Benefits of High-Intensity Exercise Training to Patients with Chronic Obstructive Pulmonary Disease: A Controlled Study

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Keywords

Chronic obstructive pulmonary disease · Strength exercise · Training · High intensity · Quality of life · Six-minute walk test

Abstract

Background: Various exercise training programs are used for patients with chronic obstructive pulmonary disease (COPD) of different severity. **Objectives:** To investigate the impact of individualized high-intensity training on exercise capacity with COPD. **Methods:** A total of 49 patients agreed to participate. Of these, 31 were assigned to the training group and 18 served as controls. The training group exercised twice a week for 90 min with consecutively increasing loads. At the time of enrollment (T_0), as well as after 3 (T_1) and 6 (T_2) months, a 6-min walk test (6-MWT) was performed and data on health-related quality of life, femoral muscle thickness, and various serum markers were obtained. **Results:** The

training group improved in their 6-MWT results ($T_0 = 407 \pm 152$ m vs. $T_1 = 459 \pm 127$ m, $p = 0.002$, vs. $T_2 = 483.2 \pm 130.1$ m, $p = 0.004$), in their cross-sectional area of the musculus rectus femoris ($T_0 = 6.2 \pm 1.2$ cm² vs. $T_1 = 6.9 \pm 1.2$ cm², $p = 0.003$, vs. 7.5 ± 1.6 cm², $p = 0.002$), and in their St. George's Respiratory Questionnaire (SGRQ) score ($T_0 = 43.3 \pm 18.0$ vs. $T_1 = 36.0 \pm 18.4$, $p = 0.001$, vs. $T_2 = 34.7 \pm 18.0$, $p = 0.004$). Serum levels of myostatin, irisin, resistin, and α -Klotho did not change significantly within the training period. Of note, the exercise group showed an inverse relationship between serum levels of resistin and those of α -Klotho after 6 months ($r = -0.608$, $p = 0.021$). **Conclusions:** COPD patients undergoing an individualized, structured, high-intensity training program improved their exercise capacity, gained muscle mass, and improved their quality of life.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive airway disease and a common cause of morbidity and mortality. The prevalence of COPD increases with age and is associated with reduced physical activity [1]. COPD patients are at increased risk of entering a vicious circle of symptom progression causing reduced physical activity, social isolation, increased anxiety, and depression [2], as well as further inactivity, which is expected to lead to structural and biochemical muscular alterations associated with increased discomfort during exercise [3]. The most frequently observed pathologic features of skeletal muscles of COPD patients are myopathic changes due to pulmonary cachexia and/or steroid therapy [4].

During the last 2 decades, various well-designed, randomized, controlled clinical trials have shown that pulmonary rehabilitation is an effective nonpharmacological intervention for improving the health status in COPD patients [5], and it has become an established part of care for COPD patients. Various training programs have been shown to provide positive effects on patients' physical and mental well-being [6], as well as on muscle composition [7] and quality of life [8]. Several studies have demonstrated that exercise training-induced improvements are accompanied by a decrease in inflammatory markers, such as IL-8, and an increase in muscle activity parameters, such as peroxisome proliferator-activated receptor- γ coactivator 1- α and irisin [9–11]. Finally, exercise training is a cost-effective intervention and reduces the number of hospitalizations [12].

In this context, different training modalities have been proposed to optimize exercise tolerance and to maximize training effects in patients with COPD. Nevertheless, it still remains unclear which exercise modalities are the most effective. Guidelines [13] recommend strength training 2–3 times a week and endurance training at moderate intensity 3–5 times a week; less is known about more intensive training concepts, including a quick escalation of exercise intensity.

We hypothesized that high-intensity training leads to an improvement of exercise capacity and reduced inflammatory activity. Therefore, we examined the effects of high-intensity exercise training of COPD patients on walking distance during the 6-min walk test (6-MWT) and on serum biomarker levels when compared to controls.

Subjects and Methods

Study Outline

Between January 2009 and December 2014, we invited 119 patients with mild to very severe COPD to participate in the study. Finally, 49 COPD patients without exacerbations for at least 4 weeks were enrolled in our prospective, nonrandomized interventional study conducted in the outpatient clinic of the University Hospital of Marburg. Thirty-one patients wished to be allocated to the exercise group, and each had an individualized outpatient strength training twice a week over a 3-month period with a fast increase in load. A subgroup of 14 patients agreed to continue the assigned training program for an additional 3 months.

Eighteen patients refused to participate in the training group due to different causes and gave written consent to serve as controls. In order to fulfil the study protocol, a training participation of at least 80% was required. The primary endpoint of this study was a difference in 6-MWT distance from baseline to 3 months between the exercise and the control group. Every patient gave informed written consent to participate in the study. The study was approved by the Ethics Committee of the Philipps-Universität Marburg (Ethics Committee AZ 7/13, Marburg, Germany) and registered (DRKS00006842).

Training Program

The exercise group underwent an individualized physical strength outpatient training 2 times a week for 90 min at the Department of Physiotherapy of the University Hospital of Marburg. The group was led by a specially educated physiotherapist. The training program was split into two 3-month exercise phases. The composition of the training was based on the guidelines of the American Association of Cardiovascular and Pulmonary Rehabilitation (ACCP/AACVPR) [14].

Each patient underwent a training schedule based on his/her exercise capacity, i.e., maximal force and endurance time in the different modalities (repetition method of Radlinger et al. [15]). In the first training session, a test of maximal force was repeated to adjust the training schedule at weeks 3, 7, and 11. Measurement of endurance capacity was performed on a bicycle ergometer: each patient started to cycle on an ergometer set at 25 W. The exercise load was increased by 25 W every minute. At the same time, we asked the participants to estimate their grade of exertion and dyspnea (Borg scale, ranging from 0 to 10). Simultaneously, oxygen saturation was monitored. The test was stopped when a patient reached 20 on the Borg scale or the oxygen saturation decreased below 90%. Disease-specific techniques (body positions and different breath and cough techniques, such as pursed-lip breathing) were communicated to the group.

There was a special focus on the following muscle groups: thigh muscles (especially musculus quadriceps femoris), lateral hip and trunk stabilizers, anterior shoulder muscles, rotator cuff muscles, different muscles of the upper extremities and dorsal trunk, and scapular stabilizers. The training equipment used was a leg press, leg squats, a cable pulldown, and a cable row. During the first 3 months, the intensity of the training changed from 35 to 75% of the maximal muscle strength of exercise. An overview of training strength, repetition, and series parameters is given in Table 1.

During the second session, the exercise intensity was kept constant but was switched towards muscle strength retention. The pa-

Fig. 1. Flowchart of patient recruitment, enrollment (T₀), and follow-up measurements (T₁, T₂).

Table 1. Overview of the training schedule

	Week											
	1	2	3	4	5	6	7	8	9	10	11	12
Intensity of maximal force, %	35	40	40	45	60	65	65	65	70	75	75	75
Repetitions	3	2	2	3	2	2	2	2	2	2	3	3–4
Series	20	20	20	20	20	15	15	15	15	15	15	15

The intensity of the training changed during the first 3 months from 35 to 75% of the maximal muscle strength of exercise. The training was adjusted in weeks 3, 7, and 11 in the first session (bold type).

tients trained with 70% of their maximal muscle strength of exercise, each with 2 repetitions and 20 series. The training schedule was adjusted if a patient was under- or overchallenged.

No intervention was performed in the control group. These patients were observed for 3 months.

Monitoring Training Benefits

Patient assessment was performed before the start of the training (T₀), after 3 months (T₁), and, in a subgroup of 14 patients, after 6 months (T₂). Assessments included the 6-MWT [16] and an assessment of health-related quality of life by the St. George's Respiratory Questionnaire (SGRQ) [17]. Measurement of the

cross-sectional area of the rectus femoris muscle was performed using ultrasonography as described by Seymour et al. [18]. While the patients were in a supine position, the transducer was placed perpendicular to the long axis of the thigh on its superior aspect, three-fifths of the distance from the anterior superior iliac spine to the superior patellar border. The area was calculated as an average of 3 consecutive measurements.

Analysis of Serum Markers

Serum concentrations of irisin and soluble α -Klotho were analyzed using commercially available ELISA kits (irisin: Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA; detection range:

Table 2. Baseline characteristics of the participants completing the study (per protocol)

Measures and comorbidities	All (<i>n</i> = 37)	Control group (<i>n</i> = 17)	Exercise group (<i>n</i> = 20)	<i>p</i> value
<i>Baseline characteristics</i>				
Age, years	65.73±8.3	65.59±8.65	65.85±8.21	ns
Gender (male/female), <i>n</i>	26/11	10/7	16/4	ns
BMI	29.41±5.55	29.69±6.0	29.16±5.28	ns
Current smokers, <i>n</i>	4	3	1	ns
<i>Spirometry</i>				
COPD stage				
I	15	5	10	ns
II	14	9	5	ns
III	4	2	2	ns
IV	4	1	3	ns
FEV ₁ , % predicted	67.66±24.10	67.37±17.1	67.91±29.23	ns
FEV ₁ /FVC, %	52.24±14.45	54.22±12.83	50.55±15.83	ns
R _{tot} , kPa × s/L	0.43±0.20	0.40±0.09	0.45±0.26	ns
ITGV, % predicted	129.48±37.16	126.22±22.20	132.25±46.74	ns
<i>Symptoms and oxygen saturation during the 6-MWT</i>				
Borg scale, RPE	2.17±1.38	2.1±1.6	2.4±1.2	ns
SaO ₂ , %	95.71±1.58	95.5±1.7	96±1.4	ns
<i>COPD treatment, <i>n</i></i>				
LAMA	15	8	7	ns
ICS	10	4	6	ns
ICS + LABA	14	8	6	ns
<i>Comorbidities, <i>n</i></i>				
Obesity	14	8	6	ns
Arterial hypertension	11	6	5	ns
Cardiac diseases	5	3	2	ns
Diabetes mellitus type 2	3	1	2	ns
<i>Comorbidity treatment</i>				
β-Blocker	16	7 (41%)	9 (45%)	ns
ACE inhibitor/ARB	17	8 (47%)	9 (45%)	ns
Diuretic agent	14	6 (35%)	8 (40%)	ns
Calcium antagonist	7	3 (18%)	4 (20%)	ns
Aldosterone antagonist	5	2 (12%)	3 (15%)	ns

Data are presented as the mean ± SD unless specified otherwise. BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; R_{tot}, total airway resistance; ITGV, intrathoracic gas volume; 6-MWT, 6-min walk test; RPE, rating of perceived exertion (0–10); SaO₂, oxygen saturation; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids; LABA, long-acting β-adrenoceptor agonist; ARB, angiotensin receptor blocker.

0.066–1,024 ng/mL, serum dilution 1:2; α-Klotho: Immuno-Biological Laboratories Co., Phoenix, AZ, USA; detection range: 93.75–6,000 pg/mL, serum dilution 1:2). Myostatin (CDF-8) was quantified using precoated Quantikine ELISAs (R&D Systems, Bio-Techne, Wiesbaden-Nordenstadt, Germany; detection range: 31.3–2,000 pg/mL, serum dilution 1:4). Resistin was measured using Duo Set ELISA kits (R&D Systems, Bio-Techne; detection range: 31.2–2,000 pg/mL, serum dilution 1:20). All samples were

measured in duplicate using a plate reader (Infinite® F200pro; Tecan, Männedorf, Switzerland) as described elsewhere [13].

Statistics and Data Analysis

Sample size calculation was performed using G*Power 3.1 and yielded a total sample size of 18 subjects considering 2 degrees of freedom with a power (1 – beta) of 95% and an alpha of 5% (primary endpoint). Based on the study protocol, all data were calcu-

Fig. 2. a Improvement in exercise capacity (6-MWT). **b** Increase in the cross-sectional area of the musculus rectus femoris (m. rect. femoris). **c** Significant improvement in SGRQ total score. 6-MWT, 6-min walk test; SGRQ, St. George's Respiratory Questionnaire.

lated using SPSS 22 (IBM SPSS Statistics version 22.0; SPSS, Armonk, NY, USA) and Prism 5.03 (GraphPad Software, Inc., La Jolla, CA, USA). Two groups were compared using the Mann-Whitney U test for unpaired samples. Comparisons within a group were made with the Wilcoxon rank-sum test for paired samples. To compare measurements from several time points, Friedman's test for continuous and Fisher's exact test for categorical variables were used. All tests were 2-sided ($p < 0.05$ was considered to be significant). For independent samples, the Kruskal-Wallis test was applied.

Results

Baseline Characteristics of the Patients

A total of 49 of 119 screened patients (41.18%) agreed to participate in the study; 31 were primarily assigned to the exercise group, and 18 to the control group. Twelve patients (35% dropout rate) refused further participation, and thus 20 of the exercise group and 17 of the control group completed the first 3 months of the study. Subsequently, a further 6 patients dropped out during the second phase. In the control group, 1 patient withdrew informed consent (6% dropout rate). Thus, 14 patients

completed the 6-month training program (Fig. 1). The patients' baseline characteristics are given in Table 2.

6-min Walk Test

When compared to baseline ($T_0 = 407.9 \pm 152.09$ m), a significant improvement in 6-MWT distance was observed in the exercise group after the first ($T_1 = 459.3 \pm 126.6$ m; $p = 0.002$) and the second training period ($T_2 = 483.2 \pm 130.1$ m; $p = 0.004$). No change was found in the control group ($T_0 = 399.1 \pm 129.4$ m, $T_1 = 397.2 \pm 119.1$ m; $p = 0.979$). In addition, a significant difference was found between the training and the control group ($p = 0.027$; Fig. 2a).

Area of Musculus Rectus Femoris

The exercise group demonstrated an increase in the cross-sectional area of the m. rectus femoris ($T_0 = 6.2 \pm 1.2$ cm², $T_1 = 6.9 \pm 1.2$ cm², $p = 0.003$, $T_2 = 7.5 \pm 1.6$ cm², $p = 0.002$), whereas the control group showed no change ($T_0 = 8.2 \pm 4.9$ cm², $T_1 = 7.5 \pm 4.0$ cm², $p = 0.249$). Furthermore, a significant difference was observed at T₂ between the control and the training group ($p = 0.007$; Fig. 2b).

Fig. 3. Percent change in maximum force over 11 weeks. * $p < 0.05$, Friedman's test.

Quality of Life

If compared to baseline (T_0), clinically relevant improvements in SGRQ total score were found within the exercise group after the first ($T_0 = 43.3 \pm 18.0$, $T_1 = 36.0 \pm 18.4$; $p = 0.001$) and the second period of training ($T_2 = 34.7 \pm 18.0$; $p = 0.004$). In the control group, the SGRQ total score did not change ($T_0 = 44.4 \pm 22.3$, $T_1 = 43.4 \pm 22.2$; $p = 0.687$). The comparison of the groups at T_2 showed a significant difference between the control and the training group ($p = 0.038$; Fig. 2c).

Intervention Setting within the First 3 Months

The maximum force determination for training adjustment took place at baseline, as well as in the third, fifth, and eleventh training week. The lowest increase in maximum power was observed in cable pulldown (38%) and in guided squats (50%). However, leg press showed an increase in maximum force of 71%, and cable row an increase of 84% compared to the baseline measurement. The percent changes in maximum force are shown in Figure 3.

Serum Markers of Inflammation, Muscle-Derived Markers, and B-Type Natriuretic Peptide

In the control and the training group, serum levels of myostatin, irisin, resistin, and α -Klotho did not change significantly within the training period (Table 3). It is

noteworthy, however, that after the 6-month training program the exercise subgroup showed an inverse relationship between serum levels of resistin and those of α -Klotho ($r = -0.608$, $p = 0.021$) (Fig. 4). No changes in the above measures were found in the controls.

B-type natriuretic peptide (BNP) was within the normal range in both groups during the study. It is noteworthy that a small, nonsignificant decrease was observed in the exercise group.

Discussion

The main finding of the present study is an improvement in 6-MWT distance of 52–76 m after high-intensity training. This represents a clinically important change and reflects an improvement in the patient's condition. 6-MWT distance is a potentially useful biomarker of COPD severity, which is influenced by muscle weakness, pulmonary vascular disease, or depression [19]. 6-MWT distance has also been a surrogate for predicting survival in observational studies [20]. The observed increase in 6-MWT distance is thought to be clinically relevant [21]. A few small studies have compared interval training with continuous training among patients with COPD, and the results are somewhat inconsistent. There have been sev-

Fig. 4. Correlations between serum levels of resistin and α -Klotho in a training group at the time points T₀, T₁, and T₂.

Table 3. Changes in serum markers within the study period

Marker	Control group			Exercise group			<i>p</i> value
	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂	
Irisin, pg/mL	6.6±2	6.6±1.6	6.9±0.7	7.8±1.7	7.5±1.6	7.7±1.6	ns
α -Klotho, pg/mL	655±120	641±127	602±158	584±195	590±180	633±235	ns
Myostatin, ng/mL	3.2±1.6	3.2±1.6	2.6±1.2	2.8±1.1	2.7±1.2	2.9±1.1	ns
Resistin, ng/mL	10±3.6	9.6±3.2	11±4.4	9.7±3.9	8.9±2.8	10.2±3.7	ns

Data are presented as the mean ± SD.

eral randomized controlled trials comparing high- and low-intensity training among patients with COPD [22]. Some studies show that the magnitude of improvement in physiological responses is significantly greater in high-intensity training than in low-intensity training [23, 24]. On the other hand, in patients with severe COPD it can be difficult to sustain a high intensity with the continuous training modality, because lung hyperinflation (air trapping) may contribute to exercise intolerance [25]. The latest publication by Schaadt et al. [26] showed that in their small-sized study, the mortality risk increased among COPD patients after a biweekly high-intensity rehabilitation program. Furthermore, Greening et al. [27] demonstrated in a randomized trial that training of hospitalized COPD patients, including strength, endurance, and neuromuscular stimulation, resulted in short-term effects and higher mortality, although the study was not powered for mortality assessment. It is therefore suggested

that COPD rehabilitation programs should be designed carefully for every individual patient, and that additional studies are needed to determine the optimal duration, intensity, and frequency of rehabilitation programs.

Nevertheless, in our study 35% of the patients dropped out after 3 months and 30% after a 6-month training program. The reasons for dropout were varied and not specifically related to the severity of COPD. For example, 1 patient was not able to leave his work, 1 patient received a new hip, and 2 patients were not able to complete all the measurements. Another 2 patients with severe COPD were ill for a longer period of time. We could observe that the dropout rate in the high-intensity COPD group was not above the 50% previously published for individualized and nonindividualized training groups [14, 28–30].

High-intensity rehabilitation exercise is known to increase the muscular aerobic metabolism that allows tolerating a higher magnitude of activity without limiting dys-

pnea [31]. Previous studies have demonstrated that measurement of the m. rectus femoris is a useful tool for monitoring changes in muscle strength [18]. Parallel to the increase in 6-MWT distance, the high-intensity exercise group showed an increase in cross-sectional area of the m. rectus femoris after 3 months of 0.7 cm², and after 6 months of 1.3 cm². Our results confirm data from an earlier study showing an increase in cross-sectional area of the m. rectus femoris of 0.57 cm² after 8 weeks of high-intensity isokinetic knee extensor resistance training [28]. The greater effect in our cohort can at least in part be explained by the higher intensity and more individualized resistance training. Due to the limited number of patients in our study, further research is needed to draw any final conclusions.

We also demonstrated an improvement in SGRQ score of at least 8 points after high-intensity and low-frequency strength training in the exercise group, while no effect was detected in the control group. This finding is in line with other studies also showing improvements in quality of life after a period of exercise training [32, 33]. Regular meetings of patients play a key role in quality of life; training could promote group dynamics with regard to psychosocial support [32].

Finally, we assessed the levels of a few serum markers, such as myostatin (a myokine produced and released by myocytes that inhibits muscle cell growth and differentiation), irisin (a myokine linked to the positive benefits of exercise), resistin (a signal molecule associated with inflammation in COPD), and α -Klotho (a novel β -glucuronidase associated with human aging). We did not observe any significant changes in the measured biomarkers; however, it is interesting to note that after 6 months of high-intensity training, we found an inverse correlation between serum levels of resistin and those of α -Klotho. Klotho is an antiaging protein having anti-inflammatory functions [34, 35]. Klotho expression has been found to be reduced in the lungs of smokers and patients with COPD. Many clinical studies have suggested that soluble Klotho exerts strong cardioprotective effects, since higher Klotho levels were related to a lower incidence of mortality and cardiovascular disease [36]. In contrast, resistin is linked to inflammation and senescence. For example, the results from a cross-sectional study which included 412 subjects of different ages revealed that in old subjects resistin is inversely associated with muscle strength [37]. In older adults, higher resistin levels have also been found to be associated with cardiovascular events [38]. An experimental study suggested that resistin may induce hepatocyte senescence [39]. Hence, the inverse relationship between serum levels of Klotho and resistin levels after a

6-month high-intensity training further supports the clinical improvements among COPD patients discussed above.

A variety of cardiopulmonary interactions have been described in COPD [40]. Besides common shared risk factors, pathophysiological mechanisms linking heart size, morphology, and function to COPD should be taken into account. BNP is a surrogate marker for increased ventricular distending forces and wall stress [41, 42]. BNP levels were not increased in the present study, which argues against patent heart failure and increased wall stress [43]. However, it is noteworthy that a nonsignificant decrease within the normal range was observed in the training group. This is in accordance with previous findings showing physiological cardiac hypertrophy caused by exercise training in COPD [44].

In sum, our results show that high-intensity training twice a week during 3–6 months is feasible for many patients at different stages of COPD and results in a significant improvement of exercise capacity, muscle mass, and quality of life if compared to untrained patients. The baseline characteristics of those in the exercise and control groups who completed the study indicate that overall the control group was less health conscious, including more cases with obesity, smoking habits, and comorbidities. This supports the notion that high-intensity training twice a week during 3–6 months is feasible only for very highly motivated COPD patients. We assessed depression and anxiety via standardized questionnaires. The patients did not show any values within the range which defines clinically relevant anxiety and depression. However, we detected a trend toward reduced values after 3 and 6 months in the exercise group. This could indicate an elevation of mood after exercising.

It is a limitation of this study that only a small number of patients were enrolled. This might reflect a well-known characteristic of COPD patients, namely, that they are hard to motivate to perform exercises, particularly with a training concept with increased loads. Based on our results, we conclude that it is feasible for COPD patients to undergo a high-intensity training 2 times a week. We cannot exclude a potential bias that led to the overproportionate inclusion of highly motivated patients.

Conclusion

Different training programs have been shown to exhibit positive effects on COPD patients who were able to complete their exercise training programs. Nevertheless,

it is still unclear which exercise modalities are the most effective. High-intensity training twice a week during 3–6 months is feasible for patients with mild COPD and results in a significant improvement of exercise capacity, muscle mass, and quality of life. It is important to point out that 50% of the study population of the high-intensity training arm who completed the nonrandomized study were COPD patients at GOLD stage I. Therefore, a second conclusion is that patients with mild-to-moderate COPD who are able to complete the training program are assumed to benefit from it.

Statement of Ethics

Every patient gave informed written consent to participate in the study. The study was approved by the Ethics Committee of Philipps-Universität Marburg (Ethics Committee AZ 7/13, Marburg, Germany) and registered (DRKS00006842).

References

- Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al: Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J* 2006;27:397–412.
- Caspersen CJ, Powell KE, Christenson GM: Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985;100:126–131.
- Cooper CB: The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. *Am J Med* 2006;119(suppl 1):21–31.
- Wagner PD: Skeletal muscles in chronic obstructive pulmonary disease: deconditioning, or myopathy? *Respirology* 2006;11:681–686.
- Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, et al: Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002;3:CD003793.
- Spruit MA, Augustin IM, Vanfleteren LE, Janssen DJ, Gaffron S, Pennings HJ, et al: Differential response to pulmonary rehabilitation in COPD: multidimensional profiling. *Eur Respir J* 2015;46:1625–1635.
- McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y: Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015;2:CD003793.
- Vincent E, Sewell L, Wagg K, Deacon S, Williams J, Singh S: Measuring a change in self-efficacy following pulmonary rehabilitation: an evaluation of the PRAISE tool. *Chest* 2011;140:1534–1539.
- Puente-Maestu L, Lázaro A, Tejedor A, Camacho S, Fuentes M, Cuervo M, et al: Effects of exercise on mitochondrial DNA content in skeletal muscle of patients with COPD. *Thorax* 2011;66:121–127.
- Remels AH, Gosker HR, Schrauwen P, Hommelberg PP, Sliwinski P, Polkey M, et al: TNF- α impairs regulation of muscle oxidative phenotype: implications for cachexia? *FASEB J* 2010;24:5052–5062.
- Tang K, Wagner PD, Breen EC: TNF- α -mediated reduction in PGC-1 α may impair skeletal muscle function after cigarette smoke exposure. *J Cell Physiol* 2010;222:320–327.
- Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA: Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001;56:779–784.
- Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester 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–e64.
- Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al: Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest* 2007;131(suppl):4S–42S.
- Radlinger L, Bachmann W, Homburg J, Leuenberger U, Thaddey G: Rehabilitatives Krafttraining. Stuttgart/New York, Thieme, 1998.
- Jenkins SC: 6-minute walk test in patients with COPD: clinical applications in pulmonary rehabilitation. *Physiotherapy* 2007;93:175–182.
- Jones PW, Quirk FH, Baveystock CM, Littlejohns P: A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321–1327.
- Seymour JM, Ward K, Sidhu PS, Puthucherry Z, Steier J, Jolley CJ, et al: Ultrasound measurement of rectus femoris cross-sectional area and the relationship with quadriceps strength in COPD. *Thorax* 2009;64:418–423.
- Spruit MA, Polkey MI, Celli B, Edwards LD, Watkins ML, Pinto-Plata V, et al: Predicting outcomes from 6-minute walk distance in chronic obstructive pulmonary disease. *J Am Med Dir Assoc* 2012;13:291–297.
- Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR: The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004;23:28–33.
- Hui KP, Hewitt AB: A simple pulmonary rehabilitation program improves health outcomes and reduces hospital utilization in patients with COPD. *Chest* 2003;124:94–97.
- Tanaka T, Arizono S, Hanada M, Senjyu H: High-intensity lower limb endurance training in chronic respiratory disease. *Nagasaki Univ Acad Output Site* 2015;27:1–11.
- Punzal PA, Ries AL, Kaplan RM, Prewitt LM: Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. *Chest* 1991;100:618–623.
- Gimenez M, Servera E, Vergara P, Bach JR, Polu JM: Endurance training in patients with chronic obstructive pulmonary disease: a comparison of high versus moderate intensity. *Arch Phys Med Rehabil* 2000;81:102–109.

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The authors declare that they have no competing interests.

Author Contributions

T.B. contributed to the study hypothesis and study design as well as to writing of the manuscript and shared in scientific discussions. C.N. contributed to the study hypothesis and study design and performed the statistical analysis of the study and data collection. M.S. contributed to writing of the manuscript and shared in scientific discussions. L.L. contributed to writing and reviewing of the manuscript and shared in scientific discussions. K.K. contributed to the organization of the study and data collection and shared in scientific discussions. J.K. supervised the training sessions and performed the data collection. S.A., M.V., B.B., T.G., C.F.V., K.K., S.J., and P.A. reviewed the manuscript and shared in scientific discussions. A.R.K. contributed to the study design, reviewed the manuscript, and shared in scientific discussions.

- 25 O'Donnell DE, Revill SM, Webb KA: Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:770–777.
- 26 Schaadt L, Christensen R, Kristensen LE, Henriksen M: Increased mortality in patients with severe COPD associated with high-intensity exercise: a preliminary cohort study. *Int J Chron Obstruct Pulmon Dis* 2016;11:2329–2334.
- 27 Greening NJ, Williams JE, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, et al: An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ* 2014;349:g4315.
- 28 Menon MK, Houchen L, Harrison S, Singh SJ, Morgan MD, Steiner MC: Ultrasound assessment of lower limb muscle mass in response to resistance training in COPD. *Respir Res* 2012;13:119.
- 29 Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al: Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:155–161.
- 30 Effing T, Zielhuis G, Kerstjens H, van der Valk P, van der Palen J: Community based physiotherapeutic exercise in COPD self-management: a randomised controlled trial. *Respir Med* 2011;105:418–426.
- 31 Gibala MJ, Little JP, Macdonald MJ, Hawley JA: Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J Physiol* 2012;590:1077–1084.
- 32 Göhl O, Linz H, Schönleben T, Otte B, Weineck J, Worth H: Benefits of a multimodular outpatient training program for patients with COPD (in German). *Pneumologie* 2006;60:529–536.
- 33 Zambom-Ferraresi F, Cebollero P, Gorostia-EM, Hernández M, Hueto J, Cascante J, et al: Effects of combined resistance and endurance training versus resistance training alone on strength, exercise capacity, and quality of life in patients with COPD. *J Cardiopulm Rehabil Prev* 2015;35:446–453.
- 34 Avin KG, Coen PM, Huang W, Stolz DB, Sowa GA, Dubé JJ, et al: Skeletal muscle as a regulator of the longevity protein, Klotho. *Front Physiol* 2014;5:189.
- 35 Matsubara T, Miyaki A, Akazawa N, Choi Y, Ra SG, Tanahashi K, et al: Aerobic exercise training increases plasma Klotho levels and reduces arterial stiffness in postmenopausal women. *Am J Physiol Heart Circ Physiol* 2014;306:H348–H355.
- 36 Kuro-o M: Klotho as a regulator of oxidative stress and senescence. *Biol Chem* 2008;389:233–241.
- 37 Bucci L, Yani SL, Fabbri C, Bijlsma AY, Maier AB, Meskers CG, et al: Circulating levels of adipokines and IGF-1 are associated with skeletal muscle strength of young and old healthy subjects. *Biogerontology* 2013;14:261–272.
- 38 Gencer B, Auer R, de Rekeneire N, Butler J, Kalogeropoulos A, Bauer DC, et al: Association between resistin levels and cardiovascular disease events in older adults: the Health, Aging and Body Composition study. *Atherosclerosis* 2016;245:181–186.
- 39 Yu A, Zheng Y, Zhang R, Huang J, Zhu Z, Zhou R, et al: Resistin impairs SIRT1 function and induces senescence-associated phenotype in hepatocytes. *Mol Cell Endocrinol* 2013;377:23–32.
- 40 Alter P, van de Sand K, Nell C, Figiel JH, Greulich T, Vogelmeier CF, et al: Airflow limitation in COPD is associated with increased left ventricular wall stress in coincident heart failure. *Respir Med* 2015;109:1131–1137.
- 41 Alter P, Rupp H, Rominger MB, Vollrath A, Czerny F, Figiel JH, et al: B-type natriuretic peptide and wall stress in dilated human heart. *Mol Cell Biochem* 2008;314:179–191.
- 42 Alter P, Rupp H, Rominger MB, Czerny F, Vollrath A, Klose KJ, et al: A new method to assess ventricular wall stress in patients with heart failure and its relation to heart rate variability. *Int J Cardiol* 2010;139:301–303.
- 43 Alter P, Koczulla AR, Nell C, Figiel JH, Vogelmeier CF, Rominger MB: Wall stress determines systolic and diastolic function – characteristics of heart failure. *Int J Cardiol* 2016;202:685–693.
- 44 Alter P, Luetteken L, Nell C, Haid D, Kehr K, Greulich T, et al: Exercise training leads to physiological left ventricular hypertrophy in COPD. *Int J Cardiol* 2014;174:156–157.