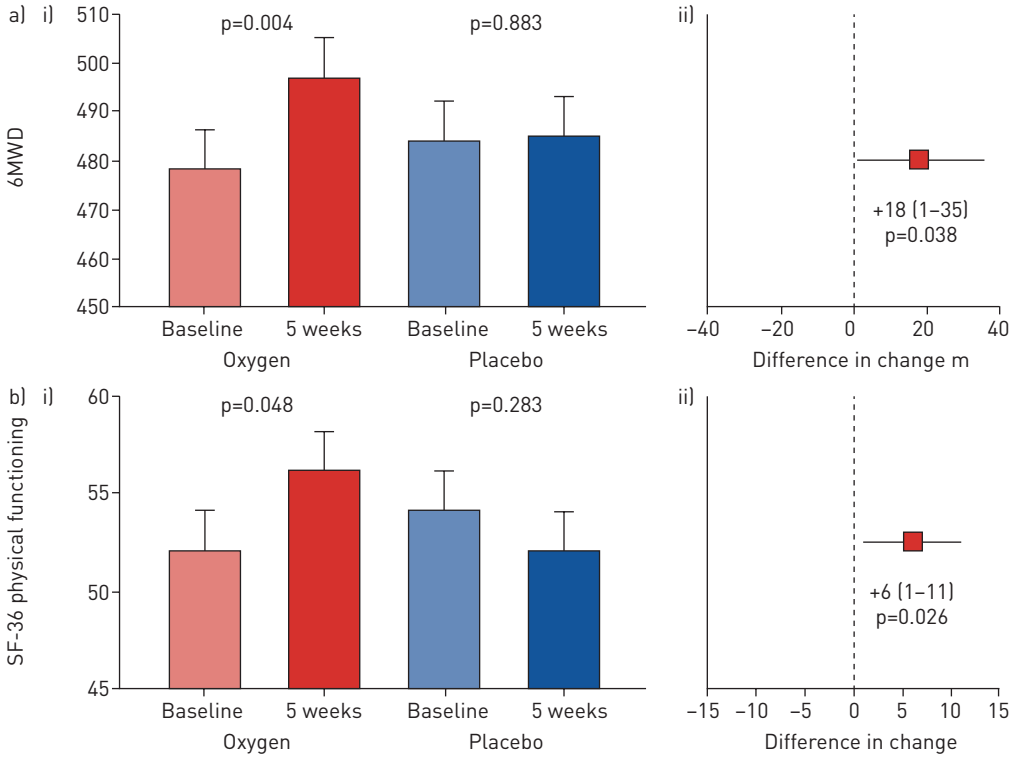

FIGURE 2 Effect of domiciliary oxygen therapy for 5 weeks on the a) 6-minute walk distance (6MWD) and b) physical functioning scale of the 36-item short form medical outcome quality-of-life questionnaire (SF-36). Data are presented as i) mean±SE adjusted values and ii) treatment effect of oxygen compared to placebo calculated as adjusted mean difference (95% CI) of changes during oxygen therapy minus corresponding vales during placebo therapy (regression models are shown in supplementary tables S1 and S2).

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 per day (table 3).

No serious adverse events occurred. Episodes of mild epistaxis were reported by seven out of 30 patients during the DOXT period and by six out of 30 patients during the placebo period.

Discussion

The current randomised placebo-controlled double-blind, crossover trial is the first to evaluate the effect of DOXT in patients suffering from PAH/CTEPH with mild resting hypoxaemia 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 physical functioning quality-of-life score compared to placebo treatment. Moreover, DOXT improved NYHA functional class and aspects of cognitive performance and it increased and stabilised the nocturnal S_{pO_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 randomised 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 European Society of Cardiology/European Respiratory Society guidelines [1] have suggested the use of data from studies in patients with COPD performed >30 years ago [11, 23, 24] as a guidance to prescribe DOXT to patients with PH "when P_{aO_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

TABLE 3 Secondary outcomes

	Baseline	End of 5-week placebo treatment (ambient air)	End of 5-week domiciliary oxygen therapy	Treatment effect[#]	p-value
Functional class and quality of life					
NYHA class (I/II/III/IV) % patients	(7/30/53/10)	(14/28/45/14)	(21/32/43/4)	0.13 (0.03–0.61)[¶]	0.010
Physical component score SF-36 %	38±11	39±11	39±11	0 (−2–3)	0.819
Mental component score SF-36 %	49±11	50±11	51±11	0 (−2–3)	0.904
CAMPHOR, symptoms	8.0±6.3	7.2±6.3	6.5±5.4	−0.8 (−2.3–0.8)	0.333
CAMPHOR, activity	7.3±5.9	7.4±5.9	6.7±5.9	−0.7 (−2.1–0.7)	0.316
CAMPHOR, quality of life	4.0±5.3	4.7±5.4	3.7±5.4	−1.0 (−2.2–0.3)	0.120
MLHF, general	30.4±22.8	29.6±22.9	27.9±23.0	−1.7 (−6.3–2.8)	0.457
MLHF, physical	14.1±10.1	14.5±10.2	13.5±10.2	−1.0 (−3.1–1.0)	0.329
MLHF, emotional	7.4±7.0	6.9±7.0	6.7±7.0	−0.3 (−1.7–1.2)	0.713
Echocardiography					
Tricuspid pressure gradient mmHg	NA	46±22	47±22	1 (−6–8)	0.822
Right atrial pressure mmHg	NA	5.3±2.1	5.3±2.2	−0.1 (−0.9–0.8)	0.918
Tricuspid annular plane systolic excursion cm	NA	1.9±2.8	2.6±2.9	0.7 (−0.7–2.2)	0.305
Right ventricular fractional area change %	NA	33±11	38±11	5 (−2–11)	0.158
Right ventricular area, systolic cm^2	NA	17.3±7.7	14.0±7.7	−3.2 (−5.3–−1.2)	0.002
Right ventricular area, diastolic cm^2	NA	25.1±9.1	21.6±9.0	−3.4 (−5.8–−1.1)	0.005
NT-proBNP ng·L^{-1}	495±993	555±986	586±990	32 (−142–206)	0.722
Arterial blood gas analysis					
P_{aO_2} kPa	10.0±1.6	9.3±1.6	9.4±1.6	0.1 (−0.4–0.6)	0.627
P_{aCO_2} kPa	4.5±0.7	4.8±0.7	4.6±0.7	−0.2 (−0.5–0.0)	0.099
Sleep studies					
Mean nocturnal S_{pO_2} %	89±4	89±4	91±4	1 (0–2)	0.006
Oxygen desaturation index events·h^{-1}	8.7±8.9	9.2±9.0	6.2±9.1	−3.0 (−5.4–−0.7)	0.011
AHI events·h^{-1}	10.7±14.6	10.5±14.6	8.6±14.8	−1.9 (−5.4–1.5)	0.279
Mean nocturnal pulse rate ppm	65±9	66±9	64±8	−2 (−5–0)	0.058
Cognitive performance					
Stroop 1 time s	15±3	14±3	13±3	−1 (−2–0)	0.033
Stroop 2 time s	19±4	17±4	17±4	0 (−1–1)	0.868
Stroop 3 time s	29±10	28±10	26±10	−2 (−5–1)	0.270
Activity recordings					
Steps per day	5654±3274	5055±3279	5222±3290	167 (−407–742)	0.568

Data are presented as mean±SD, unless otherwise stated. NYHA: New York Heart Association; SF-36: 36-item short-form medical outcome questionnaire; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; MLHF: Minnesota Living with Heart Failure questionnaire; NT-proBNP: N-terminal pro-brain natriuretic peptide; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; AHI: apnoea–hypopnoea index; NA: echocardiography not available at baseline. [#]: mean difference (95% CI) between outcomes at the end of 5-week oxygen treatment period minus corresponding values at the end of the 5-week placebo treatment period; [¶]: for NYHA class, treatment effects were computed by logistic regression and expressed as odds ratio of reducing the NYHA class by one class with domiciliary oxygen therapy *versus* placebo.

COPD and PAH/CTEPH, the urgent need for robust evidence evaluating the role of oxygen therapy in PAH/CTEPH is obvious. The current randomised 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 hypoxaemia at rest that exacerbates during physical activity.

The symptoms and limitations of exercise performance in PH and its distinct characteristic, exercise-induced hypoxaemia, 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 pulmonary vascular resistance (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 hypoxaemia 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 pathophysiological 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 carbon dioxide 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 of DOXT, performance was improved compared to placebo. Presumably, alleviation of hypoxaemia by DOXT reflected in the higher nocturnal S_{pO_2} with DOXT (table 3) may have contributed to a reduction of the ventilatory drive with enhanced ventilatory efficiency and a stabilising 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 right ventricular dimensions documented by echocardiography (table 3) is consistent with right ventricular unloading by DOXT.

Physical activity is of paramount importance for living a normal life, and inability to participate in daily physical activities is associated with a reduced quality of life [27]. Thus, the improvements in the NYHA functional class and in the physical functioning scale of SF-36 quality of life by DOXT are important, patient-centred outcomes of our study (table 3). The quality-of-life 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 physical functioning score. 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 shown previously 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 physical functioning. Interestingly, patients used DOXT for more hours per day (+2.8 $h \cdot day^{-1}$ 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 randomised studies (up to 1 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 $h \cdot day^{-1}$ would have improved pulmonary haemodynamics 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 crossover design of our trial even though our analysis did not indicate any carry-over or order effect (supplementary tables S1 and S2).

In conclusion, our randomised, placebo-controlled trial demonstrates that 5 weeks of DOXT improves exercise performance, quality of life and NYHA functional class in patients with PAH/CTEPH who have exercise-induced hypoxaemia. 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 hypoxaemia at rest that is exacerbated during exercise.

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