Effects of downhill walking in pulmonary rehabilitation for patients with COPD: a randomised controlled trial

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Downhill walking is a feasible, acceptable and safe training modality that increases the likelihood of achieving clinically important gains in functional exercise tolerance in patients with COPD
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ABSTRACT The development of contractile muscle fatigue (CMF) affects training responses in patients with chronic obstructive pulmonary disease (COPD). Downhill walking induces CMF with lower dyspnoea and fatigue than level walking. This study compared the effect of pulmonary rehabilitation (PR) comprising downhill walking training (DT) to PR comprising level walking (conventional training (CT)) in patients with COPD.

In this randomised controlled trial, 35 patients (62±8 years; forced expiratory volume in 1 s (FEV_1) 50±17% predicted) were randomised to DT or CT. Exercise tolerance (6-minute walk test distance (6MWD); primary outcome), muscle function, symptoms, quality-of-life and physical activity levels were assessed before and after PR. Absolute training changes and the proportion of patients exceeding the 30 m 6MWD minimally important difference (MID) were compared between groups. Quadriceps muscle biopsies were collected after PR in a subset of patients to examine physiological responses to long-term eccentric training.

No between-group differences were observed in absolute 6MWD improvement (mean 6MWD change 77±46 m DT *versus* 56±47 m CT; p=0.45), however 94% of patients in DT exceeded the 6MWD MID compared to 65% in CT (p=0.03). Patients in DT tended to have larger improvements than CT in other outcomes. Muscle biopsy analyses did not differ between groups.

PR incorporating downhill walking confers similar magnitudes of effects to PR with conventional walking across clinical outcomes in patients with COPD, however, offers a more reliable stimulus to maximise the achievement of clinically relevant gains in functional exercise tolerance in people with COPD.

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This work is registered at ClinicalTrials.gov with identifier NCT02113748. Individual deidentified data from participants from the present study can be shared upon request to researchers who provide a methodologically sound proposal. Only data regarding the results presented in this manuscript can be shared beginning 3 months and ending 12 months after publication.

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Introduction

Exercise training is a fundamental component of pulmonary rehabilitation (PR) and primary source of benefit for outcomes such as exercise tolerance and quality of life [1]. High-intensity exercise can stimulate more profound physiological muscular adaptation than lower intensity exercise [2]. However, some patients with chronic obstructive pulmonary disease (COPD) may have limited potential to sustain such training loads. This could be due to a range of factors such as symptoms (*e.g.* dyspnoea, fatigue [3, 4]), ventilatory impairment (*e.g.* dynamic hyperinflation, gas exchanges disturbances and obstructive airways) or skeletal muscle dysfunction (*e.g.* low muscle mass, mitochondrial dysfunction, oxidative stress) [5]. The development of contractile muscle fatigue (CMF) after exercise has been associated with enhanced exercise tolerance after training [6, 7]; yet, interestingly, almost one-third of patients with COPD do not exhibit CMF after pulmonary rehabilitation despite incorporating "fatigable" modalities such as cycling [8].

Downhill walking is an exercise modality characterised by high volumes of eccentric activity in the quadriceps femoris muscles. This is due to a "braking" pattern during walking, which increases the duration of the eccentric component of gait [9]. Repeated eccentric contractions *via* downhill walking associates with enhanced mechanical stress to the muscle [10] and induces CMF more reliably, and with lower ventilatory requirements, than level walking in patients with COPD [11]. This modality may therefore help improve training responses in those who do not develop CMF during conventional pulmonary rehabilitation. Little data currently exists regarding the potential role for downhill walking in pulmonary rehabilitation in people with COPD [12] as the modality could potentially cause more knee instability and injury [13, 14] precluding the safe use of downhill walking in training programmes.

This study aimed to determine the feasibility, safety and effectiveness of pulmonary rehabilitation including downhill walking training (DT) compared with pulmonary rehabilitation including conventional walking training (CT) on the primary outcome of functional exercise tolerance. We also explored the effects of downhill walking training on other conventional training outcomes, progression of training intensity and muscle physiology (*i.e.* quadriceps tissue biomarkers). We hypothesised a larger intervention effect on exercise tolerance (*i.e.* 6-min walk test (6MWT)) would be observed in patients following downhill walking training, especially those without CMF at randomisation.

Methods

Study population

All patients with COPD [15] referred to outpatient pulmonary rehabilitation at University Hospital Leuven (Belgium) between April 2014 and January 2016 were screened for eligibility. Patients were ineligible if they had significant comorbid conditions that restricted their ability to safely perform exercise training or precluded them from training completion (*e.g.* awaiting lung transplantation). Furthermore, patients in whom evaluation of contractile muscle fatigue *via* magnetic femoral nerve stimulation was contraindicated (*e.g.* bilateral metallic hip prothesis or bilateral intravenous femoral bypass) were ineligible for recruitment. Ethics approval was obtained from the University Hospital Leuven ethics committee (ML10278) and written, informed consent was obtained from all participants. The study was registered at clinicialtrials.gov (identifier NCT02113748).

Study procedures

An overview of the study and outcome measurements is provided in figure 1. Participants underwent comprehensive baseline evaluation 1 week prior to commencing pulmonary rehabilitation. This comprised assessment of complete lung function [16], peripheral muscle force (dynamometry [17]) and respiratory muscle force (maximal respiratory pressures [18]), maximal exercise tolerance (cardiopulmonary exercise test (CPET) [19]), cycle endurance test (CET) [20]), functional exercise tolerance (6MWT [21–23]; physical activity levels based on 1 week assessment (GT3X; Actigraph, Pensacola, FL, USA) [24], quality of

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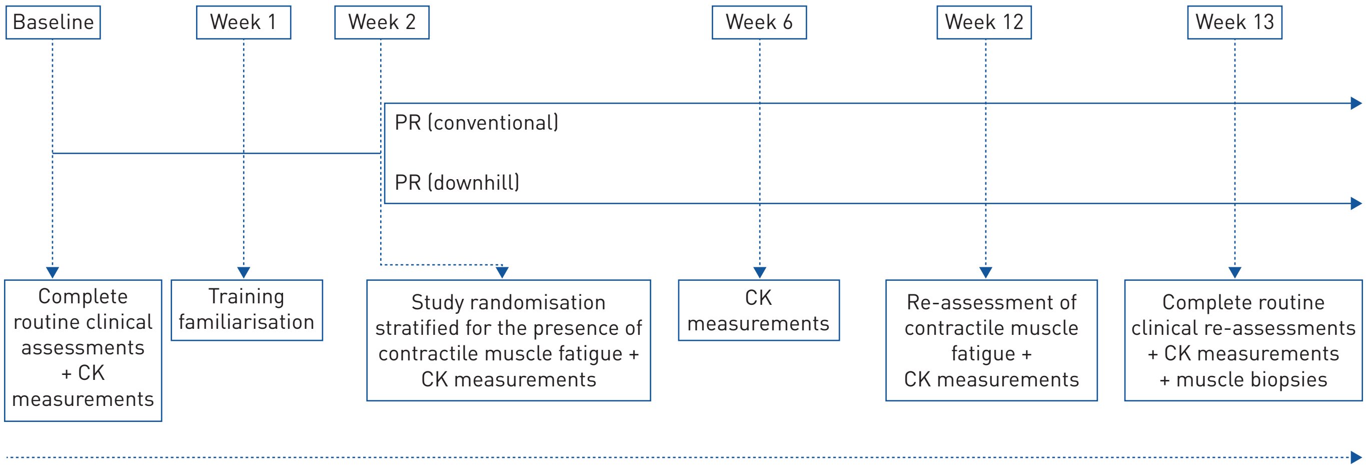

FIGURE 1 Study overview. PR: Pulmonary rehabilitation; conventional: training including conventional treadmill walking; downhill: training including downhill walking; CK: creatine kinase.

life (Chronic Respiratory Disease Questionnaire (CRDQ) [25]), perceived breathlessness (modified Medical Research Council scale (mMRC) [26]) and health status (COPD Assessment Test (CAT) [27]). Pulmonary rehabilitation training then commenced three-times per week for 12 weeks with all patients familiarised to conventional treadmill walking during the first week.

Quadriceps CMF was evaluated after an exercise session in week two, to enable stratification of patients according to CMF absence/presence. CMF was assessed using a protocol described previously [6]. Potentiated twitch contractions (TW_{qpot}) were measured in a sitting position before and 15-minutes after a PR session. The femoral nerve was stimulated through a 45 mm figure-of-eight coil powered by a double Magstim stimulator (Magstim Co. Ltd, Whitland, UK). Force was measured by a strain-gauge force transducer (DS Europe 546QD), amplified (Model 811A amplifiers; Hewlett-Packard) and stored on a computer. CMF was defined as ⩾15% decrease of pre-exercise TW_{qpot} [28].

Patients were then randomly assigned to undertake the remaining 10 weeks of pulmonary rehabilitation as conventional or downhill walking training. Random sequence generation was undertaken *via* web-based software (www.randomisation.com) in block sizes of four and six for both strata by personnel external to the study team. Allocation was concealed *via* sealed, opaque, sequentially numbered envelopes. Patients and pulmonary rehabilitation staff were not blinded to knowledge of interventions; however, data for the primary outcome were collected by a blinded therapist (not involved in the study). All baseline assessments were re-evaluated after pulmonary rehabilitation completion (week 13). Serum creatine kinase (CK) was measured at baseline, week 2, 6 and 12 to assess intervention safety. Feasibility was defined *a priori* as ⩾75% protocol completion, while acceptability was evaluated *via* custom questionnaires (supplementary material). In order to evaluate physiological adaptations in response to long-term eccentric training, muscle biopsies of the right vastus lateralis muscle were collected in a subset of consenting patients in the week after pulmonary rehabilitation re-evaluations (week 14). This was performed *via* the suction-modified Bergström muscle biopsy technique [29]. Blood and fat tissue were dissected, and samples fixed in isopentane cooled in liquid nitrogen for analysis. Histological analyses comprised determination of cross-sectional area, proportion of fibres I, IIa and IIx, number of capillaries per fibre, and number of nuclei and satellite cells [30–32].

Training regimens in conventional and downhill walking training

Full details regarding the pulmonary rehabilitation programme used at our centre have been previously reported [6, 33]. Briefly, it involves cycling, walking (up to 20 mins), upper and lower limb strength training, arm cranking and stair climbing. Sessions last 60–90 min and intensity is progressed weekly. Patients who desaturate below 90% on transcutaneous pulse oximetry are offered titrated supplementary oxygen. For our study, downhill walking training differed from conventional walking training only on the basis of the treadmill training protocol. While conventional walking training involved walking on a motorised treadmill with neutral inclination, progressed *via* increases in duration, speed and inclination (positive), downhill walking training was performed at a fixed −10% inclination [11] (*i.e.* a 10 m decline for every 100 m walked) *via* insertion of a customised bracket underneath the treadmill, secured against the rear feet [11]. After familiarisation during initial sessions, participants were encouraged to walk without handrail support to optimise the eccentric quadriceps stimulus. Downhill walking training was only progressed in terms of duration and speed. No treadmill running was allowed in either group.

Analysis

The primary endpoint was change (week 12 minus baseline) in 6MWD. Based on previous work from our group suggesting a mean±SD 6MWD change between patients with and without CMF after pulmonary rehabilitation of 38±40 m [6], a sample size of 42 patients was deemed necessary to have 80% power to detect a true difference between groups, allowing for a typical (17%) dropout rate at our centre. Findings were also expressed as the proportion of patients who exceeded the minimally important difference (MID) for the 6MWT (30 m) [21].

Secondary endpoints were changes in peripheral muscle force, CET, CPET, physical activity levels, symptoms and quality of life. Physiological adaptations were evaluated during CET *via* isotime comparison of ventilation, oxygen consumption, perceived dyspnoea and fatigue (modified Borg scale (0–10)) [34]. Weekly training progression and symptoms for treadmill and cycling stations was compared between groups *via* linear mixed models using compound symmetry as covariant structure and a *post hoc* Bonferroni adjustment. Area under the curve (AUC) was calculated for symptoms for each plot and expressed as absolute units (U). Responder analyses comparing the proportion of patients exceeding MIDs for secondary outcomes were also conducted. Patients who completed <75% of pulmonary rehabilitation sessions were excluded from data analysis (specified *a priori*).

Statistical analyses were performed with SAS 9.4 (SAS Institute Inc, San Diego, CA, USA). Data normality was verified using the Shapiro–Wilk test and expressed as mean±SD or medians (interquartile range) according to data distribution. Changes in longitudinal outcomes were compared within groups using paired t-test or Wilcoxon test. Comparison of training responses between groups were done *via* analysis of covariance adjusted for baseline levels of that outcome and reported as mean (95% confidence interval) and/or effect size (Cohen's d) considering values ⩽0.5 small, ⩽0.8 moderate and >0.8 large [35]. Change in physical activity levels were corrected for seasonality using a daylight time proxy [24]. Muscle biopsy data were compared between groups *via* unpaired t-tests or Mann–Whitney tests. Categorical data were compared using Chi-squared test. Consistent with the stratification, one pre-planned sub-analysis was conducted to compare training responses between patients who did *versus* did not develop CMF to explore whether this factor was an effect modifier. α was set at 0.05 for all analyses.

Results

44 patients were recruited and randomised after screening 105 for eligibility. 38 patients completed their end-pulmonary rehabilitation assessment (86% retention); however, three were excluded from the final analysis (full details in figure 2). Participant characteristics are described in table 1. All presented with airflow obstruction and reduced peripheral muscle force, exercise tolerance and physical activity levels.

Training responses

Improvements across a range of clinical outcomes were observed in patients of both groups (table 2). Significant and clinically relevant 6MWD increases were observed within both groups (mean±SD downhill walking training change (ΔDT) of 77±46 m (18±15%), p<0.001; conventional walking training change (ΔCT) of 56±47 m (14±14%), p<0.001; table 2, figure S1); however, differences between groups were modest (ΔDT minus ΔCT: 21 (−11–53)m; d=0.45) and not statistically significant. 28 out of 38 patients exceeded the MID for 6MWD; however, this proportion was greater in downhill walking training compared with conventional walking training (17 out of 18 (94%) *versus* 11 out of 17 (65%); p=0.033). Downhill walking training was associated with faster weekly progression of treadmill speed and lower perceived dyspnoea after week 6 than conventional walking training (AUC=34.73U in downhill walking training compared with 46.92U in conventional walking training; p=0.04); figure 3). Perceived fatigue was consistently reported as being lower in downhill than in conventional walking training; however, this was not statistically significant (AUC=40.66U in downhill compared with 49.65U in conventional walking training; p=0.15).

Performance on CET improved in both groups (median (interquartile range) ΔDT 660 (80–880) s *versus* ΔCT 250 (60–420) s, p<0.05 for both; p=0.056 between groups), with similar proportions of patients exceeding the MID of >100 s (12 out of 18 (67%) for downhill walking training, 10 out of 17 (59%) for conventional walking training; p>0.05). Minute-by-minute responses for ventilation and oxygen consumption are summarised in figure 4. At week 12, improvements were observed in the downhill, but not conventional walking training, group for isotime measures of ventilation (median (interquartile range) change of -8.8 (−10.93 – −1.96) $L{\cdot}min^{-1}$, p<0.001; *versus* change -3.72 (−13.8–1.63) $L{\cdot}min^{-1}$, p=0.07, respectively) and oxygen consumption (median (interquartile range) change of -0.13 (−0.30–0.00)

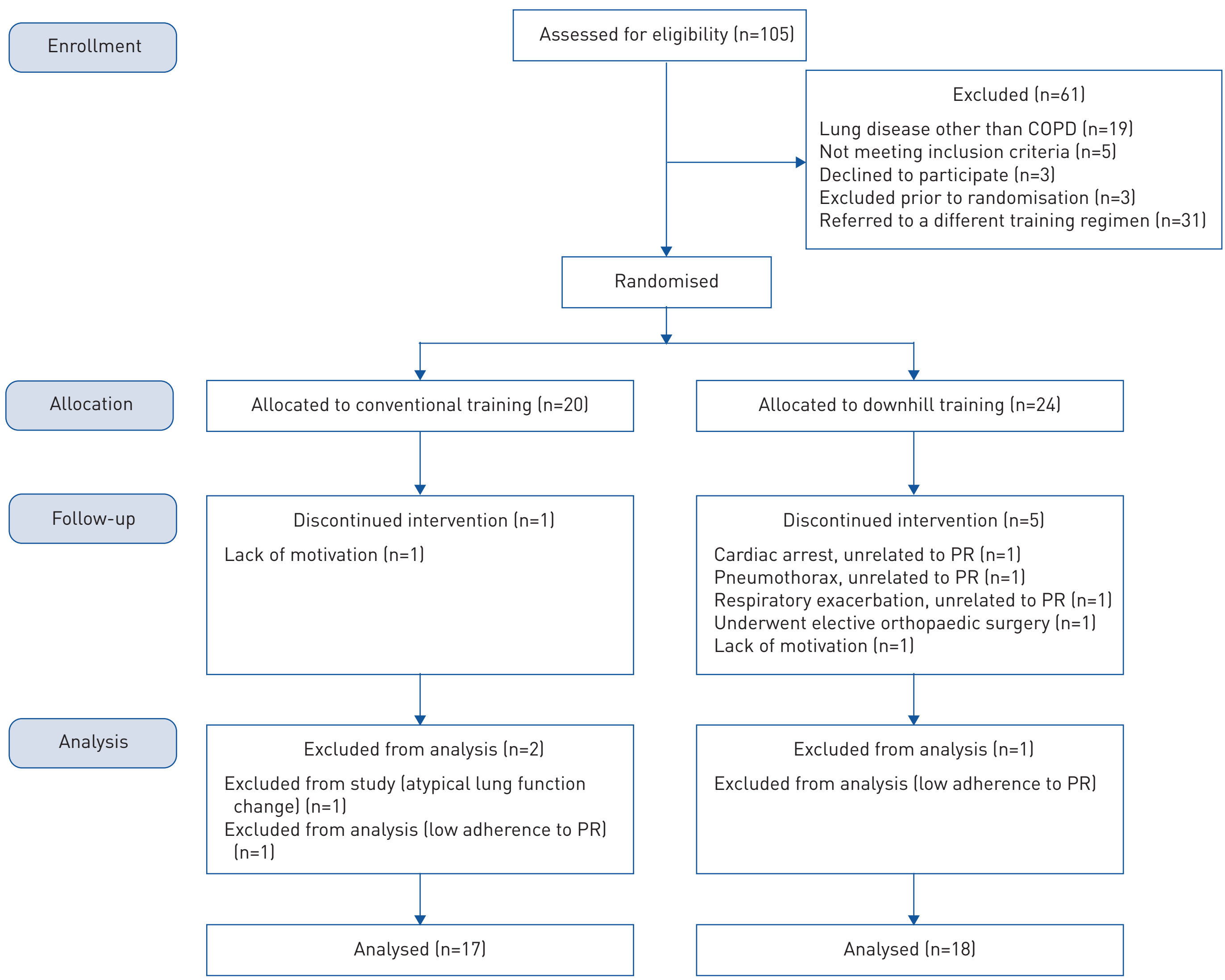

FIGURE 2 Consort flow diagram of patients in the study.

L·min^{-1}, p=0.05; *versus* change of -0.005 (−0.20–0.10) L·min^{-1}, p=0.56, respectively) with no significant between-group differences (p>0.05). Self-reported isotime dyspnoea decreased in the downhill, but not the conventional walking training, group (median (interquartile range) change in Borg score −3 (−4 – −1), p<0.0001 *versus* −1 (−4.5–1), p=0.11, respectively), while fatigue levels decreased similarly in both groups (median (interquartile range) change in fatigue score −3 (−4 – −1) in downhill walking training *versus* −2 (−3–0) in conventional walking training; p<0.01 for both). Changes in mMRC (table 2) and the proportion of patient exceeding MID of the scale (10 out of 13 (77%) in downhill walking training two out of 10 (20%)) were significantly larger on patients in downhill than in conventional walking training (p<0.05 for both).

Effect of pulmonary rehabilitation in patients without CMF

Training responses in the subgroup of 20 participants who did not exhibit CMF at the time of randomisation (n=11 in downhill walking training, n=9 in conventional walking training) are summarised in table 3. Significant improvements in 6MWD (median (interquartile range) change of 93 (45–102) m in downhill walking training *versus* 41 (−1–70) m, d=2.75) and mMRC (median (interquartile range) change -1 (−2–0) points in downhill walking training *versus* 0 [0–0] in conventional walking training; d=1.00) were only observed in downhill walking training (p<0.05 for both). Improvements across other outcomes were similar in both groups (table 3).The proportion of patients who exceeded the MID was greater in downhill than conventional walking training for 6MWD (10 out of 11 (91%) in downhill walking training;

TABLE 1 Baseline characteristics of included participants

		Training intervention	
	All subjects	Conventional walking therapy	Downhill walking therapy
Subjects n	44	20	24
Demographic characteristics			
Age years	62±8	62±9	62±8
Male/female n (% male)	28/16 (64)	11/9 (55)	17/7 (71%
BMI kg·m^{-2}	25±6	27±6	24±7
Lung function			
FEV_1 % predicted	50±18	54±20	47±16
FEV_1/FVC %	44±14	44±12	45±15
FRC % predicted	161±41	166±38	158±43
D_{LCO} % predicted	47±15	48±16	46±14
Peripheral muscle strength			
QF Nm	115±31	120±34	108±28
QF % predicted	74 (65–93)	70 (62–93)	78 (66–98)
Exercise tolerance			
6MWD m	442±112	415±123	464±100
6MWD % predicted	67±16	64±19	68±12
Cycle endurance test s	285±128	265±105	301±145
Maximal oxygen uptake % predicted	45±15	48±18	42±13
Maximal oxygen uptake mL·kg·min^{-1}	15±4	15±4	15±4
Max workload % predicted	41 (30–58)	45 (30–61)	38 (30–50)
Daily physical activity levels			
Steps per day n	4711±2599	4842±2819	4562±2928
Health-related quality of life			
CRDQ dyspnoea	14 (12–16)	14 (13–16)	14 (11–16)
CRDQ total	75 (66–83)	76 (68–80)	74 (63–88)
Symptoms			
CAT questionnaire	20 (14–23)	20 (12–23)	18 (13–22)
mMRC	3 (2–3)	3 (1–3)	3 (2–4)

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FRC: functional residual capacity; D_{LCO}: diffusion capacity of the lung for carbon monoxide; QF: quadriceps force; 6MWD: 6-min walk distance; CRDQ: Chronic Respiratory Disease Questionnaire; CAT: Clinical Assessment Test for COPD; mMRC: modified Medical Research Council scale.

five out of nine (55%) in conventional walking training, p=0.06 between groups) and mMRC scale (eight out of 11 (75%) in downhill walking training; one out of nine (11%) in conventional walking training; p=0.005 between groups), but not for CPET, CET or CRDQ.

Feasibility, acceptability and safety of downhill walking training

The downhill walking training protocol was completed by 79% of participants, with most participants finding it safe (89%) and easy (72%) to perform and feeling it helped them walk more in their daily life (78%). Adverse events occurred in a small number of patients, mostly unrelated to training (supplementary material). Serum creatine kinase levels were consistently low and did not differ between groups (figure S3). Muscle biopsy analyses were undertaken in 25 patients who completed training. No differences were observed between groups for markers of muscle damage or training adaptations, with cross-sectional area, proportion of fibres I, IIa and IIx, number of capillary contacts per fibre, number of nuclei per fibre, satellite cells per fibre and number of central nuclei per fibre being all similar (figure 5). No differences in biopsy outcomes or serum levels of creatine kinase were apparent between patients who did or did not exhibit CMF upon randomisation.

Discussion

This study confirms that pulmonary rehabilitation incorporating downhill walking is safe and confers similar magnitudes of effects to pulmonary rehabilitation with conventional walking across clinical outcomes in patients with COPD. Downhill walking training patients walked at faster speed with lower perceived dyspnoea and progressed more rapidly during pulmonary rehabilitation. Furthermore, downhill

TABLE 2 Training responses for each training programme

	Conventional training programme		Downhill training programme		Mean (95% CI) difference of responses between groups	Difference of responses between groups p-value	Cohen's d between groups
	Baseline	12 weeks	Baseline	12 weeks			
Subjects n	17		18				
Peripheral muscle strength							
QF Nm	109±28	145±43¶	120±34	145±41¶	−13 (−31–5)	0.1265	0.54
Exercise tolerance							
6MWD m	435±107	491±111¶	473±96	550±90¶	21 (−11–53)	0.1914	0.45
Δ6MWD ⩾30 m n (% of total)	11 (65%)		17 (94%)			**0.0279**	-
Endurance cycle test s	280 (220–330)	430 (310–750)¶	300 (210–400)	1200 (320–1200)¶	213 (−34–460)	0.0560	0.59
Δ Endurance cycle test >100 s n (% of total)	10 (59%)		12 (67%)			0.6316	-
Oxygen uptake mL·kg·min^{-1}	16±4	17±5	14±4	17±4*	0.9 (−1.5–3)	0.4672	0.25
Δ Oxygen uptake % baseline	7 (−6–22)		7 (1–27)*		14 (−16–43)	0.3555	0.32
Max workload Watts	60 (50–100)	80 (60–80)	60 (50–70)	70 (60–90)*	4 (−9–17)	0.5073	0.23
Δ Max workload % baseline	20 (0–31)		20 (0–33)¶		10 (−13–33)	0.3942	0.29
Daily physical activity levels							
Steps per day n	5032±2754	5316±2877	4567±2927	5027±3063	294 (−692–1281)	0.5448	0.13
Health-related quality of life							
CRDQ dyspnoea	14 (13–15)	20 (16–23)¶	14 (11–15)	20 (16–23)¶	−0.5 (−4–2.5)	0.7667	0.10
CRDQ total	76 (67–79)	86 (76–99)¶	72 (63–88)	92 (86–100)¶	4 (−4–11)	0.3159	0.35
Symptoms							
CAT questionnaire	20 (14–24)	19 (14–26)	20 (13–23)	16 (14–19)	−1 (−5–2)	0.3963	0.29
mMRC	3 (2–3)	2 (2–3)	3 (2–4)	2 (2–2)¶	−1 (−1–0)	**0.0080**	0.95

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. QF: Quadriceps force; 6MWD: 6-min walking distance; CRDQ: Chronic respiratory disease questionnaire; CAT: Clinical assessment test for COPD; mMRC: modified Medical Research Council scale. *: p<0.05 compared with baseline; ¶: p<0.01 compared with baseline. Difference between groups (intervention−control) reported as mean (95% CI). Bold indicates significance.

walking training offers a more reliable stimulus to maximise the achievement of clinically relevant gains in functional exercise tolerance in people with COPD.

The most striking finding from our study was the high reliability of downhill walking training to elicit clinically meaningful improvements on the 6MWT (MID change of 30 m: 94% for downhill walking training *versus* 65% for conventional walking training; p=0.033 between-groups), even in the subgroup of patients who did not exhibit CMF (p=0.06). This CMF-resistant subgroup represents an important target phenotype that has proven challenging to optimally target *via* conventional pulmonary rehabilitation [6, 7]. Downhill walking may help overcome this issue as our data show CMF resistance attenuated 6MWD improvements in conventional walking training (mean±SD change of 39±48 m *versus* 74±40 m in patients without and with CMF, respectively) but not in downhill walking training (mean±SD change of 74±32 m *versus* 82±65 m). Eccentric training maximises the force and work performed by muscles [36] and augments cortical feedback from peripheral sensory receptors during lengthening contractions [37]. Eccentric contractions [38] and eccentric training [39] reduce cortical inhibition more than concentric training, and improves muscle activation during movement due to withdrawal of inhibitory descending inputs to the spinal cord. The effects of downhill walking training may therefore be explained by improved patterns of muscle activation that contributed, at least in part, to gait improvements. Furthermore, exercise progression in terms of speed of walking occurred faster in downhill than conventional walking therapy most likely due to less evoked symptoms during downhill [11]. Whether the benefit of downhill walking therapy is due to a faster physiological adaptation of the muscles to the eccentric stimuli or due to allowing training to occur under higher workloads remains to be confirmed.

Walking is a core component of pulmonary rehabilitation due to its functional relevance in daily life; however, this "whole-body" modality can elicit high metabolic loads in people with COPD [40]. Downhill

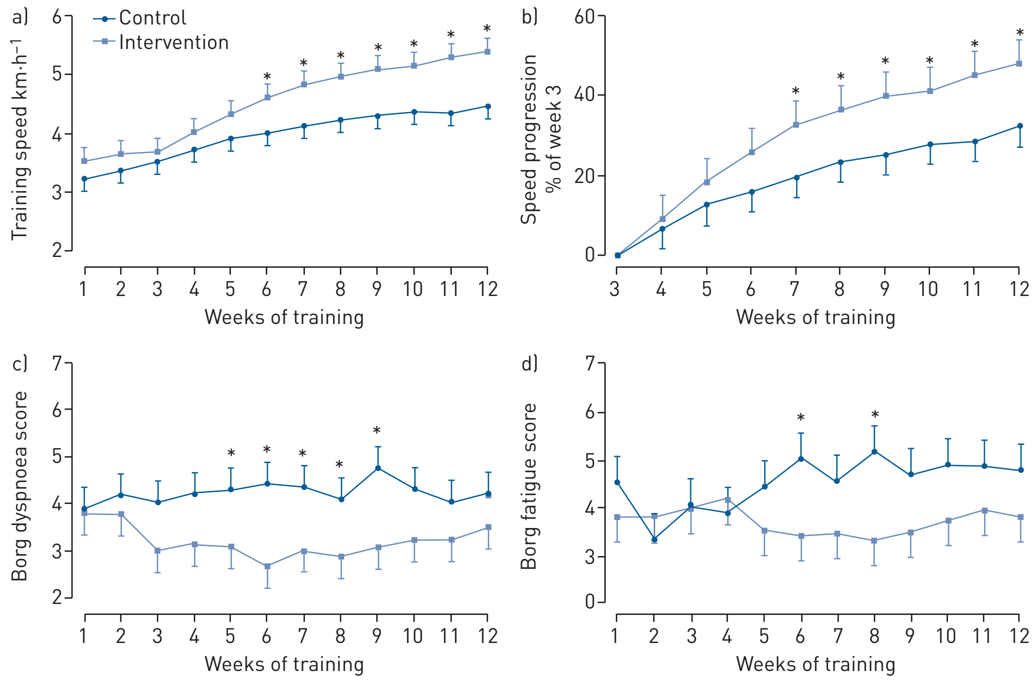

FIGURE 3 Intensity progression of treadmill component of the exercise programmes. Data described as estimated mean and standard error (estimates from mixed model) for conventional training (dark blue lines) and training including downhill (light blue lines). a) progression of treadmill speed in km·h^{-1}; b) progression of treadmill speed in % of week 3 (first week after randomisation moment); c) exertional dyspneoa; and d) exertional fatigue. *: p<0.05 for between-groups *isotime*.

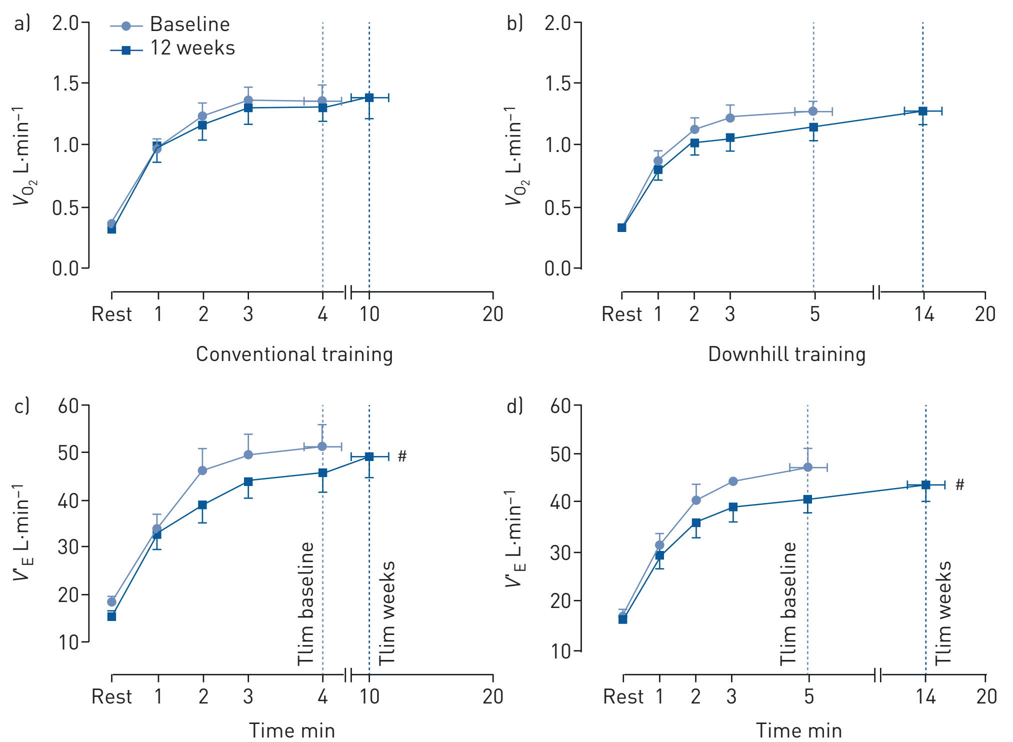

FIGURE 4 Ventilation and oxygen consumption at baseline and 12 weeks for both interventions. Data plotted as mean and standard error. Left hand panes depict oxygen consumption (V_{O_2}) (a) and ventilation (V'_E) (c) in the conventional training group; Right hand panels depict oxygen consumption (b) and ventilation (d) in the downhill training group. Dotted lines mark mean cycled time (time limit (Tlim), at baseline (light blue) and 12 weeks (dark blue). *: p<0.05 at isotime (Baseline compared with week 12). #: p<0.05 for Tlim (Baseline compared to week 12).

TABLE 3 Training responses in the subgroup of patients without quadriceps contractile muscle fatigue

	Conventional training programme		Downhill training programme		Mean (95% CI) difference of responses between groups	Difference of responses between groups p-value	Cohen's d between groups
	Baseline	12 weeks	Baseline	12 weeks			
Subjects n	9		11				
Peripheral muscle strength							
QF Nm	116±88	147±53¶	127±33	147±32¶	−14 (−41–13)	0.4030	0.57
Exercise tolerance							
6MWD m	461±120	501±135	480±106	554±106¶	34 (−6–75)	0.0732	2.75
Δ6MWD ⩾30 m n (% of total)	5 (55%)		10 (91%)			0.0693	–
Endurance cycle test s	280 (110–500)	330 (140–1200)	320 (210–410)	1200 (320–1200)¶	205 (−168–577)	0.2633	0.53
Δ Endurance cycle test >100 s n (% of total)	4 (44%)		7 (63%)			0.3907	–
Oxygen uptake mL·kg·min^{-1}	17±5	17±6	15±3	17±3¶	2.5 (−0.1–5)	0.0570	0.93
Δ Oxygen uptake % baseline	−3 (−19–3)		11 (1–22)*		17 (2–33)	0.0246	1.14
Max workload W	70 (50–100)	70 (60–80)	60 (50–95)	75 (60–100¶	13 (−8–34)	0.2145	0.58
Δ Max workload % baseline	14 (−30–20)		18 (0–33)¶		26 (−7–58)	0.1150	0.75
Daily physical activity levels							
Steps per day n	5704±2912	7139±3876	4673±3219	5604±3518¶	266 (−1225–1758)	0.7073	0.05
Health-related quality of life							
CRDQ dyspnoea	14 (13–15)	20 (16–24)¶	13 (11–15)	19 (14–23)¶	−1 (−6–3)	0.6030	0.23
CRDQ total	76 (67–79)	86 (76–99)¶	67 (63–79)	92 (87–100)¶	8 (−2–18)	0.1072	0.78
Symptoms							
CAT questionnaire	15 (11–20)	18 (9–20)	21 (15–24)	16 (13–18)¶	−4 (−8–1)	0.0852	0.80
mMRC	2 (1–3)	2 (2–3)	3 (3–4)	2 (2–3)¶	−1 (−2–0)	0.0393	1.00

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. QF: Quadriceps force; 6MWD: 6-min walking distance; CRDQ: Chronic respiratory disease questionnaire; CAT: Clinical assessment test for COPD; mMRC: modified Medical research council scale. *: p<0.05 compared with baseline; ¶: p<0.01 compared with baseline. Differences between groups (intervention−control) reported as mean (95% CI).

walking may be an attractive alternative modality for this patient group due to its inducement of greater quadriceps CMF at lower metabolic loads than level walking [11]. The mean magnitude of absolute change in 6MWD in our study was fairly high, and numerically greater in downhill than conventional walking therapy (but not statistically significantly different). This outcome should be considered with respect to some factors: 1) despite robust methods of randomisation and allocation concealment, initial mean 6MWD was 49 m higher in downhill compared with conventional walking therapy, a magnitude that exceeds the MID for this outcome [21]; 2) a mean 77 m improvement in 6MWD after 10 weeks of downhill walking therapy represents a large treatment effect in a short period of time, and greater physiological adaptations may be limited by realistic ceiling effects. Precisely what constitutes an acceptable MID for therapies "added on" to already highly beneficial treatments is a challenging issue that has been previously raised [41]; and 3) a lack of statistical power may have contributed to the lack of significance for some outcomes in the sub-group analysis of patients who did not develop CMF.

A notable strength of our study was the comprehensive evaluation of safety and clinical effectiveness of downhill walking therapy in pulmonary rehabilitation. Findings from the 6MWT corroborated well with those of the more sensitive CET, with differences in isotime measures of pulmonary ventilation potentially explaining some of the observed benefits in symptoms of dyspnoea. We adopted a rigorous approach to monitoring safety of this relatively unknown treatment, and feel our muscle biopsy, blood and symptom data should reassure clinicians that downhill walking training can be implemented into pulmonary rehabilitation with far simpler designs without undue safety concerns. Of note, downhill walking has been associated with knee pain in patients with osteoarthritis due to the combination of quadriceps muscle weakness and joint instability [14]. It is of utter importance, therefore, to screen patients for chronic knee

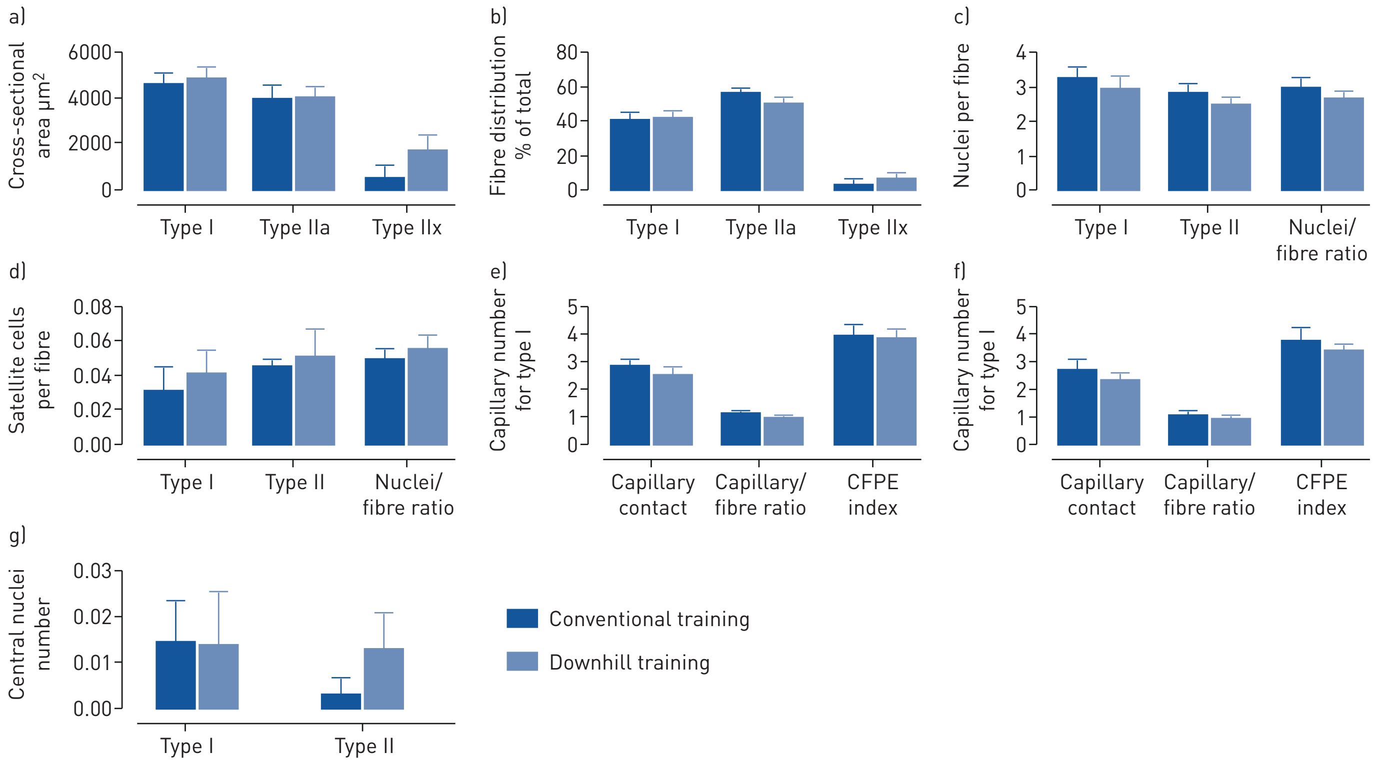

FIGURE 5 Vastus lateralis muscle histological data at 12 weeks in 25 patients following both training regimens. Data reported as mean±SD. a) Cross-sectional area of fibres; b) proportion of fibres I, IIa and IIx; c) number of nuclei per fibre; d) number of satellite cells per fibre; e) capillary in fibre Type I; f) capillary in fibre Type II and; and g) number of central nuclei per fibre. CFPE index: capillary-to-fibre perimeter exchange index. No statistically significant between-groups differences for any outcome.

pain, or severe orthopaedic deformities such as varus/valgus knee prior to the implementation of downhill walking into pulmonary rehabilitation. It was beyond the scope of the present study to explore the effect of greater durations of downhill walking therapy (>12 weeks) on physiological muscle targets, hence we urge caution extrapolating findings to such contexts. Furthermore, it is unlikely that downhill is needed during a much longer period than the 12 weeks of training proposed in the present study. As virtually all patients responded to downhill walking therapy, future studies may want to investigate exercise modalities to sustain these training benefits.

A remarkable characteristic of downhill walking is the ease of its implementation as it does not require sophisticated equipment. In the present investigation, an adaptation using an iron bar placed under the rear part of the treadmill allowed the patients to train with negative inclination. The relatively inexpensive adaptation associated with virtually inexistent changes on training protocol (*i.e.* duration) supports the implementation of downhill walking in pulmonary rehabilitation for patients with COPD.

Limitations

Our study did not detect the expected benefit on our *a priori* primary endpoint of 6MWD change. Clinically relevant differences in 6MWD between groups were better observed in the subgroup of patients who did not exhibit CMF. While this supports our underlying hypothesis, we lacked sufficient statistical power to prove this. Results from our secondary outcomes should, therefore, be interpreted with appropriate respect to their status as secondary outcomes. Additional confirmatory data from future studies may be indicated to increase our confidence in realistic effect estimates arising from this type of training. Our study sample is also unlikely to represent all patients with COPD who are referred to pulmonary rehabilitation. We noted, for example, the incidence of patients who did not exhibit CMF was greater than that previously demonstrated in studies from our own group [6]. As the subgroup analysis of training responses stratified by CMF status represented a modest sample size, its broader generalisability may be potentially limited. In addition, the assessment of quadriceps muscle fatigue by advanced equipment limits the general applicability in conventional pulmonary rehabilitation centres. Further studies are therefore needed to delineate the optimal target group in a clinical setting.

Conclusion

Downhill walking is an affordable, implementable eccentric training modality that is safe, acceptable and feasible to implement as part of comprehensive pulmonary rehabilitation for patients with COPD. Its use increases the likelihood of patients achieving clinically meaningful gains in functional exercise tolerance, thereby representing a highly reliable training stimulus. Incorporating downhill walking into pulmonary rehabilitation may be a valuable strategy to target the subgroup of patients resistant to developing CMF during conventional pulmonary rehabilitation, thus playing a potentially important role in optimising outcomes for such individuals. The definitive benefits of downhill waking in patients with COPD, especially those resistant to developing CMF remains to be confirmed in a larger, fully powered effectiveness study targeting the specific subgroup of patients where regular training is less likely to enhance functional exercise tolerance.

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