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# Time-Course of Changes in Multidimensional Fatigue and Functional Exercise Capacity and Their Associations during a Short Inpatient Pulmonary Rehabilitation Program

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**ABSTRACT**

This study aimed to assess the time-course of changes in multidimensional fatigue and functional exercise capacity and their associations during an inpatient pulmonary rehabilitation (PR) program. Seventy COPD patients from three centres were enrolled for a four-week PR program and were evaluated before (T0) and at the end of each week (T1, T2, T3, and T4). Weekly change in multidimensional fatigue was assessed by the multidimensional inventory questionnaire (MFI-20) and functional exercise capacity by the 6-minute walking distance (6MWD). Reaction time (RT) and heart rate variability (HRV) were also assessed as complementary markers of fatigue. HRV did not change during the study (all $p > 0.05$). MFI-20 score and RT decreased during the first part of the program ($p < 0.001$) and levelled off at T2 (all $p > 0.05$ compared with each preceding time). While 6MWD improved by almost 70% during the first part of the PR, it continued to increase, albeit at a greatly reduced pace, between T2 and T4 ($p < 0.05$). In parallel, a negative association was found between MFI-20 score and 6MWD at each evaluation time (r ranged from 0.43 to 0.71), with a significantly stronger T3 correlation compared with the other time periods (all $p < 0.05$). The strengthening of the association between fatigue and functional exercise capacity at T3, which occurred concomitantly with the slowdown of functional exercise capacity improvement, is consistent with a role for fatigue in the limitation of performance changes during PR. The limitation of fatigue during PR is thus an interesting aspect to improve the magnitude of performance changes.

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Respiratory tract diseases; chronic obstructive pulmonary disease; fatigue; exercise tolerance; rehabilitation outcome

## Introduction

Pulmonary rehabilitation (PR) is one of the most efficient therapies for chronic obstructive pulmonary disease (COPD), resulting in improvement in daily symptoms, exercise capacity, health status, and survival, as well as reduction in hospitalisation rates [1–3]. PR is defined as a comprehensive intervention, based on a thorough patient assessment. The contents are tailored to patients and mainly include exercise training, education, and behavioural change techniques [4].

Improvement of functional exercise capacity is one of the main objectives of pulmonary rehabilitation in patients with COPD. Indeed, functional exercise capacity is a strong predictor of health status in these patients, and more generally, of survival [5–7]. A 30-meter decrease in the 6-minute walking distance (6MWD) doubles the risk of death in the subsequent 12 months [5]. In addition, 92% of patients with a 6MWD less than 100 metres die within a year [6]. Conversely, improvement in the 6MWD after PR is associated with better survival at 5 to 12 years of follow-up [3,8]. However, this improvement is not systematic, since almost one-third of patients do not improve their performance after a PR program [9–11]. Furthermore, in those for whom it improves, the progression of the 6MWD levels off in 75% of cases, with no further improvement beyond 24 sessions [12]. Such a logarithmic progression of performance has also been reported in several other studies after approximately 20 sessions of PR [13–15]. This phenomenon appears to be a specific COPD maladaptation, as in healthy controls, the 6MWD continues to rise linearly until the end of the PR [14]. Altogether, these results suggest that the efficacy of the current PR programs is suboptimal.

The fitness-fatigue model, derived from the conceptual framework of physical training, could be a relevant candidate to explain such a levelling off in performance during PR in COPD. This model, which has been developed for

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decades, introduces athletic performance as the result of two competing responses: a positive one – the fitness after-effect – and a negative one – the fatigue after-effect [16]. Training at an optimal workload is thus paramount to avoid excessive fatigue, which would mitigate the amplitude of adaptions. And yet, with baseline levels of physical activity that are often low [17], most COPD patients progress from little or no physical activity to several hours of exercise training per week when enrolled in a PR program. In light of the fitness-fatigue model applied to COPD, this abrupt resumption of exercise could induce substantial fatigue that could limit the effects of exercise training. This hypothesis is also consistent with previous studies reporting a correlation between baseline fatigue levels and functional exercise capacity [18] and a negative association between changes in fatigue and in functional exercise capacity after PR in COPD [19]. However, the interaction between time course of changes in fatigue and performance during PR has not been considered to date. In addition, the change in fatigue all along a PR program has been poorly described. First, and as for other PR outcomes, fatigue evolution after PR exhibit heterogeneous individual responses [19,20]. Furthermore, in all studies to date, fatigue was only assessed before and after the PR program, while potential fluctuations during the program have not been studied [2,19,20]. Another important limitation is that the majority of the previous studies only performed unidimensional assessments of fatigue [2]. Given the multidimensional and multifactorial characteristics of fatigue, its overall assessment cannot be achieved with a single test [21]. A better evaluation of fatigue change during PR, through the use of multidimensional questionnaires and complementary indicators such as heart rate variability and visuomotor reaction time [21,22], is needed.

The objectives of this study were (i) to assess the weekly changes in multidimensional fatigue markers and functional exercise capacity, and (ii) to study their associations over the course of a PR program. Given the absence of increased performance beyond 20 sessions of exercise training in COPD patients and the potential interaction between fatigue and performance, we hypothesised that there would be an increase in fatigue between the 1st and the 20th sessions of exercise training, during a short inpatient PR program of 40 sessions lasting four weeks.

## Methods

### Participants

This prospective observational study was conducted at three pulmonary rehabilitation centres (Clinique du Souffle la Solane, Osseja, France; Clinique du Souffle les Clarines, Riom-ès-Montagnes, France, and Clinique du Souffle La Vallonie, Lodeve, France) between July 2019 and March 2021, with an interruption of five months between March 2020 and July 2020 due to the COVID-19 pandemic (French lockdown and restrictions in PR centres). Patients were invited to participate at the beginning of the four-week inpatient PR program if they: (1) had a diagnosis of COPD confirmed by a forced expiratory volume in one second ($FEV_1$)/forced vital capacity (FVC) ratio < 0.70 after bronchodilator intake, (2) were between 40 and 80 years of age, and (3) had healthcare cover. They were not eligible to participate if they had an exacerbation in the past four weeks, recent PR program participation (<1 year prior to inclusion), a cardiac device, any unstable cardiac condition (e.g. atrial fibrillation or arrhythmias), or neuromuscular or orthopaedic diseases affecting gait. Cardiac integrity was checked by an electrocardiogram at rest and during a symptom-limited exercise tolerance test on a cycle ergometer. During the entire PR program, the patients were asked to keep taking their usual medication.

All included patients signed a written consent form prior to joining the study. The procedures were approved by an independent French ethics committee (CPP IDF7 Ile-de-France, reference number: 2019-A00582-55) and complied with the principles of the Declaration of Helsinki for human experimentation. The protocol was registered on clinicaltrials.gov (Clinical Trial registration number: NCT04279730).

### Pulmonary rehabilitation program

The four-week inpatient PR program was performed 3 h/day for 5 days/week. In accordance with the official ATS/ERS statement [4], the multidisciplinary PR consisted of: (i) exercise training (10 sessions of 45 min per week, 30 h in total, including endurance training on a cycle ergometer, treadmill, and ground-based walking; resistance training for upper and lower trunk and respiratory muscles; balance training; coordination training and flexibility), (ii) relaxation therapy (8 h in total), (iii) breathing therapy (8 h in total), and (iv) group and individual education sessions (15 h in total, mainly including symptoms management, nutrition counselling, psychological support, and smoking cessation support).

### Study design

Patients received a standard comprehensive assessment (clinical evaluation, body composition, respiratory function, cardiopulmonary exercise testing, and blood gas analysis) before and after the PR program. In addition, prior to the program (T0) and at the end of each week (T1, T2, T3, and T4), they were evaluated for functional exercise capacity, multidimensional fatigue, heart rate variability (HRV), and visuomotor reaction time (RT). The five weekly evaluations (T0, T1, T2, T3, and T4) were performed in the morning (between 9:00 a.m. and 12:00 p.m.) by the same clinician. Patients were asked to abstain from physical activity, smoking, and the consumption of alcohol or any beverages containing stimulants in the six hours prior to the experimental session.

### Experimental procedures

#### Functional exercise capacity

Functional exercise capacity was assessed through a 6-minute walking test. The 6-minute walking tests were performed in accordance with good clinical practices and the official

ATS/ERS statement of the American Thoracic and European Respiratory Societies [4]. At T0, two 6-minute walking tests were performed for each patient, separated by a 30-minute interval. Patients were instructed to walk as far as possible in 6 min, in a 30-meter hallway. The total distance (6MWD) covered in 6 min was recorded. For T0, only the second test was retained for the analysis.

### *Multidimensional fatigue*

Perceived fatigue was evaluated using the French version of the Multidimensional Fatigue Inventory (MFI-20) questionnaire [23,24]. This is a 20-item self-report questionnaire designed to measure fatigue and covers the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, and Reduced Activity. Each dimension comprises four questions, and each of these questions is rated from 1 to 5. The highest scores correspond to the highest levels of fatigue. Subscores were calculated for each dimension (MFI-20gen, MFI-20phy, MFI-20men, MFI-20motiv, and MFI-20act) by calculating the sum of the four questions, and a total fatigue score (MFI-20tot) was calculated by calculating the sum of all the dimensions.

### *Heart rate variability (HRV)*

The HRV (i.e. R-R intervals) was recorded in a quiet room at rest and in supine position by a portable heart rate monitor, Polar V800, and with a Polar H10 chest strap (Kempele, OY, Finland). The polar V800 system consists of a watch worn on the left wrist that is connected by Bluetooth to an electrode belt fitted on the chest that records R-R intervals at a sampling frequency of 1000 Hz. Before the start of R-R interval recording, the patient's skin was cleaned and prepared to be fitted with the polar V800 electrode belt. The belt was then moistened and tightly but comfortably adjusted just below the chest muscles in accordance with the instructions for use of the device. The HRV recording lasted 10 min. Only the last five minutes were considered for analysis to ensure that only data from a stable state were taken into account. The raw R-R intervals were exported from the Polar FlowSync (Polar Electro™, OY, Kempele, Finland) as a space-delimited .txt file. Processing and artefact corrections in the recorded R-R intervals were carried out using the RHRV package of R software [25]. First, R-R interval series were visually inspected to detect a stable window for analysis of at least 400 R-R intervals, with few artefacts.

Putative artefacts were identified from the selected windows and removed if they were not 95% similar to the 10 previous ones and the 10 following ones. In cases where several artefacts were grouped together and not automatically detected, but visually identified, they were removed manually *via* the RHRV package. After artefact correction, a series of 300 R-R intervals was retained for each participant [26]. The RR interval series were then analysed in the temporal and frequency domains as previously described [26]. The following parameters were calculated: the standard deviation of normal-to-normal intervals (SDNN), the root mean square of the R-R intervals (RMSSD), the power spectral component at low and high frequencies (LF and HF, respectively) expressed in absolute values ($ms^2$) and in normalised units (% of total power), and the LF/HF ratio. HRV variability (SDNN and RMSSD) generally decreases with fatigue and overtraining, as well as HF, while LF and the LF/HF ratio increase [22,27–29].

### *Visuomotor reaction time (RT)*

The RT was assessed according to the process previously described by Volker et al. [21] using the free software PsyToolKit (Glasgow University, Glasgow, United Kingdom) [30,31]. The participants were seated comfortably and faced a computer screen and a keyboard in a quiet room. The task consisted of pressing the space bar on the keyboard as quickly as possible whenever a black cross appeared within a white square on the computer screen. Each evaluation session started with a short training session comprising five stimuli. The main task was then started, with a total of 15 stimuli that were presented at random time intervals varying from 2500 to 3500 ms. The average RT was calculated after removal of any aberrant responses (RT < 150 ms or > 1000 ms). The RT is known to increase with the occurrence of fatigue [32].

## *Statistical analyses*

All statistical analyses were performed using Statistica software (StatSoft, Inc., version 6.0, Tulsa, OK, USA), unless specified otherwise.

The changes in functional exercise capacity, multidimensional fatigue, HRV, and RT during the PR program were assessed using one-way analyses of variance (ANOVA) for repeated measures. The underlying assumptions of ANOVA were checked using Skewness-Kurtosis coefficients (normality of distribution) and the Mauchly test (sphericity of variance). In case of violation of the assumptions, non-parametric Friedman tests were used. When the analyses revealed a significant difference between the five times, Tukey post hoc analyses were conducted (or the Wilcoxon test with Bonferroni corrections in case of non-parametric data).

The associations between the 6MWD and the different fatigue indicators (MFI-20 total score, mean RT, and HRV variables) at each time point were assessed with Pearson's test. In case of any significant correlation between the 6MWD and a given fatigue indicator at one or several PR times, the correlation coefficients were compared with a two-tailed test of non-overlapping variables and dependent groups using Zou's confidence interval, as implemented in the "cocor" library available for R [33,34].

The data are reported as means and the standard deviation in case of a normal distribution, or otherwise by the median [lower quartile (LQ) - upper quartile (UQ)].

## Results

### *Patient characteristics*

Of the 2122 patients expected to participate in PR and assessed for eligibility during the period of inclusion, 96 met the inclusion criteria and agreed to participate. The final sample included 70 patients (Figure 1). Twenty-six patients were excluded after inclusion due to several reasons: COPD diagnosis invalidated during the comprehensive assessment ($n = 12$), early exit due to COVID-19 epidemic (lockdown) ($n = 5$), upon patient request ($n = 5$), degradation of health status incompatible with continuation of the protocol or exacerbation ($n = 3$), and a fall ($n = 1$). The baseline characteristics of the participants are presented in Table 1.

### Change in functional exercise capacity during the PR program

The 6MWD improved significantly during the PR ($F_{4.252}$ = 24.720, $p < 0.001$; Figure 2A). Post hoc tests indicated a significant increase between T0 and T1 (459.8 ± 93.5 vs. 473.4 ± 103.2, $p = 0.02$) and between T1 and T2 (473.4 ± 103.2 vs. 486.9 ± 101.5, $p = 0.02$). Although T2 and T3 (486.9 ± 101.5 vs. 491.8 ± 101.4 $p = 0.82$) and T3 and T4 (491.8 ± 101.4 vs. 499.7 ± 101.8, $p = 0.39$) were not different, the 6MWD continued to increase between T2 and T4 (486.9 ± 101.5 vs. 499.7 ± 101.8, $p = 0.04$).

### Change in fatigue markers during the PR program

Multidimensional fatigue as assessed by the $MFI\text{-}20_{tot}$ decreased significantly during the PR ($Fr_{70.4}$ = 70.5, $p < 0.001$; Figure 2B). Multiple comparison through Wilcoxon tests with Bonferroni corrections at $p = 0.01$ showed that the MFI-20tot decreased significantly between T0 and T1 (59.6 ± 12.4 vs. 52 ± 11.7, $p < 0.001$) and between T1 and T2 (52 ± 11.7 vs. 48.10 ± 13.28, $p < 0.01$). Then, it remained unchanged between T2 and T3 and between T3 and T4 (T2 vs. T3: 48.10 ± 13.28 vs. 49 ± 11.5, $p = 0.50$ and T3 vs. T4: 49 ± 11.5 vs. 47.5 ± 12.4, $p = 0.02$).

All five MFI-20 subscores ($MFI\text{-}20_{gen}$, $MFI\text{-}20_{motiv}$,$MFI\text{-}20_{act}$, $MFI\text{-}20_{phy}$, and $MFI\text{-}20_{men}$) decreased significantly during the PR (F ranged from 5.5 to 32.4, all $p < 0.001$). The data from the five MFI-20 subscores and the post hoc results are presented in detail in Table 2. The temporal parameters of the HRV were not significantly modified by the PR program ($F_{4.136}$ = 0.8, $p = 0.52$ for the SDNN and $F_{4.136}$ = 1.5, $p = 0.2$ for the RMSSD). The spectral parameters of the HRV also did not change during the PR ($F_{4.128}$ = 1.2, $p = 0.32$ for LF power, $F_{4.128}$ = 0.71, $p = 0.59$ for HF power, and $F_{4.128}$ = 0.41, $p = 0.63$ for LF/HF).

The RT decreased significantly during the PR ($F_{4.264}$ = 4.68, $p = 0.001$). Post hoc analyses revealed a significant decrease for T1 compared with T0 ($p = 0.003$), with no further decrease after T1 (all $p > 0.99$).

The changes in the spectral and temporal HRV data and the RT are presented in detail in Table 2.

### Associations between functional exercise capacity and fatigue markers during the PR program

The 6MWD was inversely related to the $MFI\text{-}20_{tot}$ at each T0, T1, T2, T3, and T4 evaluation time (r ranged from −0.43 to −0.71, all $p < 0.01$). The comparison of correlation coefficients according to Zou's confidence interval method showed that the T3 correlation coefficient was significantly higher than all the other ones (all $p < 0.05$, Figure 3).

The 6MWD was also inversely related with RT at T3 ($r = -0.28$, $p = 0.03$). Comparison of the correlation coefficients showed that the T3 correlation coefficient was significantly different ($p < 0.05$) from T2 ($r = 0.043$, $p = 0.74$), but not from T0 ($r = -0.11$, $p = 0.41$), T1 ($r = -0.08$, $p = 0.51$), and T4 ($r = -0.13$, $p = 0.31$).

Regarding the HRV data, significant associations were only found between the 6MWD and LF power at T0 ($r = 0.38$, $p = 0.03$), T1 ($r = 0.37$, $p = 0.04$), and T2 ($r = 0.39$, $p = 0.03$). The correlation coefficients from these associations

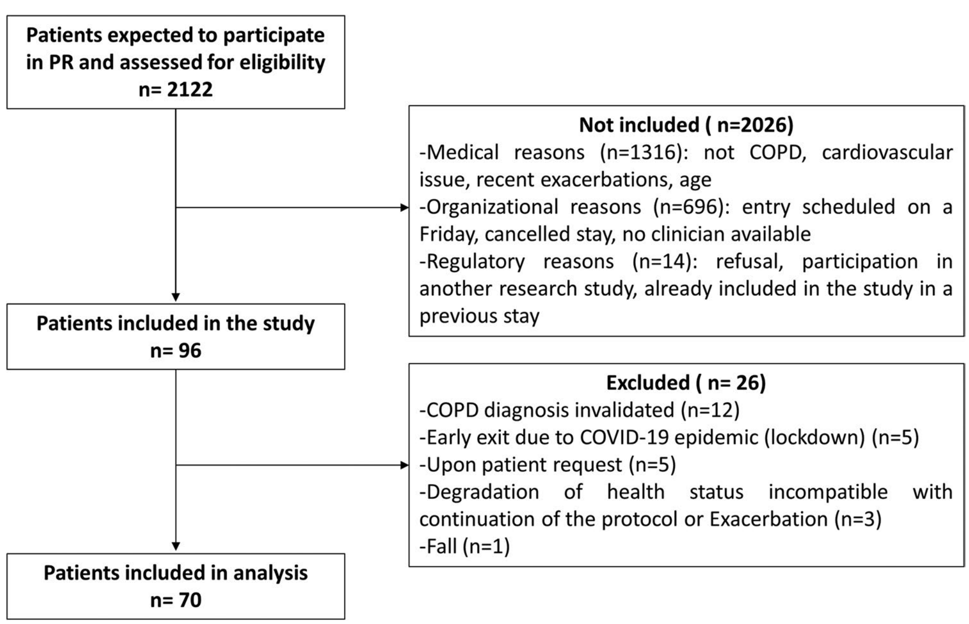


**Figure 1.** Flowchart of the study.

**Table 1.** Descriptive characteristics of the sample.

| Variables | Mean/median | Standard deviation/ [LQ-UQ] |
|---|---|---|
| Demographic and anthropometric | | |
| Age (years) | 64.8 | 7.3 |
| Sex (M/F) | 37/33 (52.9%/47.1%) | – |
| Weight (kg) | 74.4 | [65.8–91.0] |
| Height (cm) | 165.5 | [163.0–173.0] |
| BMI | 27.8 | 6.09 |
| Pulmonary function | | |
| $FEV_1$ (litre) | 1.26 | [0.95–1.69] |
| $FEV_1$ (% predicted) | 51 | [36–70] |
| $FEV_1$/FVC (%) | 52 | [40.7–60.4] |
| TLC (L) | 7.1 | 1.6 |
| TLC (% predicted) | 120.6 | 20.5 |
| GOLD stage 1 n (%) | 6 (9%) | – |
| GOLD stage 2 n (%) | 29 (41%) | – |
| GOLD stage 3 n (%) | 23 (33%) | – |
| GOLD stage 4 n (%) | 12 (17%) | – |

BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; GOLD: global initiative for chronic obstructive lung disease; LQ: lower quartile; UQ: upper quartile.

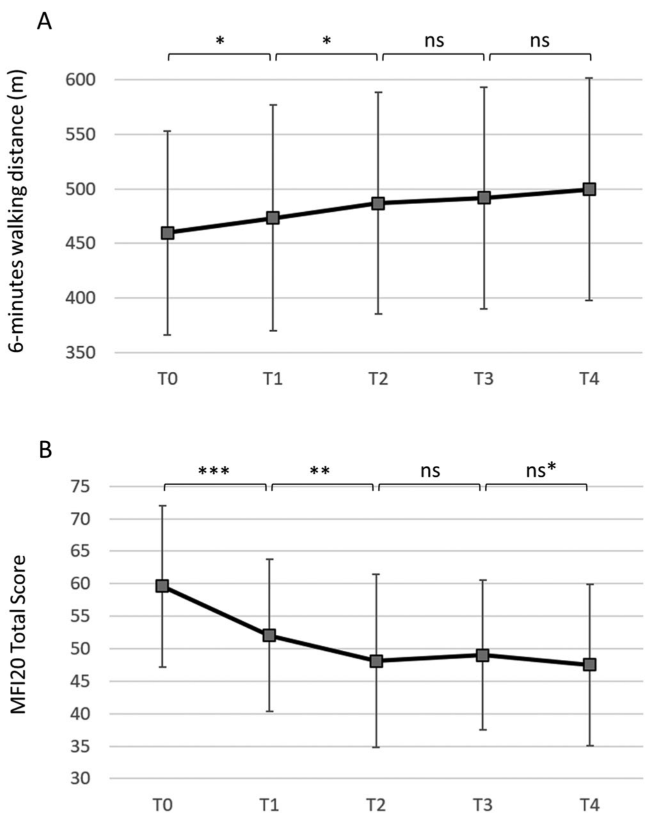


**Figure 2.** Change in the 6-minute walking distance (A) and the total fatigue MFI-20 score (B), before (T0) and at the end of the 1st (T1), 2nd (T2), 3rd (T3), and 4th (T4) week of pulmonary rehabilitation. ***, **, *: significantly different with $p < 0.001$, 0.01, and 0.05, respectively. ns and ns*: not significantly different and $p < 0.05$ but not significantly different after Bonferroni correction, respectively. The data are means ± SD.

were not significantly different from those of T3 and T4, despite the absence of a significant correlation at these times. In addition, the correlation coefficients at T0, T1, and T2 were not significantly different from each other. No significant association between the 6MWD and the other HRV data was found.

## Discussion

The present study sought to assess the changes in multidimensional fatigue markers and functional exercise capacity over the course of an inpatient PR program lasting four weeks. Our main results revealed that all the fatigue markers, except the HRV, decreased from the very beginning of the program. However, contrary to our hypothesis, they did not increase towards the middle of the program, but instead levelled off, i.e. the rate of change decreased from the middle of the program onward. In parallel, we observed that most of the improvement in functional exercise capacity, as assessed by the 6MWD, also occurred in the first part of the program. Lastly, the major finding of the study was a strengthening of the association between the 6MWD and the fatigue markers MFI-20 score and the RT at the end of the 3rd week of the program, which coincided with the slowdown of improvement in functional exercise capacity.

In our study, the PR program induced a mean increase of 40 metres in the 6MWD. In the largest ever systematic review and meta-analysis conducted on this topic, the mean improvement in the 6MWD was 44 metres, irrespective of the PR setting or duration [2]. Therefore, our short inpatient PR program delivered benefits close to those reported previously. However, unlike previous studies, the 6MWD did not change in a strict logarithmic manner [12–14]. Indeed, in these studies, the authors found that much of the improvement in the 6MWT occurred during the first part of the program, with no significant improvement beyond 18–21 sessions. In the current study, although almost 70% of the 6MWD improvement occurred in the first half of the program between the 1st and the 20th session, the 6MWD continued to improve, albeit at a greatly reduced rate, between the middle and the end of the program. The absence of a plateau in achievement after 20 sessions in our study could be explained by the difference in program duration. Indeed, although the total number of exercise training sessions was close to those of the three aforementioned studies (40 vs. 36 sessions), our program was three times shorter (4 weeks versus 12 weeks). Thus, irrespective of the number of exercise sessions, the results suggest that a minimum amount of time could be required to reach the levelling off in performance benefits during PR. Nevertheless, our results confirm that most of the performance improvement occurs early on, in the beginning of PR, even in a short inpatient PR program.

In parallel to the functional exercise capacity, multidimensional fatigue as assessed by the MFI-20 questionnaire decreased in the first part and levelled off from the middle of the program onward. Thus, our study shows that multidimensional fatigue exhibits a similar change as other PR outcomes such as functional exercise capacity and quality of life [12–14]. In addition, to date, change in fatigue had only been evaluated before and after PR [2,19,20]. Although in contradiction with our initial hypothesis that fatigue could increase at certain times of the program, our results complete current knowledge regarding the change in fatigue during PR, indicating that the decrease in fatigue only occurred during the first part of the program.

**Table 2.** Associations and changes in the associations between functional exercise capacity and fatigue markers.

| Variables | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|
| MFI-20 subscores | | | | | |
| $MFI\text{-}20_{gen}$ | 13.3 (3.3) | 11.3 (3.3)*# | 10.7 (3.4)* | 10.7 (3.2)* | 10.2 (3.1)* |
| $MFI\text{-}20_{phy}$ | 13.8 (3.4) | 11.6 (3.4)*# | 10.6 (3.2)*# | 10.5 (3.2)* | 10 (3.3)* |
| $MFI\text{-}20_{men}$ | 9.9 (3.3) | 9.2 (3.4) | 8.5 (2.8)* | 8.9 (3.1) | 8.7 (3.2)* |
| $MFI\text{-}20_{motiv}$ | 10.2 (2.9) | 9.1 (3.1)*# | 8.4 (2.9)* | 8.4 (2.7)* | 8.4 (2.8)* |
| $MFI\text{-}20_{act}$ | 12.4 (3.4) | 10.8 (2.5)*# | 10.4 (2.7)* | 10.5 (2.4)* | 10.4 (2.5)* |
| Reaction time | | | | | |
| Mean RT, ms | 351.4 (46.7) | 332.9 (38.9)*# | 333.1 (44.8)* | 334.5 (45)* | 333.7 (42.5)* |
| HRV data | | | | | |
| RMSSD, ms | 27.2 (12.8) | 29.5 (13) | 28.8 (15.3) | 29.1 (14.7) | 30.5 (16.8) |
| SDNN, ms | 16.7 (10.9) | 20.3 (12.1) | 18 (13.1) | 19.1 (14.2) | 20.5 (14.9) |
| LF power, $ms^2$ | 69.7 (95.9) | 73.2 (95.1) | 62.5 (76.6) | 67.4 (76.2) | 69.2 (93.8) |
| HF power, $ms^2$ | 36 (52.7) | 45.5 (52.2) | 32.1 (46.1) | 41.3 (59.1) | 45 (67.7) |
| LF power, % | 68 (19) | 62 (19) | 69 (17) | 65 (20) | 65 (20) |
| HF power, % | 32 (19) | 38 (19) | 31 (17) | 35 (20) | 35 (20) |
| LF/HF | 3.19 (2.41) | 2.47 (2.25) | 3.3 (2.34) | 3.5 (3.95) | 3.49 (3.91) |

$MFI\text{-}20_{gen}$: General Fatigue; $MFI\text{-}20_{phy}$: Physical Fatigue; $MFI\text{-}20_{men}$: Mental Fatigue; $MFI\text{-}20_{motiv}$: Reduced Motivation; $MFI\text{-}20_{act}$: Reduced Activity; RT: reaction time; RMSSD: root mean square of R-R intervals; SDNN: standard deviation of normal-to-normal intervals; LF: low frequency; HF: high frequency. *Significantly different from T0 and #significantly different from preceding time. Data are mean ± SD.

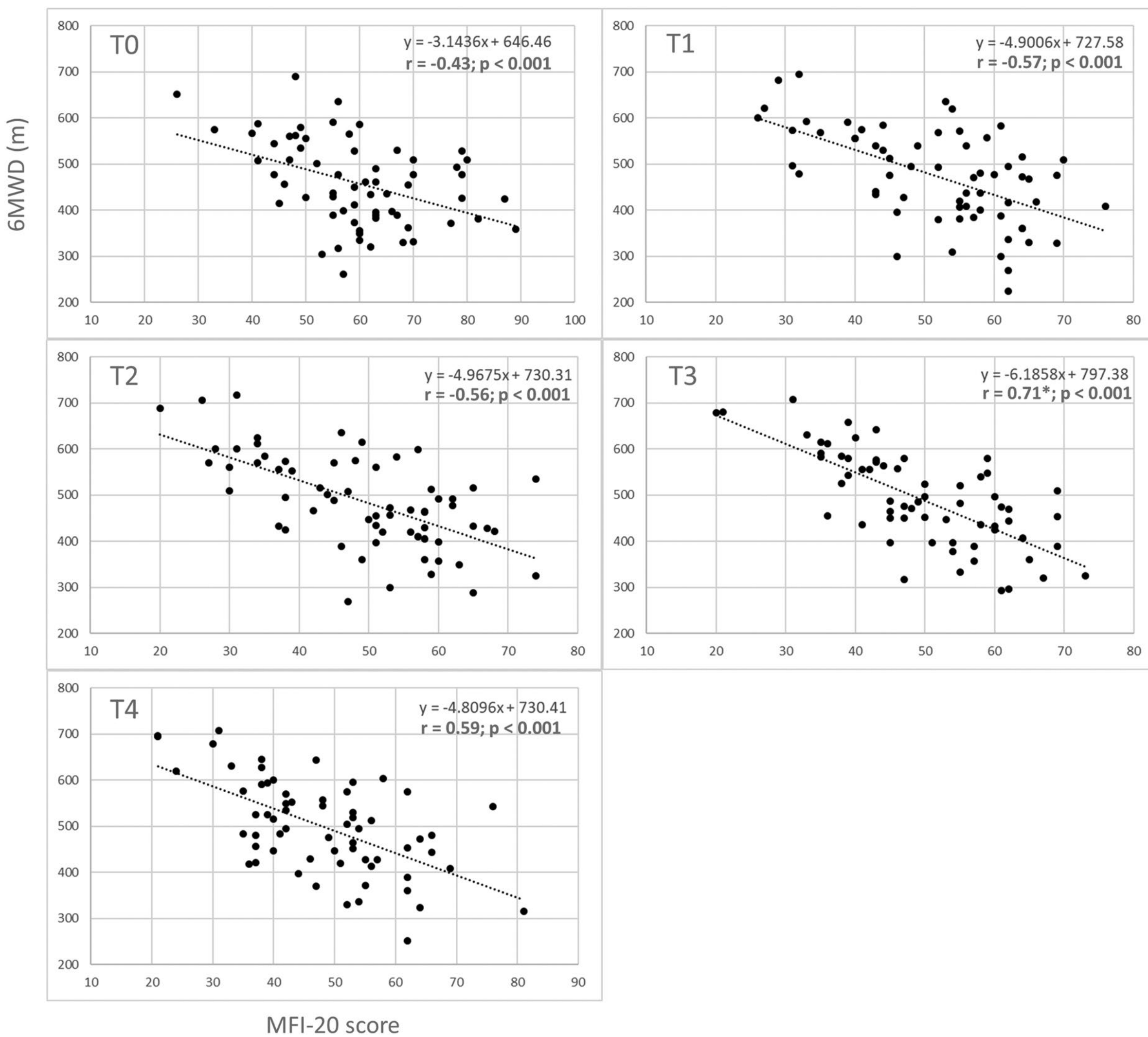


**Figure 3.** Correlations between the 6-minute walking distance (on the y-axis) and the total fatigue MFI-20 score (on the x-axis) before (T0) and at the end of the 1st (T1), 2nd (T2), 3rd (T3), and 4th (T4) week of pulmonary rehabilitation. *: correlation coefficient significantly different from T0, T1, T2, and T4.

In regard to the five individual dimensions of the MFI-20, our results show that they did not change in a consistent manner. While the “general”, “reduced activity”, and “reduced motivation” dimensions levelled off immediately after T1, the “mental” dimension of fatigue improved later on. Furthermore, only the physical dimension decreased consistently with the MFI-20 total score, exhibiting a further decrease between T1 and T2. Although statistical direct comparison is not feasible, it would appear that physical fatigue exhibited a greater change than the other subscores. These data suggest that a substantial part of the decrease in multidimensional fatigue reported in the study was the consequence of the reduction of the perceived physical fatigue.

For other fatigue markers, and especially the RT, our results indicate that they can be rapidly enhanced from the very beginning of PR. Indeed, the mean RT decreased immediately after the first week of PR and then levelled off, with no further decrease beyond the first week. While considered to be a good surrogate marker of fatigue [32], the RT is also a valid measure of cognitive function (a decrease in the RT indicates better cognitive function) [35]. This result is consistent with several studies providing evidence of cognitive function improvements after PR in COPD, although there is usually no specific cognitive intervention in such programs [36–38].

In parallel, none of the HRV parameters changed significantly over the course of the PR program. We anticipated that the HRV could be an interesting complementary and more objective marker of fatigue change than traditional questionnaires in PR because it has notably been shown to be useful and sensitive to detect overtraining syndrome in athletes [27,28,39]. The absence of HRV changes was very unexpected given that several studies have reported increases in the RMSSD, SDNN, and LF after exercise training in COPD patients [13,26,40]. It is unlikely that this can be explained by any differences in the program setting or duration, as the study of Hognon et al. [26], from our team, was conducted in the same PR centres as ours. However, another possible explanation could be a lack of power due to the binding design of the study. Indeed, while Hognon et al. [26] and Borghi-Silva et al. [13] had three evaluation times, and Camillo et al. [40] only had two, we had as many as five evaluation times. In addition, unlike other measurements, the HRV could not be collected adequately in a significant number of participants at some of the measurement times, leading to several missing values (see degrees of freedom in the Results section). Although methodologically not acceptable, when analyses are performed with only two (T0 vs. T4) or three (T0 vs. T2 vs. T4) times of evaluation instead of five, the changes in the SDNN and RMSSD become significant (data not shown). This was further confirmed by the low beta power of the five times of HRV data analysis (all < 0.46). Therefore, our study can neither confirm nor rule out the absence of HRV improvement during a PR program, mostly due to a lack of power in relation with the multiplicity of measurement.

Beyond the characterisation of the weekly change in fatigue and functional exercise capacity, this study also sought to assess the associations between the various fatigue markers and functional exercise capacity. First, we found a positive association between LF power and the 6MWD at T0, T1, and T2, which disappeared at T3. Interestingly, the disappearance of this relationship coincided with the reinforcement of the association between the 6MWD and the MFI-20 total fatigue and the RT. It is, however, not possible to conclude whether or not these two phenomena are linked, especially as no significant correlation was found between the HRV data and the MFI-20 total fatigue or the reaction time (data not shown). LF power is considered to be a marker of baroreflex function [41,42]. The fact that LF power is correlated with baseline physical performance in COPD is not a new result, since a similar relationship has been reported in healthy young subjects [43] and in patients with cardiac syndrome X [44]. The disappearance of the association between LF power and the 6MWD during the second part of the PR program may suggest a decoupling between baroreflex function and functional exercise capacity with exercise training in COPD. Whether any causal relationship could exist between this decoupling and the levelling off in performance improvement, as well as whether this decoupling is a positive or negative adaptation will require further investigation.

Additionally, we also found a negative association between total fatigue and functional exercise capacity at each evaluation time. Although both fatigue and physical performance improved over the course of the PR program, the question of optimal improvement remained. Indeed, the results on change in the functional exercise capacity confirmed the slowdown in performance improvement during the second part of PR, which is known to be specific to COPD [14]. The aforementioned association between total fatigue and functional exercise capacity indicates that the less the fatigue, the higher the performance is at any time of the program. This result is in line with several other studies that have reported negative baseline correlations between fatigue and numerous physical capacity indicators, including the 6MWD, as well as the incremental shuttle walk distance, symptom-limited cycle exercise performance, and upper and lower extremities muscle strength [45]. We also observed strengthening of the association between total fatigue and functional exercise capacity at T3, as well as between the reaction time and functional exercise capacity. This strengthening of the association occurs concomitant to the slowdown in performance improvement. Altogether, and with regard to the fitness-fatigue model of performance, these data are consistent with a role for fatigue in the limitation of performance changes during PR.

From a clinical point of view, the limitation of fatigue during PR is an interesting aspect to improve the magnitude of performance changes in COPD. Flexible non-linear periodized (FNLP) models of training warrant being considered [46]. These methods consist of assessing fatigue markers before starting each session of an exercise program, and then adjusting the workload if the markers are not in the expected range [46]. For example, using HRV-guided training (i.e. training at high intensity only when the HRV is in the normal range, otherwise moderate intensity), Vesterinen et al. [47] found a greater performance increase compared with a control group, and despite a lower total workload in the HRV-guided training group. The implementation of such FNLP models of training in PR could help to definitively confirm the impact of fatigue on benefits limitation and to overcome the levelling off in performance during PR in COPD [14].

### Study limitations

While the validated MFI-20 questionnaire has been used as a main outcome to assess multidimensional fatigue in COPD patients [48], a potential limitation is the use of RT and HRV as other fatigue markers. Although RT and HRV are both considered as valid fatigue markers in general population or in patients with other conditions that COPD [22,27,29,32], their validation in the specific COPD population is lacking.

Another limitation refers to the design of the study, which required to perform walking tests each week. It is not possible to verify whether the repetition of 6MWT could have contributed to the weekly adaptations and the evolutions of the outcomes that we found.

## Conclusions

During a short inpatient PR program, most of the change in functional exercise capacity occurred during the first part of the program. In parallel, fatigue also decreased during the first part of the program and then levelled off. Functional exercise capacity and fatigue were associated at each time period of the program, but the association strengthened in the second half of the program. In the light of the fitness-fatigue model of performance, the strengthening of the association is consistent with a role for fatigue in the limitation of benefits in terms of functional exercise capacity in the last part of the PR program. Although our hypothesis that fatigue increases in the middle of PR was not verified, the current study has important clinical implications as it identifies modulation of fatigue as a potential lever for optimisation of PR benefits.

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## Declaration of interest

The authors have no conflicts of interest to declare

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## Data availability statement

Data are available upon request by mailing to the corresponding author

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