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Assessing the Impact of Pulmonary Rehabilitation on Functional Status in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Rationale - The optimal way of assessing the impact of pulmonary rehabilitation on functional status in chronic obstructive pulmonary disease (COPD) is currently unknown. The minimal clinically important difference for the constant workrate cycling exercise also needs to be investigated to facilitate its interpretation.

Objective – Evaluate the changes in the 6-minute walking test and in the constant workrate cycle endurance test immediately following and 1-year after pulmonary rehabilitation, along with the importance of these changes in term of health status in patients with COPD.

Methods - Patients with COPD (age: 65 ± 8 years, mean ± SD; FEV_1: 45 ± 15 % predicted) were recruited from a multicenter prospective cohort study and were evaluated at baseline, immediately after a pulmonary rehabilitation program (n=157) and at 1 year (n=106). The 6-min walking test and the cycle endurance test were performed at each evaluation. Health status was evaluated with the St. Georges Respiratory Questionnaire.

Measurements and Main Results - Following pulmonary rehabilitation, cycle endurance time increased (198 ± 352s, $p<0.0001$) and stayed over baseline values at 1 year ($p<0.0001$). The 6-minute walking distance also showed improvements following rehabilitation (25 ± 52m, $p<0.0001$) but returned to baseline values at the 1 year follow-up. Changes in cycle endurance time were more closely associated with changes in health status than those of the 6-min walking test. A 100-200s improvement in the cycle endurance time was associated with clinically meaningful changes in the St. Georges Respiratory Questionnaire scores.

Conclusions - The cycle endurance test was more responsive that the 6-min walking test to detect improvement in exercise tolerance following pulmonary rehabilitation and was also better correlated with improvements in health status. An improvement in the cycle endurance time ranging from 100-200s appeared to be clinically meaningful.

INTRODUCTION

Exercise intolerance is a foremost complaint in patients with chronic obstructive pulmonary disease (COPD) and is associated with decreased quality of life and survival.[1] Exercise capacity in COPD may be evaluated using walking or cycling exercise protocols. While maximal progressive cycle tests are more widely used[2-4], cycling or walking endurance protocols are gaining popularity and have shown responsiveness to bronchodilatation[5,6] and pulmonary rehabilitation.[7,8] The 6-minute walking test (6-MWT) is also a commonly employed test used to assess functional capacity in COPD[9] although its responsiveness to interventions such as bronchodilatation[10] and pulmonary rehabilitation[11] may not be optimal.

The current literature suggests that the cycle endurance test (CET) is more responsive to detect improvement in functional capacity immediately after pulmonary rehabilitation compared to the 6-MWT.[2,12,13] Despite this notion, the 6-MWT is still largely used to evaluate the effects of pulmonary rehabilitation because of its simplicity and ease of administration.[9] Furthermore, the 6-MWT has demonstrated clinical significance compared to the CET which has yet to show similar importance.

One interesting feature of the 6-MWT also contributing to its popularity is the knowledge of a minimal clinically important difference, a key information when interpreting the results of a given test. Redelmeier and colleagues[14] previously reported that a 54-m [95% CI 37-71m] change in the 6-min distance walked is likely to be perceived by patients. Although a similar evaluation has not been reported for the constant workrate cycling exercise test, Casaburi[15] recently proposed that a minimal improvement of 105s in the endurance time of the CET should be considered as clinically meaningful. This estimate was derived from a study by O'Donnell[16] on the effects of bronchodilatation on constant workrate endurance time and from the fact that an improvement in endurance time greater than half the SD of the change in endurance time has a high likelihood of being clinically important.[17] Whether a similar estimate would be obtained in a study relating the changes in cycling endurance time to those of health status assessment following pulmonary rehabilitation is unclear. This is an important research question; if the endurance time to constant workrate cycling exercise is to become widely utilized, a clinically significant threshold needs to be established for this parameter.

The present study was undertook to test the hypothesis that the CET would be more responsive to rehabilitation than the 6-MWT, immediately following the intervention and after one year of follow-up. We also hypothesized that the changes in the endurance time in the CET seen after rehabilitation would be clinically meaningful as indicated by correlation analyses with the changes in health status. Lastly, we felt that it would be possible to identify a minimal clinically important difference for the changes in the endurance time to constant workrate cycling exercise. To address these issues, we took advantage of a multicenter prospective cohort of patients with COPD entering pulmonary rehabilitation in the province of Quebec, Canada.

METHODS

Subjects and study design

One hundred and sixty-eight patients with moderate to severe COPD were recruited in two centres (Hôpital Laval in Quebec City and Montreal Chest Institute in Montreal**,** Canada). Patients were part of a prospective cohort entering pulmonary rehabilitation initiated in the province of Quebec with the intention of testing a number of hypotheses regarding the responsiveness of the 6-MWT and of the CET to rehabilitation. Inclusion criteria were: clinical diagnosis of COPD for at least 4 weeks, non completely reversible airflow obstruction (post-bronchodilator $FEV_1/FVC < 70\%$), no asthma, heart failure, dementia or unstable psychological conditions. Patients were required to have completed the baseline evaluation (before rehabilitation) and at least one evaluation after rehabilitation (immediately after and/or one year after). Patients' assessment included a complete medical history, pulmonary function tests at rest, CET, 6-MWT and health status as measured by the St. George Respiratory Questionnaire (SGRQ). Patients were included if they had not participated in a pulmonary rehabilitation program in the past 12 months and were in stable state (i.e. no exacerbation of their disease in the preceding month) at study entry.

Rehabilitation program consisted of 6 to 12 weeks of tri-weekly 90-minutes exercise sessions that integrated endurance training (cycling and walking), muscle strengthening exercises and patient education, which has been described in details elsewhere.[18] There was no formal maintenance program after the 6-12 weeks of rehabilitation. The study procedures were standardized by one of the investigator (SB) who monitored the study sites. All patients gave informed consent to participate in the study. Ethics committee from the two study sites approved this research project.

Pulmonary function testing

Spirometry and lung volumes were measured according to recommended procedures.[19] Results were compared with predicted normal values from the European Community for Coal and Steel/European Respiratory Society.[20]

Incremental cycle ergometry

Peak cycling capacity was determined with progressive cycle ergometry with workload increments of 10 watts/minute until exhaustion.[21] Peak work capacity was related to the normal values of Jones et al.[21]

Cycle endurance test (CET)

The CET was performed on an electromagnetically braked cycle ergometer and the workload was set at 80% of peak work capacity achieved during incremental cycle ergometry. Patients were asked to cycle for as long as possible and no encouragement was provided during the tests to avoid any potential confounding effect on exercise performance.[22]

Six-minute walking test (6-MWT)

The 6-MWT was administered in an enclosed corridor in accordance to the procedures recommended by the American Thoracic Society (ATS)[9] except for the course which was 20-meter long and the addition of a practice walk. An elliptical walking course was used at both research centers. Before each test, patients were instructed to cover as much ground as possible in

the allotted time period. Patients were also notified that no encouragement would be provided to them during the test, but that they would be kept aware of time, as per ATS guidelines.[9]

Health status

Health status was evaluated using a formally validated French version of the St-Georges Respiratory Questionnaire (SGRQ).[23] The SGRQ is a disease-specific measure that has been extensively validated in patients with all grades of respiratory disease including advanced COPD.[24] The questionnaire consists of 76 items divided into three domains (symptoms, activity, and impact). Scores range from zero (perfect health) to 100 (worst possible) for each component; a total score which summarizes the responses to all items is obtained. A change in score of 4 units may be considered clinically significant.

Statistical analysis

Results are reported as mean ± SD. A p value < 0.05 was considered as statistically significant. Paired t-tests were used to evaluate the comparative sensitivity of the CET and the 6-MWT to detect improvements induced by pulmonary rehabilitation. Pearson correlations were calculated between baseline SGRQ scores and both the endurance time to CET and distance walked during the 6-MWT, and also between changes in SGRQ scores and changes in endurance time to CET and distance walked during the 6-MWT.

Two approaches were used to define a minimal clinically important difference (MCID) or range for the CET. The first method – the anchor-based approach – related the changes in the endurance time to CET to those of the SGRQ total scores. Changes immediately after rehabilitation and at one year were pooled for this analysis (n=263 observations). The SGRQ is a validated health status instrument[24] for which a negative change ≥ 4 units is clinically important. Cycle endurance time improvements (dependent variable) were plotted with improvements in SGRQ (independent variable) in a linear regression and the 95% CI of endurance time yielding an improvement of at least 4 units in SGRQ was calculated.[25]

The second method – the distribution based approach – to assess the MCID is based on the observations that half the standard deviation of the change in a given variable has a high likelihood of being perceived by the subjects[26]. The MCID range for the CET was categorized in a lower, intermediate and upper boundary.

The validity of the estimated MCID for the CET was separately tested in 52 patients with COPD that were not involved in the original analysis (they were subsequently recruited). These patients fulfilled the inclusion/exclusion criteria of the study and also participated in the prospective cohort. These patients completed baseline and immediately post rehabilitation and/or 1 year follow-up visits after analysis for this study were completed. We calculated the mean difference in the change in endurance time to CET between patient showing a change in SGRQ ≤ -4 (improvement) and patients in whom change in SGRQ >-4 (no improvement or deterioration).

The effect size for each of the different estimates of the MCID of the CET was obtained by dividing the average change in SGRQ total score (post - pre rehabilitation value) by the standard deviation of the baseline value (pre-rehabilitation) for this variable.[27] An effect-size of 0.20 indicates a small change, while effect sizes of 0.50 and 0.80 denote moderate and large changes, respectively.[28] Patients were separated according to their response to the 6-MWT and CET into

those showing no clinically meaningful improvement in both tests, those improving only the 6-MWT, those improving only the CET, and those showing clinically meaningful improvement to the 6-MWT and the CET. Significant clinical improvement was defined as ≥54m for the 6-MWT[14] and 100s for the CET. SGRQ improvements following rehabilitation for the four groups were compared using an ANOVA.

RESULTS

Table 1. Patients characteristics (n=168)

	Mean	Range
Age	65 ± 8	36 - 82
Sex (M/F)	99/69	
Body mass index (kg/m^2)	27.2 ± 5.5	16.2 - 43.6
Pack*years	61 ± 30	2 - 168
FEV_1, L	1.11 ± 0.40	0.43 - 2.52
FEV_1,% predicted	45 ± 15	16 - 83
FVC, L	2.43 ± 0.81	1.02 - 5.94
FVC, % predicted	84 ± 21	27 - 193
FEV_1/FVC	0.43 ± 0.13	0.17 - 0.76
Peak, $\dot{V}O_2$ ml•kg^{-1}•min^{-1}	12.8 ± 4.3	3.4 - 25.6
Peak $\dot{V}O_2$, % predicted	69 ± 47	13 - 447
Peak work capacity, watts	68 ± 30	0 - 190
Peak work capacity, % predicted	64 ± 37	0 - 298
SGRQ Symptoms	52.4 ± 22.0	6.0 - 100
SGRQ Activity	65.1 ± 18.7	5.6 - 100
SGRQ Impact	33.1 ± 17.2	0 - 76.4
SGRQ Total	46.0 ± 15.8	12.7 - 83.2

Values are mean ± SD. Definition of abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; $\dot{V}O_2$: maximum oxygen consumption; SGRQ: St. Georges Respiratory Questionnaire

Patient characteristics

Of the 168 patients who fulfilled the inclusion criteria, 157 (93%) completed the baseline and post-rehabilitation evaluation, and 106 (63%) completed the baseline and 1-year follow-up. Of the 157 patients who completed baseline and post rehabilitation evaluations, 62 were not evaluated at 1 year because of death (n=2), dropping-out (n=12), one of the three tests needed for this study was missing (n=34) or had not yet completed the 1-year evaluation (n=14). Eleven patients could not be evaluated immediately after rehabilitation (because of a COPD exacerbation or impossibility to schedule the visit) and were evaluated only at the 1-year follow-up. The characteristics of the study group are shown in Table 1. Patients had on average moderate to severe airflow obstruction and markedly limited exercise capacity.

Changes in exercise capacity and health status following pulmonary rehabilitation

Improvements in CET, 6-MWT and SGRQ immediately following the rehabilitation program and at 1-year follow-up are reported in table 2 and figure 1. The mean improvement for the 6-MWT was smaller than the reported MCID for this parameter (54m, 95% CI 37-71). Immediately after rehabilitation, 43 (27%) subjects had a clinically significant improvement of their walking distance (> 54m).

Table 2. Cycle endurance time, 6 minute walking distance and St-Georges respiratory questionnaire improvements following pulmonary rehabilitation

	Post rehabilitation changes	
	Immediate n = 157	1 year n = 106
Δ CET, s	198 ± 352†	137 ± 335*
Δ 6-MWT, m	25 ± 52†	-5 ± 58
Δ SGRQ symptoms	-6.1 ± 17.1†	-6.3 ± 22.5‡
Δ SGRQ activity	-5.9 ± 13.2†	-2.9 ± 15.6
Δ SGRQ impact	-7.4 ± 12.7†	-6.0 ± 14.5†
Δ SGRQ total	-6.9 ± 10.1†	-5.1 ± 12.0†

Values are mean ± SD. Definition of abbreviations: CET: cycle endurance test; 6-MWT: 6 minute walking test; SGRQ: St. Georges Respiratory Questionnaire. A change of -4 or less on the SGRQ is considered clinically significant.
† $p<0.0001$; * $p<0.05$; ‡ $p<0.005$

There was a statistically and clinically (≥ 4 units) significant improvement in all domains of the SGRQ immediately after completing the rehabilitation program and at one year except for the activity domain (table 2).

The correlations between baseline exercise values and SGRQ scores are shown in table 3 while table 4 provides the correlations between the changes in measures of exercise capacity and those in health status.

Table. 3 Correlation coefficients between baseline exercise tests and SGRQ scores

	CET time	6-MWT	SGRQ sym	SGRQ act	SGRQ imp	SGRQ tot
CET time	x	0.19*	-0.08	-0.21*	-0.15	-0.18*
6-MWT	-	x	0.05	-0.41†	-0.26‡	-0.28‖

Definition of abbreviations: CET: Constant-workrate Cycle Endurance Test; 6-MWT: 6 Minute Walking Test, SGRQ: St. Georges Respiratory Questionnaire.
* $p<0.05$; † $p<0.0001$; ‡ $p<0.005$; ‖ $p<0.0005$

Baseline SGRQ scores correlated with the CET and 6-MWT (table 3) while the changes in SGRQ scores and in the 6-MWT did not correlate (table 4). In contrasts, the changes in endurance time to CET correlated moderately with changes in SRGQ scores (table 4).

Table. 4 Correlation coefficient between pre and post rehabilitation changes (Δ) in exercise tests and SGRQ scores

	Δ CET time	Δ 6-MWT	Δ SGRQ symptoms	Δ SGRQ activity	Δ SGRQ impact	Δ SGRQ total
Δ CET time	x	0.05	-0.10	-0.23§	-0.28‖	-0.31†
Δ 6-MWT	-	x	-0.01	0.04	-0.15	-0.09

Definition of abbreviations: CET: Constant-workrate Cycle Endurance Test; 6-MWT: 6 Minute Walking Test, SGRQ: St. Georges Respiratory Questionnaire.
§ $p<0.001$; ‖ $p<0.0005$; † $p<0.0001$

Minimally clinically important difference (MCID)
A linear regression analysis was performed between changes in SGRQ total scores and endurance time to CET for the pooled changes immediately after rehabilitation and at 1 year follow-up

(n=263). The slope of this relationship was -9.21s [95% CI -12.9:-5.6s] and the intercept of 116.4s [95% CI 70.8:162.1s] illustrating that for an individual to show a clinically meaningful improvement in the SGRQ (at least 4 units), a variation of 153s [95% CI 93-213s] in endurance time to CET was necessary. A similar analysis could not be performed for the 6-MWT since changes in 6-MWT were not significantly correlated with changes in SGRQ scores. A 170s change in endurance time to CET was estimated to represent the clinically significant threshold based on the half standard deviation approach. Among the 52 patients in whom this MCID estimate for CET was subsequently tested, 29 completed baseline and post rehabilitation evaluations and 39 completed the baseline and 1 year follow-up evaluations (a total of 68 pairs of data). Mean age (67 ± 8 years) and FEV_1 (1.01 ± 0.28 l; 45 ± 16 % predicted) were similar to those of the 168 patients involved in the initial analysis. The mean difference in CET between patients showing a change in the SGRQ ≤ -4 (improvement) and those in whom the change in SGRQ was >-4 (no improvement or deterioration) was 178s ($p<0.05$), consistent with our MCID estimate for this parameter.

Table 5 reports the mean changes in CET and SGRQ total scores obtained in patients reaching the lower (100s), intermediate (150s) and upper (200s) boundaries of the clinically significant range for the CET. The corresponding effect-size for the improvement in the SGRQ is also provided.

Table 5. Functional and health status correlates of different threshold for the change in CET

Clinically meaningful range for the CET	n	Δ CET (s)	Δ SGRQ total	Effect Size for SGRQ
Lower boundary >100s	117	482 ± 292	-9.4 ± 10.0	0.59
Intermediate boundary >150s	103	527 ± 278	-9.8 ± 10.3	0.62
Upper boundary >200s	88	598 ± 251	-10.1 ± 10.3	0.63

Definition of abbreviations: CET: Constant-workrate Cycle Endurance Test; SGRQ: St. Georges Respiratory Questionnaire.

Clinical significance of change in measures of exercise capacity

Using an 100s improvement in the CET and a 54m improvement for the 6-MWT[14] as the respective clinically significant threshold for these two measures of exercise capacity, subjects

were separated into responders and non-responders for each exercise test, thus resulting in 4 categories of patients (figure 2). Immediately following the rehabilitation program, approximately a third of the patients did not show any clinically meaningful improvement to either test after rehabilitation. Despite this, these individuals had, on average, a 4.3-unit improvement in the SGRQ total score. More than twice as many patients showed a clinically meaningful improvement in the CET without improving the 6-MWT (n = 50) as compared to patients not improving the CET despite a clinically meaningful improvement in the 6-MWT (n = 21). Patients exhibiting a sole increase in the 6-MWT showed a 6.6-unit improvement in the SGRQ total score. Patients improving CET only or CET and the 6-MWT had a large (8.9 units) average gain in the SGRQ score. When using the lower boundary for the MCID of the 6-MWT (37m)[14], 44 patients improved solely on the CET and 29 on the 6-MWT only, corresponding to improvements on the SGRQ total score of -9.7±10.3 and -6.0±10.4 respectively. Thus the conclusions from figure 2 remain whether the mean value or the lower boundary of the 95% CI of the MCID for the 6-MWT was used in the analysis. The progressively greater improvement in SGRQ total score when going from no improvement in measures of exercise capacity to clinically meaningful changes in both exercise tests was statistically significant ($p < 0.001$). The proportion of patients showing an improvement in SGRQ total score ≥ 4 units in the subgroup showing no improvement in both exercise tests, improving only on the 6-MWT, improving only on the CET, and for the subgroup improving on both tests was 53%, 67% 68% and 91%, respectively ($p < 0.05$).

DISCUSSION

The objectives of this study were to compare the responsiveness of the 6-MWT and of the CET to detect changes following pulmonary rehabilitation and to identify a clinically significant threshold for the CET in patients with COPD. Our results can be summarized as follow: *i)* the CET is more sensitive to the acute and long-term effects of pulmonary rehabilitation than the 6-MWT; *ii)* the improvements in CET correlated with gains in health status, while the changes in 6-MWT did not; *iii)* a 100-200s change in the CET was associated with clinically significant improvements in health status as assessed by the SGRQ.

Few studies have compared the effects of pulmonary rehabilitation on the 6-MWT and the CET, but available reports[2,13,29] accounted much larger improvements in cycle endurance than 6-MWT. Taken together, these studies and ours clearly indicate that the 6-MWT is not the best tool to evaluate the efficacy of pulmonary rehabilitation. Having confirmed a greater responsiveness of the CET over the 6-MWT, one may wonder about the clinical significance of improving solely the CET when no changes in the 6-MWT are observed. The present study supports the idea that the modifications in the CET are clinically relevant since they are associated with improvement in health status (table 5 and figure 2) even in the absence of a significant change in the 6-MWT. These findings have practical implications in evaluating the overall response to pulmonary rehabilitation.

An emerging discussion in pulmonary rehabilitation concerns the observation that a portion of patients with COPD does not seem to respond to this intervention.[30] The present results underscore the difficulty in addressing the important issue of response versus non-response to pulmonary rehabilitation. For instance, relying solely on the 6-MWT to assess the response to pulmonary rehabilitation will lead to a gross underestimation of the response rate. We would therefore suggest that the response to rehabilitation should not be defined based on only one parameter, but rather on a combination of factors that should include a constant-workrate exercise protocol.

The absence of correlation between changes in 6-MWT and changes in SGRQ total scores found in the present study are consistent with previous report.[31] In contrast, the baseline values of the 6-MWT and of the SGRQ total scores were significantly correlated. These results are consistent with the current knowledge about the 6-MWT. The distance walked during a 6-min period is statistically associated with health status[32] and is a good predictor of mortality[33], indicating adequate discriminative properties of the test. On the other hand, the responsiveness of the 6-MWT, a self-paced walking test, is smaller than that of externally-paced walking or cycling protocols[10,34], indicating suboptimal evaluating properties. It is becoming clear in the field of COPD that the clinical use of the 6-MWT should be to assess disease severity (discriminative properties) and prognostic (predictive properties) but not to evaluate response to treatment.

The exploration of the mechanisms explaining the differences in responsiveness to rehabilitation between the 6-MWT and the CET was beyond the scope of the present study. The 6-MWT is a self-paced test (i.e. patients determine their own walking speed) with a fixed duration. Patient may learn to self-pace in pulmonary rehabilitation which could also influence responsiveness. In contrast, the CET is an externally-paced test (i.e. workload is dictated to patients) with an indefinite duration. Accordingly, improvements in performance are achieved differently for the

two tests. Patients have to increase walking speed to cover more distance on the 6-MWT, while they have to increase endurance time to achieve the same outcome on the CET.

In a previous study evaluating the responsiveness of the 6-MWT to acute bronchodilation[10], cardiorespiratory kinetics and walking speeds were remarkably similar during two 6-MWT performed on separate days indicating that patients reproduce the same walking pattern during repeated six-minute walking. In the present study, the improvement in the 6-MWT was small but consistent with the magnitude of improvement usually seen after rehabilitation[35] suggesting that changing walking speed is a difficult goal to achieve in this setting. In contrast, patients were more likely to increase their cycling endurance time after rehabilitation. These findings indicate that it is easier to increase endurance time than to modify walking pattern, thereby suggesting that the tests' different designs had an impact on their respective response to bronchodilation.

The changes in endurance time to CET are currently difficult to interpret given the lack of data relating the changes in this parameter with patient-centered outcomes such as health status. There is no convention as to which method is preferable to compute a MCID value. However, some authors[36] have suggested that the use of only one method is likely to result in imprecision and that combining statistical estimates with clinically based anchors is recommended. Combining the anchor and distribution-based approaches as well as on other's data[15], we found that a 100-200s improvement in CET is clinically relevant. In 52 additional patients not involved in the original analysis, the mean difference in endurance time to CET between patients who improved SGRQ and those who didn't was 178s, a value comprised within the confidence interval of our estimate. Based on the findings that a 100s improvement in CET (the lower estimate of the clinically relevant zone) was associated with large gains in health status, we propose that an intervention associated with such an improvement in CET should be viewed as clinically relevant.

Study limitations

We used the anchor-based approach in correlating the changes in the endurance time to CET to those of the SGRQ total scores as an attempt to estimate the minimal important difference for the CET. The precision of this estimate is obviously dependant on the tightness of the correlation between the target instrument (CET) and the anchor (SGRQ).[37] In the present study, this correlation was modest ($r = -0.31$), but in the expected range for a correlation between physiological and health status measurements. Because of the imprecision inherent to this method of assessing the minimal clinically significant difference, we felt that it was more appropriate to report a range (100-200 seconds) of clinically meaningful improvements based on the 95% CI of the regression analysis between the changes in the CET and in the SGRQ than reporting only a discrete threshold. This information should help interpreting the results of clinical trials reporting the effects of interventions aimed at improving functional status as assessed by the endurance time to CET. Another potential limitation of the present study is that we cannot be absolutely certain whether our estimation of the minimal clinically important difference for the CET would also apply to pharmacological interventions since all measurements were obtained during rehabilitation. It is however reassuring that, using data collected during a pharmacological trial, it was estimated that the minimal clinically important difference for the CET was 105s, an improvement falling into the range proposed in the present study.

CONCLUSION

In summary, the present study provides clinically useful information about the assessment of the impact of pulmonary rehabilitation in patients with COPD. We first confirmed the greater responsiveness of the CET over the 6-MWT. More importantly, in a significant proportion of patients with COPD, improvements in the CET were seen without changes in the 6-MWT. This finding was clinically relevant, as suggested by the clear association with changes in health status. Lastly, a 100s (range 100-200s) gain in CET is proposed as a clinically meaningful difference for this exercise test.

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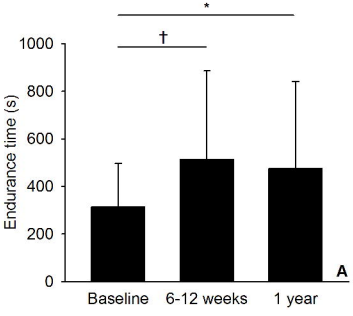
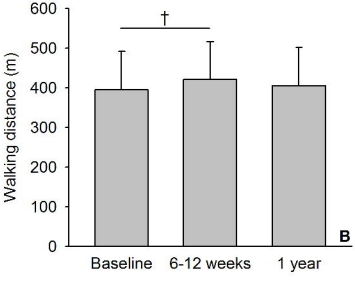
Figure 1. Improvements in endurance time and walking distance after pulmonary rehabilitation. Panel A: Improvements in cycle endurance test (CET, s). Panel B: Improvements in the distance walked during the 6-minute walking test (6-MWT, m). Panel C: Improvements in CET and 6-MWT after rehabilitation (n=157) and at one year (n=106) in % baseline values. Values are mean ± SD. * p<0.05; † p<0.0001





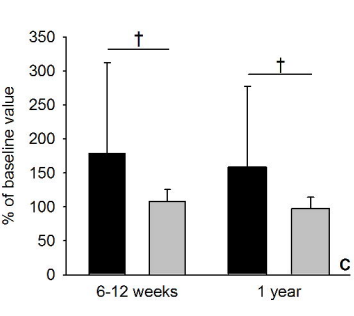


Figure 2. Changes in St. Georges Respiratory Questionnaire (SGRQ) immediately after rehabilitation according to the presence (↑) or absence (↔) of a clinically meaningful improvement in the 6-minute walking test (6-MWT, > 54 m) and cycle endurance test (CET, > 100 s). Dashed line represents the clinical meaningful change for the SGRQ. Values are mean ± SD.