





OPEN ACCESS

Original research

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

Dario Kohlbrenner <sup>1,2</sup>, Manuel Kuhn,<sup>1,2</sup> Anastasios Manettas,<sup>3,4</sup> Céline Aregger,<sup>3</sup> Matthias Peterer,<sup>3</sup> Nicola Greco,<sup>3</sup> Noriane A Sievi <sup>2</sup>, Christian Clarenbach<sup>1,2</sup>

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thorax-2023-220546>).

<sup>1</sup>Faculty of Medicine, University of Zurich, Zurich, Switzerland

<sup>2</sup>Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland

<sup>3</sup>Physiotherapy Occupational Therapy, University Hospital Zurich, Zurich, Switzerland

<sup>4</sup>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](mailto:dario.kohlbrenner@usz.ch)

Received 1 June 2023

Accepted 18 November 2023

Published Online First

21 December 2023



► <http://dx.doi.org/10.1136/thorax-2023-221218>



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Kohlbrenner D, Kuhn M, Manettas A, *et al.* *Thorax* 2024;**79**:340–348.

## 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.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) elicits a characteristic, progressive loss in skeletal muscle mass and function.<sup>1,2</sup> It is well established that exercise training may counteract the COPD associated skeletal muscle dysfunction by augmenting muscle protein synthesis, inducing

## 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.

angiogenesis and increasing mitochondrial function.<sup>1</sup> Consequently, structured concurrent (ie, same-session endurance and strength type exercises) exercise training programmes were introduced.<sup>3</sup> 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.<sup>2,4</sup>

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.<sup>5</sup> 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.<sup>6</sup> 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.<sup>7–9</sup> The reason, therefore, is the



ventilatory limitation caused by airflow obstruction, dynamic hyperinflation and increased dead-space.<sup>10</sup>

In summary, despite PR being effective,<sup>4</sup> muscle strength impairment remains a persisting problem in COPD, reinforcing the vicious circle of breathlessness and deconditioning.<sup>11</sup> 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.<sup>12</sup> 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.<sup>12–14</sup> 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.<sup>12–14</sup> 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.<sup>15</sup> 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,<sup>16</sup> and a rationale for the potential of the method was published.<sup>7</sup> 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.<sup>17–19</sup>

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

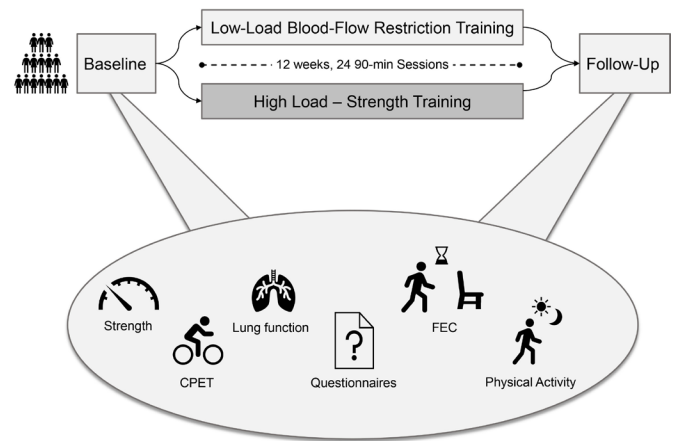
### Study participants

Patients with a COPD diagnosis according to the Global Initiative for Chronic Obstructive Lung Disease,<sup>2</sup> referred to our centre for outpatient PR, aged  $\geq 40$  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.<sup>9 21 22</sup> 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



**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).

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.

## General components

### Endurance exercise

Endurance exercise was performed using a continuous methodology.<sup>22</sup> 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),<sup>23</sup> 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  $\geq 8/10$ , 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.<sup>9 22</sup> 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  $\geq 14$  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.<sup>23</sup>

#### 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.<sup>24</sup> 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).<sup>23</sup>

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.<sup>25</sup> 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.<sup>26 27</sup> 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.<sup>28</sup> 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,<sup>29</sup> and for the 1MSTST 3 repetitions.<sup>30</sup>

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<sub>1</sub>), 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.<sup>31</sup> Literature reports drop-out rates of 17% in studies investigating PR.<sup>32</sup> 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.<sup>33</sup>

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

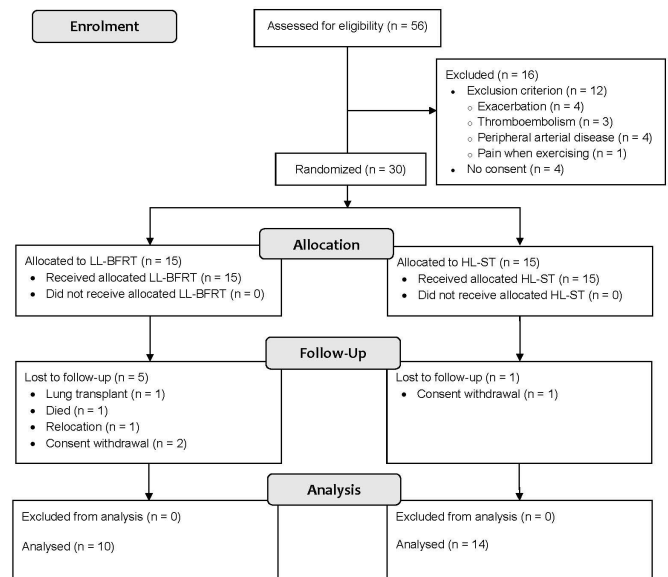
## RESULTS

### 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<sub>1</sub> 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 <sub>1</sub> , l	1.4 (0.6)	1.3 (0.6)	1.4 (0.7)
FEV <sub>1</sub> , % 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 <sub>2</sub> max, 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 <sub>1</sub> , 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; 1MSTS, 1 min sit-to-stand test; 6MWT, 6 min walk test; nm, newton metres; VO <sub>2</sub> max, 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

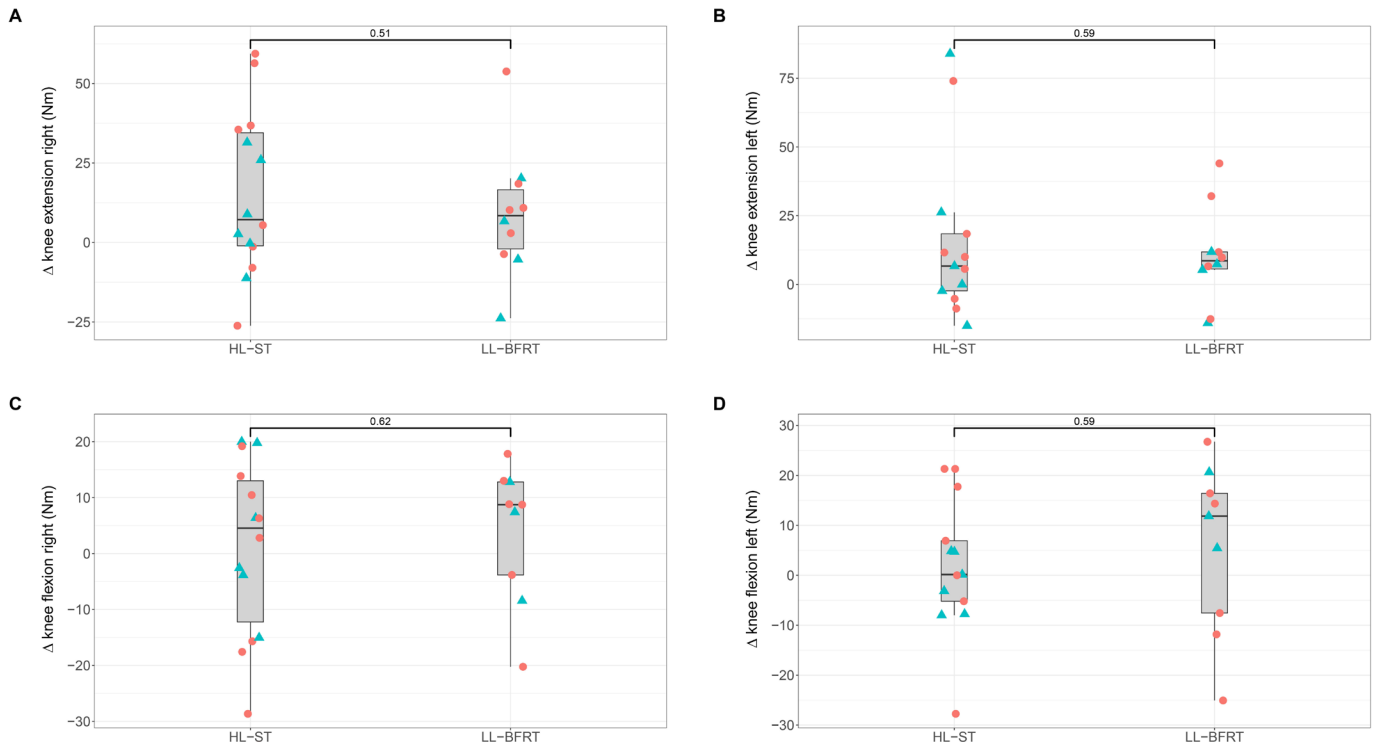
Scores in the PCS of the SF-12 increased by 0.9 (6.7) points, from 39.3 (7.0) to 40.2 (9.8) points in the LL-BFRT group and decreased by  $-1.5$  (8.6), from 36.4 (9.9) to 35.0 (7.5) points in the HL-ST group. The between-group difference of the change ( $t=-0.66$ ,  $p=0.52$ ). Two participants improved 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).  $\Delta$ , 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**

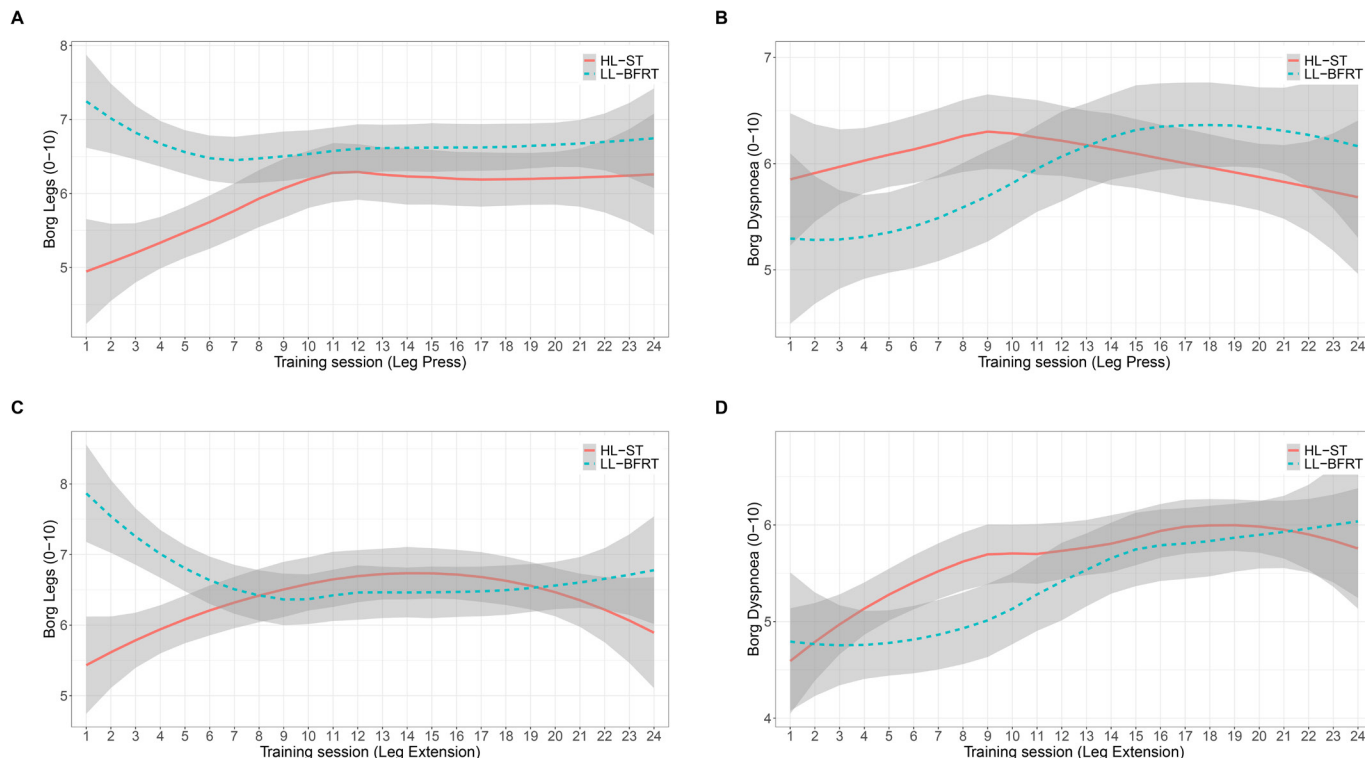
Here, we report on the first study investigating LL-BFRT in participants with COPD. We found encouraging results, suggesting similar strength gains from LL-BFRT in comparison to HL-ST while reducing perceptions of dyspnoea during the exercise training.

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%.<sup>34</sup> 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
<b>1-repetition maximum</b>							
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
<b>1 min sit-to-stand test</b>							
Repetitions	22 (7)	24 (8)	1 (5)	23 (6)	27 (7)	4 (4)	0.25
<b>6 min walk test</b>							
Distance (m)	460 (95)	465 (98)	5 (30)	424 (136)	442 (116)	18 (88)	0.68
<b>Physical activity</b>							
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.<sup>35</sup> Especially since the knee flexors seem to have an important predictive role regarding mortality in COPD patients.<sup>36</sup>

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
<b>COPD Assessment Test</b>							
Score	15 (6)	13 (6)	-1 (7)	15 (4)	14 (6)	-1 (3)	0.98
<b>Chronic Respiratory Questionnaire</b>							
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
<b>Short-form 12</b>							
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
<b>Hospital Anxiety and Depression Scale</b>							
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 iPP0 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.<sup>24</sup> In the same time horizon, LL-BFRT already induces muscle mass gains, which HL-ST fails to achieve.<sup>24</sup> 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

**Acknowledgements** We thank our study participants for dedicating their time to research. Furthermore, we thank Andras Gürth and Noëmi Bachmann with Physiotherapy Occupational Therapy, University Hospital Zurich for their assistance with the study measurements.

**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.

**Funding** This study was supported by project grants from the Heubergstiftung, Switzerland (no award/grant number) and the Foundation for Physiotherapy Science, Switzerland (no award/grant number).

**Competing interests** DK, MK, AM, CA, MP, NG and NAS have nothing to disclose. CC reports personal fees from Roche, personal fees from Novartis, personal fees from Boehringer, personal fees from GSK, personal fees from Astra Zeneca, personal fees from Sanofi, personal fees from Vifor, personal fees from Mundipharma, personal fees from Daiichi Sankyo, personal fees from CSL Behring, all outside the submitted work.

**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.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

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

#### REFERENCES

- 1 Maltais F, Decramer M, Casaburi R, *et al*. An official American Thoracic society/ European respiratory society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014;189:e15–62.
- 2 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2023 report). 2023.
- 3 Casaburi R, ZuWallack R. Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. *N Engl J Med* 2009;360:1329–35.
- 4 McCarthy B, Casey D, Devane D, *et al*. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015;2015:CD003793.
- 5 Armstrong M, Vogiatzis I. Personalized exercise training in chronic lung diseases. *Respirology* 2019;24:854–62.



- 6 Almadana Pacheco V, Pavón Masa M, Gómez-Bastero Fernández AP, *et al.* Patient profile of drop-outs from a pulmonary rehabilitation program. *Arch Bronconeumol* 2017;53:257–62.
- 7 S. Thiebaud R, P. Loenneke J, Abe T. COPD and muscle loss: is blood flow restriction a potential treatment. *J Trainol* 2014;3:1–5.
- 8 Spruit MA, Singh SJ, Garvey C, *et al.* An official American Thoracic society/European respiratory society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188:e13–64.
- 9 American College of Sports Medicine. American college of sports medicine position stand. progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009;41:687–708.
- 10 Neder JA, Marillier M, Bernard AC, *et al.* The integrative physiology of exercise training in patients with COPD. *COPD* 2019;16:182–95.
- 11 ZuWallack R. How are you doing? What are you doing? differing perspectives in the assessment of individuals with COPD. *COPD* 2007;4:293–7.
- 12 Centner C, Wiegel P, Gollhofer A, *et al.* Effects of blood flow restriction training on muscular strength and hypertrophy in older individuals: A systematic review and meta-analysis. *Sports Med* 2019;49:95–108.
- 13 Loenneke JP, Wilson JM, Marin PJ, *et al.* Low intensity blood flow restriction training: a meta-analysis. *Eur J Appl Physiol* 2012;112:1849–59.
- 14 Lixandrão ME, Ugrinowitsch C, Berton R, *et al.* Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance training associated with blood-flow restriction: A systematic review and meta-analysis. *Sports Med* 2018;48:361–78.
- 15 Hughes L, Paton B, Rosenblatt B, *et al.* Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med* 2017;51:1003–11.
- 16 Kohlbrenner D, Aregger C, Osswald M, *et al.* Blood-flow-restricted strength training combined with high-load strength and endurance training in pulmonary rehabilitation for COPD: A case report. *Phys Ther* 2021;101:pzab063.
- 17 Declaration of Helsinki. n.d. Available: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
- 18 Human research act (HRA). n.d. Available: <https://www.admin.ch/opc/de/classified-compilation/20061313/index.html>
- 19 Ordinance on human research with the exception of clinical trials (HRO). n.d. Available: <https://www.admin.ch/opc/en/classified-compilation/20121177/index.html>
- 20 Eldridge SM, Chan CL, Campbell MJ, *et al.* CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ* 2016;355:i5239.
- 21 Human Kinetics, Incorporated. *Guidelines for Pulmonary Rehabilitation Programs*. 2019.
- 22 Liguori G, Feito Y, Fountaine C, *et al.* *ACSM's guidelines for exercise testing and prescription (11th edn)*. Philadelphia: Wolters Kluwer, 2021.
- 23 Borg E, Borg G, Larsson K, *et al.* An index for Breathlessness and leg fatigue. *Scandinavian Med Sci Sports* 2010;20:644–50. 10.1111/j.1600-0838.2009.00985.x Available: <https://onlinelibrary.wiley.com/toc/16000838/20/4>
- 24 Patterson SD, Hughes L, Warmington S, *et al.* Blood flow restriction exercise: considerations of methodology, application, and safety. *Front Physiol* 2019;10:1332.
- 25 Mentiplay BF, Perraton LG, Bower KJ, *et al.* Assessment of lower limb muscle strength and power using hand-held and fixed Dynamometry: A Reliability and validity study. *PLoS One* 2015;10:e0140822.
- 26 Wikholm JB, Bohannon RW. Hand-held Dynamometer measurements: tester strength makes a difference. *J Orthop Sports Phys Ther* 1991;13:191–8.
- 27 Lu TW, Hsu HC, Chang LY, *et al.* Enhancing the Examiner's resisting force improves the reliability of manual muscle strength measurements: comparison of a new device with hand-held Dynamometry. *J Rehabil Med* 2007;39:679–84.
- 28 Vaidya T, Beaumont M, de Bisschop C, *et al.* Determining the minimally important difference in quadriceps strength in individuals with COPD using a fixed Dynamometer. *Int J Chron Obstruct Pulmon Dis* 2018;13:2685–93.
- 29 Holland AE, Spruit MA, Troosters T, *et al.* An official European respiratory society/American Thoracic society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44:1428–46.
- 30 Vaidya T, de Bisschop C, Beaumont M, *et al.* Is the 1-minute sit-to-stand test a good tool for the evaluation of the impact of pulmonary rehabilitation? determination of the minimal important difference in COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11:2609–16.
- 31 Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics* 2005;4:287–91. 10.1002/pst.185 Available: <https://onlinelibrary.wiley.com/toc/15391612/4/4>
- 32 Bjoernshave B, Korsgaard J, Nielsen CV. Does pulmonary rehabilitation work in clinical practice? A review on selection and dropout in randomized controlled trials on pulmonary rehabilitation. *Clin Epidemiol* 2010;2:73–83.
- 33 Cleveland WS, Devlin SJ. Locally weighted regression - an approach to regression-analysis by local fitting. *J Am Stat Associat* 1988;83:596–610.
- 34 De Brandt J, Spruit MA, Hansen D, *et al.* Changes in lower limb muscle function and muscle mass following exercise-based interventions in patients with chronic obstructive pulmonary disease: A review of the English-language literature. *Chron Respir Dis* 2018;15:182–219.
- 35 Pearson SJ, Hussain SR. A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Med* 2015;45:187–200.
- 36 Pleguezuelos E, Guirao L, Moreno E, *et al.* Ischiocrural strength may be a better Prognostic marker than quadriceps strength in COPD. *Lung* 2018;196:665–8.