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Effects of Vibration Training in Interstitial Lung Diseases: A Randomized Controlled Trial

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Keywords
Whole-body vibration training · Interstitial lung disease · Health-related quality of life

Abstract
Background: Numerous studies have reported positive effects of exercise training in patients with interstitial lung disease (ILD) on physical capacity and quality of life. However, evidence is rare on the effects of specific forms of training and further pathophysiological mechanisms in these patients. ***Objectives:*** In this multicenter study we aimed to explore the clinical effects of whole-body vibration training (WBVT) in patients with ILD on various outcome measures, including proinflammatory cytokines and myostatin. ***Methods:*** We randomly assigned 26 patients with different forms of multidisciplinary confirmed fibrotic ILDs either to the WBVT group ($n = 11$; 55% male, 61 ± 14 years old, forced vital capacity 83.2 ± 29.3% predicted, 6-min walking distance [6MWD] 478 ± 79 m) performing 3 months of a standardized training (3 times per week), or to a control training group (CTG, $n = 15$; 60% male, 63 ± 9 years old, FVC 74.6 ± 20.5% predicted, 6MWD 455 ± 85 m) performing sham WBV training. Training in the two groups was performed on a Galileo™ vibration plate (6–20 vs. 5 Hz). The functional assessments before and after the intervention period included pulmonary function, 6MWD test, chair rise test, ultrasonographic measurement of quadriceps muscle thickness (cross-sectional area), quality of life questionnaires, and serum samples. ***Results:*** We observed a significant increase in 6MWD ($\Delta_{Training} = 30$ m [12–67], $p = 0.024$) and a decrease of myostatin ($\Delta_{Training} = -465$ pg/mL [−713 to −166], $p = 0.008$) in the WBVT group. In contrast, no significant differences were observed in the CTG. ***Conclusions:*** The present study demon-

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strates that WBVT is able to significantly increase 6MWD and decrease myostatin in patients with fibrotic ILDs. Therefore, WBVT seems to be a beneficial and feasible training modality in ILD patients. ***Clinical Trial Registry:*** German Clinical Trials Registry (DRKS00012930).

Introduction

Interstitial lung disease (ILD) comprises a heterogeneous group of >200 entities [1]. The most common symptoms in ILD patients are dyspnea, cough, fatigue associated with a high burden of disease, and thus a reduced health-related life quality [2, 3]. Usually, in many fibrotic ILDs, disease progresses over time and is thus associated with worsened symptoms. ILD patients frequently suffer from comorbid conditions and consequences of the disease, such as pulmonary hypertension, arrhythmias, exercise-induced hypoxemia, and skeletal muscle weakness [4]. Historically, physical activity in patients with ILDs with breathlessness at resting conditions was not recommended. In contrast, recent data demonstrated that exercise training in ILD may improve 6-min walking distance (6MWD), dyspnea, health-related quality of life, and peak exercise capacity [5, 6].

Whole-body vibration training (WBVT) is a complementary exercise training tool which has been shown to be effective in several diseases, for example in osteoporosis [7], anti-synthetase syndrome [8], multiple sclerosis [9], diabetic neuropathy [10], chronic arthritis [11], and type 2 diabetes mellitus [12]. WBVT was also used in both stable [13] and exacerbated chronic obstructive pulmonary disease (COPD) [14], leading to improved 6MWD and quality of life [13–15] if added to a common endurance and strength-training program [16]. In exacerbated COPD patients it has been shown that WBVT altered the serum levels of myokines like peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) and the hormone irisin [14]. Even use in the intensive care unit with intubated and ventilated patients has been proven to be safe and feasible [17]. The method of WBVT is based on cyclic sinus wave oscillations with various frequencies and amplitudes transmitted to the body. The frequencies in the Galileo™ device range between 5 and 30 Hz. The teetering oscillation of the platform leads to a repetitive muscular stretch of the lower limbs which transmits a reflex signal to the spine that again induces muscular activation. It has been assumed that the high-frequency alternation between contraction and relaxation cycles improves the muscle function of lower limb and trunk muscles [16].

While the low-frequency area (5–10 Hz) is primarily thought to relax muscles, higher frequencies, usually above 10 up to 20 Hz, are recommended for proprioception training. High frequencies (20–30 Hz) diminish muscle relaxation and therefore induce adaptations in muscle performance, including power, endurance, and proprioception.

Although WBVT is a promising training tool to further enhance exercise capacity, there is no literature about WBVT in patients with ILD. We therefore aimed to analyze the effects of WBVT in patients with fibrotic ILD with regards to functional assessments and quality of life, as well as cytokine and myokine levels.

Materials and Methods

Setting and Study Design

A prospective, 3-center, randomized controlled clinical trial was performed at the Philipps University of Marburg (Germany), the Chest Clinic of the University of Heidelberg (Germany), and the Chest Clinic Wangen (Germany). Between April 2015 and May 2016, a total of 111 subjects were screened according to the inclusion and exclusion criteria. Ninety-three patients were excluded due to not fulfilling the inclusion criteria. Finally, 31 patients were randomized by T.B. and J.K. into the study (Fig. 1).

To be included in the trial, patients must have had a multidisciplinary confirmed diagnosis of fibrosing ILD under stable drug treatment of >3 months, including idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia, or sarcoidosis, and consented to the study procedures.

Patients were excluded if they had significant comorbid conditions that could interfere with the intervention, including significant COPD, pulmonary hypertension, unstable musculoskeletal conditions, or severe cardiovascular disease (e.g., congestive heart failure), psychiatric or cognitive impairment that prevented understanding the purpose of the study, or neurological disorders. Furthermore, other conditions such as walking limitations or prior limb surgery (e.g., artificial joint in the lower extremities) which prevented patients from performing WBVT were excluded. Patients were also excluded if a pulmonary rehabilitation program during the trial period was planned or had been performed within the last 6 months before inclusion into this trial.

Randomization

A computer-generated list was used to produce envelopes with the allocation to one of both treatment groups based on block randomization of 5 as described before [18]. The study was approved by the Ethical Board of the Philipps University of Marburg (Germany; ID 143/14) and was registered at the German Clinical Trials Registry (www.drks.de, ID DRKS00012930).

Intervention

Subjects in the WBVT group trained 3 times per week over a period of 3 months using a side-alternating vibration platform (Galileo, Novotec Medical, Pforzheim, Germany). WBVT sessions consisted of a warm-up (10 min treadmill-walking or cycling with

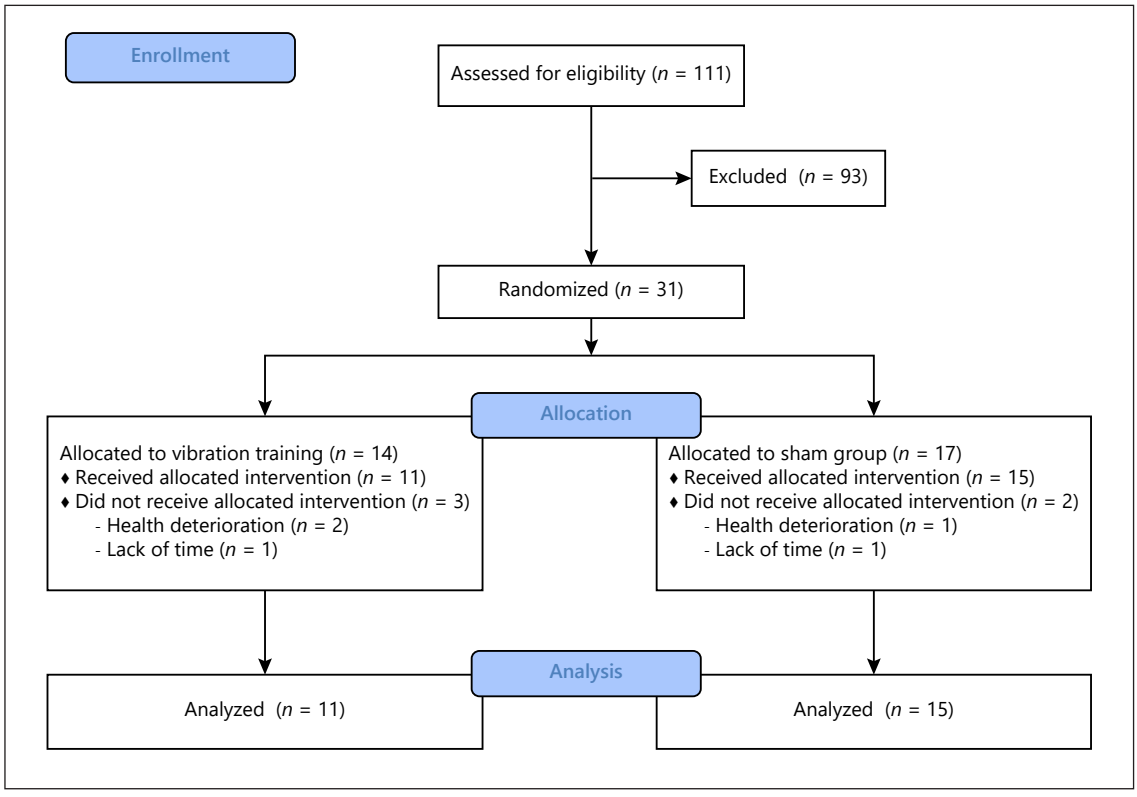

Fig. 1. Study flow chart.

low intensity, stretching exercises), WBVT (8–13 min), and a cool-down (5 min). Training started with 2 sets of 3 min duration (2 min of rest in between) at a frequency which was continuously increased from 6 to 20 Hz (2-Hz increase each week) and a mean peak-to-peak displacement of 4–6 mm. From week 9, patients performed 3 sets of 3 min WBVT. In week 12, all subjects finally reached a frequency of 24–26 Hz. Subjects stood on the WBVT platform shoeless in an isometric squat position with knees slightly bended (knee angle of ~150°) and arms by their sides or on the armrest of the device. During the breaks subjects were allowed to sit or to walk around as individually preferred. Exercise duration as well as the vibration frequency was progressively increased over time. The control training group (CTG) also trained 3 times per week for 3 months. CTG participants performed an identical warm-up (10 min, as described above), a sham training on a vibration platform for 2 × 3 min at a sustained frequency of 5 Hz, and a cool-down (5 min) as in the intervention group. Both exercise training groups were supervised by an exercise therapist as described before [19].

Outcome Measures

All measurements were performed at baseline and at the end of the 3-month study period. The outcome assessors were blinded for the randomized groups.

6-Min Walking Test

The primary endpoint of this study was the difference in the 6MWD from baseline to 3 months between the WBVT and CTG subjects. For that purpose, a standardized 6MWT was performed according to the American Thoracic Society (ATS) guidelines [20] without performing a learning 6MWT.

Lung Function Testing

Spirometry and body plethysmography were performed in accordance with the guidelines of the ATS [21–24]. Reference values were used from the European Respiratory Society (ERS) [25].

Chair Rise Test

The chair rise test (CRT) was performed using a chair with a standard height of 46 cm. Subjects were asked to stand up and sit down 5 times as quickly as possible with their arms folded across their chest. During the standing position, knees and hips had to be fully extended. The outcome of this test was the time needed to complete the test [26].

Muscle Cross-Sectional Area

The muscle cross-sectional area of the quadriceps muscles rectus femoris and intermedius were measured by ultrasound at predefined points of the thigh as described before [27].

St. George Respiratory Questionnaire

The St. George Respiratory Questionnaire (SGRQ) is a multidimensional questionnaire that assesses disease-specific health-related quality of life in subjects with chronic lung diseases. The SGRQ is a self-administered questionnaire with 50 items comprising 3 domains (symptoms, activity, and impact) each scored from

Table 1. Patient characteristics of WBVT and CTG at baseline

	WBVT (n = 11)	CTG (n = 16)
Age, years	62 (49–74)	63 (55–69)
Male/female	6/5 (54.5/45.5)	10/6 (60/40)
BMI	31 (23.4–32.9)	25.9 (22.8–30.8)
Diagnosis		
IPF	2 (18)	4 (25)
Idiopathic NSIP	1 (9)	1 (6)
Smoking-associated ILD	0 (0)	2 (13)
HP	0 (0)	4 (25)
Granulomatous ILD	2 (18)	0 (0)
Connective tissue disease	1 (9)	0 (0)
Unclassifiable ILD	5 (46)	5 (31)
VCmax, %	94.3 (52.1–103.2)	64.9 (58.4–91.9)
FEV_1, %	86.5 (58.2–107.5)	69.5 (63.3–92.2)
FEV_1 %/FVC (Tiffeneau index)	90.5 (85.7–101.4)	85.7 (81.7–90.3)
DLCO-SB, %	48.6 (28.7–59.9)	27.7 (22.4–43.5)
6MWD, m	480 (424–520)	457 (399–500)
Myostatin, pg/mL	3,623 (2,681–4,125)	2,597 (2,023–3,708)
Comorbidities		
Pulmonary hypertension	2 (18)	0 (0)
Type II diabetes	0 (0)	1 (6)
Coronary heart disease	2 (18)	2 (13)
Osteoporosis	1 (9)	0 (0)
Arterial hypertension	4 (36)	3 (19)
GERD	3 (27)	3 (19)

Values are the median (IQR) or n (%). WBVT, whole-body vibration training; CTG, control training group; BMI, body mass index; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia; ILD, interstitial lung disease; HP, hypersensitivity pneumonitis; VC, vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO-SB, diffusion capacity of the lung for carbon monoxide, single breath; 6MWD, 6-min walking distance; GERD, gastroesophageal reflux disease.

0 to 100, with higher scores corresponding to worse health-related quality of life [28].

Short Form 36

The Short Form 36 (SF-36) health survey evaluates the burden of the physical and emotional functioning, general pain, overall feeling of health, social functioning, vitality, and psychological well-being. Each domain can be scored from 0 points (maximal impaired) to 100 points (not impaired). A high-scale value is correlated to lower limitations in each area of life and a better health-related quality of life. A summary score for physical and mental health can be calculated from the mean values of the 8 single domains.

Hospital Anxiety and Depression Scale

The 14 items contained in the hospital anxiety and depression scale (HADS) evaluate the symptoms of anxiety and depression. Each sub-scale can be scored from 0 points (not impaired) to 21 points (maximal impaired). Accordingly, a score from 0 to 7 points is not associated with the symptoms of anxiety and depression. A score higher than 11 reflects a strong correlation to the symptoms.

Statistical Analyses

The 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 – β) of 95% and an alpha of 5% [29]. Results are provided as the median with interquartile range (25th percentile; 75th percentile). Delta values were calculated for each parameter between pre- (baseline) and post- (3 months) measurements. Statistical analyses for between-group comparisons were performed using the Mann-Whitney U test. Comparisons between baseline parameters were done by χ^2 test (for frequency distributions) or the U test. Intragroup differences were compared using the Wilcoxon signed-rank test. All statistical tests were performed two sided with a significance level of α at 5%.

Results

Baseline Characteristics

Twenty-six out of 31 subjects (WBVT: n = 11, CTG: n = 15) completed the study and were included in the final

Table 2. Effects of a 3-month WBVT in comparison with the CTG on lung function, exercise capacity, quality of life, anxiety and depression, and muscle cross-sectional area

	WBVT				CTG				WBVT vs. CTG
	baseline	3 months	delta	*p* value	baseline	3 months	delta	*p* value	*p* value
Lung function									
VCmax, % predicted	94.3 (52.1 to 103.2)	89.8 (50.9 to 103.2)	−0.3 (−5.7 to 0.3)	0.359	64.9 (58.4 to 91.9)	70.8 (60.4 to 82.9)	−1.3 (−3.7 to 4.1)	0.977	0.736
FEV_1, % predicted	86.5 (58.2 to 107.5)	76.4 (54 to 104.8)	−3.3 (−6.7 to 1.2)	0.050	69.5 (63.3 to 92.2)	69.2 (66.6 to 89.9)	−0.7 (−4.8 to 4)	0.755	0.186
FEV_1, %/FVC (Tiffeneau index)	90.5 (85.7 to 101.4)	85.4 (84.3 to 99.3)	−0.9 (−5.0 to 1.0)	0.213	85.7 (81.7 to 90.3)	86.5 (82.2 to 93.0)	−0.5 (−2.5 to 4.6)	0.820	0.350
DLCO-SB, %	48.6 (28.7 to 59.9)	45.9 (−33.8 to 52.6)	−2.3 (−7.3 to 8.1)	0.790	27.7 (22.4 to 43.5)	27.4 (20.4 to 40.6)	−1.4 (−5.8 to 2.7)	0.443	1.00
6MWD, m	480 (424 to 520)	540 (450 to 600)	30.0 (12 to 67)	**0.047**	457 (399 to 500)	452 (409 to 525)	4 (−9 to 20)	0.730	**0.026**
CRT, s	10.7 (8.6 to 11.3)	9.9 (7.2 to 14.0)	−1.4 (−1.8 to 0.2)	0.110	10.0 (8.6 to 13.9)	10.4 (8.3 to 12.4)	−0.3 (−1.4 to 0.5)	0.331	0.287
Quality of life									
SF-36	70.7 (59.3 to 82.0)	73.3 (58.7 to 83.3)	2.0 (−0.7 to 3.3)	0.328	69.3 (60.0 to 76.0)	66.7 (56.0 to 75.3)	0 (−4.3 to 2.7)	0.950	0.585
SGRQ	36.4 (28.6 to 52.0)	36.4 (28.0 to 55.0)	1.7 (−7.5 to 4.1)	0.657	30.8 (22.5 to 56.2)	39.1 (24.4 to 56.8)	3.8 (−6.4 to 13.8)	0.650	0.421
Anxiety and depression									
HADS A	6 (3 to 11)	5 (3 to 7)	−1 (−2 to 1)	0.101	5 (1 to 12)	5 (2 to 9)	0 (−1 to 2)	0.751	0.412
HADS D	3 (2 to 7)	4 (2 to 6)	0 (−1 to 1)	0.952	5 (2 to 9)	5 (1 to 7)	−1 (−4 to 0)	0.089	0.259
Sonography									
Rectus femoris, cm^2	8.8 (6.7 to 10.4)	9.1 (6.1 to 10.2)	−0.5 (−1.0 to 0.4)	0.182	6.1 (5.2 to 8.4)	6.7 (4.8 to 7.6)	−0.4 (−1 to 0.4)	0.233	0.876
Intermedius, cm^2	3.8 (2.3 to 7.0)	4.7 (2.4 to 6.6)	0.5 (0.1 to 0.7)	0.182	2.7 (1.4 to 4.8)	3.5 (1.7 to 5.9)	0.2 (−0.7 to 1.1)	0.281	0.938
Biomarker									
Myostatin, pg/mL	3,623 (2,681 to 4,125)	2,991.2 (2,147.1 to 3,726.2)	−464.8 (−713 to −166.3)	**0.008**	2,597 (2,023 to 3,708)	2,553 (2,177 to 3,888)	150 (−306 to 4745)	0.281	**0.009**
IL-6, pg/mL	3.0 (1.9 to 4.8)	2.7 (1.9 to 4.7)	−1 (−1.9 to 0)	0.173	3.9 (2.5 to 5.6)	3.5 (1.9 to 9.2)	0 (−0.7 to 2.8)	0.091	**0.034**

Values are mean from baseline to 3 months (IQR). Bold *p* values are significant. WBVT, whole-body vibration training; CTG, control training group; VC, vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO-SB, diffusion capacity of the lung for carbon monoxide, single breath; 6MWD, 6-min walking distance; CRT, chair rise test; SF-36, Short Form 36; SGRQ, St. George Respiratory Questionnaire; HADS A, Hospital Anxiety and Depression Scale, anxiety score; HADS D, Hospital Anxiety and Depression Scale, depression score; IL-6, interleukin 6.

per-protocol analysis. For the intention to treat analysis mandatory follow-up data were not collected. Baseline characteristics were comparable between groups. At baseline, there were no significant differences in patient characteristics between the groups (Table 1).

Changes after WBVT

The results are summarized in Table 2. On comparing the deltas between both groups no significant difference was detected (p = ns).

Subjects in the WBVT group were able to increase the 6MWT significantly by 30 m, but not in the control group, with −5 m (WBVT: from 480 [424–520] to 540 [450–600] m, $p < 0.05$, and CTG: from 457 [399–500] to 452 [409–525] m; p = ns). The difference between the delta of both groups was significant (WBVT: 30.0 [12–67] vs. 4 [−9–20] m, $p < 0.05$; Fig. 2). Furthermore, there was no significant intra- or intergroup differences in the CRT.

Measurements of the cross-sectional area of the M. rectus femoris or the M. quadriceps intermedius did not yield any significant changes in any group. In the WBVT group and in the CTG the training period increased the median (IQR) SGRQ values (1.7 [−7.5 to 4.1] vs. 3.8 [−6.4 to 13.8], p = ns). Changes in the different SGRQ domains did not reach significance. Of note, in the therapy group SGRQ remained stable, while there was a non-significant but clinically meaningful worsening in quality of life in the control group.

In the WBVT group serum IL-6 values decreased by −1 pg/mL (−1.9 to 0), whereas in the CTG group serum IL-6 remained unchanged (0 pg/mL [−0.7 to 2.8]; Fig. 3).

Adverse Events

No adverse or sever adverse events were observed during the study period.

Discussion

This study investigated the effects of WBVT in patients with fibrosing ILDs for the first time. It was found that WBVT significantly improved 6MWD after 3 months of WBVT compared to controls. Although the participants were heterogeneous, they were able to increase the 6MWD by 30 m by performing WBVT, which also reflects a minimal important difference [20].

In the international guidelines, pulmonary rehabilitation and exercise training are recommended for patients with chronic lung diseases including, for example, ILD and IPF [5, 30]. To our knowledge, no trials

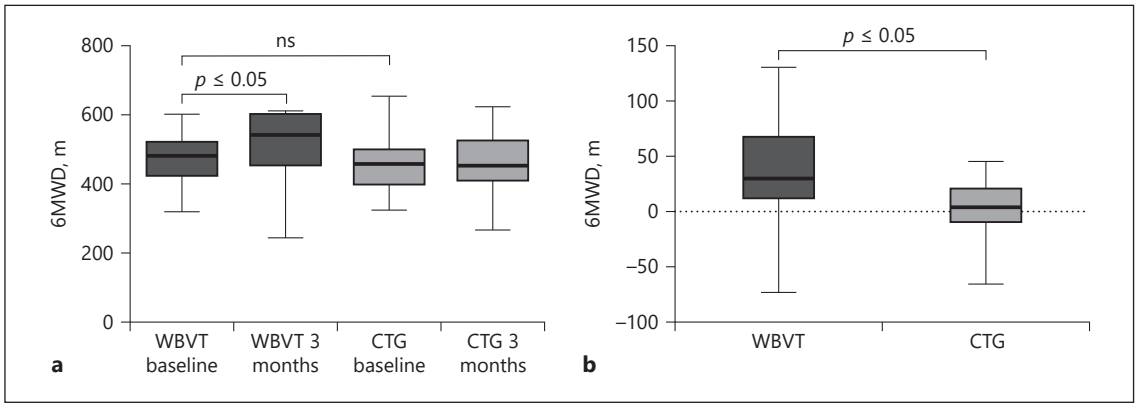

Fig. 2. 6MWD at baseline and after 3 months of training (**a**) and the change in 6MWD (**b**) in WBVT and CTG subjects.

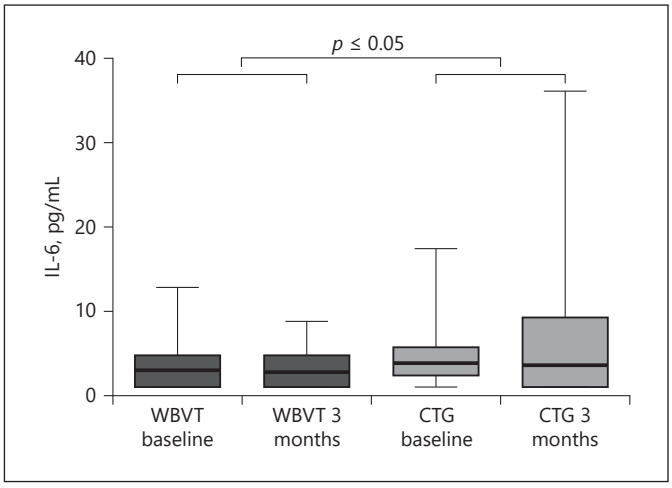

Fig. 3. IL-6 serum levels in the WBVT and CTG groups.

exist which already investigated the effects of WBVT in ILD patients.

Significant effects of WBVT therapy on 6MWD, health-related quality of life, and biological parameters like PGC1α and irisin have been previously described for COPD in stable as well as exacerbated conditions [14, 31]. In a randomized controlled trial including 60 stable COPD patients (FEV_1 34.3% predicted) WBVT patients showed a significant increase in the 6MWD of 81.2 ± 9.2 m [15]. Similar effects were shown for 49 hospitalized exacerbated COPD patients in a German single-center trial. Patients were randomized (1:1) to undergo physiotherapy alone or physiotherapy with the addition of WBVT. Compared to physiotherapy alone, complementary WBVT therapy led to a significant increase in 6MWD (96 ± 76 vs. 6 ± 82 m; $p = 0.007$) [14]. In a Cochrane Review where 168 ILD patients were analyzed following an 8- to 12-week pulmonary rehabilitation, the relative effect in 6MWD was +44.34 m, which is in the range of the 6MWD change observed in our trial [5].

Beside slowing down the decline in lung function, optimal disease management of fibrosing ILD requires supportive care to maintain patients' quality of life [32]. However, no significant difference could be observed between baseline and follow-up quality of life measurements in our trial. In contrast, in a systemic review and meta-analysis in patients with IPF, it could be demonstrated that a comprehensive pulmonary rehabilitation program showed short-term effects in enhancing exercise capacity and health-related quality of life measured with the SGRQ/IPF-specific SGRQ (SGRQ-I) total score (WMD = –8.40, 95% CI –11.44 to –5.36, $I^2 = 0\%$; $p < 0.00001$) [33]. As our intervention consisted of an exercise training program but not of a comprehensive pulmonary rehabilitation program as described in the review of Cheng et al. [33], both interventions were not comparable. This and the fact that the time of each exercise training session with stimulating intensity was short (10 min warm-up and 5 min cool-down) might be the reason for the divergent effects on health-related quality of life in our ILD participants.

Beside proven benefits of WBVT on exercise capacity, we postulated an WBVT effect in biological regulatory proteins. In the included ILD patients, we analyzed the myostatin levels of WBVT and CTG patients. It has been shown that patients who received WBVT therapy reached a significantly lower myostatin level [34]. The protein myostatin is released by myocytes and inhibits myogenesis. In patients with liver cirrhosis, higher serum myo-

statin levels has been shown to correlate with muscle mass loss and impaired protein synthesis, as reflected by lower serum albumin levels and lower branched-chain amino acid to tyrosine ratio levels [35]. High serum myostatin levels were also associated with a reduced survival rate in liver cirrhosis [35]. Animal experiments with mice demonstrated that mechanical vibration therapy with 30 Hz is highly effective in downregulating atrophy genes like atrogin-1 and myostatin, both in vivo and in vitro [36]. Given that the previous observations refer to animal experiments and other study subject than ILD, it is unclear whether the results can be transferred to ILD. In our ILD patients, it could be shown that WBVT therapy significantly reduced myostatin levels, which can be speculated to subsequently result in an increase of muscle mass [37]. Furthermore, WBVT training had an effect on IL-6 serum levels. IL-6 is secreted by T cells, macrophages, fibroblasts, and endothelial cells, and acts as a proinflammatory cytokine. Following intervention in the current study, WBVT patients had lower IL-6 levels than the controls. It is very likely that IL-6 accounts for the age-associated skeletal muscle deterioration (sarcopenia); furthermore, increased levels of IL-6 were significantly associated with sarcopenia [38]. Higher levels of IL-6 (>5 pg/mL) were found to lead to an increased risk of loss of muscle mass and a reduction of muscle strength [38–40]. To speculate, WBVT might enhance skeletal muscle mass by reducing regulatory proteins like myostatin and IL-6.

Limitations

The study has some limitations. The major limitation of our study is the small number of included patients. However, our study was conceived as a feasibility trial and, despite the small sample size, it clearly shows that WBVT improves the 6MWD and decreases myostatin levels.

One could argue that the relatively short training period of 3 months might be a limitation. We designed the trial with training periods of 3 times per week over a period of 3 months. This goes in line with the training duration of other training trials or in-patient rehab programs.

Conclusions

The study findings suggest that whole-body vibration therapy is an effective and key intervention across the range of fibrotic ILDs. In summary, it has been found that WBVT is feasible in patients with fibrotic ILD. WBVT therapy was associated with a significant and substantial improvement in the 6MWD. A potential explanation of the clinical benefit beside the improvement of postural balance might be the lower levels of myostatin observed after WBVT therapy, which might have a significant effect on muscle mass. However, a causal relation cannot be deduced from the present study. Since WBVT is feasible, easy to perform, and has shown beneficial effects, it could also be a useful treatment option in ILD patients.

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Statement of Ethics

All subjects gave their written informed consent. The study protocol was approved by the Ethics Committee on Human Research.

Conflicts of Interest Statement

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A.R.K. and T.B. made substantial contributions to the conception and design of the work and the data acquisition. A.R.K., T.B., and C.N. made substantial contributions to the analysis. All of the listed authors designed the study and were involved in the interpretation of the data. A.R.K. and T.B. drafted the work. J.K., F.K., M.V., C.N., I.J., M.S., P.A., C.K., T.G., C.F.V., R.G., T.S., K.K., N.C.K., F.J.F.H., and M.K. revised the report critically for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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