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Original research

Low-load blood flow restriction strength training in patients with COPD: a randomised single-blind pilot study

Dario Kohlbrenner ,[1,2] Manuel Kuhn,[1,2] Anastasios Manettas,[3,4] Céline Aregger,[3] Matthias Peterer,[3] Nicola Greco,[3] Noriane A Sievi ,[2] Christian Clarenbach[1,2]

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[1]Faculty of Medicine, University of Zurich, Zurich, Switzerland
[2]Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland
[3]Physiotherapy Occupational Therapy, University Hospital Zurich, Zurich, Switzerland
[4]Biomechanics and Ergonomics, ErgoMech Laboratory, Department of Physical Education and Sport Science, University of Thessaly, Trikala, Greece

Correspondence to
Dr Dario Kohlbrenner, Faculty of Medicine, University of Zurich, Zurich, Switzerland; dario.kohlbrenner@usz.ch

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ABSTRACT

Objective The objective of this study is to compare the effectiveness of lower limb low-load blood flow restriction training (LL-BFRT) with high-load strength training (HL-ST) as part of an outpatient pulmonary rehabilitation programme on leg strength in patients with chronic obstructive pulmonary disease (COPD).

Methods Participants were randomised to LL-BFRT or HL-ST (24 sessions). LL-BFRT was done at 30% 1-repetition maximum (1-RM) with 70% arterial occlusion pressure. HL-ST was done at 70% 1-RM. Primary outcome was isometric strength of knee extensors and flexors. Secondary outcomes were 1-RM, functional exercise capacity, physical activity, symptom burden and health-related quality of life. Perceptions of dyspnoea and leg fatigue were recorded after every exercise. We compared groups with t-tests.

Results We included 30 participants (13 women, 17 men, 64 (9) years, forced expiratory volume in 1 s 47 (18)% pred.), 24 completed the study. Isometric knee extensor strength improved to a clinically relevant degree in both legs in both groups (LL-BFRT: right leg 9 (20) Nm, left leg 10 (18) Nm; HL-ST: right leg 15 (26) Nm, left leg 16 (30) Nm, data are mean (SD)), without statistically significant or clinically relevant between-group differences (right leg mean difference= −6.4, 95% CI= −13.20 to 25.92 Nm, left leg mean difference= −5.6, 95% CI= −15.44 to 26.55 Nm). 1 min sit-to-stand test performance improved to a clinically relevant degree only in the LL-BFRT group (4 (4) vs 1 (5) repetitions). Interestingly, physical activity improved to a clinically relevant degree only in the LL-BFRT group (1506 (2441) vs −182 (1971) steps/day). LL-BFRT lowered perceived in-exercise dyspnoea and increased leg fatigue compared with HL-ST in the initial 12 trainings.

Conclusion In patients with stable COPD undergoing outpatient pulmonary rehabilitation, LL-BFRT was not superior to HL-ST in improving leg strength. LL-BFRT led to similar strength gains as HL-ST while reducing perceptions of dyspnoea in the initial training phase.

Trial registration number NCT04151771.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Low-load blood flow restriction training (LL-BFRT) enhances strength equal to high-load strength training (HL-ST) in healthy populations. Since high training loads exacerbate in-exercise dyspnoea in patients with chronic obstructive pulmonary disease (COPD), LL-BFRT is an interesting option.

WHAT THIS STUDY ADDS

⇒ Twelve weeks of LL-BFRT induced similar strength gains as HL-ST. Thereby, perceived in-exercise dyspnoea tended to be lower during the initial 6 training weeks.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This is the first study on LL-BFRT in COPD and enters a new research field in pulmonary rehabilitation. The training programme applied in this study can be translated into clinical practice.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) elicits a characteristic, progressive loss in skeletal muscle mass and function.[1 2] It is well established that exercise training may counteract the COPD associated skeletal muscle dysfunction by augmenting muscle protein synthesis, inducing angiogenesis and increasing mitochondrial function.[1] Consequently, structured concurrent (ie, same-session endurance and strength type exercises) exercise training programmes were introduced.[3] The effectiveness of pulmonary rehabilitation (PR), in terms of improving muscle strength, endurance capacity and health-related quality of life (HrQoL) has been thoroughly investigated.[2 4]

Given the effectiveness of PR in COPD, current research focuses on optimising exercise training methods, aiming to further augment its effects. More, as a first step, COPD-specific dosing of exercise and personalised exercise planning is the overarching goal in current PR research.[5] As such, addressing the most pressing limitations of PR builds the initial challenge. In detail, up to 38% of the patients with COPD being enrolled in a structured outpatient PR drop-out before completion.[6] Although psychological and social factors, aside medical reasons, seem to play an important role in the explanation of the high non-completion rate, it has been shown that a significant number of participants may have difficulties to tolerate the training loads required to elicit the clinical benefits of exercise training.[7–9] The reason, therefore, is the

ventilatory limitation caused by airflow obstruction, dynamic hyperinflation and increased dead-space.[10]

In summary, despite PR being effective,[4] muscle strength impairment remains a persisting problem in COPD, reinforcing the vicious circle of breathlessness and deconditioning.[1 11] An underlying reason might be the unavailability of tolerable and sustainably gain-inducing strength training loads.

Low-load blood flow restriction training (LL-BFRT), whereby arterial inflow to the trained limb is reduced and venous outflow is prevented by inflation of a cuff at its most proximal point, is a method to increase muscle strength with low training loads.[12] LL-BFRT is usually performed at 20%–30% of the 1-repetition maximum (1-RM) compared with the conventional high-load strength training (HL-ST) that uses 60%–80% of the 1-RM.[12–14] Despite the drastically reduced mechanical stress on the musculature, comparable muscle mass and strength gains were shown in healthy individuals and patients with musculoskeletal disorders.[12–14] It is proposed that the metabolic stress, induced through the local ischaemia during the exercise, together with the reperfusion stimulus after cuff deflation account for the effects of LL-BFRT.[15] However, the exact mechanisms are not conclusively explained yet.

To date, the potential effectiveness of LL-BFRT in patients with COPD has only been demonstrated and discussed in a single-case study,[16] and a rationale for the potential of the method was published.[7] Thus, we aimed to investigate the effectiveness of LL-BFRT on isometric leg strength (primary outcome), dynamic leg strength, functional exercise capacity, physical activity, symptom burden and HrQoL (secondary outcomes) as part of an outpatient PR programme in patients with COPD.

METHODS

Study design

We performed a single-centre, two-arm randomised, single (assessor)-blind pilot study at the University Hospital Zurich, Switzerland. The study ran from January 2020 to completion in December 2022.[17–19]

This manuscript is in accordance with the Consolidated Standards of Reporting Trials 2010 statement: extension to randomised pilot and feasibility trials.[20]

Study participants

Patients with a COPD diagnosis according to the Global Initiative for Chronic Obstructive Lung Disease,[2] referred to our centre for outpatient PR, aged ≥40 years were deemed eligible for this study. We excluded participants in case of: recent acute COPD exacerbation (ie, within the last 6 weeks), PR within the last 3 months, pregnancy, history of thromboembolism in the lower extremity, diagnosed polyneuropathy, diagnosed peripheral artery disease, resting systolic blood pressure <100 mm Hg, and pain when conducting leg strength or endurance training.

Experimental procedures

All participants took part in an outpatient PR as part of their usual care, delivered according to clinical practice guidelines.[9 21 22] A researcher not involved in study procedures randomised participants on a 1:1 ratio using computerised randomisation with permuted random block sizes of 2 or 4. The assessor collecting baseline and follow-up data was blinded to group allocation.

The PR consisted of 2 weekly 90 min exercise training sessions for 12 weeks, totalling at 24 sessions. Exercise sessions incorporated LL-BFRT or HL-ST for the lower limbs, on plate-loaded leg press and leg extension machines, alongside concurrent endurance exercise. The upper limb strength training was done as HL-ST. A separate educational and behavioural counselling programme complemented the rehabilitation. Thus, the groups differed solely in terms of their lower limb strength training methodology. The exercise training sessions were group trainings led by a specialised respiratory therapist. Figure 1 provides a study overview including details on the baseline and follow-up testing days.

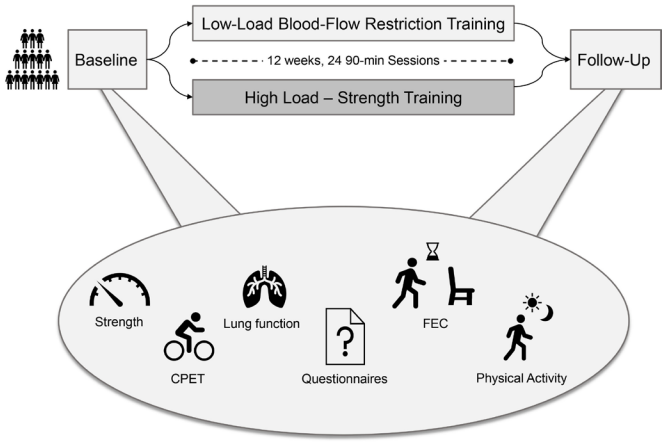

Figure 1 Overview of the study design and outcomes. CPET, cardiopulmonary exercise testing; FEC, functional exercise capacity (ie, 6 min walk test and 1 min sit-to-stand test).

General components

Endurance exercise

Endurance exercise was performed using a continuous methodology.[22] Participants trained on stationary seated or semirecumbent bicycle ergometers for 20 min at an initial training load of 65% of the incremental peak power output (iPPO), as determined by cardiopulmonary exercise testing (CPET) at baseline. Target exhaustion was at a modified Borg scale rating of 7/10 (numeric rating scale ranging from 0 to 10),[23] evaluated every 5 min throughout the exercise. Training load was increased if a participant's mean exhaustion throughout two consecutive training sessions was <7/10, and decreased if ≥8/10, respectively.

Educational programme

Participants attended four 90 min lessons of educational and behavioural counselling. The lessons delivered knowledge about COPD and its treatment, diet, physical activity and psychological/behavioural topics. Specialists (ie, pulmonologists, dietitians, respiratory physiotherapists and psychologists) designed and led the lessons.

High-load strength training

HL-ST was performed using the three-set methodology with an initial training load of 70% 1-RM.[9 22] Each set was performed to volitional muscular failure, supposed to occur within 8–12 repetitions. Training rhythm was 1-0-1-0 (ie, one second concentric phase, no pause, 1 s eccentric phase, no pause). Training loads were determined through the estimation of the 1-RM in the first training session and increased every time the participant achieved to reach ≥14 repetitions in every set of the individual exercise for two consecutive training sessions. Training load was decreased when the participant reached muscular failure <8 repetitions in any set on two consecutive training sessions. The set breaks were standardised to 60 s. During the break,

Table 1 Frequency, intensity, type and time (FITT) components of the experimental procedures

		LL-BFRT group	HL-ST group
Frequency		► 2×/week for 12 weeks, Tuesdays and Thursdays	
Intensity	Volume	► LL-BFRT: 4 sets with a total of 75 repetitions (30, 15, 15, 15 repetitions) under BFR ► Endurance: 20 min continuous	► HL-ST: 3 sets with a total of 24–36 repetitions (8–12 RM each) ► Endurance: 20 min continuous
	Initial load	► LL-BFRT: 30% of 1-RM ► Endurance: 65% of iPPO	► HL-ST: 70% of 1-RM ► Endurance: 65% of iPPO
	Rest	► LL-BFRT: 45 s between sets, ≥5 min between LL-BFRT exercises ► Endurance: none	► HL-ST: 60 s between sets ► Endurance: none
	Progression	► LL-BFRT: volitional muscle failure ≥33 repetitions in the first set ► Endurance: mean Borg <7/10 (dyspnoea)	► HL-ST: muscular failure ≥14 repetitions in every set in two consecutive exercises ► Endurance: mean Borg <7/10 (dyspnoea)
Type		► LL-BFRT strength training for the lower limb and high-load strength training for the upper limb, continuous endurance training	► High-load strength training for the lower and upper limb, continuous endurance training
Time		► 90 min per training session	

BFR, blood flow restriction; HL-ST, high-load strength training; iPPO, incremental peak power output; LL-BFRT, low-load blood flow restriction training; 1-RM, 1-repetition maximum; RM, repetition maximum.

participants remained seated. After completion of each exercise, participants rated their perceived leg exertion and dyspnoea on the modified Borg scale.[23]

Low-load blood flow restriction strength training

LL-BFRT was performed using a four-set methodology with an initial training load of 30% 1-RM and an arterial occlusion pressure (AOP) of 70%, in accordance with available evidence-based application guidelines.[24] Inflatable cuffs were mounted bilaterally at the most proximal part of the lower limb and inflated with a manometer (Slim Cuff (width 11 cm) and Hand Inflator with Manometer, VBM Medical, Sulz a.N., Germany). The pressure was constantly adjusted to keep the targeted AOP during the exercise. The first set was performed to volitional muscular failure, ensuring appropriate metabolic stress and fatigue throughout the subsequent sets. Each exercise consisted of 75 repetitions during 4 sets. The first set covered 30 repetitions, and the subsequent sets 15 repetitions each. Training rhythm was 1-0-1-0. Training loads were determined through the estimation of the 1-RM in the first training session and increased every time participants exceeded 33 repetitions in the first set. Training load was decreased when participants reached volitional muscle failure <27 repetitions in the first set. During the subsequent sets, training load stayed unchanged. The set breaks were standardised to 45 s. During the break, participants remained seated and the cuffs remained inflated. After the exercise, the cuffs were deflated immediately. A minimum of 5 min reperfusion time was granted before proceeding with the second lower limb exercise. After completion of each exercise, participants rated their perceived leg exertion and dyspnoea on the modified Borg scale (Numeric Rating Scale from 0 to 10).[23]

The exercise dosing is presented in table 1 for both groups.

Arterial occlusion pressure determination

Lower limb AOP was determined according to a Standard Operating Procedure (SOP) by the respiratory physiotherapist in charge of the exercise training supervision. In detail, the participant was assessed in a supine lying position on a treatment bench after 5 min of rest and the pressure cuff was placed around the most proximal part of the thigh. The Arteria dorsalis pedis was identified using a handheld acoustic Doppler (SD3, Edan, San Diego, California, USA). Subsequently, the cuff was rapidly inflated to a pressure of 200 mm Hg, so that audible pulse was lost. If audible pulse was still present at 200 mm Hg, the cuff was inflated further in steps of 10 mm Hg until disappearance. AOP was identified through a stepwise decrease in cuff pressure of 10 mm Hg until reidentification of audible pulse. After a 2 min rest period with a completely deflated cuff, an additional inflation was carried out to the previously identified AOP plus 10 mm Hg. Thereafter, the cuff was deflated in steps of 5 mm Hg, until reidentification of audible pulse. This procedure allowed identification of the AOP to the nearest±5 mm Hg. AOP was assessed immediately before the 1st, 8th and 16th exercise training session and the training pressure was adjusted accordingly.

Study outcomes

Participants attended two baseline visits, the first consisting of lung function assessment and CPET, the second of the remaining functional tests. The follow-up visit was identical to the second baseline visit.

Primary outcome

The primary outcome was volitional isometric strength of the leg extensor and flexor muscles. We used a handheld dynamometer (MicroFET2, Hoggan Industries, West Jordan, Utah, USA), which has shown excellent reliability in assessing muscle strength of knee extensor and flexor muscles, as well as excellent concurrent validity with an isokinetic dynamometer.[25] Measurements were performed according to an SOP. Participants sat on a treatment bench with their feet off the floor. They placed their hands on the bench's edges and their hips were fixed to the bench with a strap to ensure standardisation and maximal effort. The break technique was used and bias through rater strength was minimised by fixating the leg during the knee extensor assessment.[26 27] Three reproducible measurements were recorded and the highest value was used for analysis. We measured moment arms to express the results as torque in newton metres (Nm). The minimal clinical important difference (MCID) for isometric knee extensor strength is considered 7.5 Nm.[28] For knee flexor strength, no MCID is available.

A single rater performed all measurements. Intrarater reliability between the three attempts recorded per visit was excellent (0.94 (0.89, 0.97) at baseline visits, 0.96 (0.92, 0.98) at follow-up visits).

Secondary outcomes

Dynamic leg strength was measured by submaximal 1-RM estimation on the leg press and the leg extension machines (Leg Press VR2 and Eagle, Cybex International, Medway, Massachusetts, USA).

Functional exercise capacity was measured with the 6 min walk test (6MWT) and the 1 min sit-to-stand test (1MSTST). The MCID for the 6MWT is considered 30 m,[29] and for the 1MSTST 3 repetitions.[30]

CPET with an incremental ramp protocol was performed at baseline to inform initial endurance training loads.

Lung function parameters, forced expiratory volume in 1 s (FEV_1), forced vital capacity and lung diffusion capacity of carbon monoxide (DLCO) were obtained after short-acting bronchodilator inhalation.

Physical activity (PA) was recorded with an accelerometer (SenseWear Pro, Bodymedia, Pittsburgh, Pennsylvania, USA). We applied an MCID of 1000 steps/day to our analysis.

We assessed symptom burden with the COPD Assessment test (CAT), HrQoL with the Chronic Respiratory Questionnaire (CRQ) and the Short-Form-12 (SF-12), depression and anxiety symptoms with the Hospital Anxiety and Depression Scale (HADS). Finally, participants filled a purpose-designed questionnaire at the end of their study participation concerning perceptions on the programme.

Further details on the secondary outcomes are given in the online supplemental file.

Statistical analysis

In pilot studies, a sample size of 24 (ie, 12/group) participants is recommended, providing optimal precision in mean and variance estimates in relation to the feasibility and risk exposure of participants to a novel intervention.[31] Literature reports drop-out rates of 17% in studies investigating PR.[32] Therefore, we aimed to include 30 participants (ie, 15/group). Data were analysed on an intention-to-treat basis. Distribution of variables was determined visually using quantile-quantile plots and showed normality. Group characteristics and baseline measurements are presented using descriptive statistics. Differences between groups at the primary and secondary endpoints were calculated using independent samples t-tests. No corrections for multiple testing were applied since no statistically significant results were found. We used locally estimated scatterplot smoothing (LOESS) to display lines on group level for perceptions of dyspnoea and leg effort.[33]

Statistical analyses were done in R V.4.2.3 for Windows (R Core Team 2023, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participant characteristics

Thirty participants were included, of whom 24 (80%) completed the study (see figure 2). The sample had a mean (SD) age of 64 (9) years, and a FEV_1 of 47 (18) % predicted. Detailed baseline characteristics stratified by group allocation are presented in table 2. Participants showed high adherence, all of them completed 24 exercise training sessions. No adverse and serious adverse events related to the intervention were reported.

Muscle strength

Isometric muscle strength of the right knee extensors improved by mean (SD) 9 (20) Nm, from 125 (61) to 134 (63) Nm in the LL-BFRT group and by 15 (26) Nm, from 137 (40) to 153 (50) Nm in the HL-ST group. The between-group difference

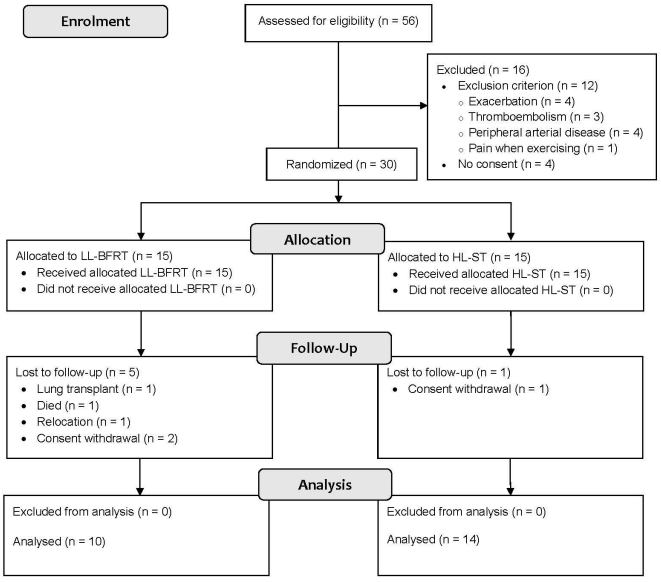

Figure 2 Study participant flow chart. Exacerbation, experienced an acute COPD exacerbation in the last 6 weeks; thromboembolism, history of thromboembolism in the lower limb. COPD, chronic obstructive pulmonary disease; HL-ST, high-load strength training; LL-BFRT, low-load blood flow restriction training.

(mean difference=−6.4, 95% CI=−13.20 to 25.92 Nm) of the improvement was not statistically significant (t=0.67, p=0.51). Five (50%) participants improved beyond the MCID in the LL-BFRT group, while seven (50%) did in the HL-ST group. Isometric muscle strength of the left knee extensors improved by 10 (18) Nm, from 125 (67) to 135 (67) Nm in the LL-BFRT group and by 16 (30) Nm, from 136 (45) to 152 (54) Nm in the HL-ST group. The between-group difference (−5.6, 95% CI=−15.44 to 26.55 Nm) of the improvement was not statistically significant (t=0.55, p=0.59). Five (50%) participants improved beyond the MCID in the LL-BFRT group, while six (43%) did in the HL-ST group. Sex did not modify the effects in both right and left knee extensors (p=0.68 for knee extension left, p=0.21 for knee extension right)

Isometric muscle strength of the right knee flexors improved by 4 (12) Nm, from 100 (35) to 104 (30) Nm in the LL-BFRT group and by 1 (16) Nm, from 110 (33) to 112 (36) Nm in the HL-ST group. The between-group difference of the improvement (2.9, 95% CI=−15.10 to 9.28 Nm) was not statistically significant (t=−0.50, p=0.62). Isometric muscle strength of the left knee flexors improved by 6 (17) Nm, from 96 (41) to 102 (28) Nm in the LL-BFRT group and by 2 (14) Nm, from 106 (29) to 108 (33) Nm in the HL-ST group. The between-group difference of the improvement (3.7, 95% CI=−18.27 to 10.81 Nm) was not statistically significant (t=−0.55, p=0.59). Individual and grouped data for the changes in isometric strength are shown in figure 3.

There were no statistically significant between-group differences in changes in 1-RM in the leg press and the leg extension exercise, see table 3.

Functional exercise capacity

There were no statistically significant between-group differences in changes in 1MSTST repetitions, though only the LL-BFRT group improved to a clinically relevant degree (see table 3). Five (50%) participants improved beyond the MCID in the LL-BFRT group, while four (29%) did in the HL-ST group.

Table 2 Participant characteristics at baseline

	Overall	HL-ST	LL-BFR-ST
N	30	15	15
Age, years	64 (9)	65 (9)	62 (8)
Sex, female/male (% female)	13/17 (43)	6/9 (40)	7/8 (47)
GOLD stage, n (%)			
1	1 (3)	0 (0)	1 (7)
2	9 (30)	4 (27)	5 (33)
3	14 (47)	8 (53)	6 (40)
4	6 (20)	3 (20)	3 (20)
COPD risk group, n (%)			
A	4 (13)	3 (20)	1 (7)
B	17 (57)	8 (53)	9 (60)
E	9 (30)	4 (27)	5 (33)
FEV_1, l	1.4 (0.6)	1.3 (0.6)	1.4 (0.7)
FEV_1, % predicted	47 (18)	46 (16.5)	49 (19.4)
FVC, l	2.8 (1.0)	2.7 (0.9)	2.9 (1.1)
FVC, % predicted	76 (18)	72 (16)	79 (20)
VO_2max, ml/min/kg	14.2 (4.0)	15.4 (4.1)	13.4 (3.8)
iPPO, W	85 (41)	92 (40)	79 (42)
Knee extensor strength, nm right/left	132 (47)/130 (50)	138 (39)/137 (42)	126 (54)/123 (58)
Knee flexor strength, nm right/left	106 (33)/103 (34)	111 (32)/110 (29)	102 (34)/97 (37)
1MSTS, repetitions	22 (7)	21 (8)	23 (6)
6MWT, m	420 (126)	408 (139)	432 (114)
Steps per day, n	3143 (2351)	3048 (2649)	3246 (2103)

Data are mean (SD) or n (%).
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease ; HL-ST, high-load strength training; iPPO, incremental peak power output; LL-BFR-ST, low-load blood flow restriction strength training; 1MSTST, 1 min sit-to-stand test; 6MWT, 6 min walk test; nm, newton metres; VO_2max, maximal oxygen uptake.

There were no statistically significant between-group differences in changes in 6MWT distance (see table 3). Six (60%) participants improved beyond the MCID in the LL-BFRT group, while 5 (36%) did in the HL-ST group.

Physical activity

We had valid accelerometer data at both time points from eight participants in each group. There were no statistically significant between-group differences in changes in PA (see table 3). The within-group difference exceeded the MCID only in the LL-BFRT group. Five (63%) participants improved beyond the MCID in the LL-BFRT group, while 3 (38%) did in the HL-ST group.

Rating of perceived leg exertion and dyspnoea during exercise

Borg scale ratings for perceived leg exertion after the leg press and the leg extension exercise for every training session are shown in figure 4A,C. The initial training sessions revealed diverging perceptions of effort between the LL-BFRT and the HL-ST group. While the LL-BFRT group perceived high leg exertion, the HL-ST group reported rather low numbers. Halfway through the training period, the reportings reached a plateau that is comparable between groups. Patterns were largely similar between the leg press and the leg extension exercises. Borg scale ratings for perceived dyspnoea after the leg press and the leg extension exercise for every training session are shown in figure 4B,D. Both groups started with similar values during the first training session, thereafter the HL-ST group showed higher reportings for about half of the training sessions. In the second half of the training period, dyspnoea reportings were largely similar between the groups.

COPD-related symptom burden

Scores in the CAT decreased by −1 (3) points, from 15 (4) to 14 (6) points in the LL-BFRT group and by −1 (7), from 15 (6) to 13 (6) points in the HL-ST group. The between-group difference of the change (−0.1, 95% CI=−4.81 to 4.94) was not statistically significant (t=0.03, p=0.98). Three participants improved beyond the MCID in the LL-BFRT group, while five did in the HL-ST group.

Health-related quality of life

Scores in the PCS of the SF-12 increased by 0.9 (6.7) points, from 39.3 (7.0) to 40.2 (9.8) points in the LL-BFRT group and decreased by −1.5 (8.6), from 36.4 (9.9) to 35.0 (7.5) points in the HL-ST group. The between-group difference of the change (2.3, 95% CI=−9.89 to 5.20) was not statistically significant (t=−0.66, p=0.52). Two participants improved beyond the MCID in the LL-BFRT group, while three did in the HL-ST group. Scores in the MCS of the SF-12 increased by 0.7 (7.0) points, from 50.6 (5.8) to 51.3 (7.5) points in the LL-BFRT group and by 4.3 (9.9), from 49.7 (10.4) to 50.6 (5.8) points in the HL-ST group. The between-group difference of the change (−3.6, 95% CI=−4.62 to 11.79) was not statistically significant (t=0.93, p=0.37). Two participants improved beyond the MCID in the LL-BFRT group, while five did in the HL-ST group.

Scores in the Mastery domain of the CRQ increased by 0.4 (0.5) points, from 5.1 (1.8) to 5.5 (1.3) points in the LL-BFRT group and by 0.2 (1.5), from 5.2 (1.6) to 4.1 (1.6) points in the HL-ST group. The between-group difference of the change (0.2, 95% CI=−1.27 to 0.80) was not statistically significant (t=−0.49, p=0.63). Three participants improved beyond the MCID in the LL-BFRT group, while five did in the HL-ST group.

Anxiety and depression risk

Scores in the Anxiety subscale of the HADS increased by 1.3 (3.5) points, from 6.1 (2.4) to 7.4 (2.2) points in the LL-BFRT group and decreased by −2 (3.8), from 8.4 (5.1) to 7.4 (2.2) points in the HL-ST group. The between-group difference of the change (3.2, 95% CI=−6.47 to 0.08) was not statistically significant (t=−2.07, p=0.06). Two participants improved beyond the MCID in the LL-BFRT group, while five did in the HL-ST group. Scores in the Depression subscale of the HADS increased by 0.7 (3.2) points, from 5.0 (3.4) to 5.7 (2.6) points in the LL-BFRT group and decreased by −3.1 (4.9), from 7.3 (5.4) to 4.2 (3.6) points in the HL-ST group. The between-group difference of the change (3.2, 95% CI=−6.82 to 0.48) was not statistically significant (t=−1.84, p=0.08). Two participants improved beyond the MCID in the LL-BFRT group, while five did in the HL-ST group.

Effects on the CAT, CRQ, SF-12 and HADS are summarised in table 4

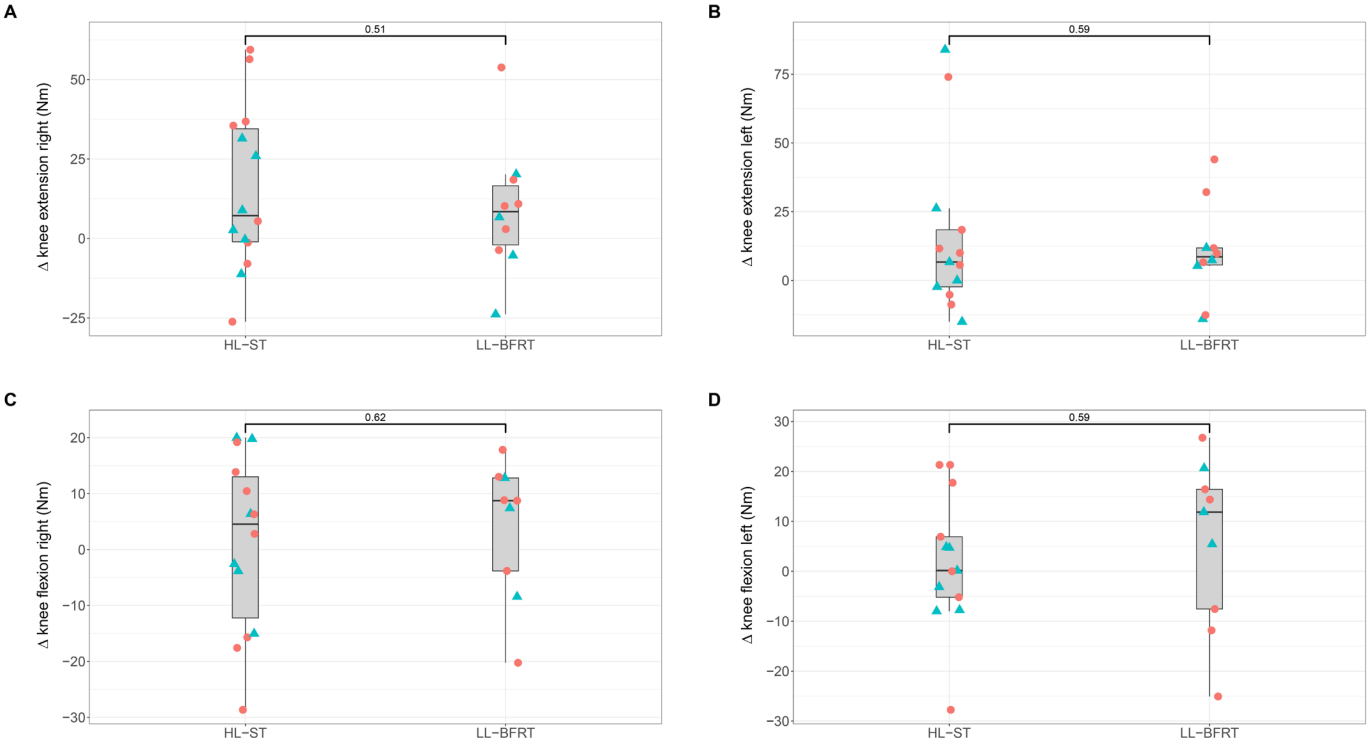

Figure 3 Changes in isometric leg strength stratified by group. (A) right knee extensors; (B) left knee extensors; (C) right knee flexors; (D) left knee flexors. Individual data are stratified for females (blue triangles) and males (red circles). Δ, change post–pre study intervention; HL-ST, high-load strength training; LL-BFRT, low-load blood flow restriction training; Nm, newton metres.

Participant experiences

The LL-BFRT group rated their overall physical improvement with 7 (1) points, general exhaustion from exercise with 6 (2) points and muscle soreness from exercise with 5 (2) points. Similarly, the HL-ST group rated their overall improvement with 7 (2) points, general exhaustion from exercise with 6 (1) points and muscle soreness from exercise with 5 (3) points.

Online supplemental material provides details on the course of AOP over the course of the study and online supplemental figure S1 (1-RM), S2 (6MWT) and S3 (1MSTST) display the secondary outcomes graphically.

DISCUSSION

Here, we report on the first study investigating LL-BFRT in participants with COPD. We found encouraging results, suggesting similar strength gains from LL-BFRT in comparison to HL-ST while reducing perceptions of dyspnoea during the exercise training.

Our study did not find any statistically significant or clinically relevant differences in isometric strength gains in the knee extensors between the LL-BFRT and the HL-ST group, while both groups improved their strength to a clinically relevant degree. A recent literature review quantified the magnitude of knee extensor strength gains from concurrent PR programmes between 7% and 32%.[34] Improvements observed in our work

Table 3 Changes in dynamic strength, functional exercise capacity and physical activity across study groups

	HL-ST			LL-BFRT			Between groups
	Pre	Post	Delta	Pre	Post	Delta	P value
1-repetition maximum							
Leg press (kg)	103.4 (29.8)	138.7 (43.0)	35.3 (16.5)	87.0 (36.0)	113.1 (42.3)	26.1 (20.8)	0.28
Leg extension (kg)	39.4 (20.8)	48.9 (25.8)	9.5 (11.7)	35.8 (21.4)	45.3 (22.6)	9.5 (8.5)	0.99
1 min sit-to-stand test							
Repetitions	22 (7)	24 (8)	1 (5)	23 (6)	27 (7)	4 (4)	0.25
6 min walk test							
Distance (m)	460 (95)	465 (98)	5 (30)	424 (136)	442 (116)	18 (88)	0.68
Physical activity							
Steps/day (n)	3609 (3110)	3426 (3092)	−182 (1971)	3436 (2333)	4941 (3149)	1506 (2441)	0.15

Data are mean (SD).
HL-ST, high-load strength training; LL-BFRT, low-load blood flow restriction training.

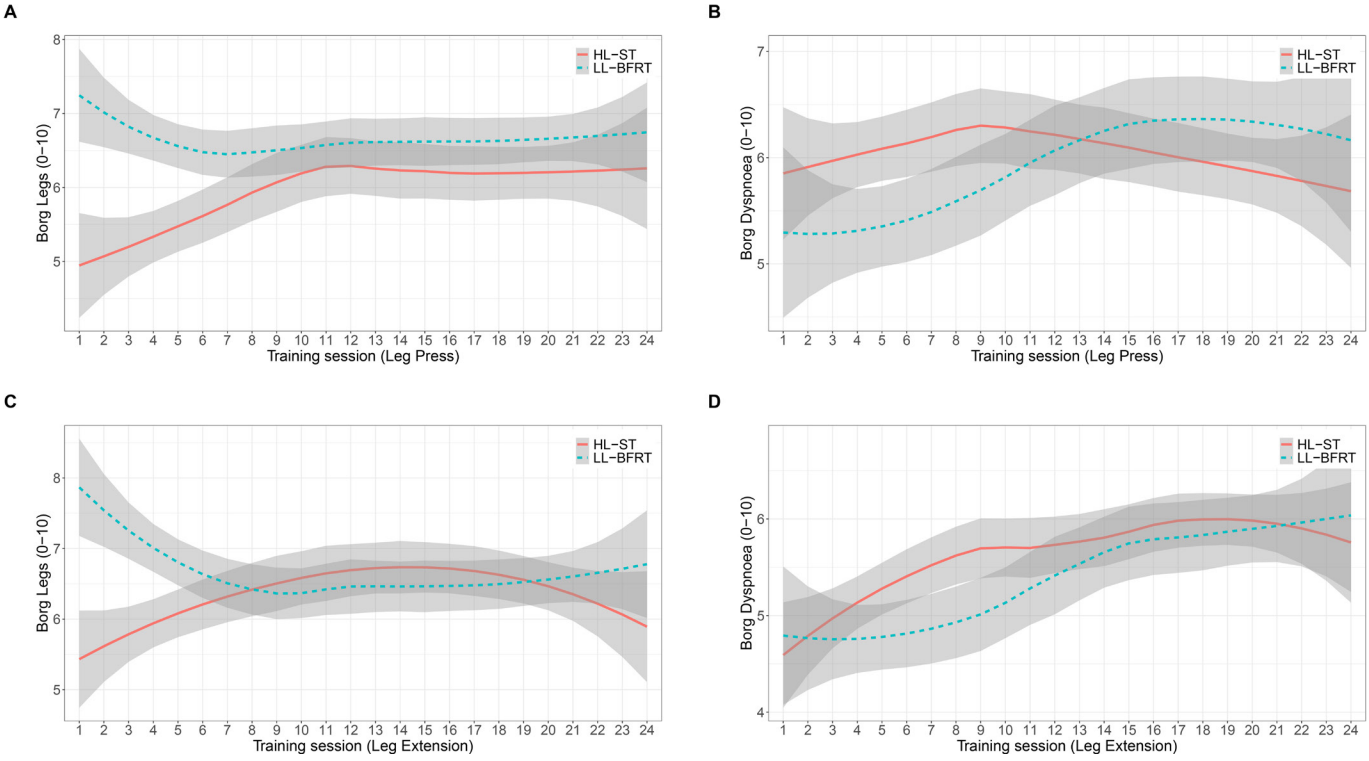

Figure 4 Perceived dyspnoea and leg exertion for each training session measured with the modified Borg scale. Locally estimated scatterplot smoothing (LOESS) lines are stratified by group. (A) perceived leg exertion during the leg press exercise; (B) perceived dyspnoea during the leg press exercise; (C) perceived leg exertion during the leg extension exercise; (D) perceived dyspnoea during the leg extension exercise. HL-ST, high-load strength training; LL-BFRT, low-load blood flow restriction training.

are in line with these results, showing changes of 10%–12%. Regarding knee flexors, both groups did not improve to a clinically relevant degree. This is not surprising, considering that knee flexors were not trained in isolation. In our study, the LL-BFRT group gained more knee flexor strength. However, the magnitude is likely not clinically relevant. Nevertheless, the BFR stimulus leads to augmented activation of secondary muscles and future studies should therefore assess knee flexor strength as well.[35] Especially since the knee flexors seem to have an important predictive role regarding mortality in COPD patients.[36]

Considering dynamic strength measures (ie, 1-RM) we observed larger increases in the leg press exercise for the HL-ST group. However, it needs to be considered that the HL-ST group trained at loads very similar to the 1-RM estimation procedure. Thus, we attribute the between-group difference to the fact that

Table 4 Changes in questionnaire scores across study groups

	HL-ST			LL-BFRT			Between groups
	Pre	Post	Delta	Pre	Post	Delta	P value
COPD Assessment Test							
Score	15 (6)	13 (6)	−1 (7)	15 (4)	14 (6)	−1 (3)	0.98
Chronic Respiratory Questionnaire							
Mastery	5.2 (1.6)	5.3 (1.4)	0.2 (1.5)	5.1 (1.8)	5.5 (1.3)	0.4 (0.5)	0.63
Dyspnoea	5.0 (1.4)	4.1 (1.6)	−0.9 (2.1)	4.4 (1.4)	4.8 (0.9)	0.4 (1.0)	0.16
Emotion	4.8 (1.5)	5.3 (1.4)	0.5 (1.4)	4.7 (1.5)	5.2 (1.2)	0.4 (1.0)	0.97
Fatigue	4.1 (1.3)	4.6 (0.9)	0.5 (1.6)	3.6 (1.3)	3.9 (1.5)	0.4 (1.0)	0.81
Short-form 12							
PCS	36.4 (9.9)	35.0 (7.5)	−1.5 (8.6)	39.3 (7.0)	40.2 (9.8)	0.9 (6.7)	0.52
MCS	49.7 (10.4)	54.0 (9.1)	4.3 (9.9)	50.6 (5.8)	51.3 (7.5)	0.7 (7.0)	0.37
Hospital Anxiety and Depression Scale							
Depression	7.3 (5.4)	4.2 (3.6)	−3.1 (4.9)	5.0 (3.4)	5.7 (2.6)	0.7 (3.2)	0.08
Anxiety	8.4 (5.1)	6.4 (4.1)	−2.0 (3.8)	6.1 (2.4)	7.4 (2.2)	1.3 (3.5)	0.06

Data are mean (SD).
COPD, chronic obstructive pulmonary disease; HL-ST, high-load strength training; LL-BFRT, low-load blood flow restriction training; MCS, mental component subscale; PCS, physical component subscale.

the HL-ST group was more accustomed to handle the load experienced during the test.

Considering the baseline characteristics of our sample, there is a possibility that the LL-BFRT group had more severe skeletal muscle dysfunction. In detail, the LL-BFRT group showed clinically relevant lower isometric muscle strength and iPPO than the HL-ST group. However, their functional exercise capacity was preserved and PA higher. We applied sensitivity analyses, using linear regression models with baseline adjustment regarding these variables to determine the impact of the baseline indifference. Adjusting the tests for baseline differences did not change the results. In addition, we applied imputation with predictive mean matching to account for missing data in the isometric strength measurements. This did not change the results, implying robustness of our data.

During our study, no adverse events associated with the intervention were reported and our study participants showed excellent adherence to the intervention. In particular, none of the participants requested to change the study group. From the six participants not completing the study, five were allocated to the LL-BFRT group. In detail, three of the dropouts in the LL-BFRT group were due to health or logistic reasons (see figure 2 for details).

We hypothesised that LL-BFRT would result in lower in-exercise dyspnoea because of the drastically lower load. This hypothesis was partially confirmed. As visualised in figure 4, LL-BFRT seems to induce increased perceptions of leg fatigue while reducing perceived dyspnoea in comparison to HL-ST. However, this effect levels off halfway through the 12-week training period (ie, after 10–12 trainings). From studies in healthy participants, it is known that LL-BFRT induces short-term (ie, 1–3 weeks) strength improvements equal to HL-ST.[24] In the same time horizon, LL-BFRT already induces muscle mass gains, which HL-ST fails to achieve.[24] Pairing these physiological findings to our insights on the perceptions, we suggest the design of PR incorporating an initial LL-BFRT period, progressing to HL-ST after 6 weeks. We could well imagine that this procedure would increase tolerability of PR, especially in participants with a dyspnoea and peripheral muscle dysfunction dominant COPD phenotype. In addition, the early hypertrophic response from LL-BFRT might even augment the HL-ST stimulus.

To our surprise, the LL-BFRT group showed clinically relevant increases in PA while the HL-ST group did not show an increase. We may only hypothesise on the underlying mechanism of this interesting finding, which could be due to LL-BFRT eliciting less neuromuscular fatigue and thus providing the participants with more capacity to translate their strength gains. This hypothesis is supported by the 1MSTST showing clinically relevant improvement only in the LL-BFRT group. Ultimately, this finding needs confirmation in larger studies, adequately powered for the PA outcome.

This study has some limitations. First, this is the first study on LL-BFRT in COPD and its findings need confirmation in well-powered studies. Second, the endurance training stimulus in our study seemed to be ineffective. Both groups did not show a relevant training response in the 6MWT. Unfortunately, we did not follow up with CPET, which would have provided more insights. Third, we used handheld dynamometry to quantify leg strength. This approach may show more variation than fixed strain gauge or isokinetic testing. Nevertheless, the measure is commonly used and we standardised the procedure as far as possible. Last, we did not incorporate a muscle mass outcome. Data on increases in muscle mass would be an interesting asset to our strength and functional measures.

In conclusion, this pilot study suggests that LL-BFRT seems to be equally effective in improving leg strength as HL-ST in patients with stable COPD while reducing perceptions of dyspnoea in the initial training phase. Future studies may investigate a combined approach, transitioning from LL-BFRT to HL-ST after 12 trainings. In addition, physiological studies on acute cardiorespiratory responses to LL-BFRT would show if the reduced perceived dyspnoea reflects reduced ventilatory work.

Twitter Dario Kohlbrenner @d_kohlbrenner

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Contributors Conception and study design: DK, CC and NAS; Data collection: DK, MK, CA, MP, AM and NG; Data analysis: DK; Drafting of manuscript: DK; Critical revision of manuscript: all authors. Approval of final manuscript: all authors; Guarantor of the work: DK.

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Patient consent for publication Not applicable.

Ethics approval We conducted this study in accordance with the Declaration of Helsinki, the principles of Good Clinical Practice, the Human Research Act (HRA) and the Ordinance on Human Research with the Exception of Clinical trials (HRO). All subjects provided written informed consent. The Ethics Committee of the Canton of Zurich approved the study (EK-ZH-NR: 2019–01641).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data generated in this study are available on reasonable request directed to the corresponding author.

ORCID iDs
Dario Kohlbrenner http://orcid.org/0000-0001-6674-5193
Noriane A Sievi http://orcid.org/0000-0003-1758-4586

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Online Supplementary Material

Low-load blood-flow restriction strength training in patients with COPD:

a randomised single-blind pilot study

Dario Kohlbrenner[1,2], Manuel Kuhn[1,2], Anastasios Manettas[3,4], Céline Aregger[3], Matthias Peterer[3], Nicola Greco[3], Noriane A. Sievi[2], Christian F. Clarenbach[1,2]

[1]Faculty of Medicine, University of Zurich, Zurich, Switzerland

[2]Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland

[3]Physiotherapy Occupational Therapy, University Hospital Zurich, Zurich, Switzerland

[4]Biomechanics and Ergonomics, ErgoMech Laboratory, Department of Physical Education and Sport Science, University of Thessaly, Trikala, Greece

Corresponding author:
Dario Kohlbrenner, PhD
University Hospital Zurich
Department of Pulmonology
Rämistrasse 100
8091 Zurich
Switzerland
dario.kohlbrenner@usz.ch

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Methods

Participants were asked to refrain from exercise and strenuous activities for the 24h preceding the visits. In addition, they were ask to avoid intake of caffeine and heavy meals 4h before the visits.

Secondary outcomes

We used the 3-8 repetition maximum (RM) test [1], performed after a warm-up procedure (i.e., 15 repetitions with a weight estimated to be approximately 50% of the individual 1-RM). For the test, participants performed as many technically correct and full range of motion repetitions as possible. If muscular failure in the first set of testing did not occur within 3-8 repetitions, an additional set was carried out after 5min of rest. No more than three sets of testing were done to ensure reproducible values. The 1-RM was estimated using the equation:

$$\text{1-RM predicted} = \frac{weight\ lifted}{1.0278 - 0.0278\ x\ the\ number\ of\ repetitions\ performed}$$

Results were recorded in kilograms. The results of this test were also used to set the initial exercise training loads.

Functional exercise capacity was measured with the 6-minute walk test (6MWT) according to American Thoracic Society / European Respiratory Society (ATS/ERS) technical standards [2], and the 1-minute sit-to-stand test (1MSTST), which is a valid and reliable test in COPD [3].

Cardiopulmonary exercise testing (CPET) was performed in accordance with published ERS standards [4]. We used a bicycle ergometer (ergoselect33 100, ergoline GmbH, Sitz, Germany) with an incremental ramp protocol (initial load 20W +10W/min for women and 30W +10W/min for men). Respiratory parameters were collected breath-by-breath (Ergostik, Geratherm Respiratory GmbH, Bad Kissingen, Germany).

Lung function was measured according to ATS/ERS technical standards [5, 6].

Physical activity (PA) was recorded with a triaxial accelerometer of a multisensory activity monitor (SenseWear Pro, Bodymedia Inc., Pittsburgh, PA, USA). We used the number of steps per day as an indicator for PA. The device was worn as an armband on the left upper arm for seven days, around the clock except during water-based activities (e.g., showering, swimming). Days with a minimum of 22.5h on-body time were considered valid days [7]. Over the 7-day assessment period, a minimum of four valid recording days were required to include PA data for final analysis [7]. Minimal clinical important differences (MCIDs) reported for PA in COPD populations are relatively broad (i.e., between 350 and 1100 steps/day) [8]. We applied a rather high threshold of 1000 steps/day to our analysis.

Participants were asked to complete a number of questionnaires. We assessed symptom

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burden with the COPD Assessment test (CAT), a valid and reliable questionnaire specifically designed for the COPD population [9]. The MCID of the CAT is considered -2 points [10]. We assessed health-related quality-of-life (HrQoL) with the Chronic Respiratory Questionnaire (CRQ) and the Short-Form-12 (SF-12). While the CRQ is specifically designed for chronic respiratory disease populations, the SF-12 is generically targeting HrQoL [11, 12]. The MCID for the CRQ is 0.5 points for the dyspnoea, fatigue, emotion, and mastery subscales [13]. The MCID for the SF-12 is 3 points in the physical component subscale (PCS), and 3.5 points in the mental component subscale [14]. Depression and anxiety symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS), a valid and reliable questionnaire in the COPD population [15]. The HADS consists of an Anxiety and a Depression subscale, the MCID is considered -1.5 points in both [15]. Finally, participants were asked to fill a purpose-designed questionnaire at the end of their study participation (see below for the original and a translated version of the questionnaire).

Results

Lower limb arterial occlusion pressure

AOPs in the LL-BFRT group were 154 (43), 149 (38), 143 (33), and 162 (27) mmHg at the first, 8th, 16th training, and follow-up, respectively. AOPs in the HL-ST group were 172 (28), 168 (24), 159 (25), and 167 (29) mmHg at the first, 8th, 16th training, and follow-up, respectively.

Purpose-designed questionnaire (original)

Fragebogen zum Abschluss der Studie LL-BFRT in COPD

Inwiefern hat sich Ihre körperliche Leistungsfähigkeit während der Studie verändert?

1	2	3	4	5	6	7	8	9	10
Hat stark abgenommen				Gleich geblieben					Hat sich stark verbessert

Wie anstrengend empfanden Sie das Krafttraining durchschnittlich?

1	2	3	4	5	6	7	8	9	10
Überhaupt nicht anstrengend									Extrem anstrengend

Hatten Sie Muskelkater aufgrund des Trainings in der ambulanten pulmonalen Rehabilitation?

1	2	3	4	5	6	7	8	9	10
Nie				Mässiger Muskelkater					Extremer Muskelkater

Purpose-designed questionnaire (translated from German)

Questionnaire to conclude your study participation

How did your physical fitness change during the study?

1	2	3	4	5	6	7	8	9	10
Strongly declined				Unchanged					Strongly improved

How hard did you perceive the exercise training on average?

1	2	3	4	5	6	7	8	9	10
Not exhausting at all									Extremely exhausting

Did you have muscle soreness from the exercise training? How intense did it feel?

1	2	3	4	5	6	7	8	9	10
Never				Moderate muscle soreness					Extreme muscle soreness

Supplementary Figures

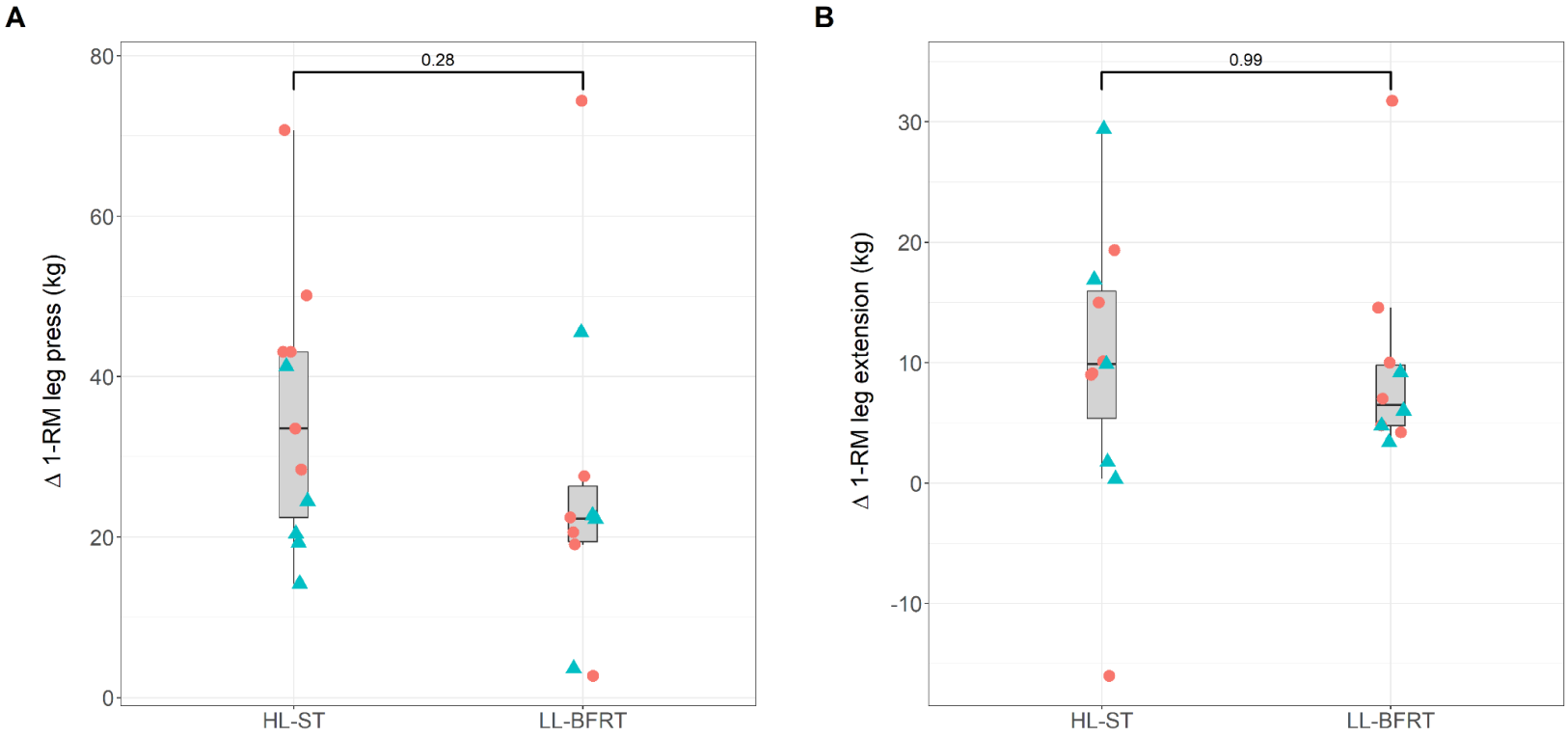

Figure S1. Changes in estimated 1-RM stratified by group. A, leg press; B, leg extension. Individual data is stratified for females (blue triangles) and males (red circles). Δ, change post-pre study intervention; 1-RM, 1-repetition maximum; kg, kilogram; HL-ST, high-load strength training; LL-BFRT, low-load blood-flow restriction training.

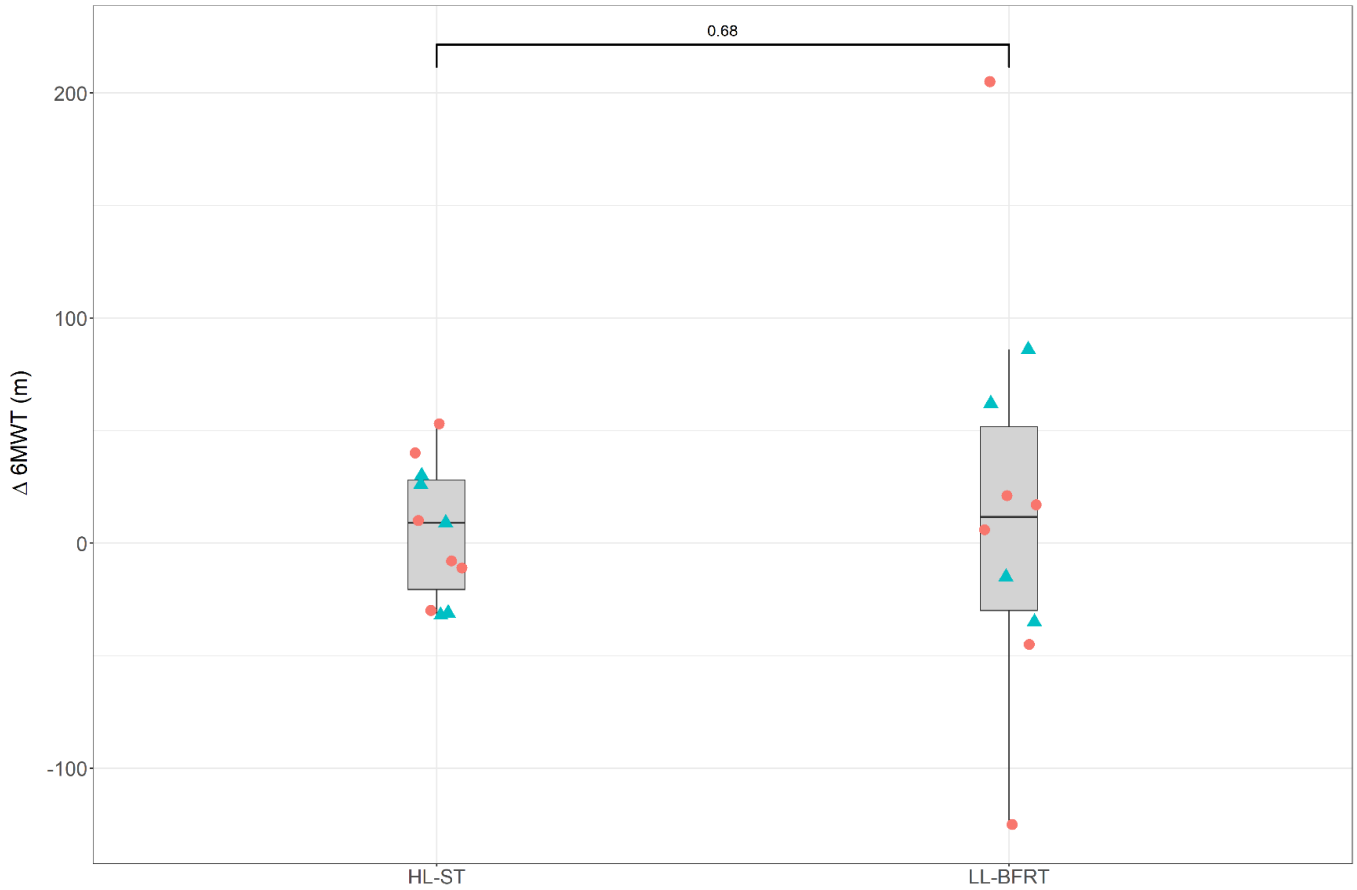

Figure S2. Changes in 6MWT distance stratified by group. Individual data is stratified for females (blue triangles) and males (red circles). Δ, change post-pre study intervention; 6MWT, 6-minute walk test; m, meters; HL-ST, high-load strength training; LL-BFRT, low-load blood-flow restriction training.

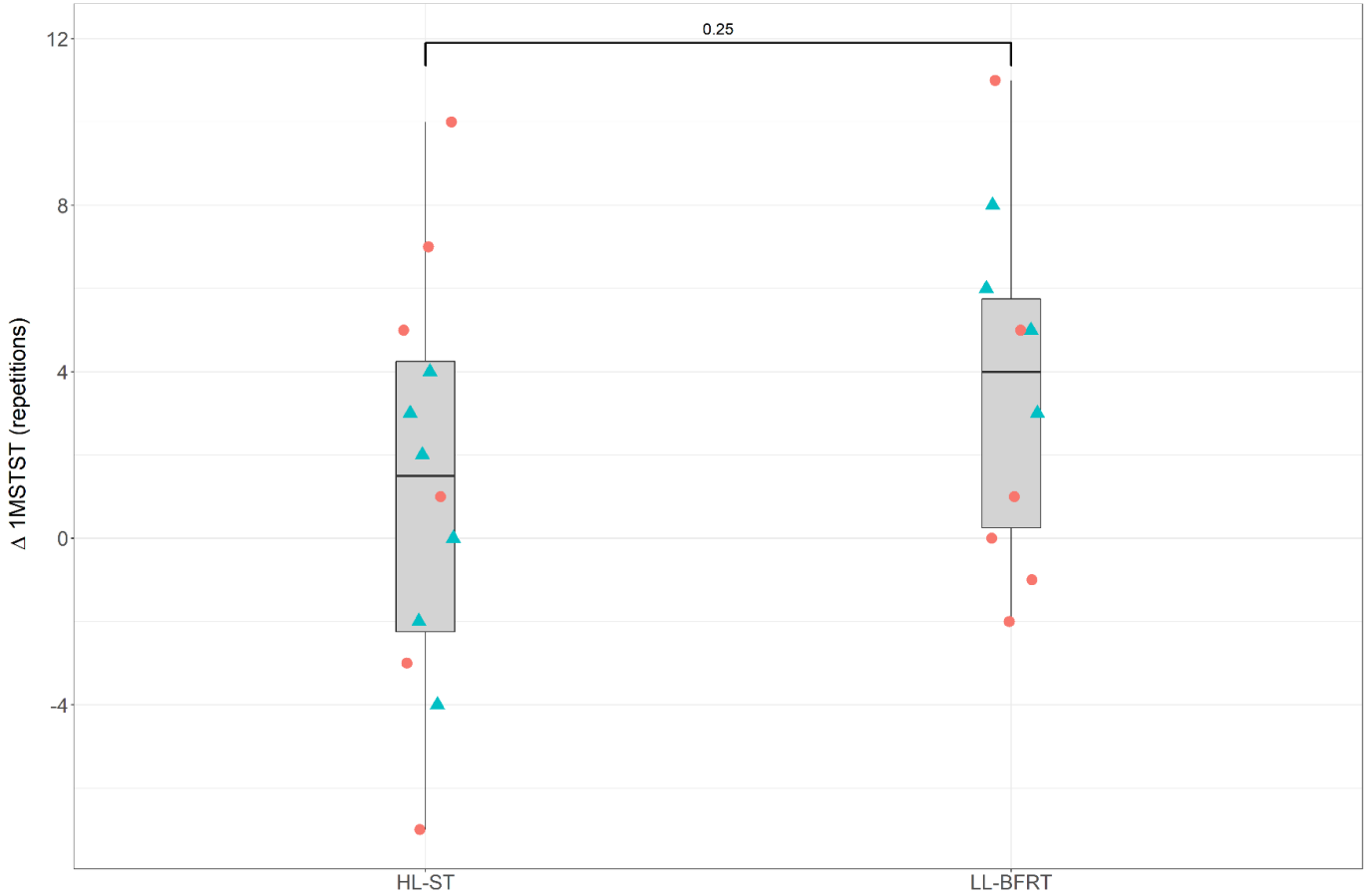

Figure S3. Changes in 1MSTST stratified by group. Individual data is stratified for females (blue triangles) and males (red circles). Δ, change post-pre study intervention; 1MSTST, 1-minute sit-to-stand test; HL-ST, high-load strength training; LL-BFRT, low-load blood-flow restriction training.

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