Inspiratory muscle training does not improve clinical outcomes in 3-week COPD rehabilitation: results from a randomised controlled trial

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IMT added to a 3-week PR programme improved P_{Imax} and FIV_1, but not exercise capacity, dyspnoea or QoL #COPD http://ow.ly/hPGK30gfqej

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ABSTRACT The value of inspiratory muscle training (IMT) in pulmonary rehabilitation in chronic obstructive pulmonary disease (COPD) is unclear. The RIMTCORE (Routine Inspiratory Muscle Training within COPD Rehabilitation) randomised controlled trial examined the effectiveness of IMT added to pulmonary rehabilitation.

In total, 611 COPD patients (Global Initiative for Chronic Obstructive Lung Disease stage II–IV) received a 3-week inpatient pulmonary rehabilitation, of which 602 patients were included in the intention-to-treat analyses. The intervention group (n=300) received highly intensive IMT and the control group (n=302) received sham IMT. The primary outcome was maximal inspiratory pressure (P_{Imax}). The secondary outcomes were 6-min walk distance, dyspnoea, quality of life and lung function. Outcomes were assessed pre- and post-pulmonary rehabilitation. ANCOVA was used.

The intervention group showed higher effects in P_{Imax} ($p<0.001$) and forced inspiratory volume in 1 s ($p=0.013$). All other outcomes in both study groups improved significantly, but without further between-group differences. Sex and pulmonary rehabilitation admission shortly after hospitalisation modified quality of life effects.

IMT as an add-on to a 3-week pulmonary rehabilitation improves inspiratory muscle strength, but does not provide additional benefits in terms of exercise capacity, quality of life or dyspnoea. A general recommendation for COPD patients to add IMT to a 3-week pulmonary rehabilitation cannot be made.

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Introduction

Inspiratory muscle training (IMT) aims to improve inspiratory muscle function using different training techniques that selectively load the inspiratory muscles. IMT has been widely studied in patients with chronic obstructive pulmonary disease (COPD) and several systematic reviews support the effectiveness of IMT as a stand-alone therapy [1–5]. IMT improves maximal inspiratory muscle strength (maximal inspiratory pressure (P_{Imax})), dyspnoea, functional capacity and health-related quality of life (QoL) [1–3].

Pulmonary rehabilitation is recommended in COPD guidelines as a key element in the long-term management of COPD [6]. The most essential pulmonary rehabilitation component is physical training, especially endurance and strength training [7–9]. The effects of pulmonary rehabilitation might increase further by adding IMT, but the evidence is inconsistent. Although meta-analyses indicate that additional IMT may improve P_{Imax}, effects on other clinically relevant outcomes such as dyspnoea, QoL or functional exercise capacity remain unclear [3, 5]. Only one meta-analysis showed a nonsignificant trend regarding 6-min walk distance (6MWD) [3]. Therefore, pulmonary rehabilitation guidelines do not recommend routinely adding IMT to pulmonary rehabilitation [8].

Moreover, positive effects of additional IMT on P_{Imax} have been demonstrated, predominantly in studies that did not use a placebo control group or for IMT programmes with a longer duration (*e.g.* 6 months) [10–13]. In Germany, according to legal stipulations, pulmonary rehabilitation is usually provided on an inpatient basis for 3 weeks. However, a 3-week intensive inpatient pulmonary rehabilitation with daily IMT might be comparable to an 8-week pulmonary rehabilitation with three sessions per week [14]. Currently, it is unclear whether adding IMT to an intensive 3-week pulmonary rehabilitation programme leads to an improvement of P_{Imax} and other clinical outcomes.

Based on the comparison of studies with higher and lower mean values in baseline P_{Imax} (cut-off P_{Imax} <6 kPa), Gosselink *et al.* [3] hypothesised that IMT is more effective in patients with inspiratory muscle weakness. However, no study has examined this hypothesis on the patient level.

Most randomised controlled trials (RCTs) regarding IMT as an add-on had a small sample size. Thus, a lack of statistical power may have inhibited the detection of beneficial effects in clinical outcomes. Moreover, a lack of power precludes examining moderation effects (*e.g.* whether effects between groups were influenced by sex or baseline P_{Imax}). Therefore, studies with adequately powered samples are required [15].

The main hypothesis of this RCT (RIMTCORE (Routine Inspiratory Muscle Training within COPD Rehabilitation)) was that IMT routinely added to a 3-week pulmonary rehabilitation programme (intervention group) improves P_{Imax} (primary outcome) in comparison with a control group receiving pulmonary rehabilitation and sham IMT. Secondary hypotheses were that IMT (compared with sham IMT) improves lung function (*e.g.* forced inspiratory volume in 1 s (FIV_1), forced expiratory volume in 1 s (FEV_1) and vital capacity), dyspnoea, functional capacity and QoL. Furthermore, modifying effects on these outcomes were examined for sex, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, smoking status, "pulmonary rehabilitation admission directly or up to 2 weeks after hospitalisation due to acute exacerbations of COPD" (Hosp_AECOPD) *versus* "pulmonary rehabilitation in stable COPD" and baseline P_{Imax}.

Methods

Study design and subjects

This RCT used a parallel group design: COPD patients who underwent a 3-week inpatient pulmonary rehabilitation in the Bad Reichenhall Clinic (Bad Reichenhall, Germany) were recruited from February 2013 to July 2014. All admitted patients with GOLD stage II–IV fulfilling inclusion and exclusion criteria (table 1) were asked to participate. Participants were randomised without stratification according to a computer-generated randomisation list (provided by the University of Würzburg, Würzburg, Germany) to receive either highly intensive strength IMT (intervention group) or sham IMT (control group). Based on results of a nonrandomised pilot study, a sample size of n=420 patients was planned (for details regarding sampling and randomisation procedures, see supplementary material).

The study was approved by the local ethics committee (Bayerische Landesärztekammer; 12107) and was registered at the German Clinical Trials Register (identifier DRKS00004609). All participants provided

This study is registered at the German Clinical Trials Register with identifier number DRKS00004609.

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TABLE 1 Inclusion and exclusion criteria for chronic obstructive pulmonary disease (COPD) subjects screened for trial participation[#]

Inclusion criteria
Medical history of COPD
Forced expiratory volume in 1 s (FEV_1)/vital capacity <70% and FEV_1 % pred <80% post-bronchodilation
Exclusion criteria
Lack of language or cognitive abilities to fill out questionnaires
Hypercapnic respiratory failure (arterial carbon dioxide tension >50 mmHg at rest)
Indication for intermittent noninvasive ventilation
Contraindications for inspiratory muscle training (*e.g.* a history of recent lung surgery, recent pulmonary embolism, history of recurrent spontaneous pneumothorax)
Severe comorbidities that confer significantly greater morbidity than COPD (*e.g.* active cancer without successfully completed curative tumour therapy)

[#]: a pulmonologist verified the diagnosis of Global Initiative for Chronic Obstructive Lung Disease stage II–IV COPD at study start in each patient.

written informed consent. RIMTCORE was funded by Deutsche Rentenversicherung Bayern Süd (German statutory pension insurance scheme).

Interventions

All patients received an intensive pulmonary rehabilitation programme tailored to each patient's individual needs. Obligatory components (mostly 30- to 60-min sessions) included physical training (endurance training: four or five sessions per week; strength training: three sessions per week; whole-body vibration muscle training: seven sessions per week), patient education (seven or more sessions) and respiratory physiotherapy in groups (two to four sessions per week). Optional components were smoking cessation (eight sessions), mucolytic physiotherapy, saline inhalation, psychological interventions, social counselling, nutritional counselling and occupational therapy.

Inspiratory muscle training

The intervention group received high-intensity interval-based IMT routinely added to the pulmonary rehabilitation programme according to the protocol of Hill *et al.* [14], using a threshold training device (POWERbreathe Medic; POWERbreathe International, Southam, UK). Training intensity was individually adjusted based on the previously determined P_{Imax}. The initial training load was at least 30% of P_{Imax} and was progressively increased to at least 60%. High-intensity interval-based IMT took place 7 times per week (21 min; seven cycles of 2 min of IMT each followed by 1 min of rest). Experienced coaches supervised three sessions per week to ensure adequate training and instructed the patients regarding further training at home.

Sham IMT

The control group received sham IMT (also supervised 3 days per week). The sham training device looked identical to the verum device, but had no valve within it. Patients were instructed to breathe slowly and in a relaxed manner. Thus, the training load was <1 cmH_2O, which represented no effective IMT and thus making this a placebo procedure [4].

Outcomes

Lung function, functional capacity and questionnaire data were assessed at the beginning (T0) and end (T1) of the pulmonary rehabilitation programme.

Primary outcome

The primary outcome was P_{Imax}, *i.e.* the maximum static inspiratory pressure a subject can generate at the mouth [16], measured using a commercially available mouth occlusion pressure device (CareFusion, Höchberg, Germany) as recommended by German guidelines [16].

Secondary outcomes

Lung function measurement

FEV_1, FIV_1, vital capacity, residual volume and total specific resistance were determined before and after bronchodilation by spirometry and body plethysmography (MasterLab; CareFusion) [17, 18].

6-min walk distance

6MWD measurement was carried out on a track length of 30 m according to the 2002 American Thoracic Society statement [19]. At both T0 and T1 each patient performed two tests with an interval of 1 h. The best test of each was included for analysis.

Quality of life

QoL was assessed by the St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT) and Clinical COPD Questionnaire (CCQ) [20–22].

Dyspnoea

Baseline and transition dyspnoea indexes (BDI and TDI, respectively) provided measurements of breathlessness at T0 (BDI) and T1 (TDI) [23, 24].

Statistical analysis

Intention-to-treat (ITT) and per-protocol analyses were performed. Results of the ITT analysis are presented unless otherwise stated. Pre–post changes within groups were estimated *via* the standardised response mean, with mean differences between T1 and T0 divided by the standard deviation of the difference scores. ANCOVA with T1 values as outcomes and treatment group (intervention group/control group) as predictor was used to estimate treatment effects. Adjusted mean differences (AMDs) with 95% confidence intervals and Cohen's d were calculated to quantify the between-group effects. We computed two models for each outcome. The unadjusted model only included corresponding T0 values as covariates. The adjusted model also included sex, GOLD stage, smoking status (active *versus* ex-/never-smoker) and baseline P_{Imax} as covariates. The residuals of all models were checked for distortions of model assumptions (*e.g.* normality and linearity) and robust regression analyses were computed if model assumptions did not hold. Neither adjusted/unadjusted nor linear/robust regression analyses differed in results; therefore, only results of the adjusted analyses with linear models are presented, as stated in the study protocol.

Moderator effects of sex, Hosp_AECOPD, GOLD stage, smoking status and baseline P_{Imax} were examined by (separately) including the moderator and interaction term (group membership (intervention group/control group) and moderator) in the respective model. Significant interactions with categorical moderators were further analysed by simple effect analyses.

Missing data arose for two reasons: 1) discontinuation of pulmonary rehabilitation (*i.e.* no data available at T1) and 2) missing data in some items (0–3%). All missing data were imputed with a multiple imputation procedure creating 10 imputed data sets. Pooled results are reported. TDI could not be imputed due to the scaling of the items and thus listwise deletion was applied (for missing data procedure details, see supplementary material). All analyses were performed using SPSS Statistics version 23 (IBM, Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). $p<0.05$ was considered significant.

Results

In total, 983 subjects with pre-diagnosed COPD were screened for eligibility (figure 1). Of these, 611 patients with confirmed COPD II–IV were randomised to the intervention group or the control group. Data of nine patients could not be analysed because no data regarding the primary outcome P_{Imax} at T0 or T1 were available, leaving data for 602 patients for the ITT analysis. During inpatient rehabilitation, 50 patients discontinued participation in the study for various reasons, leaving data for 561 patients for the per-protocol analysis. For details on planned and recruited sample size, see the supplementary material.

Baseline data

At baseline, 64.6% of the patients were male, mean±SD age was 57.8±7.4 years and mean±SD P_{Imax} was 6.71 ±2.29 kPa. The intervention group received a mean±SD of 19.4±4.5 IMT sessions; mean±SD training load was increased from 21±7 cmH_2O (30.6% of mean P_{Imax}) at T0 to 47±14 cmH_2O (68.5% of mean P_{Imax}) at T1. Table 2 presents further sample characteristics.

Comorbidities

97.5% of the patients had clinically relevant comorbidities (mean (range) 4 (1–11)). Cardiovascular (63.5%), musculoskeletal (58.1%) and metabolic disorders (54.7%) were the most frequent (table 3).

Primary and secondary outcomes

Both groups improved significantly in P_{Imax} (table 4). The intervention group improved significantly more than the control group (AMD 0.94, 95% CI 0.72–1.16). The intervention group also improved significantly more in FIV_1 (AMD 0.10, 95% CI 0.02–0.19). All other secondary outcomes improved significantly in both arms, mostly with moderate to high effect sizes, but without significant differences between groups.

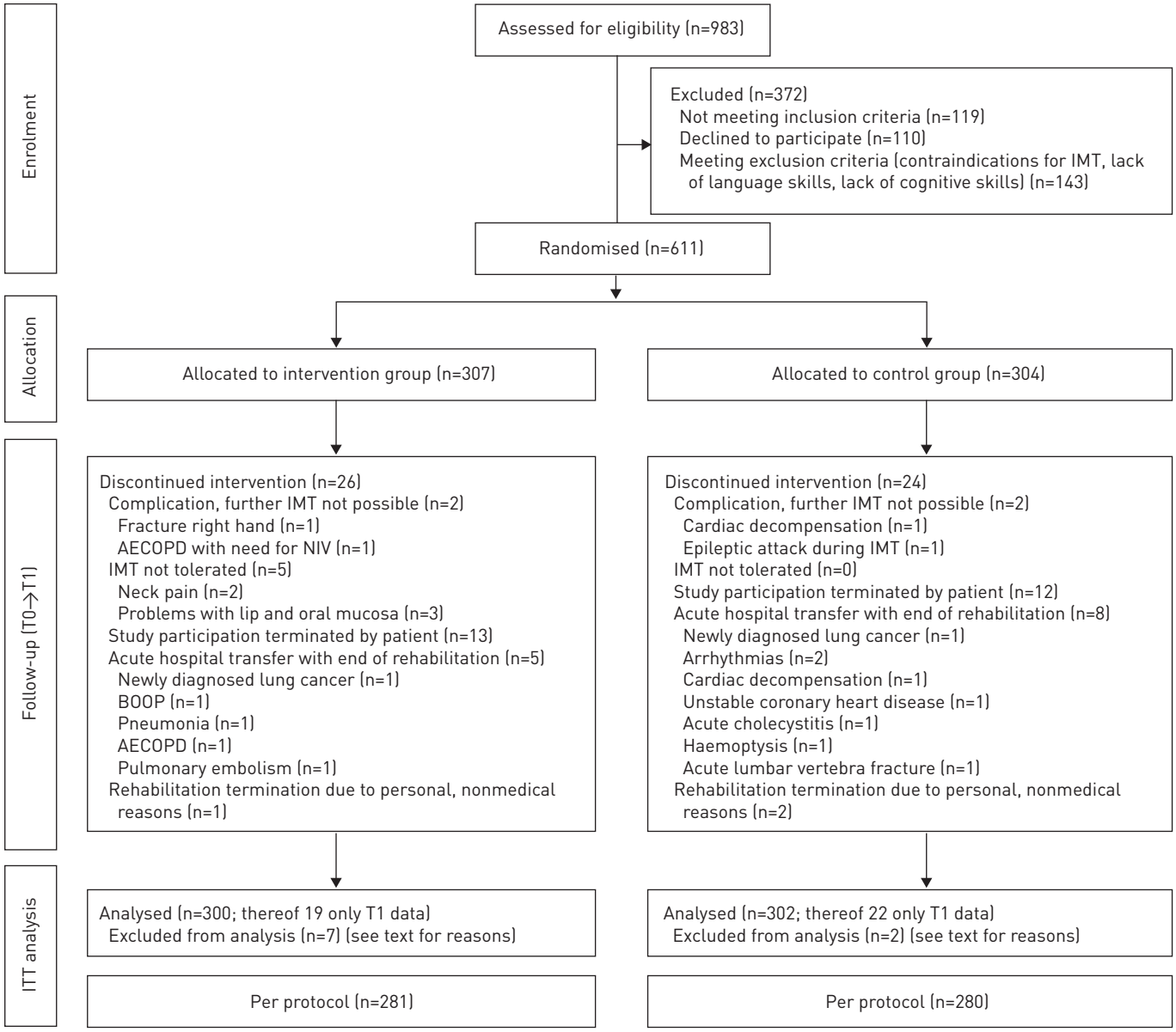

FIGURE 1 Flowchart of participant selection. T0: baseline; T1: after rehabilitation; ITT: intention-to-treat; IMT: inspiratory muscle training; AECOPD: acute exacerbations of chronic obstructive pulmonary disease; NIV: noninvasive ventilation; BOOP: bronchiolitis obliterans organising pneumonia.

Effect modifiers

Sex was a significant effect modifier for CAT (p<0.001), CCQ-Total (p=0.011), CCQ-Mental (p=0.001), CCQ-Symptoms (p=0.002) and SGRQ-Total (p=0.042) (table 5). In females, the intervention group showed significantly larger effects regarding CAT and CCQ-Mental compared with the control group. In contrast, in males, the control group showed larger effects regarding CAT, CCQ-Mental, CCQ-Symptoms and SGRQ-Total than the intervention group.

Moreover, sex modified the effects for 6MWD, but only in the per-protocol analysis (p=0.038). Females in the intervention group showed higher improvements in 6MWD than in the control group, whereas no group difference was found in males (table 5).

Significant interaction effects for Hosp_AECOPD (yes/no) were found in CCQ-Total (p=0.038), CCQ-Function (p=0.021), SGRQ-Impacts (p=0.028) and SGRQ-Total (p=0.041) (table 6). In patients with pulmonary rehabilitation after Hosp_AECOPD, the control group tended to show greater improvements in these outcomes than the intervention group, whereas no differences were found for patients with stable COPD.

TABLE 2 Patient characteristics at baseline

	Intervention group	Control group
Subjects	300	302
Age years	57.7±8.2	57.9±6.6
Female	112 (37.3)	101 (33.4)
BMI kg·m^{-2}	26.6±6.4	26.9±6.6
FEV$_1$ L	1.55±0.57	1.50±0.56
FEV$_1$ % pred	51.0±15.3	49.5±15.0
***P*$_{Imax}$ kPa**	6.73±2.39	6.69±2.19
GOLD stage		
II	154 (51.3)	142 (47.0)
III	114 (38.0)	124 (41.1)
IV	32 (10.7)	36 (11.9)
GOLD category		
A	11 (3.7)	7 (2.3)
B	61 (20.3)	68 (22.5)
C	14 (4.7)	16 (5.3)
D	214 (71.3)	211 (69.9)
Current smoker	118 (39.3)	115 (38.1)
Never-smoker	7 (2.3)	8 (2.6)
Pack-years	39.6±23.6	41.8±24.0
Patients with LTOT	42 (14.0)	56 (18.5)
Rehabilitation after hospitalisation due to AECOPD	90 (30.0)	99 (32.9)
BDI	6.1±2.6	5.8±2.5

Data are presented as n, mean±SD or n (%). BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; *P*$_{Imax}$: maximal inspiratory pressure; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LTOT: long-term oxygen therapy; AECOPD: acute exacerbations of chronic obstructive pulmonary disease; BDI: baseline dyspnoea index.

In addition, although not significant in the ITT analysis (p=0.242), baseline *P*$_{Imax}$ modified the change in *P*$_{Imax}$ in the per-protocol analysis: larger effects in favour of the intervention group were found for patients with lower baseline values in *P*$_{Imax}$ (B=−0.10 (95% CI −0.20–−0.01); p=0.035). However, this effect is rather small (figure 2). Even in patients with baseline *P*$_{Imax}$ ⩾7 kPa, a significant increase was found at T1.

Discussion

The main results of this RCT are that adding high-intensity interval-based IMT to an intensive 3-week pulmonary rehabilitation programme led to a significant improvement in *P*$_{Imax}$ and FIV$_1$ in patients with

TABLE 3 Clinically relevant comorbidities[#] of participants

	Total	Intervention group	Control group
Subjects	602	300	302
Cardiovascular diseases	383	183 (61.0)	200 (66.2)
Musculoskeletal disorders	350	170 (56.7)	180 (59.6)
Metabolic disorders (including cachexia and obesity)	329	150 (50.0)	179 (59.3)
Mental comorbidities	139	74 (24.7)	65 (21.5)
Nose and sinuses disorders	106	56 (18.7)	50 (16.6)
Gastrointestinal comorbidities	104	55 (18.3)	49 (16.2)
Obstructive sleep apnoea	81	35 (11.7)	46 (15.2)
Comorbid asthma (ACOS)	76	37 (12.3)	39 (12.9)
Malignancies after successful completion of therapy	32	14 (4.7)	18 (6.0)
Other respiratory diseases (ILD and restrictive lung diseases)	21	9 (3.0)	12 (4.0)
Bronchiectasis	8	4 (1.3)	4 (1.3)
α_1-Antitrypsin deficiency (homozygote)	8	6 (2.0)	2 (0.7)

Data are presented as n or n (%). ACOS: asthma–chronic obstructive pulmonary disease overlap syndrome; ILD: interstitial lung disease. [#]: total number of patients with at least one illness of the indicated disease group.

TABLE 4 Primary and secondary outcomes for the control group and intervention group

	T0	Change T1–T0	SRM	AMD (95% CI) T1	Cohen's d
P_{Imax} kPa					
Control	6.69±2.19	0.88±1.46	0.60	*0.94 (0.72–1.16)*	0.59
Intervention	6.73±2.39	1.83±1.58	1.15		
P_{Imax} cmH_2O					
Control	68.22±22.33	8.97±14.89	0.60	*0.94 (0.72–1.16)*	0.59
Intervention	68.63±24.37	18.66±16.11	1.15		
P_{Imax} % pred					
Control	63.68±21.05	8.35±13.97	0.60	*8.95 (6.87–11.03)*	0.59
Intervention	63.94±23.04	17.29±14.99	1.15		
FIV_1 L					
Control	2.93±0.87	0.25±0.52	0.48	*0.10 (0.02–0.19)*	0.20
Intervention	2.90±0.86	0.36±0.53	0.68		
FEV_1 L					
Control	1.50±0.57	0.19±0.31	0.60	0.02 (−0.03–0.07)	0.06
Intervention	1.55±0.57	0.21±0.33	0.63		
VC L					
Control	3.18±0.91	0.25±0.46	0.55	0.00 (−0.07–0.07)	0.00
Intervention	3.22±0.91	0.24±0.46	0.53		
6MWD m					
Control	420.1±115.1	83.99±65.74	1.28	1.59 (−7.94–11.12)	0.02
Intervention	425.2±113.7	85.30±62.80	1.36		
SGRQ-Total					
Control	50.79±17.8	−10.50±13.22	−0.80	1.57 (−0.44–3.59)	0.12
Intervention	51.32±17.5	−9.42±13.44	−0.70		
CAT					
Control	20.27±7.23	−3.42±5.85	−0.59	−0.09 (−0.94–0.76)	−0.02
Intervention	20.83±7.45	−3.76±5.76	−0.65		
CCQ-Total					
Control	2.85±1.15	−0.58±0.90	−0.65	0.01 (−0.12–0.15)	0.01
Intervention	2.94±1.16	−0.63±0.98	−0.64		
TDI T1					
Control[#]		4.60±3.01		−0.09 (−0.61–0.42)	−0.03
Intervention[¶]		4.57±3.17			

Data are presented as mean±SD, unless otherwise stated. T1: after rehabilitation; T0: baseline; SRM: standardised response mean; AMD: adjusted mean difference between intervention group and control group (adjusted for baseline, maximal inspiratory pressure (P_{Imax}) baseline, sex, smoking status and Global Initiative for Chronic Obstructive Lung Disease stage); FIV_1: forced inspiratory volume in 1 s; FEV_1: forced expiratory volume in 1 s; VC: vital capacity; 6MWD: 6-min walk distance; SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; TDI: transition dyspnoea index. [#]: n=268; [¶]: n=275. Italic indicates p<0.05.

moderate to very severe COPD compared with sham IMT, but failed to improve other clinically relevant outcomes such as dyspnoea, QoL, functional capacity and other lung function parameters. The mean increase in P_{Imax} in the intervention group *versus* control group of 0.94 kPa (9.59 cmH_2O) corresponds to a P_{Imax} mean difference of 8.60 cmH_2O, as achieved by much longer outpatient programmes [5]. Exploratory subgroup analyses showed that sex and Hosp_AECOPD might moderate the effects in QoL to a small extent, whereas baseline P_{Imax} showed no influence on any outcome.

The rationale for adding IMT to pulmonary rehabilitation is the assumption that changes in P_{Imax} may lead to changes in clinical outcomes. However, despite relevant improvements in P_{Imax}, no further improvements in clinical outcomes were found. There may be various reasons for this. First, the causal model may just be wrong and improvements in clinical P_{Imax} do not translate into clinical outcomes [25]. However, effects in clinical outcomes were shown by various studies comparing IMT alone with controls [1, 13, 14]. Second, an effect of 0.94 kPa might be too small to translate into clinically relevant improvements in the context of pulmonary rehabilitation. Hence, interventions of longer duration are necessary. For example, MAGADLE *et al.* [12] showed both larger effects in P_{Imax} as well as effects in functional capacity using an intervention lasting 6 months. Third, changes in P_{Imax} might lead to changes in clinical outcomes only if no other therapies produce changes in these outcomes at the same time. Therefore, effects of pulmonary rehabilitation on clinical outcomes might mask possible IMT effects.

TABLE 5 Effect modification of sex regarding specific secondary outcome values

	T0	Change T1–T0	SRM	AMD (95% CI) T1	Cohen's d
SGRQ-Total					
Female					
Control	51.17±18.49	−9.92±13.97	−0.71	−1.10 (−4.58–2.38)	−0.08
Intervention	53.71±18.18	−11.92±13.38	−0.89		
Male					
Control	50.59±17.40	−10.80±12.84	−0.84	*3.14 (0.55–5.73)*	0.24
Intervention	49.90±16.95	−7.93±13.25	−0.60		
CAT					
Female					
Control	20.25±7.83	−2.03±6.39	−0.32	*−1.95 (−3.49– −0.40)*	−0.30
Intervention	22.12±7.77	−4.70±6.07	−0.77		
Male					
Control	20.28±6.93	−4.12±5.41	−0.76	*1.03 (0.04–2.03)*	0.19
Intervention	20.06±7.15	−3.20±5.50	−0.58		
CCQ-Total					
Female					
Control	2.97±1.18	−0.58±0.98	−0.59	−0.22 (−0.46–0.02)	−0.23
Intervention	3.16±1.22	−0.87±0.95	−0.91		
Male					
Control	2.78±1.13	−0.59±0.86	−0.69	0.15 (−0.02–0.31)	0.16
Intervention	2.81±1.11	−0.48±0.97	−0.50		
CCQ-Mental					
Female					
Control	3.20±1.73	−0.55±1.50	−0.37	*−0.46 (−0.85– −0.08)*	−0.30
Intervention	3.25±1.80	−0.98±1.58	−0.62		
Male					
Control	2.69±1.65	−0.73±1.54	−0.47	*0.34 (0.08–0.59)*	0.22
Intervention	2.67±1.72	−0.42±1.52	−0.28		
CCQ-Symptoms					
Female					
Control	3.06±1.32	−0.64±1.08	−0.60	−0.24 (−0.53–0.04)	−0.21
Intervention	3.09±1.37	−0.88±1.18	−0.74		
Male					
Control	2.67±1.36	−0.69±1.13	−0.61	*0.26 (0.07–0.46)*	0.23
Intervention	2.62±1.31	−0.43±1.18	−0.37		
6MWD m					
Female[#]					
Control	394.4±116.4	77.78±69.00	1.13	13.4 (−2.8–29.6)	0.21
Intervention	404.9±109.8	89.32±59.29	1.51		
Male[#]					
Control	442.1±105.8	83.25±56.81	1.47	−2.1 (−15.7–11.5)	−0.04
Intervention	448.2±106.0	81.58±56.19	1.45		

Data are presented as mean±SD, unless otherwise stated. T1: after rehabilitation; T0: baseline; SRM: standardised response mean; AMD: adjusted mean difference between intervention group and control group (adjusted for baseline, maximal inspiratory pressure (P_{Imax}) baseline, sex, smoking status and Global Initiative for Chronic Obstructive Lung Disease stage); SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; 6MWD: 6-min walk distance. [#]: based on per-protocol analyses. Italic indicates p<0.05.

Fourth, subgroups of patients (*e.g.* females *versus* males) might differ in their response to IMT. We will discuss these points in the following paragraphs.

According to our study and contrary to Gosselink *et al.*'s [3] meta-analysis, P_{Imax} at baseline does not moderate the size of the effect in P_{Imax}. Patients with high values of P_{Imax} at T0 still benefit substantially from the intervention according to changes in P_{Imax}. Furthermore, baseline P_{Imax} did not modify the effect in any secondary outcome. Therefore, the hypothesis that (only) patients with inspiratory muscle weakness may benefit from IMT is not supported by our results. The different results of both studies may be explained by different methods. Gosselink *et al.* [3] examined relationships between variables of studies (*i.e.* mean baseline P_{Imax} and mean effect of IMT), whereas we examined relationships between patient variables. Inferences from the study level to the patient level may be misleading if patients are not drawn

TABLE 6 Comparison of pulmonary rehabilitation directly after hospitalisation due to acute exacerbation of chronic obstructive pulmonary disease (AECOPD) *versus* stable COPD regarding specific secondary outcome values

	T0	Change T1–T0	SRM	AMD (95% CI) T1	Cohen's d
SGRQ-Total					
AECOPD					
Control	54.4±19.3	−14.03±13.71	−1.03	*4.27 (0.34–8.20)*	*0.29*
Intervention	54.0±19.1	−9.77±15.50	−0.63		
Stable COPD					
Control	49.0±16.6	−8.77±12.59	−0.70	−0.04 (−2.35–2.28)	−0.01
Intervention	50.2±16.7	−9.27±12.47	−0.74		
SGRQ-Impacts					
AECOPD					
Control	44.1±21.8	−14.88±16.96	−0.88	*5.07 (0.49–9.66)*	0.29
Intervention	42.0±19.7	−9.30±17.00	−0.55		
Stable COPD					
Control	37.4±17.8	−8.21±14.61	−0.56	−0.26 (−2.83–2.32)	−0.02
Intervention	38.6±17.9	−9.02±14.03	−0.64		
CCQ-Total					
AECOPD					
Control	2.99±1.32	−0.75±0.97	−0.78	0.22 (−0.05–0.48)	0.20
Intervention	3.12±1.32	−0.61±1.15	−0.53		
Stable COPD					
Control	2.77±1.05	−0.50±0.85	−0.59	−0.10 (−0.25–0.06)	0.11
Intervention	2.86±1.08	−0.63±0.90	−0.70		
CCQ-Function					
AECOPD					
Control	3.19±1.50	−0.86±1.02	−0.84	0.25 (−0.04–0.53)	0.22
Intervention	3.18±1.56	−0.64±1.24	−0.52		
Stable COPD					
Control	2.71±1.21	−0.44±0.90	−0.48	−0.14 (−0.32–0.03)	−0.15
Intervention	2.80±1.21	−0.62±1.01	−0.61		

Data are presented as mean±SD, unless otherwise stated. T1: after rehabilitation; T0: baseline; SRM: standardised response mean; AMD: adjusted mean difference between intervention group and control group (adjusted for baseline, sex, smoking status and Global Initiative for Chronic Obstructive Lung Disease stage); SGRQ: St George's Respiratory Questionnaire; CCQ: Clinical COPD Questionnaire. Italic indicates p<0.05.

randomly from the same population, which is difficult to prove [26]. This reason and the large sample size of our study support the validity of our result.

The mean 6MWD improved statistically and clinically significantly in both study arms by >80 m. The AMD between groups in the ITT analysis was 1.9 m. However, according to the per-protocol analysis, IMT might improve 6MWD in females by >13 m (Cohen's d=0.21). The cause of the difference in the results between the ITT and per-protocol analyses remains unclear. Therefore, the finding of the per-protocol analysis should be treated with caution and, based on the ITT analysis, we conclude that sex has no moderator effect on 6MWD.

Similar results were observed for QoL. Both groups improved significantly with moderate to strong effect sizes, but IMT did not lead to further improvements. However, sex and Hosp_AECOPD modified QoL. Although females tended to profit from additional IMT in some QoL subscales, males and patients after AECOPD tended to have no benefit or even showed worsening effects. No previous study has reported similar effects, maybe for reasons of power. Several possible explanations for the sex effect exist. For example, inspiratory muscles in females may fatigue less quickly [27, 28]. Therefore, females may experience IMT as less stressful and might benefit more from the gain in P_{Imax} with regard to QoL. Furthermore, males may benefit more from "relaxation breathing" (control group) than females. Slow and relaxed breathing for 21 days may be comparable to relaxation training [29] and may affect psychological but not physiological parameters [30]. However, all effects are small and the clinical relevance is unclear.

In addition, we found a significant improvement in FIV_1. Although several authors regard changes in FIV_1 as relevant [31], the clinical significance of a difference of 100 mL remains unclear, especially as other lung function parameters did not increase.

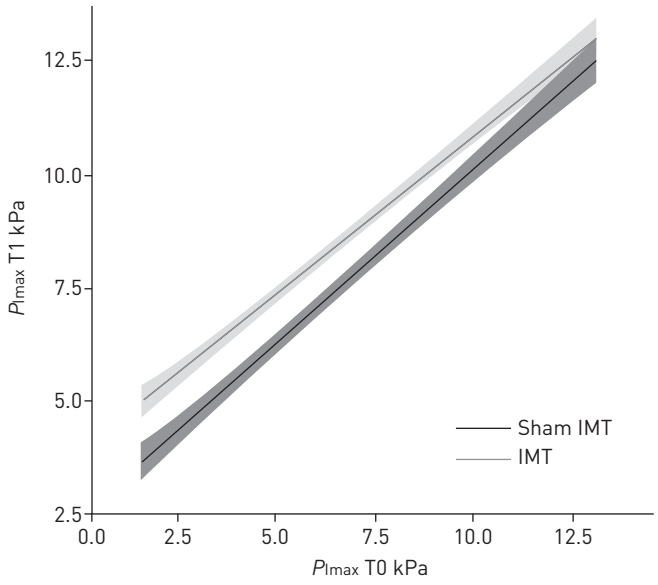

FIGURE 2 Interaction effect of baseline maximal inspiratory pressure (P_{Imax}) (T0) and intervention group on P_{Imax} after rehabilitation (T1). IMT: inspiratory muscle training. Grey shadowed areas represent 95% confidence interval regions. Differences between the lines represent the intervention effect in P_{Imax} conditioned for P_{Imax} T0. No other significant moderator effects were found.

To the best of our knowledge, this is the largest RCT evaluating add-on IMT to pulmonary rehabilitation in COPD. To enhance external validity, we did not exclude patients with comorbidities, exacerbations shortly before rehabilitation or those without inspiratory muscle weakness ("real-life study").

Nevertheless, the study has several limitations. First, this is a single-centre study, which might limit generalisability. However, the rehabilitation programme of the Bad Reichenhall Clinic conforms to the structural requirements of German healthcare insurance providers [32] and should be comparable to other inpatient pulmonary rehabilitation programmes. Second, participants and health professionals could not be fully blinded, as is common in such studies. Thus, influences of group awareness cannot be ruled out. Third, a control group without sham training was not available. As our control setting may have had effects beyond placebo (in the sense of an active control group), the effects on QoL may have been underestimated. Fourth, it is difficult to appraise the clinical relevance of the effects of IMT in females in 6MWD and some QoL scales. According to some authors, effect sizes of 0.2 can be regarded as small, but potentially meaningful [33]. However, clear guidelines on how to interpret small effects comparisons with active control groups do not exist.

Conclusions

IMT routinely added to an intensive 3-week pulmonary rehabilitation improves P_{Imax} and FIV_1. Initial P_{Imax} did not modify these effects. However, for the whole sample, IMT did not further improve functional capacity, dyspnoea or QoL. Therefore, a general recommendation to include IMT in a 3-week pulmonary rehabilitation for all COPD patients cannot be made. Concerning subgroups, IMT improved aspects of QoL, but not in males or patients after severe AECOPD.

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