Effects of inspiratory muscle training in patients with chronic obstructive pulmonary disease after stratification by the degree of static hyperinflation

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Abstract

Background: Inspiratory muscle training (IMT) is a training method in patients with chronic obstructive pulmonary disease (COPD) to improve inspiratory muscle strength, exercise capacity and health status. It is unclear whether patients with different baseline degrees of static hyperinflation respond differentially to IMT as part of a pulmonary rehabilitation (PR) program. Therefore, the aim was to study the effects of IMT as an add-on on PR after stratification for baseline degrees of static hyperinflation. Methods: In this single center retrospective study data were extracted between June 2013 and October 2020 of COPD patients. IMT was performed twice daily as part of a PR program. The primary outcome measure was maximal inspiratory mouth pressure (MIP). Secondary outcomes were endurance cycling and functional exercise capacity and disease-specific health status. Results: After screening for eligibility and exclusion because of multiple reasons, 426 COPD patients were categorized into RV categories 50%-130%, 131%-165%, 166%-197%, 198%-234% and 235%-349%. In the whole sample, MIP, endurance exercise capacity and health status improved significantly. The change in 6MWD was higher in the lowest baseline degree of static hyperinflation (+39 (9-92) m) compared with the baseline highest degree of static hyperinflation (+11 (-18-54) m) ($p<0.05$). Conclusions: IMT as part of a PR program in patients with COPD with different baseline degrees improved MIP irrespective of the degree of static lung hyperinflation. Improvement in functional exercise capacity was significantly higher in the group with the lowest degree of static hyperinflation compared with the patients with the highest degree of static hyperinflation.

Introduction

In patients with chronic obstructive pulmonary disease (COPD), worsening expiratory flow limitation together with alterations in the elastic properties of the lungs are associated with progressive lung hyperinflation which is mechanistically linked to dyspnea during exercise (1). Indeed, high levels of diaphragm activation were shown during exhaustive exercise in patients with COPD (2). Also, the load imposed on the respiratory muscles is increased in patients with COPD (3). In addition, inspiratory muscle function is altered in COPD and this altered function is most probably secondary to a mechanical disadvantage related to static lung hyperinflation (3). The increased gas volume in the lungs at the end of the expiration phase places the diaphragm at a mechanical disadvantage, thereby impairing its length-tension relationship and reducing its maximum pressure-generating capacity (4). Thus, inspiratory muscle dysfunction in patients with COPD may be caused by hyperinflation of the lung which results in a reduced inspiratory muscle strength, measured by the maximal inspiratory mouth pressure (MIP) (5).

Inspiratory muscle training (IMT) is a training method to increase MIP, by using threshold devices which provide consistent and specific pressure for inspiratory muscle strength training (6). Generally, IMT improves inspiratory muscle strength, exercise capacity and health status and decreases dyspnea in COPD patients with reduced baseline MIP (6, 7). However, there is no additional effect of IMT on the reduction in dyspnea following pulmonary rehabilitation (PR) compared with PR alone (6).

As noted before, inspiratory muscle weakness is most probably related to lung hyperinflation. However, Augustin and colleagues (8) showed that a low MIP can also occur in COPD patients without static lung hyperinflation. So, a reduced MIP without static hyperinflation is probably due to muscle weakness and therefore it can partially be trained by IMT. At present, it remains unknown whether and to what extent patients with a reduced MIP with different degrees of static lung hyperinflation respond differentially to IMT as part of a PR program. Therefore, the aim was to study the effects of IMT during a PR program after stratification for the baseline degree of static lung hyperinflation. The hypothesis of this study is that COPD patients with low degrees of static hyperinflation will respond better to IMT as an add-on on PR than COPD patients with high degrees of static hyperinflation. This is hypothesized because hyperinflation impairs the function of the diaphragm by placing it at mechanical disadvantage, shortening its operating length, and changing the mechanical linkage between its various parts.

Methods

Design

This is a single center, retrospective study. Data of 754 patients with COPD who started an inpatient PR program including IMT, between June 2013 and October 2020 were extracted from the Integrated Knowledge System at CIRO, a center of expertise for patients with chronic respiratory diseases in Horn, the Netherlands (9). The medical ethics committee of Maastricht University stated that the Medical Research Involving Human Subjects Act (WMO) did not apply for this study and that an official approval of this study by the committee was not required (METC2020-2270). The Board of Directors of CIRO approved the use of de-identified patients' records.

Participants

Inclusion criteria were: (i) primary diagnosis of COPD (10); (ii) IMT as part of PR ; (iii) MIP measurement at baseline and at the end of PR; (iv) reduced MIP (MIP <-60% of the predicted value or < 70% of the predicted value in combination with mMRC 3 or 4); and (v) measurement residual volume (RV) at baseline. Participants with RV < 50% or > 350% were excluded to limit the possible effects of extreme outliers (11). When patients participated in repeated PR programs during this period, only the first PR program was included in this analysis.

Interventions

All participants underwent an eight week comprehensive interdisciplinary inpatient PR program (9, 12). Before and after the PR program, patients underwent a thorough intake and assessment of pulmonary and extra-pulmonary features which determined the application of various treatments (9). All measurements were performed by a highly trained and skilled team of biomedical engineers and laboratory technicians. In brief, the PR program consisted of 40 sessions (8 weeks, 5 days/week) and included exercise and non-exercising components such as occupational therapy, relaxation therapy, exacerbation management strategies, educational sessions and psychosocial counselling (12). Physical exercise training was the cornerstone of PR, consisting of treadmill walking,

cycle ergometry and resistance training at moderate to high intensities. The training intensities were progressively increased during the course of the program based on symptom scores. Patients who were unable to perform endurance or interval training twice per day received lower-limb high-frequency neuromuscular electrical stimulation (13). Also, all patients underwent flexibility exercises, unsupported arm exercises, general physical exercise and outdoor walks.

IMT was performed twice daily using the Threshold IMT (Philips-Respironics, Eindhoven, Nederland), 3 times per week group-based and supervised by a physiotherapist. One session consisted of 3 series of 10 breaths (14). Training intensity was set initially at a load of approximately 50% of patients' maximal static inspiratory mouth pressure (MIP). If this load was not tolerable, that means that the patient was not able to perform 30 good breaths, the intensity was lowered to the highest tolerable intensity (14). During the supervised sessions patients received instructions and feedback on the performance of IMT and weekly was tried to gradually increase the training load to the highest tolerable intensity.

Baseline assessment

Spirometry was measured in all patients with Masterlab® (Jaeger, Würzburg, Germany) following ATS/ERS statements (15). Post-bronchodilator spirometry was performed to assess forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). Also, static lung volumes (intrathoracic gas volume, total lung capacity, residual volume) and diffusing capacity of the lung for carbon monoxide, single breath hold method were determined in all patients (Masterlab®, Jaeger, Würzburg, Germany). A symptom-limited cardiopulmonary exercise cycle test (CPET) was executed where peak VO_2 was determined in accordance with the statements of the American Thoracic Society and the American College of Chest Physicians (16). Resting arterial partial pressure of oxygen (PaO_2), carbon dioxide ($PaCO_2$) and oxygen saturation were measured (GEM4000, Instrumentation Laboratory, Peachtree City, USA) (8). Patients with long term oxygen therapy (LTOT) continued oxygen supply during the procedure. Body composition (body weight, BMI = Body Mass Index and FFMI = Fat Free Mass Index) was determined using dual-energy x-ray absorptiometry (Lunar Prodigy system, GE Healthcare, Madison, WI) (17).

Outcome measurement

The primary outcome was MIP assessed according to ATS/ERS statements (18) and expressed in reference values to Black and Hyatt (19). Secondary outcomes included functional exercise capacity measured by the 6-minute walk test (6MWT) and expressed in the achieved distance in six minutes (6-minute walk distance, 6MWD). The 6MWT was performed twice, according to the ERS/ATS statement and the best test was recorded (20). Endurance cycling exercise capacity was measured at 75% of peak work rate during the CPET (Constant Work Rate Test, CWRT) (21), muscle function was measured isokinetically with the Biodex (22) and Disease-specific health status was assessed using the COPD Assessment Test (CAT) (23).

Statistical analysis

All statistical analyses were performed using SPSS for Windows, Version 25.0 (SPSS, Inc., Chicago, Il, USA). The normality was examined with a Shapiro-Wilks test for normality and for the examination of a histogram and homogeneneity of variances was tested with Levene's test. Because there was no normal distribution, data were expressed as numbers, percentages and median (interquartile range). In the absence of homogeneity of variances of most variables, the relation between the different groups was analyzed using nonparametric tests such as Kruskal-Wallis test, Mann Whitney U test and Wilcoxon signed-rank test. Patients were categorized in quintiles to compare between degrees of static lung hyperinflation, based on their measured residual volume (RV) as a percentage of predicted RV at baseline assessment (11). A two-sided p-value of < 0.05 was considered to be indicative of statistical significance. Adjustment for multiple testing were made with a Bonferroni correction.

Results

Patients

In total 754 patients with COPD were screened for eligibility in the analysis. Of these patients, 328 were excluded for multiple reasons (Fig. 1). Eventually, 426 patients were included and categorized into RV categories 50%-130% (n = 84), 131%-165% (n = 86), 166%-197% (n = 86), 198%-234% (n = 85) and 235%-349% (n = 85).

Baseline characteristics

In general, patients generally had severe to very severe COPD (FEV_1% predicted: 33 (26–46)), high levels of dyspnea (mMRC dyspnea grade 0/1/2/3/4: 1/6/73/164/177);, a normal body composition (BMI: 25.3 (21.03–29.5) kg/m^2), a poor peak (CPET: 47 (36–63) watts) and functional exercise performance (6MWD: 321 (248–392) meters), and a poor health status (CAT: 23 (20–28) points) (Table 1). MIP was decreased in the whole group (MIP: 55% (48%-62%) predicted).

Table 1
Clinical and lung function characteristics of the whole group.

		RV Categories					
Characteristic	Whole group n = 426	RV 50–130% n = 84	RV 131–165% n = 86	RV 166–197% n = 86	RV 198–234% n = 85	RV 235–349% n = 85	p-valu
Sex (M/F), numbers	273/173	69/15	51/35 *	53/33 *	56/29	44/41 *§	< 0.0(
Age, years	68 (61–73)	73 (66–77)	72 (66–74)	68 (63–73) *	67 (60–71) *	62 (58–67) *	0.0(
mMRC dyspnea grade 0/1/2/3/4, numbers	1/6/73/164/177	0/2/18/33/30	1/2/12/36/33	0/2/18/36/30	0/0/19/26/38	0/0/6/33/46 *	0.0
Exacerbation rate in previous year (0/1/2/3/4/>4), numbers	53/57/74/67/50/122	16/12/13/15/8/20	16/17/14/12/7/18	8/8/10/15/12/32	9/12/20/9/11/24	4/8/17/16/12/28 *§	0.0(
Pulmonary function	n = 426	n = 84	n = 86	n = 86	n = 85	n = 85	
FEV_1, liters	0.86 (0.64–1.15)	1.40 (1.04–1.74)	0.93 (0.75–1.20) *	0.87 (0.71–1.21) *	0.75 (0.61–0.93) *§	0.56 (0.47–0.70) *§	< 0.0(
FEV_1, % predicted	33 (26–46)	55 (43–69)	39 (34–48) *	35 (29–42) *	28 (23–34) *§	21 (18–27) *§	< 0.0(
FVC, liters	2.71 (2.11–3.34)	2.81 (2.36–3.52)	2.74 (2.15–3.53)	2.88 (2.08–3.66)	2.74 (2.22–3.26)	2.33 (1.81–2.92) §§	0.0(
FVC, % predicted	82 (69–97)	89 (72–106)	87 (76–102)	86 (74–100)	80 (68–91) §	69 (60–82) *§ §	< 0.0(
FEV_1/FVC max, %	32 (27–41)	51 (40–60)	35 (31–43) *	32 (28–38) *	28 (24–33) *§	25 (21–29) *§§	< 0.0(
GOLD classification (I/II/III/IV), numbers	14/68/172/172	11/40/26/7	3/15/58/10 *	0/10/47/29 *	0/3/31/51 *§	0/0/10/75 *§§	< 0.0(
GOLD classification (A/B/C/D), numbers	0/22/1/403	0/14/0/70	0/6/0/80	0/2/1/83 *	0/0/0/85 *	0/0/0/85 *	< 0.0(
ITGV, liters	5.15 (4.08–6.27)	3.45 (2.88-4,07)	4.67 (3.86–5.15) *	5.34 (4.32–6.21) *	6.15 (5.38–6.54) *§	6.90 (5.62–7.84) *§	< 0.0(
ITGV, % predicted	164 (134–191)	103 (87–117)	140 (132–149) *	164 (154–175) *	181 (175–192) *§	215 (201–230) *§§	< 0.0(
RV, liters	4.14 (3.10–5.03)	2.95 (2.37–4.06)	3.58 (2.91–4.41) *	4.43 (3.72–4.90) *	4.71 (3.94–5.29) *	4.86 (3.51–6.16) *§§	< 0.0(
RV, % predicted	181 (142–222)	107 (87–118)	151 (141–159) *	181 (173–191) *	214 (205–222) *§	270 (248–291) *§§	< 0.0(

Baseline characteristics of total group and different RV categories. Data are expressed as median (interquartile range), percentages or numbers.

Abbreviations: M = males; F = females; mMRC = modified medical research council; FEV_1 = forced expiratory volume in one second; FVC max = maximum forced vital capacity; GOLD = Global Initiative for chronic Obstructive Lung Disease; ITGV = intra thoracic gas volume; RV = residual volume; TLC = total lung capacity; TLCO = the single-breath transfer factor of the lung for carbon monoxide; MIP = maximal static inspiratory mouth pressure; PaO_2 = resting arterial oxygen tension; $PaCO_2$ = resting arterial carbon dioxide tension; SaO_2 = resting arterial oxygen tension; kPa = kilopascal; LTOT = long-term oxygen therapy; BM = body mass index; FFMI = fat free mass index; kg/m^2 = kilogram per square meter.

* Significantly different compared to RV 50%-130% category at $p < 0.005$ (with Bonferroni correction).

§ Significantly different compared to RV 131%-165% category at $p < 0.005$ (with Bonferroni correction).

§ Significantly different compared to RV 166%-197% category at $p < 0.005$ (with Bonferroni correction).

§ Significantly different compared to RV 198%-234% category at $p < 0.005$ (with Bonferroni correction).

		RV Categories					
TLC, liters	6.86 (5.66–8.12)	5.35 (4.84–6.39)	6.25 (5.19–7.39) *	7.57 (5.92–8.35) *□	7.83 (6.65–8.61) *□	8.21 (6.78–9.52) *□□§	< 0.00
TLC, % predicted	117 (104–132)	91 (77–99)	108 (101–114) *	120 (112–126) *□	126 (118–134) *□□	140 (133–148) *□□	< 0.00
TLCO, % predicted	40 (32–52)	50 (40–63)	44 (34–56)	39 (33–51) *	37 (29–45) *	34 (27–40) *□□§	< 0.00
MIP, kPa	4.82 (3.91–5.83)	5.06 (4.19–5.84)	4.46 (3.82–5.79)	4.77 (3.94–5.78)	5.14 (3.86–6.02)	4.62 (3.68–5.72)	0.19
MIP, % predicted	55 (48–62)	54 (44–63)	56 (46–64)	54 (49–62)	55 (48–61)	54 (46–61)	0.74
Arterial blood gases	n = 419	n = 83	n = 86	n = 84	n = 84	n = 82	
PaO_2 (kPa)	8.9 (8.0-9.9)	9.0 (7.9–10.2)	8.9 (8.1–9.8)	9.0 (8.0-9.9)	9.3 (8.3–10.1)	8.5 (7.7–9.1)	0.01
$PaCO_2$ (kPa)	5.6 (5.1–6.5)	5.2 (4.8–5.6)	5.5 (5.0-6.2)	5.5 (5.0-6.4) *	5.8 (5.2–6.6) *	6.6 (5.6–7.7) *□□§	< 0.00
SaO_2 (%)	93 (91–95)	94 (91–96)	94 (92–95)	93 (92–95)	94 (92–95)	92 (89–94) *□	0.00
LTOT use, %	41	28	34	47	46	51 □□§	0.00
Body composition	n = 424	n = 83	n = 86	n = 84	n = 85	n = 84	
BMI (kg/m^2)	25.3 (21.03–29.5)	29.2 (26.0-33.1)	26.5 (21.8–30.1) *	24.9 (21.4–29.5) *	23.6 (19.9–27.7) *	21.2 (18.5–25.4) *□□	< 0.00
FFMI (kg/m^2)	16.6 (14.66-18.0)	18.3 (17.0–20.0)	16.7 (15.1–18.0) *	16.6 (14.6–18.2) *	16.3 (14.0-17.4) *	15.3 (13.9–16.5) *□	< 0.00

Baseline characteristics of total group and different RV categories. Data are expressed as median (interquartile range), percentages or numbers.

Abbreviations: M = males; F = females; mMRC = modified medical research council; FEV_1 = forced expiratory volume in one second; FVC max = maximum forced vital capacity; GOLD = Global Initiative for chronic Obstructive Lung Disease; ITGV = intra thoracic gas volume; RV = residual volume; TLC = total lung capacity; TLCO = the single-breath transfer factor of the lung for carbon monoxide; MIP = maximal static inspiratory mouth pressure; PaO_2 = resting arterial oxygen tension; $PaCO_2$ = resting arterial carbon dioxide tension; SaO_2 = resting arterial oxygen tension; kPa = kilopascal; LTOT = long-term oxygen therapy; BM = body mass index; FFMI = fat free mass index; kg/m^2 = kilogram per square meter.

* Significantly different compared to RV 50%-130% category at $p < 0.005$ (with Bonferroni correction).

□ Significantly different compared to RV 131%-165% category at $p < 0.005$ (with Bonferroni correction).

□ Significantly different compared to RV 166%-197% category at $p < 0.005$ (with Bonferroni correction).

§ Significantly different compared to RV 198%-234% category at $p < 0.005$ (with Bonferroni correction).

There were no statistical significant differences in baseline MIP (kPa or % predicted) between different RV categories. Patients with higher categories of RV were significantly younger, had more severe airflow obstruction, more impaired diffusion capacity, more patients with hypercapnia, lower body weight and muscle mass, worse exercise capacity, and lower isokinetic quadriceps muscle function (Tables 1 and 2).

Table 2
Baseline clinical, functional and health status characteristics of the whole sample.

		RV Categories					
	Whole group n = 426	RV 50–130% n = 84	RV 131–165% n = 86	RV 166–197% n = 86	RV 198–234% n = 85	RV 235–349% n = 85	p-value
6-minute walk test	n = 421	n = 84	n = 84	n = 85	n = 85	n = 83	
6MWD, meters	321 (248–392)	334 (234–401)	335 (268–412)	340 (277–410)	315 (243–391)	299 (233–358)	0.055
6MWD, % predicted	51 (41–61)	54 (41–66)	57 (46–68)	55 (44–65)	49 (40–57) □	46 (33–54) *□□	< 0.001
Borg dyspnea end, points	7 (5–7)	6 (4–7)	7 (5–7)	7 (4–7)	6 (5–7)	7 (5–8)	0.827
Borg fatigue end, points	5 (3–7)	5 (3–7)	5 (4–7)	4 (3–7)	5 (3–7)	4 (3–6)	0.021
Saturation end, %	87 (82–91)	90 (83–94)	87 (82–91)	87 (81–91) *	87 (81–91) *	84 (79–88) *□	< 0.001
Cardiopulmonary exercise test	n = 355	n = 75	n = 74	n = 75	n = 69	n = 62	
Peak load, watts	47 (36–63)	61 (47–76)	49 (40–64) *	50 (36–65) *	42 (35–55) *	39 (31–44) *□	< 0.001
Peak load, % predicted	35 (27–44)	38 (31–49)	39 (30–46)	36 (27–44)	33 (24–42) *	30 (22–34) *□□	< 0.001
Peak VO_2, ml/min	864 (693–1027)	995 (839–1207)	867 (751–1012)	800 (667–1009) *	811 (582–1013) *	726 (605–908) *□	< 0.001
Peak VO_2, % predicted	46 (28–57)	49 (43–58)	51 (42–61)	45 (38–56)	44 (37–55)	41 (33–49) □	0.009
Peak VE, liters	36 (28–42)	42 (34–51)	34 (30–42)	33 (26–41) *	33 (24–37) *	28 (24–36) *□	< 0.001
Peak VE, % MVV	81 (71–97)	75 (59–88)	80 (71–97)	79 (72–100)	87 (78–102) *	100 (78–117) *	< 0.001
Peak HR, bpm	113 (100–123)	113 (97–124)	115 (103–127)	112 (100–123)	109 (102–121)	113 (101–121)	0.638
Peak HR, % predicted	73 (65–80)	73 (65–85)	76 (69–82)	73 (65–79)	70 (66–78)	71 (65–78)	0.132
Borg dyspnea end, points	7 (7–9)	7 (6–8)	7 (6–9)	7 (7–9)	7 (7–9)	8 (7–9)	0.067
Borg fatigue end, points	7 (5–8)	7 (5–8)	7 (5–8)	6 (5–7)	6 (4–7)	7 (4–8)	0.490
Saturation end, %	90 (87–94)	91 (89–95)	90 (87–94)	90 (87–93)	90 (87–94)	89 (86–92) *	0.041
Constant work-rate cycling endurance test	n = 342	n = 70	n = 71	n = 73	n = 63	n = 60	
Cycle time, seconds	185 (142–266)	213 (143–303)	197 (150–251)	198 (145–275)	171 (132–239)	167 (133–234)	0.236
Borg dyspnea end, points	8 (7–9)	7 (7–10)	8 (5–9)	8 (7–9)	7 (7–9)	8 (7–10)	0.652
Borg fatigue end, points	7 (5–9)	8 (5–9)	7 (5–8)	7 (5–9)	7 (5–9)	7 (5–8)	0.413
Hospital Anxiety and Depression Scale	n = 393	n = 81	n = 85	n = 72	n = 77	n = 78	
Anxiety, points	8 (5–11)	7 (5–11)	8 (4–11)	9 (6–12)	8 (6–11)	7 (6–12)	0.151
Depression, points	8 (5–11)	8 (6–13)	8 (5–11)	9 (5–11)	8 (5–11)	7 (5–11)	0.615

Baseline characteristics of total group and different RV categories. Data are expressed as median (interquartile range), percentages or numbers.

Abbreviations: RV = residual volume; 6MWD = 6 minute walk distance; VO_2 = oxygen uptake; ml/min = milliliters per minute; VE = ventilation; HR = heart rate; bpm = beats per minute; CAT = COPD Assessment Test.

* Significantly different compared to RV 50%-130% category at $p < 0.005$ (with Bonferroni correction).

□ Significantly different compared to RV 131%-165% category at $p < 0.005$ (with Bonferroni correction).

□ Significantly different compared to RV 166%-197% category at $p < 0.005$ (with Bonferroni correction).

	RV Categories						
CAT	n = 398	n = 82	n = 86	n = 74	n = 77	n = 79	
Total score, points	23 (20–28)	23 (21–28)	23 (19–28)	24 (21–28)	24 (20–27)	24 (20–27)	0.880
Baseline characteristics of total group and different RV categories. Data are expressed as median (interquartile range), percentages or numbers.							
Abbreviations: RV = residual volume; 6MWD = 6 minute walk distance; VO_2 = oxygen uptake; ml/min = milliliters per minute; VE = ventilation; HR = heart rate; bpm = beats per minute; CAT = COPD Assessment Test.							
* Significantly different compared to RV 50%-130% category at p < 0.005 (with Bonferroni correction).							
□ Significantly different compared to RV 131%-165% category at p < 0.005 (with Bonferroni correction).							
□ Significantly different compared to RV 166%-197% category at p < 0.005 (with Bonferroni correction).							

Outcomes

In the whole sample, MIP, functional and endurance exercise capacity and health status improved significantly after eight weeks of PR including IMT (Table 3). Changes in MIP, endurance exercise capacity and health status between RV categories did not significantly differ (Table 3). Improvement in 6MWD was significantly higher in the group with the lowest degree of static hyperinflation (RV category 50%-130%) compared with the patients with the highest degree of static hyperinflation (RV category 235%-349%) (Fig. 2).

Table 3
Change with-in and between groups in maximal inspiratory mouth pressure, exercise capacity and health status

Characteristic	Whole group n = 426	RV 50–130% n = 84	RV 131–165% n = 86	RV 166–197% n = 86	RV 198–234% n = 85	RV 235–349% n = 85	p-value
MIP	n = 426	n = 84	n = 86	n = 86	n = 85	n = 85	
MIP, kPa, baseline	4.82 (3.91–5.83)	5.06 (4.19–5.84)	4.46 (3.82–5.79)	4.77 (3.94–5.78)	5.14 (3.86–6.02)	4.62 (3.68–5.72)	
MIP, kPa, end	5.68 (4.63–7.13)	5.92 (5.01–7.40)	5.62 (4.25–7.07)	5.66 (4.75–6.97)	5.89 (5.08–7.44)	5.37 (4.36–6.42)	
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	
Δ MIP, kPa	0.90 (0.18–1.71)	1.02 (0.30–1.76)	0.78 (0.04–1.66)	0.97 (0.37–1.67)	0.96 (0.29–1.94)	0.73 (-0.06-1.61)	0.883
MIP, % predicted, baseline	55 (48–62)	54 (44–63)	56 (46–64)	54 (49–62)	55 (48–61)	54 (46–61)	
MIP, % predicted, end	65 (55–75)	64 (55–76)	66 (56–76)	67 (58–76)	67 (56–76)	60 (48–72)	
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.032	
Δ MIP, % predicted	10 (2–19)	11 (3–19)	8 (0–20)	12 (4–18)	11 (3–20)	9 (-1-17)	0.891
6-minute walk test	n = 421	n = 83	n = 82	n = 82	n = 83	n = 80	
6MWD, meters, baseline	321 (248–392)	334 (234–401)	335 (268–412)	340 (277–410)	315 (243–391)	299 (233–358)	
6MWD, meters, end	358 (281–425)	385 (295–449)	361 (290–429)	375 (299–451)	342 (284–415)	310 (240–367)	
p-value	< 0.001	< 0.001	0.001	< 0.001	< 0.001	0.017	
Δ 6MWD, m	26 (-7-64)	39 (9–92)	27 (-10-63)	31 (-6-63)	25 (-4-59)	11 (-18-54) *	0.018
6MWD, % predicted, baseline	51 (41–61)	54 (41–66)	57 (46–68)	55 (44–65)	49 (40–57)	46 (33–54)	
6MWD, % predicted, end	57 (44–68)	64 (53–77)	61 (51–74)	61 (48–72)	55 (43–64)	47 (38–56)	
p-value	< 0.001	< 0.001	0.001	< 0.001	< 0.001	< 0.001	
Δ 6MWD, % predicted	4 (-1-11)	7 (2–16)	4 (-2-10)	6 (-1-10)	4 (-1-10)	2 (-3-8) *	0.005
Constant work-rate cycling endurance test	n = 337	n = 68	n = 71	n = 73	n = 61	n = 56	
Cycle time, seconds, baseline	185 (142–266)	213 (143–303)	197 (150–251)	198 (145–275)	171 (132–239)	167 (133–234)	
Cycle time, seconds, end	310 (186–631)	405 (232–730)	290 (210–629)	346 (160–769)	274 (187–420)	247 (144–673)	
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	
Δ CWRT, s	103 (15–327)	183 (52–441)	117 (15–359)	79 (-13-367)	64 (10–166)	75 (15–448)	0.057
CAT	n = 398	n = 78	n = 79	n = 72	n = 74	n = 74	
CAT, total score, baseline	23 (20–28)	23 (21–28)	23 (19–28)	24 (21–28)	24 (20–27)	24 (20–27)	
CAT, total score, end	21 (16–25)	19 (14–24)	19 (15–24)	22 (17–25)	20 (16–25)	22 (18–25)	
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.001	
Δ CAT, points	-3 (-7-1)	-5 (-9–0)	-3 (-7-1)	-3 (-6-1)	-2(-7-0)	-2 (-5-1)	0.074

Values expressed as median (interquartile range).

Abbreviations: MIP = maximal static inspiratory mouth pressure; Δ = delta (difference between end and baseline); 6MWD = 6-minute walk distance; CWRT = Constant work-rate cycling endurance test; CAT = COPD Assessment Test.

* Significantly different compared to RV 50%-130% category at p < 0.005 (with Bonferroni correction).

Discussion

This is the first study reporting the effectiveness of IMT as part of a PR program in patients with COPD with different baseline degrees of static lung hyperinflation. The main finding of this study is that MIP improves after IMT as part of a PR program, irrespective of baseline RV. So, the hypothesis that COPD patients with high degrees of hyperinflation will not benefit from IMT in combination with PR is rejected. The changes in endurance exercise capacity,

and health status following PR were comparable between RV categories. Only the change in functional exercise capacity was greater for the lowest degree of static hyperinflation compared to the highest degree.

Effectiveness of IMT in combination with PR

MIP improved significantly after eight weeks IMT in combination with PR compared to baseline. A recent study investigated whether adjunctive IMT could enhance the benefits of PR (24). In this study was a control group (sham IMT + PR) and MIP was significantly more improved in the intervention group (24). However, this gain in MIP was not translated in an improvement between groups in 6MWD (24). In the current study in all RV categories MIP increased compared to baseline after eight weeks but no significant differences were found in the change in MIP between RV categories. So it is not clear to which extent IMT contributed to an additional improvement in MIP to other training modalities of PR, irrespective of the degree of static hyperinflation. So other factors may play a more important role in improvement in MIP than the degree of static hyperinflation. Perhaps PR itself without IMT also has positive effects on MIP. After a 12-week PR program a correlation between the change in the diaphragmatic length of zone of apposition at functional residual capacity and the change in 6MWD was found (25). So, it is debatable for training the inspiratory muscles by IMT in a PR setting because the inspiratory muscles may already be trained by intrinsic mechanical loading in the setting of high ventilatory demand (26).

In the present study the change in 6MWD was significantly lower in the highest RV category compared to the lowest RV category, while there was no significant difference in the change in endurance cycling time measured with the CWRT. A probable explanation is that in this study only patients were included with a reduced MIP. Although walking and cycling are both whole body exercises and there is some carryover of training effects, there are some different physiological responses to these training types (27). Oxyhemoglobin desaturation was greater during treadmill walking compared with cycling and peak ratings of dyspnea were found to be higher for treadmill walking compared with cycling (28), and a maximum voluntary contraction force of the quadriceps after cycling was significantly reduced compared to walking (29). Besides static hyperinflation also dynamic hyperinflation plays a central role in the development of dyspnea and exercise intolerance (30). Dynamic hyperinflation is expressed as decreased inspiratory capacity and increased functional residual capacity due to a continually increasing end-expiratory lung volume (31). The major consequence of dynamic hyperinflation is an increased ventilatory workload and decreased pressure-generating capacity by the inspiratory muscles, despite compensatory mechanisms (32).

Methodological considerations

The strength of this study is the large sample size of patients with COPD with well-characterized data which represent clinical practice. This study had some limitations. First, the data are obtained retrospectively in a single-center state-of-the-art rehabilitation program, which reduces the generalizability of the results. Second, because IMT was performed twice daily individually and 3 times per week group-based the training adherence during the individual sessions is not clear. This could, at least partially, have influenced the results.

Conclusion

We conclude that IMT as part of a PR program in patients with COPD improved MIP irrespective of the degree of static lung hyperinflation. Generally, changes following PR in endurance exercise capacity and health status were not significantly different between RV categories.

Declarations

CONFLICT OF INTEREST STATEMENT

The authors do not have any conflict of interest with the contents of the present manuscript.

AUTHOR'S CONTRIBUTIONS

Trial concept and design: MJHS, and MAS; acquisition of data: MJHS, MTJG; analysis and interpretation of data: MJHS, AWV, MTJG, FMEF, and MAS; drafting the article: MJHS, AWV, FMEF, and MAS; revising it critically for important intellectual content: all authors; final approval of the version to be published: all authors. MJHS had full access to all trial data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. O'Donnell DE, Webb KA, Neder JA. Lung hyperinflation in COPD: applying physiology to clinical practice. COPD Research and Practice. 2015;1(1):4.

2. Sinderby C, Spahija J, Beck J, Kaminski D, Yan S, Comtois N, et al. Diaphragm activation during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163(7):1637-41.

3. Marchand E, Decramer M. Respiratory muscle function and drive in chronic obstructive pulmonary disease. Clin Chest Med. 2000;21(4):679-92.

4. Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. N Engl J Med. 1991;325(13):917-23.

5. Gea J, Agusti A, Roca J. Pathophysiology of muscle dysfunction in COPD. J Appl Physiol (1985). 2013;114(9):1222-34.

6. Beaumont M, Forget P, Couturaud F, Reychler G. Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. Clin Respir J. 2018;12(7):2178-88.

7. Gosselink R, De Vos J, van den Heuvel SP, Segers J, Decramer M, Kwakkel G. Impact of inspiratory muscle training in patients with COPD: what is the evidence? Eur Respir J. 2011;37(2):416-25.

8. Augustin IML, Spruit MA, Houben-Wilke S, Franssen FME, Vanfleteren L, Gaffron S, et al. The respiratory physiome: Clustering based on a comprehensive lung function assessment in patients with COPD. PLoS One. 2018;13(9):e0201593.

9. Spruit MA, Vanderhoven-Augustin I, Janssen PP, Wouters EF. Integration of pulmonary rehabilitation in COPD. Lancet. 2008;371(9606):12-3.

10. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347-65.

11. Vanfleteren MJ, Koopman M, Spruit MA, Pennings HJ, Smeenk F, Pieters W, et al. Effectiveness of Pulmonary Rehabilitation in Patients With Chronic Obstructive Pulmonary Disease With Different Degrees of Static Lung Hyperinflation. Arch Phys Med Rehabil. 2018;99(11):2279-86 e3.

12. 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(8):e13-64.

13. Sillen MJ, Franssen FM, Delbressine JM, Vaes AW, Wouters EF, Spruit MA. Efficacy of lower-limb muscle training modalities in severely dyspnoeic individuals with COPD and quadriceps muscle weakness: results from the DICES trial. Thorax. 2014;69(6):525-31.

14. Langer D, Charususin N, Jacome C, Hoffman M, McConnell A, Decramer M, et al. Efficacy of a Novel Method for Inspiratory Muscle Training in People With Chronic Obstructive Pulmonary Disease. Phys Ther. 2015;95(9):1264-73.

15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. The European respiratory journal. 2005;26(2):319-38.

16. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211-77.

17. Engelen MP, Schols AM, Heidendal GA, Wouters EF. Dual-energy X-ray absorptiometry in the clinical evaluation of body composition and bone mineral density in patients with chronic obstructive pulmonary disease. Am J Clin Nutr. 1998;68(6):1298-303.

18. American Thoracic Society/European Respiratory S. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518-624.

19. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis. 1969;99(5):696-702.

20. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. The European respiratory journal. 2014;44(6):1428-46.

21. van 't Hul A, Gosselink R, Kwakkel G. Constant-load cycle endurance performance: test-retest reliability and validity in patients with COPD. J Cardiopulm Rehabil. 2003;23(2):143-50.

22. Mathur S, Makrides L, Hernandez P. Test-retest reliability of isometric and isokinetic torque in patients with chronic obstructive pulmonary disease. Physiother Can. 2004;56:94–101.

23. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. The European respiratory journal. 2009;34(3):648-54.

24. Charususin N, Gosselink R, Decramer M, Demeyer H, McConnell A, Saey D, et al. Randomised controlled trial of adjunctive inspiratory muscle training for patients with COPD. Thorax. 2018;73(10):942-50.

25. Crimi C, Heffler E, Augelletti T, Campisi R, Noto A, Vancheri C, et al. Utility of ultrasound assessment of diaphragmatic function before and after pulmonary rehabilitation in COPD patients. Int J Chron Obstruct Pulmon Dis. 2018;13:3131-9.

26. Donaldson AV, Maddocks M, Martolini D, Polkey MI, Man WD. Muscle function in COPD: a complex interplay. Int J Chron Obstruct Pulmon Dis. 2012;7:523-35.

27. American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc. 1998;30(6):975-91.

28. Mahler DA, Gifford AH, Waterman LA, Ward J, Machala S, Baird JC. Mechanism of greater oxygen desaturation during walking compared with cycling in patients with COPD. Chest. 2011;140(2):351-8.

29. Man WD, Soliman MG, Gearing J, Radford SG, Rafferty GF, Gray BJ, et al. Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;168(5):562-7.

30. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2001;164(5):770-7.

31. Calverley PM, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. The European respiratory journal. 2005;25(1):186-99.

32. Cooper CB. The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. The American journal of medicine. 2006;119(10 Suppl 1):21-31.

Figures

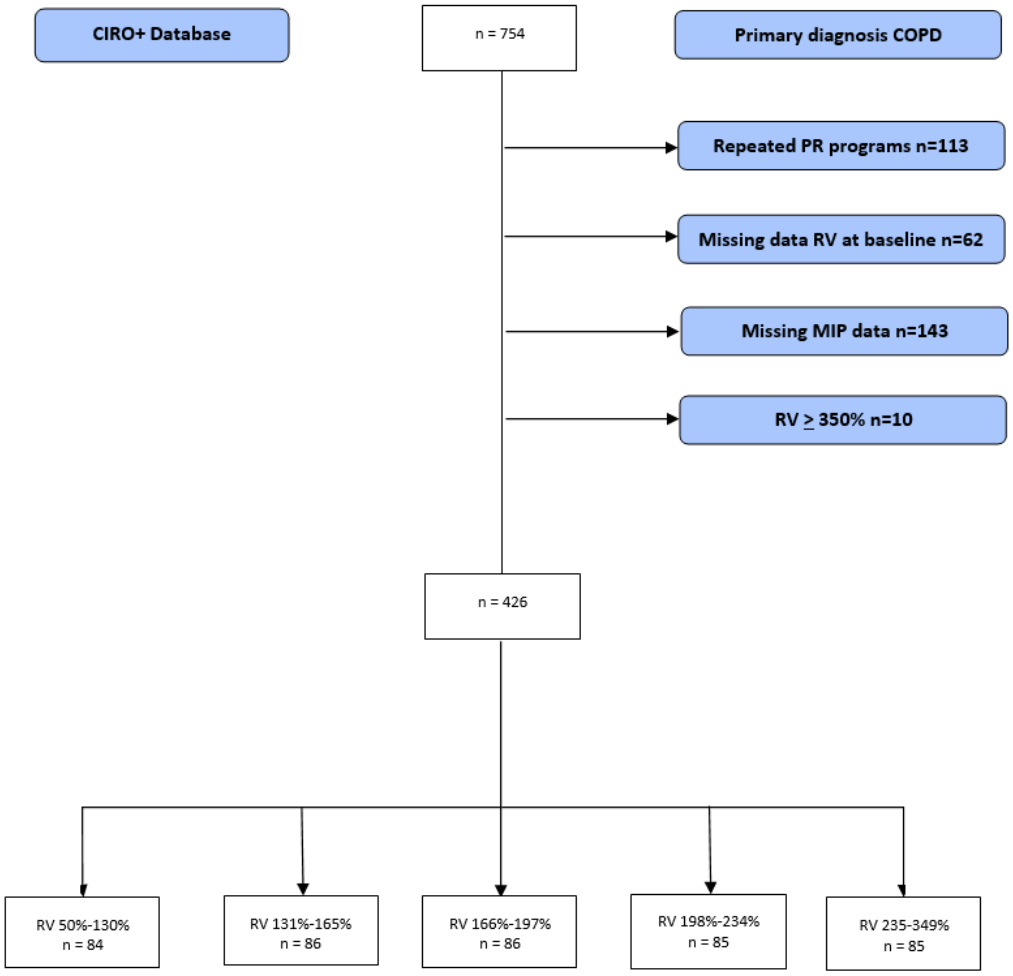

Figure 1

Flow diagram

Abbreviations: COPD=chronic obstructive pulmonary disease; PR=pulmonary rehabilitation; RV=residual volume; MIP= maximal static inspiratory mouth pressure

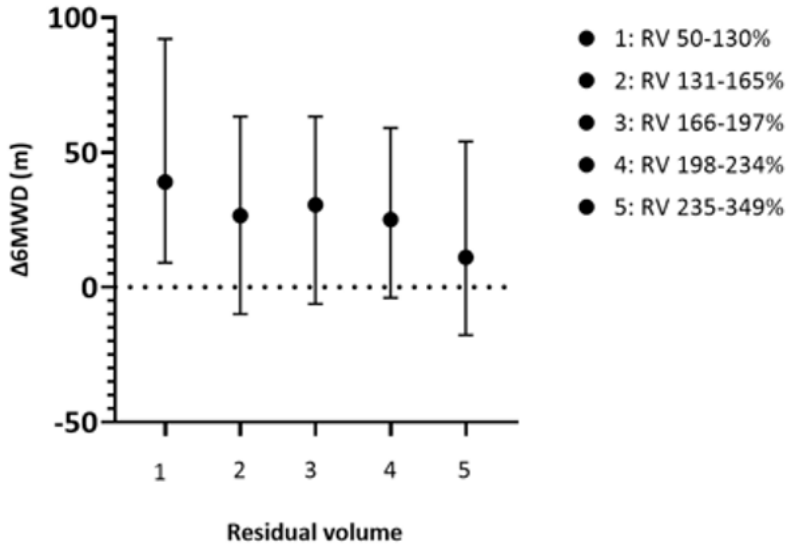

Figure 2

6-minute walk distance stratified for residual volume

Abbreviations: Δ6MWD=change in 6-minute walk distance; RV=residual volume