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Effects of downhill walking in pulmonary rehabilitation for patients with COPD: a randomized 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 chronic obstructive pulmonary disease.

Abstract

Background: The development of contractile muscle fatigue (CMF) affects training responses in patients with 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.

Methods: In this randomised controlled trial, thirty five patients (62±8years; FEV_1 50±17%pred) 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 30m 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.

Results: No between-group differences were observed in absolute 6MWD improvement (mean 6MWD Δ77±46m DT vs 56±47m 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.

Conclusion: 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.

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 characterized 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 PR. Little data currently exists regarding the potential role for downhill walking in PR 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 programs.

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

Methods

Study Population

All patients with COPD[15] referred to outpatient PR at University Hospital Leuven (Belgium) between April 2014 – 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 one week prior to commencing PR. 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 (6-minute walk test [6MWT][21-23]; physical activity levels based on one week assessment (Actigraph GT3X©, USA)[24],quality of life (Chronic Respiratory Disease Questionnaire [CRDQ][25]), perceived breathlessness (modified Medical Research Council scale [mMRC][26]) and health status (COPD Assessment Test [CAT][27]). PR training then commenced 3x/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 (TWqpot) were measured in a sitting position before and 15-minutes after a PR session. The femoral nerve was stimulated through a 45mm figure-of-eight coil powered by a double Magstim stimulator (Magstim Co Ltd., Whitland, Dyed,Wales, 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 TWqpot[28].

Patients were then randomly assigned to undertake the remaining 10 weeks of PR as CT or DT. Random sequence generation was undertaken via web-based software (www.randomization.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 PR staff were not blinded to knowledge of interventions, however data for the primary

outcome was collected by a blinded therapist (not involved in the study). All baseline assessments were re-evaluated after PR 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 (online supplement). 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 PR 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 fibers I, IIa and IIx, number of capillaries per fibre, and number of nuclei and satellite cells[30-32].

Training regimens in CT and DT

Full details regarding the PR program 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 minutes and intensity is progressed weekly. Patients who desaturate below 90% on transcutaneous pulse oximetry are offered titrated supplementary oxygen. For our study, DT differed from CT only on the basis of the treadmill training protocol. While CT involved walking on a motorized treadmill with neutral inclination, progressed via increases in duration, speed and inclination (positive), DT was performed at a fixed -10% inclination[11] (i.e. a 10m decline for every 100m 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. DT 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 six-minute walk distance (6MWD). Based on previous work from our group suggesting a mean ± standard deviation (SD) 6MWD change between patients with and without CMF after PR of 38±40m[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 metres)[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 PR sessions were excluded from data analysis (specified *a priori*).

Statistical analyses were performed with SAS 9.4 (SAS Institute Inc, California USA). Data normality was verified using the Shapiro-Wilk test and expressed as mean±SD or medians [Q1 – Q3] 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 [CI]) 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-square test. Consistent with the stratification, one pre-planned sub-analysis was conducted to compare training responses between patients who did vs did not develop CMF to explore whether this factor was an effect modifier. Alpha was set at 0.05 for all analyses.

Results

Forty-four patients were recruited and randomised after screening 105 for eligibility. Thirty-eight patients completed their end-PR 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 DT Δ77±46m [18±15%], p<0.001; CT Δ56±47m [14±14%], p<0.001; Table 2, Figure

S1), however differences between groups were modest (∆DT minus ∆CT: 21 (-11 – 53)m; *d*=0.45) and not statistically significant. Twenty-eight out of 38 patients exceeded the MID for 6MWD, however this proportion was greater in DT compared with CT (17/18 [94%] vs 11/17 [65%], p=0.033). DT was associated with faster weekly progression of treadmill speed and lower perceived dyspnoea after week 6 than CT (AUC=34.73U in DT compared to 46.92U in CT, p=0.04); Figure 3). Perceived fatigue was consistently reported as being lower in DT than CT, however this was not statistically significant (AUC=40.66U in DT compared to 49.65U in CT, p=0.15).

Performance on CET improved in both groups (median [Q1-Q3] DT Δ660 [80–880]sec vs CT Δ250 [60–420]sec, p<0.05 for both; p=0.056 between groups), with similar proportions of patients exceeding the MID of >100sec (12/18 [67%] for DT, 10/17 [59%] for CT; 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 DT, but not CT, group for *isotime* measures of ventilation (median [Q1-Q3] ∆-8.8 [-10.93 – -1.96] l/min, p<0.001; vs ∆-3.72 [-13.8 – 1.63] l/min, p = 0.07, respectively) and oxygen consumption (median [Q1-Q3] ∆-0.13 [-0.30 – 0.00] l/min, p=0.05; vs ∆-0.005 [-0.20 – 0.10] l/min, p = 0.56, respectively) with no significant between-group differences (p>0.05). Self-reported *isotime* dyspnoea decreased in the DT, but not the CT, group (median [Q1-Q3] ∆Borg -3 [-4 – -1], p<0.0001 vs -1 [-4.5 – 1], p=0.11, respectively), while fatigue levels decreased similarly in both groups (median [Q1-Q3] ∆fatigue -3 [-4 – -1] in DT vs -2 [-3 – 0] in CT, p<0.01 for both). Changes on mMRC (table 2) and the proportion of patient exceeding MID of the scale (10/13 [77%] in DT 2/10 [20%]) were significantly larger on patients in DT than in CT (p<0.05 for both).

Effect of PR 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 DT, n=9 in CT) are summarised in Table 3. Significant improvements in 6MWD (median [Q1-Q3] ∆93 [45 – 102]m in DT; median [Q1-Q3] ∆41[-1 – 70]m, *d*=2.75) and mMRC (median [Q1-Q3] ∆-1 [-2 – 0]points in DT; median [Q1-Q3] ∆0 [0 – 0] in CT; *d*=1.00) were only observed in DT (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 DT than CT for 6MWD (10/11 [91%] in DT; 5/9 [55%] in CT, p=0.06 between groups) and mMRC scale (8/11 [75%] in DT; 1/9 [11%] in CT; p=0.005 between groups), but not for CPET, CET or CRDQ.

Feasibility, acceptability and safety of DT

The DT 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 (online supplement). Serum CK 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 CK were apparent between patients who did or did not exhibit CMF upon randomisation.

Discussion

This study confirms that PR incorporating downhill walking is safe and confers similar magnitudes of effects to PR with conventional walking across clinical outcomes in patients with COPD. DT patients walked at faster speed with lower perceived dyspnoea and progressed more rapidly during PR. Furthermore, DT 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 DT to elicit clinically meaningful improvements on the 6MWT (MID Δ30m: 94% DT vs 65% CT; 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 PR[6, 7]**.** Downhill walking may help overcome this issue as our data show CMF resistance attenuated 6MWD improvements in CT (mean±SD Δ39±48m vs Δ74±40m in patients without and with CMF) but not in DT (mean±SD Δ74±32m vs Δ82±65m). Eccentric training maximizes 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 DT 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 DT than CT most likely due to less evoked symptoms during downhill[11]. Whether the benefit of DT 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 PR due to its functional relevance in daily life, however this 'whole-body' modality can elicit high metabolic loads in people with COPD[40]. Downhill 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 DT than CT (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 49m higher in DT compared to CT – a magnitude that exceeds the MID for this outcome[21]; 2) A mean 77m improvement in 6MWD after 10 weeks of DT 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 DT in PR. 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 DT can be implemented into PR 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 utterly importance, therefore to screen patients for chronic knee pain, or severe orthopedic deformities such as varus/valgus knee prior to the implementation of downhill walking into PR. It was beyond the scope of the present study to explore the effect of greater durations of DT (>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 DT, 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 PR 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 PR. 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 PR 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 PR 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 PR may be a valuable strategy to target the subgroup of patients resistant to developing CMF during conventional PR, 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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Table 1. Baseline characteristics of included participants.

		Training Intervention	
	All subjects (N=44)	**CT (N=20)**	**DT (N=24)**
Demographic characteristics			
Age (years)	62±8	62±9	62±8
Gender (% 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
$DL_{,CO}$ (% 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 (meters)	442±112	415±123	464±100
6MWD (% predicted)	67±16	64±19	68±12
Cycle endurance test (seconds)	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 (n/day)	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 reported as Mean±SD or Median [IQR]. CT= conventional training group; DT=Downhill training group; FEV_1= Forced expiratory volume in the 1^{st} second; FRC= Functional residual capacity; DL,co = Diffusion capacity for carbon monoxide; QF= Quadriceps force; 6MWD= distance covered in the 6-minute walk test; CRDQ= Chronic respiratory disease questionnaire; CAT= Clinical assessment test for COPD; mMRC= modified Medical research council scale.

Table 2. Training responses for each training program.

	Conventional training program (n=17)		Downhill training program (n=18)		Difference of responses between groups Mean (95%CI)	Difference of responses between groups p value	Cohen's d between groups
	Pre	**Post**	**Pre**	**Post**			
Peripheral muscle strength							
QF (Nm)	109±28	145±43¶	120±34	145±41¶	-13 (-31 – 5)	0.1265	0.54
Exercise Tolerance							
6MWD (meters)	435±107	491±111¶	473±96	550±90¶	21 (-11 – 53)	0.1914	0.45
Δ6MWD≥30m (N(% total))	11 (65%)		17 (94%)			**0.0279**	-
Endurance cycle test (seconds)	280 [220–330]	430 [310–750]¶	300 [210–400]	1200 [320–1200]¶	213 (-34 – 460)	0.0560	0.59
Δ Endurance cycle test >100s (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 (n/day)	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

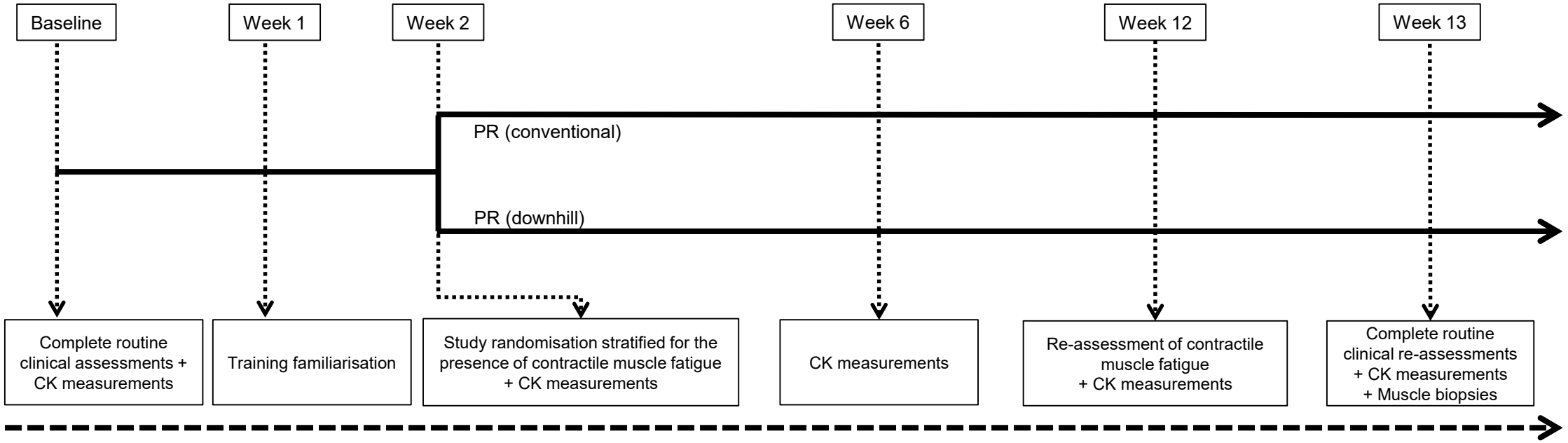
Data reported as Mean ± SD or Median [IQR]. Pre= Baseline; Post=12 weeks; QF= Quadriceps force; 6MWD= distance covered in the 6-minute walk test; CRDQ= Chronic respiratory disease questionnaire; CAT= Clinical assessment test for COPD; MRC= Medical research council scale. *=p<0.05 compared to PRE; ¶=p<0.01 compared to PRE. **Difference between groups (Intervention - Control) reported as Mean (95% CI).**

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

	Conventional training program (n=9)		Downhill training program (n=11)		Difference of responses between groups Mean (CI95%)	Difference of responses between groups p value	Cohen's d between groups
	Pre	**Post**	**Pre**	**Post**			
Peripheral muscle strength							
QF (Nm)	116±88	147±53¶	127±33	147±32¶	-14 (-41 – 13)	0.4030	0.57
Exercise Tolerance							
6MWD (meters)	461±120	501±135	480±106	554±106¶	34 (-6 – 75)	0.0732	2.75
Δ6MWD≥30m (N(% of total))	5 (55%)		10 (91%)			0.0693	–
Endurance cycle test (seconds)	280 [110–500]	330 [140–1200]	320 [210–410]	1200 [320–1200]¶	205 (-168 – 577)	0.2633	0.53
Δ Endurance cycle test >100s (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 (Watts)	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 (n/day)	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 reported as Mean ± SD or Median [IQR]. Pre= Baseline; Post=12 weeks; QF= Quadriceps force; 6MWD= distance covered in the 6-minute walk test; CRDQ= Chronic respiratory disease questionnaire; CAT= Clinical assessment test for COPD; MRC= Medical research council scale. *=p<0.05 compared to PRE; ¶=p<0.01 compared to PRE. **Differences between groups (Intervention - Control) reported as Mean (95% CI).**

Figure 1. Study overview.



PR: Pulmonary rehabilitation; Conventional: training including conventional treadmill walking; downhill: training including downhill walking; CK: Creatine Kinase.

Figure 2. Consort flow diagram of patients in the study.

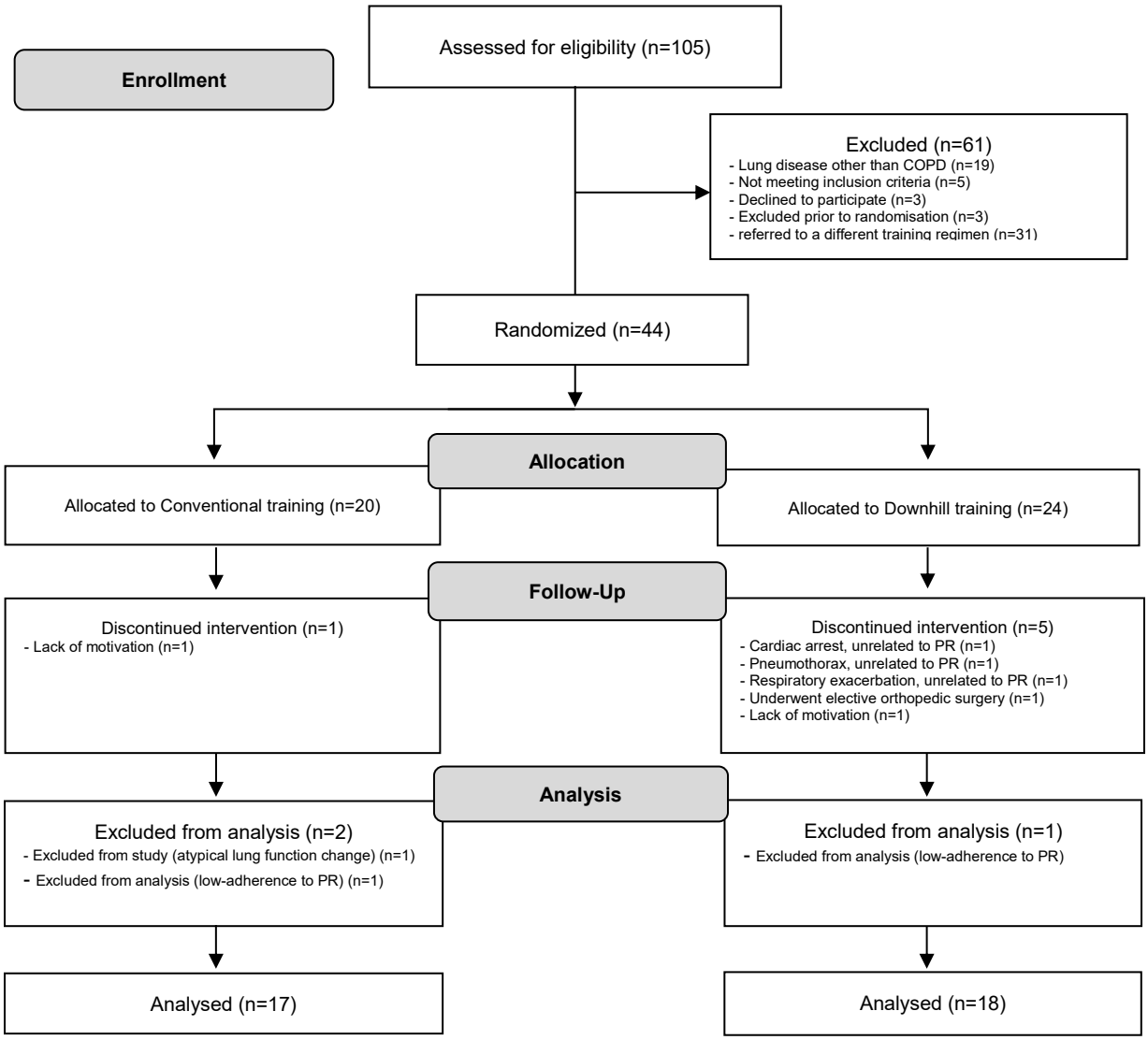
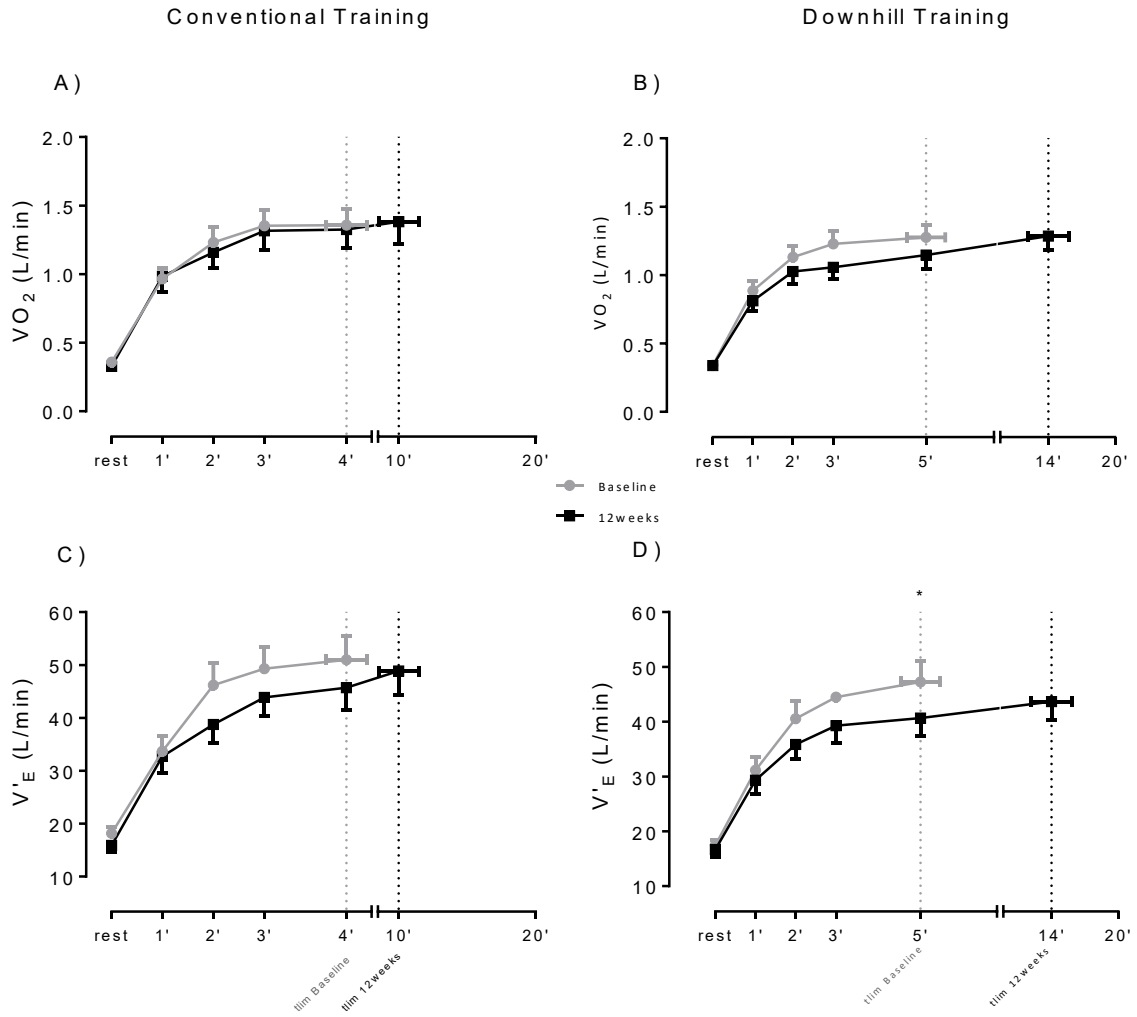
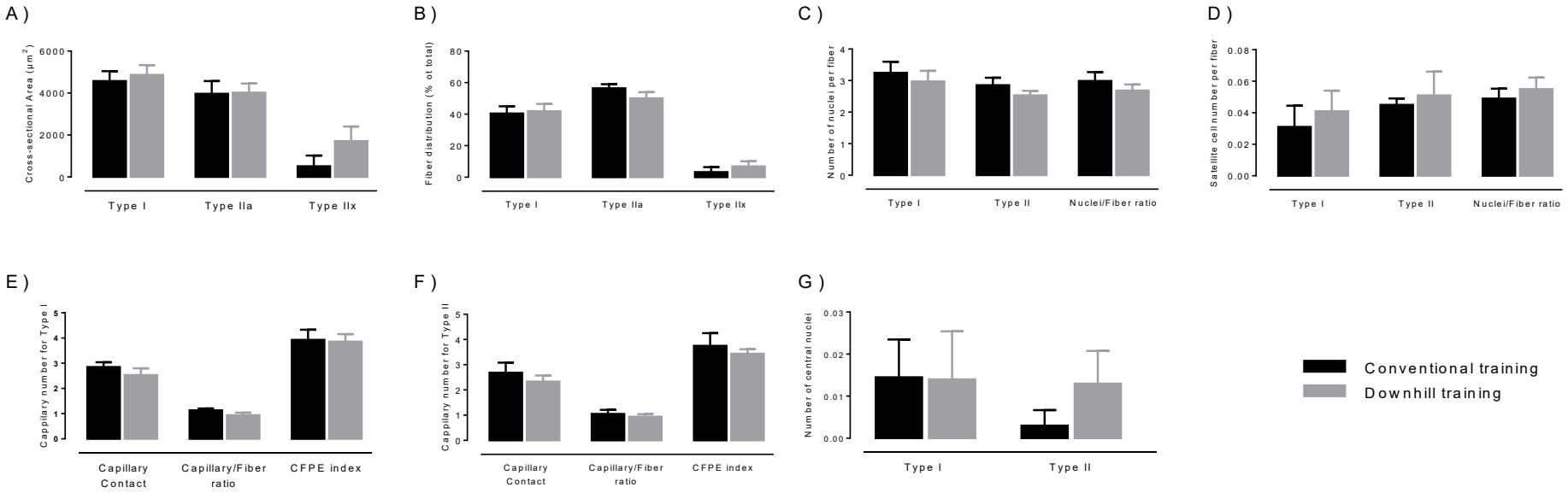


Figure 4. Ventilation and oxygen consumption at baseline and 12 weeks for both interventions.



Data plotted as mean and standard error. Left hand panes depict oxygen consumption (A) and ventilation (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 (grey) and 12 weeks (black). *<p,0.05 at *isotime* (Baseline compared to week 12). † p<0.05 for tlim (Baseline compared to week 12).

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; G) number of central nuclei per fibre. CFPE index: capillary-to-fibre perimeter exchange index. No statistically significant between-groups differences for any outcome.

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

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ONLINE SUPPLEMENTARY MATERIAL

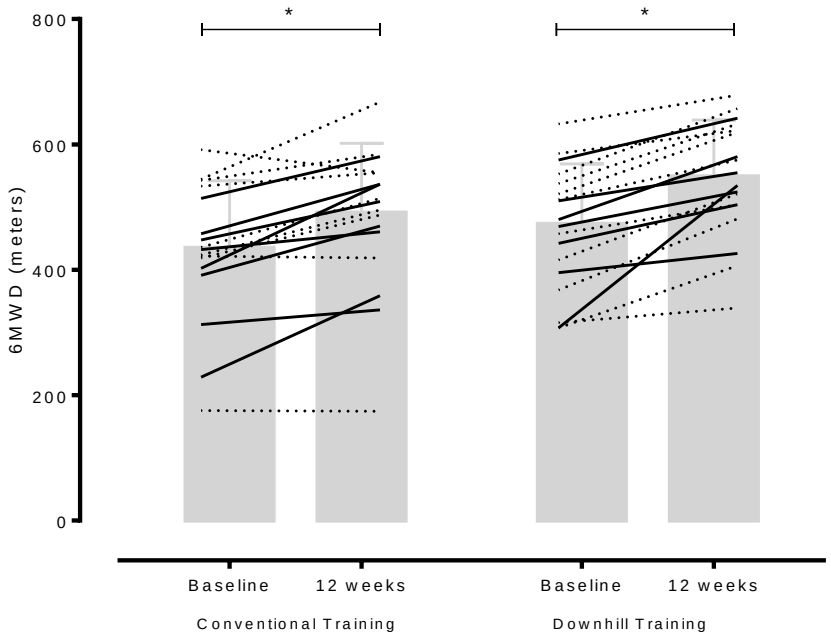
Results

Individual 6MWD responses in DT and CT

Significant and clinically relevant 6MWD increases were observed within both groups (mean±SD DT Δ77±46m [18±15%], p<0.001; CT Δ56±47m [14±14%], p<0.001; grey bars in Figure S1), however differences between groups were modest (ΔDT minus ΔCT: 21 (-11 – 53)m; *d*=0.45) and not statistically significant.

In the subgroup of patients without CMF, significant improvements in 6MWD (median [Q1-Q3] Δ93 [45 – 102]m in DT; median [Q1-Q3] Δ41[-1 – 70]m, *d*=2.75) were only observed in DT (p<0.05 for both).

Figure S1. Changes in six-minute walk distance between baseline and week 12 following pulmonary rehabilitation with conventional or downhill training.

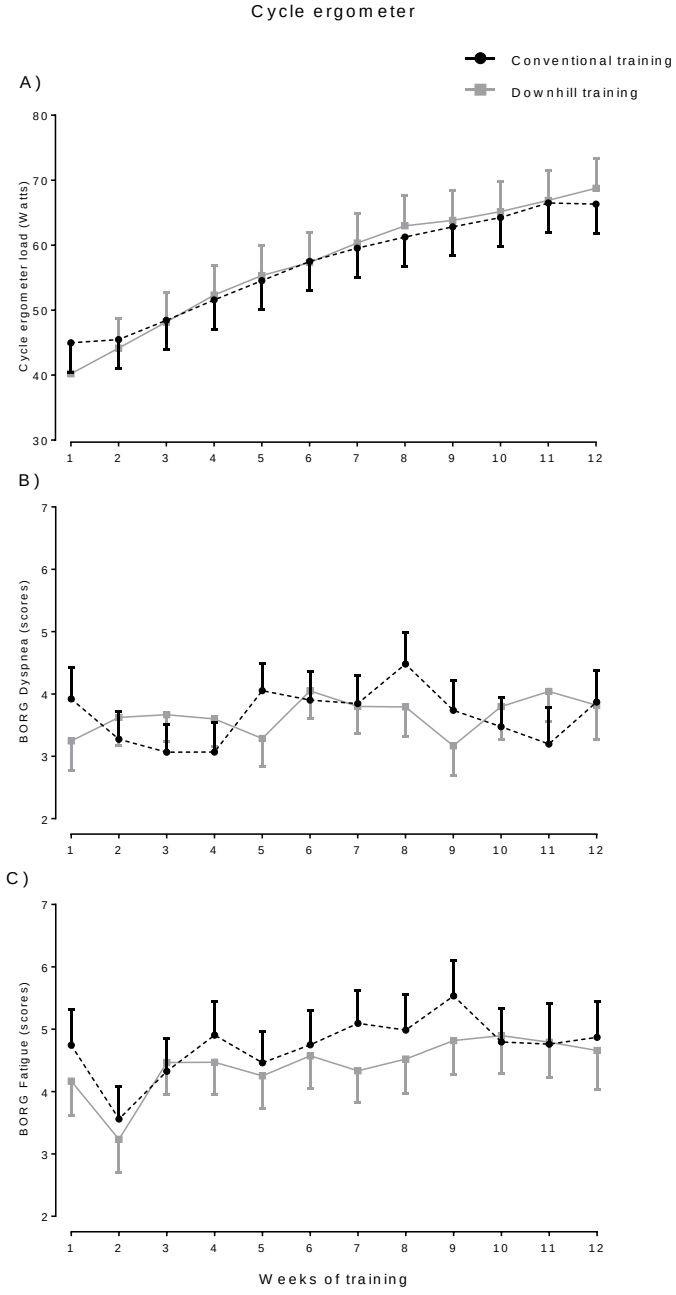


6MWD= 6-minute walk distance; *= p<0.001 from baseline. Dashed and solid lines denote participants who did or did not exhibit contractile muscle fatigue at week 2 of pulmonary rehabilitation, respectively. In the latter group, 5/9 improved 6MWD >30m with conventional training; 10/11 improved 6MWD >30m with downhill training.

Training progression.

Weekly progression of training intensity and symptoms during the cycling component of PR are summarised in Figure S2. There were no significant differences neither in workload progression nor in symptoms between the two groups across the 12 weeks of training.

Figure S2. Intensity progression of cycling component of the exercise programs.

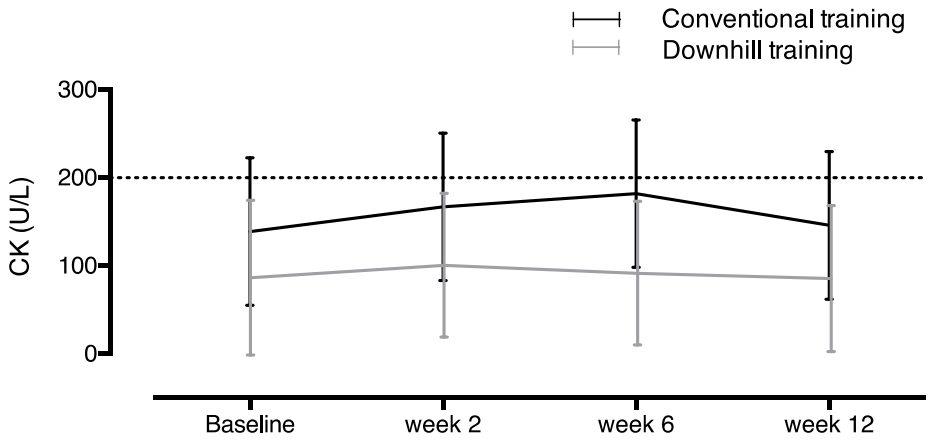


Data described as estimated mean and standard error (estimates from mixed model) for conventional training (black lines) and training including downhill (grey lines). A) progression of cycle ergometer workload in watts; B) exertional dyspneoa and; D) exertional fatigue.

Feasibility, acceptability and safety of DT

Our 75% *a priori* feasibility target for DT protocol completion was exceeded, with 19 / 24 (79%) patients completing the intervention. All participants completed a custom survey upon PR completion. Of these, 13 (72%) agreed or strongly agreed that the downhill walking component was easy to perform, 16 (89%) felt it was safe to perform and 14 (78%) felt it helped them walk more in their daily life. Thirteen (72%) disagreed or strongly disagreed that they experienced pain or discomfort whilst performing downhill walking. The only adverse events related to PR training reported by patients of either group were mild intermittent pain in the hip region (n=1; CT group); recurrence of pre-existing back pain (n=2; CT group); and 'shin-splints' during the last 2 weeks of PR training (n=2; DT group), attributed to individuals walking at advanced (fast) treadmill speeds. Two patients were diagnosed with peripheral vascular disease during the program (DT group). Serum CK levels were consistently low and did not differ between groups (Figure S3). Muscle biopsy analysis from 25 consenting patients who completed training revealed no evidence of muscle damage and no significant differences in key markers of training adaptations between the two groups. The 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 were similar between groups ($p>0.05$ for all; Figure 5 in the manuscript). No differences were apparent between patients who did or did not demonstrate CMF prior to initiation of PR.

Figure S3. Accumulation of serum levels of creatine kinase throughout the 12 weeks of training.



Data expressed as Mean (SD). CK= Creatine kinase; Serum levels collected at baseline (prior to training commencement) and 48 hours after an exercise session at weeks 2, 6 and 12. $p>0.05$ between groups in all time-points. Dotted line denotes threshold of abnormally high values (i.e. 200 U/L).