Original Research Article

CLINICAL REHABILITATION

Clinical Rehabilitation
1–12

DOI: 10.1177/02692155231174124
journals.sagepub.com/home/cre
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Determination of the minimal important difference for inspiratory muscle strength in people with severe and very severe COPD

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Abstract

Objective: Inspiratory muscle training is recommended for people with chronic obstructive pulmonary disease (COPD) with inspiratory muscle weakness. Clinical interpretation of changes in inspiratory muscle strength could be helped by the determination of cut-off values. The aim of this study was to estimate the minimal important difference for inspiratory muscle strength assessed with maximal inspiratory pressure (MIP) in people with COPD.

Design: Post hoc analysis of a randomized controlled trial (EMI2 study) including people with severe to very severe COPD undergoing a pulmonary rehabilitation program was conducted. The determination of the minimal important difference was realized using both anchor-based and distribution-based methods.

Setting: The study includes patients admitted to the rehabilitation program unit of the Centre Hospitalier des Pays de Morlaix (Morlaix, France) between March 5, 2014 and September 8, 2016.

Participants: Seventy-three people with severe to very severe COPD (age 62.2 ± 8.0 years, forced expiratory volume in 1 s 36.4 ± 9.5% of theoretical) were analyzed.

Intervention: Patients followed a standardized pulmonary rehabilitation program 5 days a week for 4 weeks. The program included aerobic training, ground-based outdoor walking training, and strengthening of lower and upper limb muscles.

Main measures: At the end of the pulmonary rehabilitation program, MIP improved by 14.8 ± 14.9 cmH_2O ($p < 0.05$). Regarding the anchor-based method, only the modified Medical Research Council was selected as an appropriate anchor. The receiver operating characteristic curve analysis reported a minimal important difference of 13.5 cmH_2O (sensibility: 75% specificity: 67.5%). Using distribution-based

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methods, the estimate of minimal important difference was 7.9 cmH_2O (standard error of measurement method) and 10.9 cmH_2O (size effect method).
Results: The estimations proposed by this study ranged from 7.9 to 13.5 cmH_2O.
Conclusions: The measurement of minimal important difference is a simple tool for assessing the changes of inspiratory muscle strength during a pulmonary rehabilitation program. We propose a minimal important difference of 13.5 cmH_2O for the improvement of MIP. Further studies are needed to confirm this estimation.
ClinicalTrials.gov identifier: NCT02074813

Keywords
COPD, pulmonary rehabilitation, respiratory muscles, minimal important difference

Received April 29, 2022; accepted April 10, 2023

Introduction

Chronic obstructive pulmonary disease (COPD) is a major worldwide medical, social, and economic concern.[1,2] In 2019, the World Health Organization estimated that COPD is the third leading cause of death.[3] COPD is a common, preventable, and treatable disease, characterized by debilitating respiratory symptoms such as dyspnea, cough, and sputum hyperproduction.[2] The evolution of the pathology is also associated with the frequent presence of various comorbidities (e.g., cardiovascular diseases, diabetes, muscular dysfunction, osteoporosis, or balance impairment).[4] This implies that the management of people with COPD is complex and must be multidimensional. Pulmonary rehabilitation aims to provide an appropriate response to these patients and is considered a central treatment for COPD.[5]

Exercise training and therapeutic education are considered as the cornerstones of pulmonary rehabilitation and additional interventions such as muscle strengthening are also recommended.[5] Inspiratory muscle training (IMT) has been extensively studied in recent years to determine its impact in people with COPD: studies have shown that IMT alone improves the strength and endurance of inspiratory muscles, decreases dyspnea during activities of daily living, improves walking distance and quality of life.[6] When IMT is added to a standard exercise program, it improves the strength and endurance of the inspiratory muscles.[5,6] Therefore, it seems interesting to use this training in patients with a significant reduction in inspiratory muscle strength.[7] Inspiratory muscle weakness is defined as "a loss of the ability to generate muscle force and/or speed of contraction at a given resistance".[8] The cut-off of maximal inspiratory pressure (MIP) < 80% of theoretical is used to indicate the presence of inspiratory muscle weakness.[8] However, studies have shown that patients with MIP < 60 cmH_2O are the most responsive to IMT. There was also a trend toward a benefit of IMT in patients with severe COPD.[9–11] Thus, IMT can be a relevant physical intervention for people with COPD, alone or included in pulmonary rehabilitation in selected patients.[6]

Currently, it is recommended to perform this training using devices with a threshold valve[12] and to assess it using respiratory manometers. To our knowledge, this is the second study to determine a minimal important difference for MIP in people with COPD. In the first study, Iwakura[13] analyzed data from 69 people with COPD (age 75 ± 6 years). This study included all grades of COPD. He had identified a minimal important difference of 17.2 cmH_2O. However, he mentioned that this result should be used with caution, because the minimal important difference was estimated only by distribution-based methods. This new study will improve the estimation of the minimal important difference for MIP and will

help the clinician to objectify the improvement after IMT.

Interpreting the changes induced by an intervention are often difficult, both in research and in clinical practice. However, some clinimetric tools have been described to help researchers and clinicians in this purpose.[14] The minimal important difference is one of these tools and represents a threshold value of change in score deemed to have an implication in clinical management.[15] The determination of a minimal important difference for the inspiratory muscle strength could help interpretation of changes induced by IMT in people with COPD. Inspiratory muscle strength could be assessed in clinical practice by the MIP.[8] On the other hand, this minimal important difference will help them to determine the sample size needed to judge the effectiveness of interventions.[16] The aim of this study was to estimate a minimal important difference for the inspiratory muscle strength assessed by MIP in people with COPD.

Methods

Designs and Population

This post hoc study was a part of a larger trial (EMI2 study).[17] The EMI2 study compared a standardized rehabilitation program with IMT to a standard rehabilitation program without IMT in people with severe and very severe COPD. This post hoc analysis focused on the IMT group of the EMI2 study.

The inclusion criteria for this study were to be admitted to the Rehabilitation Unit of the Centre Hospitalier des Pays de Morlaix (Morlaix, France), to have a severe or very severe COPD diagnosed according to American Thoracic Society/European Respiratory society criteria at admission (forced expiratory volume in 1 s (FEV_1) < 50% of predicted value).[18] The exclusion criteria were previous pneumonectomy or lobectomy within the past 6 months, spontaneous risk of pneumothorax or rib fracture, inability to complete a standard rehabilitation program (locomotor deficits, acute heart failure, and acute COPD exacerbation at baseline), and lack of written informed consent. The study was approved by the ethics committee (CPP Ouest 6, CPP803, #2013-A01180-45) in December 2013 and registered on clinicaltrial.gov as NCT02074813 number. Written informed consent was obtained from all patients.

Outcomes

At the beginning and the end of the pulmonary rehabilitation program, a complete evaluation was performed: a pulmonary function assessment (spirometry with plethysmography) was realized. To assess exercise capacity, the 6 min walk test (6MWT) was performed. Assessment of maximal voluntary quadriceps contraction (MVQC) was performed using a handheld dynamometer (MicroFET2, Hoggan Industries, Inc., West Jordan, UT, USA). Inspiratory capacity (IC) was also measured at rest using a portable spirometer (Spirobank II, MIR Medical International Research, Rome, Italy). The measure of MIP was performed using the Micro RPM manometer (Micro Medical, Rochester, UK), in accordance with recommendations.[19] The test should be performed by an experienced operator who should induce the subjects to make maximal inspiratory efforts. The equipment needed to measure inspiratory pressure at the mouth includes a mouthpiece with a labial mold, a manometer, and a nose clip.[19] The circuit must be equipped with a leakage point to avoid glottis closure and to decrease the recruitment of the mouth muscles.[20] The maneuver consists of asking the patient to perform a maximal inspiration and to maintain it for 2 to 3s. For this study, the maneuver was performed at functional residual capacity. It is recommended to perform 5 maneuvers, then the maximum value is recorded among the 3 best maneuvers, with a variability of <10%.[19,20]

Dyspnea was assessed during exercise, using the modified dyspnea Borg scale and the multidimensional dyspnea profile (MDP) questionnaire at the end of 6MWT. The evaluation of dyspnea also included the Dyspnea-12 questionnaire, the London Chest Activity of Daily Living (LCADL) and the modified Medical Research Council (mMRC) scale. Finally, to measure their quality

of life, the St George's Respiratory Questionnaire (SGRQ) was used.

Patients followed a standardized pulmonary rehabilitation program 5 days a week for 4 weeks. The program included aerobic training performed on a cycle ergometer or a treadmill (30 min per session each, per day, at anaerobic threshold determined with a cardiopulmonary exercise test for cycle ergometer sessions and at 80% of the walk speed determined during the 6MWT for the treadmill sessions, and the intensity was increased according to patient's feeling (dyspnea and heart rate)), ground-based outdoor walking training (2 times per week during 30 min), strengthening of lower and upper limb muscles, therapeutic education program, adapted physical activity in groups (3 times per week during 30 min), and smoking cessation program, sociopsychological and dietary advices if necessary (Table 1). All training sessions were supervised by a physiotherapist. Regarding

Table 1. Standardized pulmonary rehabilitation program.

Activity	Frequency	Specification
Cycle ergometer or a treadmill	5 times per week for 30 min	At anaerobic threshold determined with a cardiopulmonary exercise test for cycle ergometer sessions and at 80% of the walk speed determined during the 6MWT for the treadmill sessions
Ground-based outdoor walking training	2 times per week for 30 min	Patients must walk at a comfortable pace for 30 min
Strengthening of lower and upper limb muscles	3 times per week	2 sets of 10 repetitions with an intensity ranging from 60% to 80% of the maximum resistance measured at the beginning of the program, for resistance strengthening 3 sets of 10 to 25 repetitions with an intensity at 30% of the maximum resistance measured at the beginning of the program, for resistance strengthening This intensity (60%–80% for resistance strengthening or increase of repetitions for endurance strengthening) should be increased regularly each week, if possible, for patients
TPE		The objectives can be of 2 types, those related to the patient's problematic determined during the educational interview and the so-called "safe" objectives, notably in the management of drug treatments, oxygen therapy, NIV, which can be distant from the patient's problematic TPE sessions cover a variety of topics such as respiratory pathophysiology, breathing strategies, learning bronchial drainage, inhaled medications, oxygen therapy, the benefits of physical activity, managing exacerbations and creating an individualized action plan, help with smoking cessation, travel, and leisure activities
APA in groups	3 times per week for 30 min	A session with stretching of upper limbs and rib cage A session of functional upper and lower limbs strengthening A session of balance exercises
Smoking cessation program	If necessary	Consultation with a tobacco specialist
Sociopsychological	If necessary	Consultation with a social worker Consultation with a psychologist
Dietary advice	If necessary	Consultation with a dietician

3 sets of 10 to 25 repetitions with an intensity at 30% of the maximum resistance measured at the beginning of the program, for **endurance** strengthening

APA: adapted physical activity; TPE: therapeutic patient education.

IMT, two 15 min sessions were performed each day, supervised by a physiotherapist, 5 times a week for 4 weeks. IMT was performed using a threshold valve device (Powerbreathe Medic; Powerbreathe, Southam, UK). The patients had to breathe slowly with an increased tidal volume; after 10 inspirations, they could have a break by breathing at rest for a short time. The cycle of 10 inspirations was repeated 15 times. The device generated a pressure corresponding to 50% of the initial MIP.[21] However, there is no international consensus on the pressure to use during an IMT. The intensity was increased (+10%) after 10 days of training to reach 60% of the initial MIP.[17]

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 9, Jamovi 2.2.5, and Microsoft Excel software. All results were presented as mean ± standard deviation (SD) or median with interquartile range (Q1–Q3) for quantitative variables. The effect of pulmonary rehabilitation on dyspnea and functional parameters was analyzed using the paired Student's t-test or the Wilcoxon test (in case of non-normal distribution). Correlations were analyzed using Pearson's or Spearman's rank correlation coefficients (in case of non-normal distribution). A p-value <0.05 was considered statistically significant.

To determine the minimal important difference, both distribution-based and anchor-based methods were used as recommended.[22] The anchor-based method is based on the use of external indicators, called anchors, with an existing minimal important difference in the studied population. Anchors used in this study were: the Borg scale, the mMRC scale, the MDP questionnaire, the SGRQ, the IC, the 6MWT, the MVQC, the LCADL, and the Dyspnea-12 questionnaire.

The mMRC scale is a valid tool, reliable and has an estimated minimal clinically important difference (MCID) of −0.5 points.[23–25] The Borg scale is a valid tool, reliable and has an estimated MCID of −1 point.[25,26] The sensory component, which was studied in detail in the study by Beaumont et al.,[17] has an estimated MCID of 3.02 points.[27] The SGRQ has an estimated MCID of 4 points.[28–30] The inspiratory capacity has an estimated MCID of 150 mL.[31] The 6 min walking distance is valid, reliable and has an estimated MCID of 30 m.[32] This LCADL scale has been shown to be valid and reliable, with an estimated MCID of −3 points.[33,34] The Dyspnea-12 questionnaire validity and reliability has been demonstrated in patients with COPD.[34,35] Its MCID is estimated to be −6 points.[36] The use of a portable dynamometer for the assessment of maximal voluntary contraction of the quadriceps is a reproducible method, the MCID has been estimated at 7.8 Nm.[37–39]

For anchor-based estimation of the minimal important difference, we used the change from baseline variables that correlated with the change in MIP from baseline to the end of the pulmonary rehabilitation program with a significant correlation coefficient of at least 0.3.[22] Then, we used the sensitivity-based and specificity-based approach with receiver operating characteristic (ROC) curves to determine the best cut-off for the change in MIP with the established minimal important difference for the different anchors. The area under the curve is used to quantify the overall ability of the test to distinguish between two results, or its ability to correctly identify the sick patient from the nondiseased patient. This area ranges from 0.5 (test with no discriminatory value) to 1.0 (perfect test). A probability of 0.51 to 0.69 is considered poor, 0.7 to 0.79 acceptable, 0.8 to 0.89 excellent, and 0.9 to 0.99 outstanding.[40] A minimal important difference was estimated if area under the curve is superior to 0.7.[41,42] The cut-off was chosen to maximize the sensitivity and the specificity values at the same time.

Distribution-based methods evaluate the statistical characteristics related to the sample and provide a minimum value below which a change may be due to measurement error rather than a change in clinical status.[43] Distribution-based methods used in this study were[15]:

- The standard deviation (SD) method: $0.5 \times SDT_0$, with: T_0: baseline period.
- Standard error of measurement (SEM): $SDT_0 \times \sqrt{(1 - ICC)}$, with ICC: intraclass correlation

coefficient and T_0: baseline period. The ICC for MIP was previously described in population with COPD to be 0.87.[44]

Results

Seventy-four patients were included in the EMI2 study. However, only data from 73 patients were analyzed. One person was excluded from the analysis for incapacity to follow the program (Figure 1). The characteristics of included patients are reported in Table 2. After the pulmonary rehabilitation program, significant improvements were found for exercise capacity (6MWT), muscle strength (MVQC and MIP), dyspnea (Borg, MDP, mMRC, and LCADL) and quality of life (SGRQ) (Table 3).

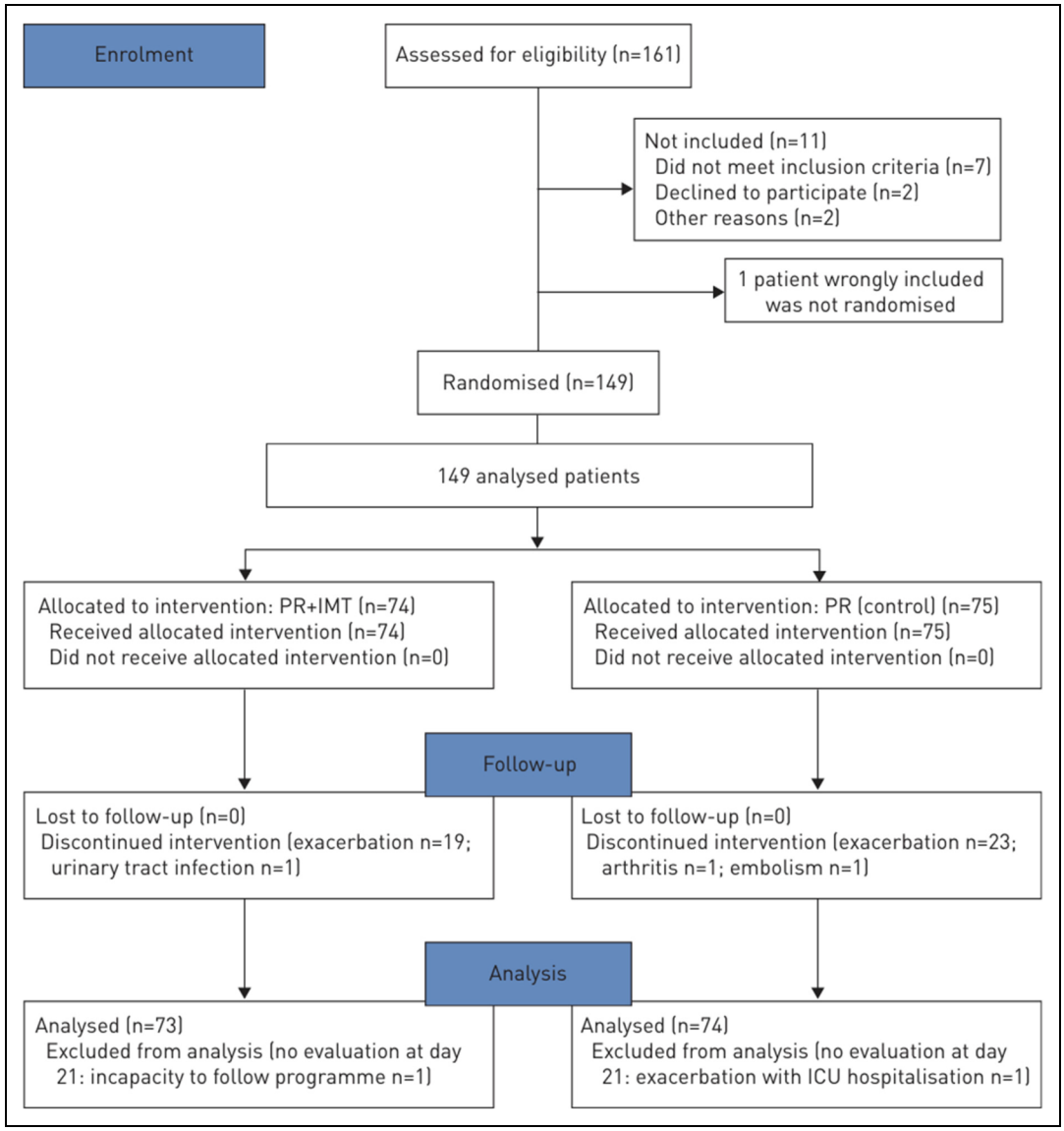

Figure 1. Flowchart.[17]

The correlations between the evolution of different anchors and evolution of MIP were reported in Table 4. Concerning the anchors, only the evolution of the mMRC was significantly correlated with the evolution of MIP during the program ($r = 0.32$, $p = 0.006$) (Figure 2). Using the existing minimal important difference for the mMRC, the ROC area under the curve was 0.71 (Figure 3) and a cut-off value of 13.5 cmH_2O was selected for the minimal important difference estimation, with a sensitivity of 75% and a specificity of 67.5%.

Table 2. Baseline patient characteristics and values of the initial tests.

N	74
Female/male	44/30
Age years	62.2 ± 8.0
BMI $kg{\cdot}m^{-2}$	26.2 ± 5.9
GOLD stage 3	37
GOLD stage 4	37
BODE index	4 (3–5)
FEV_1% pred	36.4 ± 9.5
RV % pred	210.7 ± 58.7
TLC % pred	123.5 ± 21.2
PaO_2 mmHg	67.9 ± 9.1

Data are presented as n, mean ± SD or median (interquartile range). BMI: body mass index; FEV_1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; PaO_2: arterial oxygen tension; % pred: % predicted; RV: residual volume; SD: standard deviation; TLC: total lung capacity.

Using distribution-based approach, the estimations of the minimal important difference were 7.9 and 10.9 cmH_2O. A summary of the minimal important difference estimations using both the anchor-based methods and the distribution-based is presented in Table 5.

Discussion

The aim of this study was to determine a minimal important difference for inspiratory muscle strength assessed by the MIP in people with severe and very severe COPD during a pulmonary rehabilitation program. The estimations proposed by this study ranged from 7.9 to 13.5 cmH_2O.

Regarding the distribution-based methods, the standard deviation and standard error of measurement methods estimate a minimal important difference of 7.9 and 10.9 cmH_2O, respectively. Regarding the anchor-based method, only the mMRC scale could be retained as a relevant anchor. Using this method, we found a minimal important difference of 13.5 cmH_2O. The first method relies solely on the statistical data of the population, and in this study, mainly on the measure of dispersion (standard deviation). Thus, the emphasis on the patient in this method is low. Unlike the distributional method, the anchoring method relies on patient-reported changes and

Table 3. Changes in parameters before and after pulmonary rehabilitation program.

	Baseline (n = 74)	After rehabilitation (n = 73)	Effect size	p-value
Borg (at end of the 6MWT)	5.4 ± 2.2	4.0 ± 2.0	−0.64	<0.001
mMRC dyspnea score	2.3 ± 1.1	1.3 ± 1.1	−0.93	<0.001
MDP (sensory qualities)	11.75 ± 9.6	8.2 ± 7.7	−0.38	0.001
D-12	15.3 ± 8.4	8.3 ± 6.8	−0.77	0.207
SGRQ	53.1 ± 13.9	42.6 ± 14.5	−0.76	<0.001
LCADL	26.5 ± 12.5	19.9 ± 10.8	−0.58	0.002
MIP (cmH_2O)	66.0 ± 21.8	80.8 ± 26.8	0.69	<0.001
IC at rest (L)	2.1 ± 0.6	2.2 ± 0.7	0.16	<0.001
6MWD (m)	387.5 ± 112.2	410.9 ± 117.4	0.21	<0.001
MVQC (Nm)	88.3 ± 41.2	94.2 ± 44.4	0.14	<0.001

Data are presented as n, mean ± SD. 6MWD: 6-min walking distance; D-12: dyspnea 12 questionnaire; IC: inspiratory capacity; LCADL: London Chest Activity of Daily Living scale; MIP: maximal inspiratory pressure; MDP: multidimensional dyspnea profile; mMRC: modified Medical Research Council; MVQC: maximal voluntary quadriceps contraction; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire.

Table 4. Correlations between changes of anchors and changes in maximal inspiratory pressure.

	Correlation coefficient	p-value
Borg	0.13#	0.293
mMRC dyspnea score	**−0.32##**	**0.006***
MDP (sensory qualities)	0.05##	0.653
SGRQ	−0.12#	0.327
IC at rest	0.18#	0.135
6MWD	0.19#	0.105
MVQC	−0.10#	0.473
LCADL	0.12##	0.537
D-12	−0.02#	0.938

#: Pearson test; ##: Spearman test; *$p < 0.05$. Data are presented as n, mean ± SD or median (interquartile range). 6MWD: 6-min walking distance; D-12: Dyspnea 12 questionnaire; IC: inspiratory capacity; LCADL: London Chest Activity of Daily Living scale; MDP: multidimensional dyspnea profile; mMRC: modified Medical Research Council; MVQC: maximal voluntary quadriceps contraction; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire.

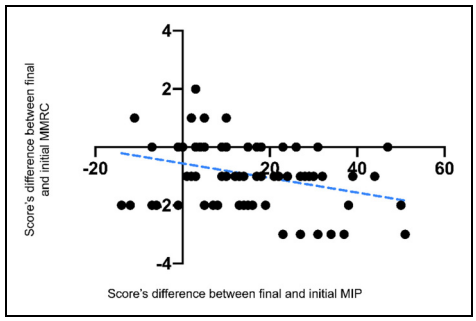

Figure 2. Correlation between changes in maximal inspiratory pressure and changes in the modified Medical Research Council.

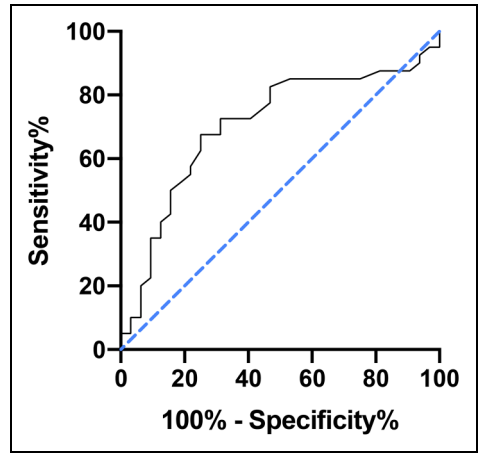

Figure 3. ROC curve to distinguish people with COPD above and below the MID of the mMRC questionnaire for maximal inspiratory pressure. We found an area under the curve of 0.71 (95% CI [0.58–0.83]). The cut-off score is 13.5 cmH_2O with a sensitivity of 75% and a specificity of 67.5%. CI: confidence interval; COPD: chronic obstructive pulmonary disease; MID: minimal important difference; mMRC: modified Medical Research Council; ROC: receiver operating characteristic;

incorporates measures reflecting the magnitude of the change.[15] In this study, we demonstrated a correlation between the change in MIP and the change in the mMRC scale, which assesses the impact of dyspnea in participants' daily lives. This result seems to agree with data found in the literature suggesting a beneficial effect of IMT on dyspnea.[9] As a result of this work, we can propose a minimal important difference of 13.5 cmH_2O for improvement in MIP. However, the estimation of this minimal important difference is based on a weak correlation between change in MIP and change in mMRC ($r = 0.32$).

Finally, in this study, the patients improved their MIP by 14.8 ± 1.8 cmH_2O ($p < 0.001$), so the improvement in inspiratory muscle strength seems to be clinically significant for the patients included in this program. This result is in accordance with systematic reviews which evaluate the effects of IMT in inspiratory muscle strength assessed by MIP measurement.[9,17] However, as stated above, IMT given as an adjunct to a respiratory rehabilitation program has an additional benefit on inspiratory muscle strength and endurance but does not correlate with improvement in dyspnea or maximal exercise capacity. This may be explained by the fact that a pulmonary rehabilitation program includes many components: exercise training, lower limb strengthening, therapeutic education. All these components contribute to the improvement of exercise capacity and the reduction of dyspnea for example.[45] It is well known that

Table 5. Summary of MID estimations.

Methods		MID
Anchor-based method		
ROC curve using change of mMRC score		13.5 cmH_2O
Distribution-based method	Formulas[15]	MID
Standard deviation	$0.5*SD_{T0}$	10.9 cmH_2O
Standard error of measurement	$SD_{T0}*\sqrt{}(1–0.87)$	7.9 cmH_2O

The standard deviation used is: $SD_{T0} = 21.80$ cmH_2O.
MID: minimal important difference; mMRC: modified Medical Research Council; ROC: receiver operating characteristic; SD: standard deviation; T_0: baseline, T_1: after rehabilitation.

exercise training is the cornerstone of pulmonary rehabilitation to improve dyspnea, exercise capacity, quality of life.[46] It is difficult to individualize the effects of each component given the large effects of exercise programs. Some studies did demonstrate that the additional effects of IMT during pulmonary rehabilitation are not significantly important.[17,47,48] This can explain the lack of correlation of changes in inspiratory muscle strength with changes of other outcomes as exercise capacity, and quality of life.

The determination of minimal important difference for the MIP will be needed in other cardiopulmonary pathologies. The effects of IMT have been demonstrated in cardiac and thoraco-abdominal surgery patients[49] and in obese patients.[50,51] In addition, interesting results have been observed in patients with heart failure[52] and bronchiectasis.[53] We could therefore consider estimating a minimal important difference for the measurement of inspiratory muscle strength in these populations.

The identification of minimal important difference in this population is important because some authors showed the benefits of IMT in people with COPD,[9,17] but the impact of improvement of inspiratory muscle strength was not clearly established. In recent years, many studies have focused on IMT.

During the implementation of an IMT, inspiratory muscle strength is assessed by the measure of the MIP performed with a manometer. The measure of the MIP with a manometer has shown good reliability and validity.[54–56] Estimating the minimal important difference adds additional significance to the results and allows us to better quantify and objective the effect we are searching. We distinguish clinical change, which is patient-based, from significant change, which is purely statistical. Consequently, it helps the clinician to judge the relevance of integrating an intervention into his clinical routine. However, this tool is still not widely used, and estimates are still rare in the scientific literature. Obtaining new minimal important difference for the main tests and questionnaires used here in people with severe and very severe COPD would also allow us to refine our estimate.

This study has some limitations: In our study, we did not use a global rating of change, which could be useful as anchor.[15] The use of a more pragmatic tool such as the global rating of change, could help determine a MCID.[57] This scale is designed to quantify the improvement or deterioration of the patient's condition over time.[58] It is a self-report tool that asks the patient to compare their current health status with their status at a previous time. Thus, it permits to obtain patient feelings directly from the interpretation of the tool. Future studies should include this type of tools to confirm and specify the clinical relevance of actual minimal important difference proposals for MIP.

MIP measure is a good tool to assess the improvement of inspiratory muscle strength after pulmonary rehabilitation. We propose a minimal important difference of 13.5 cmH_2O for the

improvement of MIP in people with severe and very severe COPD. However, further studies are required to validate this estimation.

Clinical messages

- MIP is a relevant assessment for inspiratory muscle strength evaluation of people with COPD.
- The existence of a robust minimal important difference is interesting for the design and the interpretation of studies on interventions aiming to enhance inspiratory muscle strength.
- Using the combination of anchor-based and distribution-based methods, this study proposes a minimal important difference of 13.5 cmH_2O for the MIP.

Acknowledgements

The authors would like to acknowledge colleagues from the Pulmonary Rehabilitation Unit of Morlaix who were involved in taking care of the patients and assisting with inclusion.

Authors Contributions

MB and CC were responsible for data acquisition. CC also performed formal data analysis and drafted the manuscript. MB was responsible for the conception and design of the study. All authors critically revised the manuscript, ensured accuracy of the work, approved the final version to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by a grant from the French Health Ministry.

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