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Abstract

Purpose: Not all patients with chronic obstructive pulmonary disease (COPD) experience similar benefits following pulmonary rehabilitation (PR). This pre-post PR study used a large sample of patients with COPD to determine whether PR-induced changes of oxygen uptake ($\dot{V}O_2$) kinetics and exercise responses of $\dot{V}O_2$, carbon dioxide output ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$), $\dot{V}_E/\dot{V}CO_2$, breathing frequency and tidal volume differed between responders and non-responders to PR. **Methods:** Responders to PR were defined as patients with a minimal clinically important increase in endurance time of 105 s. Isotime (=180 s) values of $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, breathing frequency and tidal volume; gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$; and $\dot{V}O_2$ mean response time of 183 patients with COPD (forced expiratory volume in 1 second: 56±19%predicted) were compared between pre- and post-PR constant work rate tests. **Results:** Following PR, only the group of responders significantly decreased $\dot{V}O_2$ mean response time ($p<0.05$), $\dot{V}CO_2$ gain, $\dot{V}_E$ gain and isotime values of $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ (all $p<0.001$), while also improving their breathing pattern (e.g. decreased breathing frequency isotime value; $p<0.0001$). These changes were not observed in the group of non-responders. Changes in physiological exercise responses were correlated with changes in physical performance (e.g. correlation between changes in $\dot{V}O_2$ mean response time and endurance time: $p=0.0002$, $r=-0.32$). **Conclusion:** PR-induced changes in physiological exercise responses differed between responders and non-responders. Physiological changes are relevant to explain the variable improvements of physical performance following PR in patients with COPD. **Key words:** Exercise physiology, Exercise training, Oxygen uptake, Kinetics

Introduction

Pulmonary rehabilitation (PR) is a comprehensive intervention, combining patient-tailored therapies such as exercise training, education and behavioural changes. It aims to increase physical performance and quality of life of patients with chronic obstructive pulmonary disease (COPD) (1). A constant work rate test (CWRT) at 75% of the individual peak work rate (WR) can be used to assess improvements of physical performance following PR (1–4). An increase in the lower-limb physiological ability can explain, at least in part, improvements in physical performance. Indeed, vastus lateralis muscle oxidative enzyme activity increased in patients with COPD following 10-12 weeks of exercise training (5, 6).

A number of studies with sample sizes ranging from 11 to 35 patients with COPD showed that exercise training also speeds oxygen uptake ($\dot{V}O_2$) kinetics at exercise onset, as quantified by a decreased $\dot{V}O_2$ mean response time (MRT) (7–9). In patients with COPD, an elevated $\dot{V}O_2$ MRT is associated with both ventilatory and physical impairments (10). Therefore, a PR-induced decrease of $\dot{V}O_2$ MRT (which reduces ventilatory and cardiovascular demands (11)) can help improve physical performance. In addition, PR has been shown to decrease carbon dioxide output ($\dot{V}CO_2$), decrease minute ventilation ($\dot{V}_E$) and alter breathing patterns during exercise in patients with COPD (7–9, 12).

Nevertheless, not all patients with COPD experience the same benefits from PR programs (4). Although improvements of physical performance can vary between patients, the previously mentioned studies that observed physiological changes following PR did not make a distinction between patients with COPD that increased endurance time more than the minimal clinically

important difference of 105 s (13) (responders) and patients who did not (non-responders). We hypothesised that the earlier described physiological changes following PR, such as speeded $\dot{V}O_2$ kinetics, might not be evident in all patients with COPD. Consequently, the objective of this study was to use a large sample of patients with COPD (n=183) to determine whether changes of $\dot{V}O_2$ MRT following PR differed between patients that did or did not respond (in terms of physical performance) to PR. In addition, we determined whether PR-induced changes of $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, breathing frequency and tidal volume responses during exercise were different between responders and non-responders to PR.

Materials and methods

Study design and participants

Clinically stable patients with COPD (no exacerbation within previous 4 weeks) were recruited at the start of an interdisciplinary PR program at CIRO (Horn, the Netherlands). Demographics, resting post-bronchodilator pulmonary function, the modified Medical Research Council dyspnoea grading, resting arterial blood gas analyses, COPD assessment test score (14) and hospital anxiety and depression scale scores (15) were collected during a pre-PR assessment (16). Physical performance was assessed by the six minute walking distance, peak isokinetic quadriceps strength and peak values of $\dot{V}O_2$ and WR during a symptom-limited incremental cardiopulmonary exercise test (16). Additionally, a symptom-limited CWRT was performed on an electrically braked cycle ergometer with a gas exchange analyser (Oxycon Pro, Carefusion, Houten, the Netherlands) for measuring CWRT endurance time. The CWRT consisted of a period of rest (3 minutes) and unloaded cycling (3 minutes), followed by an instantaneous WR increase to 75% of WR_{peak}. Borg scores for dyspnoea and fatigue were obtained during rest, unloaded cycling, every 2 minutes

during loaded cycling, at exercise cessation and after a 3-minute recovery period. Further details about the measurements described above can be found in Smid et al. (16).

COPD assessment test score, hospital anxiety and depression scale scores, six minute walking distance, peak isokinetic quadriceps strength and CWRT endurance time were measured again post-PR to quantify changes of physical performance and health and mood status following PR. Patients that increased CWRT endurance time following PR with more than 105 s, the lower bound of a minimal clinically important difference (1, 13), were classified as responders to PR, other patients as non-responders.

The described data were collected as part of the COPD, Health status and Comorbidities (CHANCE) study, a single-centre study examining health status and comorbidities in patients with COPD (16). This study was registered at the Dutch Trial Register (NTR 3416) and approved by The Medical Ethical Committee of the Maastricht University Medical Centre (METC 11-3-070). All patients provided written informed consent. The Medical Ethical Committee of the Maastricht University Medical Centre (METC 2018-0546) confirmed that additional approval by the Committee was not required for the current additional analyses. Data from the CHANCE study (i.e. the baseline kinetic feature values (10) and the effects of PR on physical performance and health status (17–20)) have already been published. The current description of the changes in physiological exercise responses following PR have not been reported before.

Pulmonary rehabilitation

Patients underwent a PR program of 40 sessions that conforms to the latest international American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation (1, 21). The interdisciplinary PR program consisted of physical exercise training, occupational therapy, nutritional counselling, psychosocial counselling, optimising medication use and adherence to medication, education and exacerbation management. Physical exercise training was the cornerstone of the program, consisting of stationary cycling, treadmill walking and exercises to strengthen muscle groups in the upper and lower extremities. Exercise training was performed at moderate-to-high intensity, i.e. ≥60% of WR_{peak} (cycling), ≥60% of six minute walking test speed (walking) and ≥60% of 1-repetition maximum (strengthening exercises). The intensity of stationary cycling and treadmill walking was adjusted weekly based on Borg scores for dyspnoea and fatigue (target score of 4-6). The load of the strengthening exercises increased 3-5% per week. Patients who were too dyspnoeic to perform endurance/interval/resistance training, received lower-limb high-frequency neuromuscular electrical stimulation (22). In addition, patients underwent flexibility exercises, general physical exercise for lower and upper extremities and daily supervised 30-minute outdoor walks. The program was implemented by an interdisciplinary team including a chest physician, respiratory nurse, dietician, occupational therapist, physiotherapist, psychologist and social worker.

Physiological responses during a constant work rate test

Ventilatory and gas exchange responses during CWRT were collected breath-by-breath (Oxycon Pro, Carefusion, Houten, the Netherlands) and pre-processed according to our previously described methodology (23). Isotime values were calculated for $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$,

breathing frequency, tidal volume, heart rate and oxygen pulse as the mean of the last 30 s before isotime at t = 180 s. Isotime was selected at 180 s as this is the minimal target duration of a CWRT (3), while the potential contribution of the slow component is also minimal during the first 180 s of a CWRT (24, 25) (see Figure, Supplemental Digital Content 1, representation of a typical $\dot{V}O2$ response at the onset of a constant work rate test and the specific phase II contribution, http://links.lww.com/MSS/C223).

At the onset of a CWRT, $\dot{V}O_2$ typically follows a three phase response (Supplemental Digital Content 1, http://links.lww.com/MSS/C223). $\dot{V}O_2$ response kinetics, i.e. $\dot{V}O_2$ MRT and gain, quantify the fundamental parameters of this $\dot{V}O_2$ response (10, 23) (Supplemental Digital Content 1, http://links.lww.com/MSS/C223). MRT describes the time needed to reach 63% of an anticipated steady state, indicating the speed of the $\dot{V}O_2$ increase at exercise onset. $\dot{V}O_2$ gain describes the $\dot{V}O_2$ increase of the fundamental component per unit increase in external WR (23).

For the calculation of $\dot{V}O_2$ MRT, Box-Jenkins transfer functions with a first order system model and a second order noise model were fitted to the $\dot{V}O_2$ time series from 30 s before the WR increase until isotime at 180 s after this step WR increase (10, 23). The system model fit was then assessed by the normalised root-mean-squared error value (10). $\dot{V}O_2$ gain was calculated as $(\dot{V}O_{2,isotime} - \dot{V}O_{2,unloaded})/\Delta WR$ where $\dot{V}O_{2,unloaded}$ was the mean of the last 30 s of unloaded cycling and ΔWR was the WR increase at t=0 s (Supplemental Digital Content 1, http://links.lww.com/MSS/C223). $\dot{V}CO_2$ and $\dot{V}_E$ gains were calculated in the same way. No gains were calculated for breathing frequency and tidal volume due to the variable nature of these responses at CWRT onset (see Figure, Supplemental Digital Content 2, examples of breathing

frequency and tidal volume responses that show the variable nature of these responses at the onset of a constant work rate cycling test, http://links.lww.com/MSS/C224).

Patient exclusion and unreliable kinetic feature values

Patients cycling until at least 105 s before the time limit pre-PR (i.e. CWRT endurance time pre-PR ≥ 1095 s) were excluded because they could not be identified as a responder (Figure 1). Patients not reaching the minimal target duration of a CWRT (i.e. 180 s (3)) pre- or post-PR were also excluded (Figure 1). Patients exhibiting unreliable kinetic feature values (i.e. unreliable $\dot{V}O_2$ MRT or gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$) pre- or post-PR were excluded for subsequent kinetic analyses (Figure 1) (10). Kinetic feature values could not reliably be calculated due to (see (10)): 1) a low increase above unloaded values of $\dot{V}O_2$ (<200 $ml \cdot min^{-1}$), $\dot{V}CO_2$ (<200 $ml \cdot min^{-1}$) or $\dot{V}_E$ (<7 $L \cdot min^{-1}$) at isotime, being lower than 2.5 standard deviations of the breath-by-breath fluctuations (26, 27); 2) a poor $\dot{V}O_2$ system model fit, defined as normalised root-mean-squared error >25%; 3) a severely slowed $\dot{V}O_2$ response ($\dot{V}O_2$ MRT >150 s). $\dot{V}O_2$ MRT values of patients with a severely slowed $\dot{V}O_2$ response were considered unreliable because these responses were rather linear in nature, leading to extremely high MRT values (10, 23).

Statistical analyses

Results are presented as mean and standard deviation or median and interquartile range for normally or non-normally distributed variables, respectively. Normality was tested using the Kolmogorov-Smirnov test. Patients with missing data were only excluded for statistical testing of the specific variable where data was missing. Patient characteristics, isotime and kinetic feature values were compared between responders and non-responders using Student's t-tests, Wilcoxon

rank-sum tests and chi-squared tests, as appropriate. Paired Student's t-tests and Wilcoxon signed rank tests were used to compare physical performance, health and mood status, Borg scores and physiological exercise responses pre- and post-PR. Pearson correlations were used to correlate changes in six minute walking distance, quadriceps isokinetic peak torque and CWRT endurance time following PR with changes in physiological exercise responses during CWRT. Statistical significance was accepted at the $p<0.05$ level. All analyses were performed using Matlab 2015b (MathWorks Inc., Natick, Massachusetts, USA).

Results

Patient characteristics

Isotime values were calculated for 183 patients with COPD (Figure 1). These elderly patients were slightly overweight, suffered from mild to very severe COPD, impaired diffusion capacities and limited physical performances (Table 1). Responders (n=117), compared to non-responders (n=66), were younger, more overweight, had a higher fat-free mass index, better resting pulmonary function and less physical impairment before PR (Table 1). Most patients that changed from unreliable (pre-PR) to reliable kinetic feature values (post-PR) were responders to PR [9/11=82%; see Figure, Supplemental Digital Content 3, amount of patients with COPD that exhibited unreliable or reliable kinetic feature values both pre- and post-pulmonary rehabilitation (PR), and the amount of patients that changed group post-PR, http://links.lww.com/MSS/C225]. Fifty six patients exhibited unreliable kinetic feature values pre- or post-PR (56/183=31%), leading to 127 patients that could be included for kinetic analyses (Figure 1). Patients with unreliable kinetic feature values pre- or post-PR were older and more ventilatory and physically impaired compared to patients with reliable kinetic feature values (Supplemental Digital Content 3,

http://links.lww.com/MSS/C225) (10). When only considering patients with reliable kinetic feature values, similar differences between responders (n=84) and non-responders (n=43) as seen in Table 1 could be observed (see Table, Supplemental Digital Content 4, pre-rehabilitation characteristics, http://links.lww.com/MSS/C226). There were missing data points for fat-free mass index (n=7), transfer factor for carbon monoxide (n=6), residual volume (n=4), quadriceps isokinetic peak torque (n=14) and six-minute walking distance (n=1).

Physical performance, health status and mood status

Before PR, responders (n=117) had significantly higher values for quadriceps isokinetic peak torque and CWRT endurance time, compared to non-responders (n=66; both $p<0.05$). Only responders increased physical performance during endurance tests ($p<0.0001$ for both tests; Table 2) following PR. Both patient groups increased quadriceps muscle strength and improved health and mood status ($p<0.0005$ for all; Table 2). The group of responders significantly decreased Borg scores for dyspnoea and fatigue during rest, unloaded cycling, after 2 and 4 minutes of loaded cycling, at exercise cessation and after the recovery period (all $p<0.0001$; Figure 2). In contrast, non-responders did not significantly decrease Borg scores for dyspnoea and fatigue after 4 minutes of loaded cycling nor at exercise cessation (Figure 2). During loaded cycling, Borg scores were only evaluated after 2 and 4 minutes of cycling, as the focus of this study was on the physiological exercise responses during the first 3 minutes of exercise (Figure 2).

Isotime values

Before PR, responders (n=117) had significantly higher isotime values for $\dot{V}O_2$, $\dot{V}CO_2$, tidal volume and heart rate, as well as significantly lower values for isotime $\dot{V}_E/\dot{V}CO_2$, compared to

non-responders (n=66; all $p<0.05$). Only responders, in contrast to non-responders, had lower $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ isotime values following PR, accompanied by a change of breathing pattern, as indicated by the reduction of isotime breathing frequency and the increase of isotime tidal volume (all $p<0.05$; Table 2; Figure 3; see Figure, Supplemental Digital Content 5, examples of changes in physiological exercise responses following pulmonary rehabilitation for responders and non-responders, http://links.lww.com/MSS/C227). Both patient groups had lower isotime heart rate values and higher isotime oxygen pulse values following PR (all $p<0.0001$; Table 2). Similar results were obtained when only the 127 patients with reliable kinetic feature values were used for these analyses (Supplemental Digital Content 4, http://links.lww.com/MSS/C226).

Kinetic feature values

Before PR, no significant differences in kinetic feature values were observed between responders (n=84) and non-responders (n=43). Only for responders, $\dot{V}O_2$ MRT significantly decreased following PR ($p<0.05$). $\dot{V}O_2$ gain increased for both responders (close to significance, $p=0.05$) and non-responders ($p<0.05$; Table 3; Figure 3). In contrast, only responders experienced a decrease in $\dot{V}CO_2$ and $\dot{V}_E$ gain after PR (both $p<0.001$), which was not observed for non-responders (Table 3; Figure 3).

Correlations between changes in physiological exercise responses and physical performance

For the 183 included patients with COPD, the change in CWRT endurance time and six minute walking distance post- compared to pre-PR was correlated with the change in isotime values of $\dot{V}CO_2$ ($p=0.002$, $r=-0.23$; $p=0.01$, $r=-0.19$, respectively), $\dot{V}_E$ ($p<0.0001$, $r=-0.29$; $p=0.0002$, $r=-$

0.27, respectively), $\dot{V}_E/\dot{V}CO_2$ (p=0.009, r=-0.19; p=0.05, r=-0.15, respectively) and breathing frequency (p=0.0006; r=-0.25; p<0.0001; r=-0.32, respectively).

When only considering the 127 patients with reliable kinetic feature values, the change in CWRT endurance time and six minute walking distance was additionally correlated with gains of $\dot{V}CO_2$ (p=0.001, r=-0.29; p=0.04, r=-0.18, respectively) and $\dot{V}_E$ (p=0.0004, r=-0.31; p=0.02, r=-0.21, respectively). Changes in $\dot{V}O_2$ MRT were correlated with changes in CWRT endurance time (p=0.0002, r=-0.32) and quadriceps isokinetic peak torque (p=0.04, r=-0.19).

Discussion

This study was the first to examine whether PR-induced changes in physiological exercise responses differed between patients with COPD who do or do not have a clinically relevant increase in CWRT endurance time following PR. Interestingly, only the group of responders (in terms of physical performance) showed a faster $\dot{V}O_2$ response (i.e. decreased $\dot{V}O_2$ MRT), a decrease in $\dot{V}CO_2$ and $\dot{V}_E$ gain, a decrease in isotime values of $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ and an improved breathing pattern following PR. These changes were correlated with changes in physical performance post-PR.

The results of the current study confirm that exercise training can speed $\dot{V}O_2$ kinetics, as quantified by a decreased $\dot{V}O_2$ MRT (7–9). Interestingly however, this could not observed in the group of non-responders. This, in combination with the association between changes of $\dot{V}O_2$ MRT and changes of physical performance, highlights the importance of a swift $\dot{V}O_2$ response at exercise onset. Enhancements in peripheral oxygen delivery (related to decreased dynamic

hyperinflation and subsequent faster cardiovascular responses (7, 9, 10, 12)) and consumption (related to improved muscle function and morphology (28)) most likely contributed to the faster $\dot{V}O_2$ response following PR in the group of responders. This faster response subsequently reduces lactate accumulation related to phosphocreatine breakdown and glycogenolysis, which decreases circulatory and ventilatory requirements, ultimately increasing CWRT endurance time (11, 29).

Decreased $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ responses post-PR (as indicated by the decreased gains and isotime values) were also only observed in the group of responders. As stated above, the faster $\dot{V}O_2$ responses in this group (combined with PR-induced improvements of muscle function and morphology (28)) can enhance aerobic ATP production and therefore reduce the need for anaerobic energy sources and subsequent lactate accumulation (11, 29). As a result, the magnitude of the $\dot{V}CO_2$ response decreases and, due to the close coupling between $\dot{V}CO_2$ and $\dot{V}_E$, also the $\dot{V}_E$ response is reduced (2, 30).

The decreased $\dot{V}_E$ response in the group of responders was related to an improved breathing pattern, indicated by a decrease in breathing frequency and a small, but significant increase in tidal volume following PR. The decrease in breathing frequency post-PR may be related to reduced dynamic hyperinflation (12). Although improved breathing patterns have been reported after exercise training in patients with COPD (3), our study is the first to indicate that these changes cannot be observed in all patients with COPD following PR. Additionally, changes in isotime breathing frequency were associated with increases of CWRT endurance time and six minute walking distance post-PR.

The observed decrease of the $\dot{V}_E$ response during exercise in the group of responders (enabled by enhancements of aerobic ATP production and improved breathing patterns) reduces the work of breathing. As a result, the oxygen requirements of ventilatory muscles are lowered, making more oxygen available for the exercising muscles and consequently reducing lactate accumulation. This ultimately results in a further decrease of the $\dot{V}CO_2$ and $\dot{V}_E$ responses following PR in the group of responders (31). The lowered isotime $\dot{V}_E/\dot{V}CO_2$ following PR indicates that the $\dot{V}_E$ decrease was more pronounced than the decrease of $\dot{V}CO_2$.

Interestingly, only the group of responders had lower Borg scores at exercise cessation following PR. We attribute this to enhanced aerobic ATP production (11, 31) and/or improvements of the ventilatory demand-capacity imbalance (1). In contrast, these changes were not observed in the group of non-responders. Therefore, they probably experienced the same exercise limitations post-PR compared to pre-PR, preventing them from increasing physical endurance.

The presented results show that physiological changes are relevant to explain the highly variable improvements of physical performance that can be observed in patients with COPD following PR. In addition, physiological exercise responses can be considered motivation-independent, in contrast to the conventional indicators of improved physical performance (e.g. CWRT endurance time or six minute walking distance) (1, 3). Another downside of these conventional indicators is that relatively large changes of CWRT endurance time could be induced by only a small shift of the power-duration curve (11). Quantifications of physiological exercise responses could thus be an interesting (additional) tool to assess physical and physiological changes of patients with COPD after an intervention such as PR.

It is important to note that improving physical performance is not the sole objective of a PR program. Even when physical performance does not improve following PR, improvements of other clinical outcomes can still be reached. In the current study, non-responders (in terms of physical performance) still experienced improvements of health and mood status following PR. This indicates that, although physiological changes were shown to be important to improve physical performance, improvements of other clinical outcomes can still be reached by patients that do not improve physical performance nor have observable changes of physiological exercise responses following PR.

Some limitations should be taken into account. First, although there were clear physiological changes of responders on a group level, this was more variable on an individual level. Second, not all patients could be included for these (kinetic) analyses due to an insufficient endurance time or unreliable kinetic feature values. Therefore, these physiological analyses might not be suitable for analysing the most severely ventilatory and physically impaired patients with COPD (10). This could be expected, as it is difficult for these patients to achieve meaningful physiological changes after exercise training (32). Third, kinetic analyses were based on a single transition from rest to exercise, as the data were collected during standard pre- and post-rehabilitation CWRTs (16). Nevertheless, this approach has been used before (9, 10, 33–35), because performing multiple CWRTs during standard patient assessments might not be practically feasible. Moreover, a more complex type of model was used to account for breath-by-breath fluctuations (23). Fourth, it cannot be excluded that breath-by-breath fluctuations could have masked minimal changes of gains or isotime values following PR in the group of non-responders. Still, even if minimal, unobservable physiological changes were present in the group of non-responders, these changes

were too limited to improve physical performance. Fifth, additional measurements of operating lung volumes and dynamic hyperinflation could provide more profound insights into the improved breathing pattern of responders after PR. Despite these limitations, the results of the current study clearly highlight that the (in-)ability to reach observable physiological changes following PR is an important element for explaining why some patients physically improve after PR, and others do not.

It would furthermore be insightful to investigate why some patients are able to reach these physiological changes following PR, while others do not. Previous studies showed that it seems unlikely to be related to the observed differences in age and airflow limitation between responders and non-responders (4, 36, 37). Based on the current results, it could be argued that non-responders were unable to reach observable physiological changes (and thus neither improvements of physical performance) because their overall lower physical performance at baseline resulted in lower exercise intensities during PR. However, previous studies reported that patients with lower physical performance were more likely to respond to PR (4, 37, 38). These combined results highlight the fact that it is currently still difficult to predict who will benefit the most from a PR program (39).

In conclusion, this study was the first to indicate that changes of physiological exercise responses following PR differed between responders and non-responders (in terms of physical performance) to PR. The large sample of included patients with COPD showed that only responders experienced a faster $\dot{V}O_2$ response, decreased $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ responses, and

an improved breathing pattern following PR. Physiological changes are thus relevant to explain the variable improvements of physical performance following PR in patients with COPD.

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The results of the present study do not constitute endorsement by ACSM. The results of the present study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Conflicts of interest

The authors declare no conflict of interest related to the submitted work.

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Figure captions

Figure 1: Overview of patient numbers included for analyses of isotime values (n=183) and for subsequent analyses of kinetic feature values (n=127). PR = pulmonary rehabilitation; CWRT = constant work rate test.

Figure 2: Median Borg score values for dyspnoea and fatigue during a constant work rate test before (grey squares) and after (black triangles) pulmonary rehabilitation (PR), for responders (left) and non-responders (right). Error bars visualise interquartile ranges. Borg scores are shown during rest (Rest), unloaded cycling (Unl), after 2 and 4 minutes of loaded cycling (2' and 4', respectively), at exercise cessation (End) and after a 3-minute recovery period (Rec). Wilcoxon signed rank tests were used to test for significant differences between the pre- and post-PR Borg scores (*: <0.05; **: <0.0001). Due to the discrete and non-normally distributed values of the scale, similar median values pre- and post-PR of non-responders could still result in significantly different Borg scores pre- compared to post-PR.

Figure 3: Examples of changes in physiological exercise responses following pulmonary rehabilitation for responders and non-responders. For clarity reasons, responses of different responders and non-responders are shown. Symbols in between the plotted responses indicate increased (upward arrow), decreased (downward arrow) or unchanged values (equality sign) for responders (symbols on the left side) and non-responders (symbols on the right side) following pulmonary rehabilitation. Framed symbols indicate differences between responders and non-responders for that specific variable.

Supplemental Digital Content

Supplemental Digital Content 1. docx—representation of a typical $\dot{V}O_2$ response at the onset of a constant work rate test (blue line) and the specific phase II contribution (orange line).

Supplemental Digital Content 2. docx—Examples of breathing frequency and tidal volume responses that show the variable nature of these responses at the onset of a constant work rate cycling test

Supplemental Digital Content 3. docx—amount of patients with COPD that exhibited unreliable or reliable kinetic feature values both pre- and post-pulmonary rehabilitation (PR), and the amount of patients that changed group post-PR

Supplemental Digital Content 4. docx—Pre-rehabilitation characteristics

Supplemental Digital Content 5. docx—Examples of changes in physiological exercise responses following pulmonary rehabilitation for responders and non-responders

Figure 1

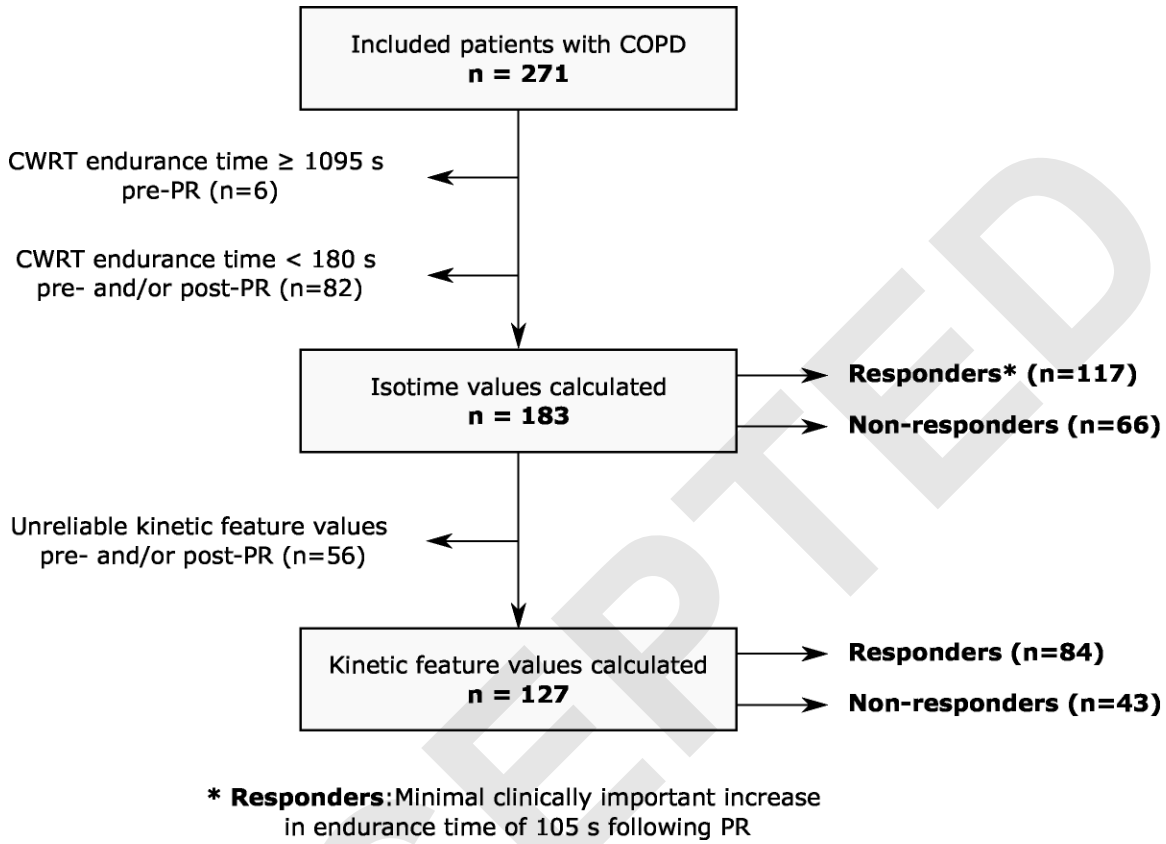


Figure 2

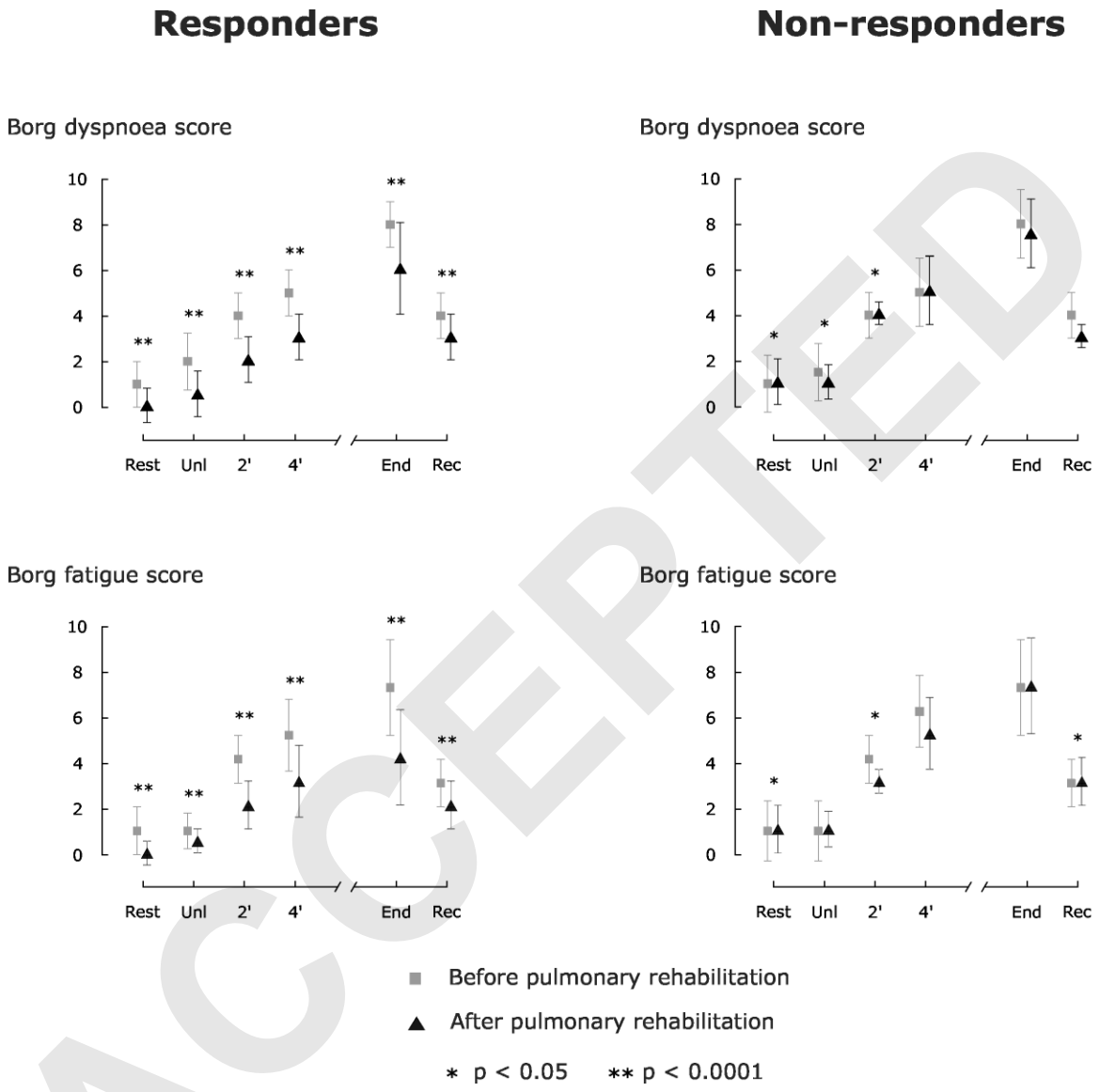


Figure 3

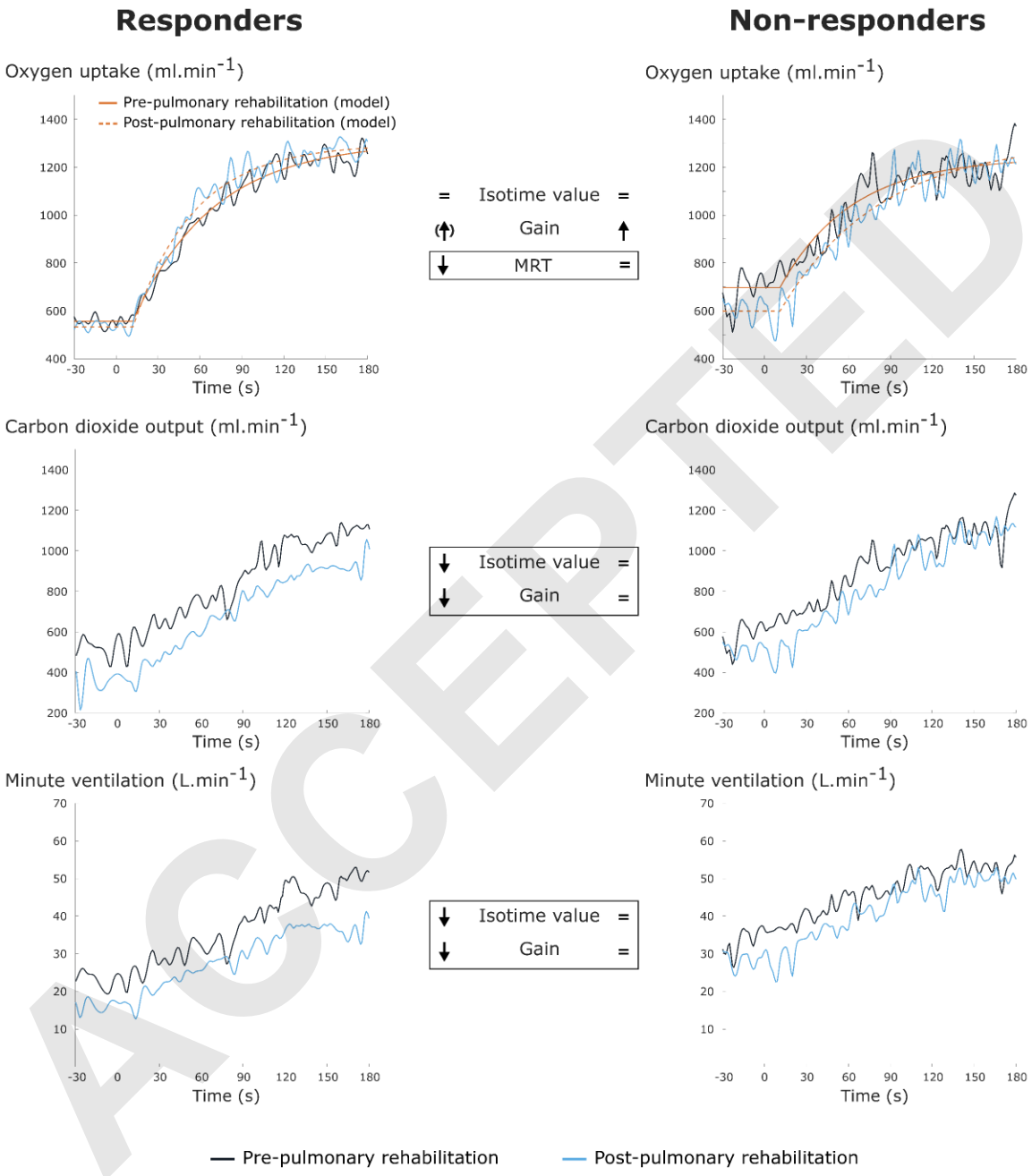


Table 1: Pre-rehabilitation characteristics, presented as mean (standard deviation), of patients with COPD that performed a constant work rate test (CWRT) pre- and post-pulmonary rehabilitation, divided as patients with (responders) and without (non-responders) clinically relevant increase of CWRT endurance time following pulmonary rehabilitation (i.e. >105 s increase).

	All patients (n=183)	Responders (n=117)	Non-responders (n=66)
Demographics			
Male – female	104 – 79	68 – 49	36 – 30
Age (years)	62 (9)	**61 (9)**	**65 (9)****
Body Mass Index ($kg \cdot m^{-2}$)	26.6 (6.0)	**27.6 (6.4)**	**24.9 (4.8)****
Fat-free mass index ($kg \cdot m^{-2}$)	17.3 (2.5)	**17.6 (2.7)**	**16.8 (2.1)***
Resting pulmonary function			
Forced expiratory volume in 1 second (FEV_1; %predicted)	56 (19)	**58 (19)**	**52 (18)***
Forced vital capacity (FVC; %predicted)	104 (18)	104 (18)	103 (19)
FEV_1/FVC (%)	41 (12)	**42 (12)**	**38 (12)***
Transfer factor for carbon monoxide (%predicted)	55 (16)	**57 (16)**	**52 (16)***
Residual volume (%predicted)	149 (44)	146 (43)	155 (47)
Intrathoracic gas volume (%predicted)	141 (33)	**137 (33)**	**148 (31)***
Total lung capacity (%predicted)	116 (17)	115 (16)	118 (19)
Modified Medical Research Council grading ≥ 2 (% patients)	72	70	76
Resting arterial blood gases			
Arterial oxygen saturation (%) [#]	94.9 (2.5)	94.9 (2.6)	94.9 (2.5)
Partial pressure of oxygen (kPa)	9.69 (1.33)	9.60 (1.30)	9.84 (1.38)
Partial pressure of carbon dioxide (kPa)	5.06 (0.59)	5.07 (0.61)	5.05 (0.55)
pH [#]	7.42 (0.03)	7.43 (0.03)	7.42 (0.03)
Health and mood status			
COPD assessment test score [#]	22 (9)	21 (8)	22 (11)
Hospital Anxiety and Depression Scale - Anxiety score [#]	6 (7)	7 (6)	6 (7)
Hospital Anxiety and Depression Scale - Depression score [#]	6 (6)	7 (6)	6 (8)
Physical performance			
Six minute walking distance (m)	487 (102)	493 (103)	476 (101)
Six minute walking distance (%predicted)	75 (14)	76 (14)	75 (15)

Peak work rate (W) [#]	80 (37)	**84 (46)**	**69 (36)***
Peak work rate (%predicted)	64 (25)	65 (24)	62 (28)
Peak oxygen uptake ($ml \cdot min^{-1}$)	1202 (410)	**1276 (428)**	**1069 (339)****
Peak oxygen uptake (%predicted) [#]	64 (33)	65 (33)	56 (30)
Isokinetic peak torque (Nm)	103 (37)	**108 (36)**	**93 (37)***
Isokinetic peak torque (%predicted)	70 (18)	72 (17)	67 (21)
Constant work rate test – Endurance time (s) [#]	295 (184)	**310 (184)**	**267 (133)****
Constant work rate test – Borg dyspnoea score at exercise cessation [#]	8 (3)	8 (2)	8 (3)
Constant work rate test – Borg fatigue score at exercise cessation [#]	7 (4)	7 (5)	7 (4)

Values in bold indicate significant differences between responders and non-responders (*: $p<0.05$; **: $p<0.005$).

[#] Variables are presented as median (interquartile range).

Table 2: Changes in health and mood status, physical performance and constant work rate test (CWRT) isotime values following pulmonary rehabilitation (PR), presented as mean (standard deviation).

	Responders: Pre-PR	***Responders: Post-PR***	***Pre-post difference (P-value)***	***Non-responders: Pre-PR***	***Non-responders: Post-PR***	***Pre-post difference (P-value)***
Health and mood status						
COPD assessment test score [#]	21 (8)	19 (11)	< **0.0001**	22 (11)	18 (10)	**0.0002**
Hospital Anxiety and Depression Scale - Anxiety score [#]	7 (6)	5 (5)	< **0.0001**	6 (7)	4 (5)	< **0.0001**
Hospital Anxiety and Depression Scale - Depression score [#]	7 (6)	5 (6)	< **0.0001**	6 (8)	4 (5)	**0.0003**
Physical performance						
Six minute walking distance (m)	493 (103)	536 (96)	< **0.0001**	476 (101)	484 (94)	0.34
Isokinetic peak torque (Nm)	108 (36)	121 (40)	< **0.0001**	93 (37)	101 (38)	< **0.0001**
CWRT endurance time (s) [#]	310 (184)	829 (675)	< **0.0001**	267 (133)	280 (138)	0.44
CWRT isotime value						
Oxygen uptake ($ml \cdot min^{-1}$)	1170 (330)	1154 (335)	0.26	1025 (246)	1029 (262)	0.74
Carbon dioxide output ($ml \cdot min^{-1}$)	1242 (401)	1136 (367)	< **0.0001**	1069 (285)	1042 (301)	0.13
Minute ventilation ($L \cdot min^{-1}$)	45.5 (12.6)	40.1 (11.0)	< **0.0001**	42.1 (11.0)	41.0 (11.2)	0.15
Minute ventilation·Carbon dioxide output^{-1} ($L \cdot L^{-1}$)	37.6 (6.7)	36.1 (5.8)	< **0.0001**	39.8 (6.0)	39.9 (6.5)	0.85
Breathing frequency ($breaths \cdot min^{-1}$)	28.8 (6.2)	25.0 (5.4)	< **0.0001**	29.6 (6.7)	28.4 (7.2)	0.05
Tidal volume ($L \cdot breath^{-1}$)	1.54 (0.48)	1.59 (0.48)	**0.04**	1.39 (0.42)	1.42 (0.46)	0.17
Heart rate (bpm)	123 (18)	111 (16)	< **0.0001**	117 (15)	111 (17)	< **0.0001**
Oxygen pulse ($ml \cdot beat^{-1}$)	9.6 (2.5)	10.5 (2.9)	< **0.0001**	8.9 (2.3)	9.4 (2.5)	< **0.0001**

Patients are classified as responders (n=117) and non-responders (n=66). Displayed p-values indicate whether there were significant differences between pre- and post-PR values for responders (third column) and non-responders (sixth column).
[#] Variables are presented as median (interquartile range).

Table 3: Changes in kinetic feature values following pulmonary rehabilitation (PR), presented as mean and standard deviation.

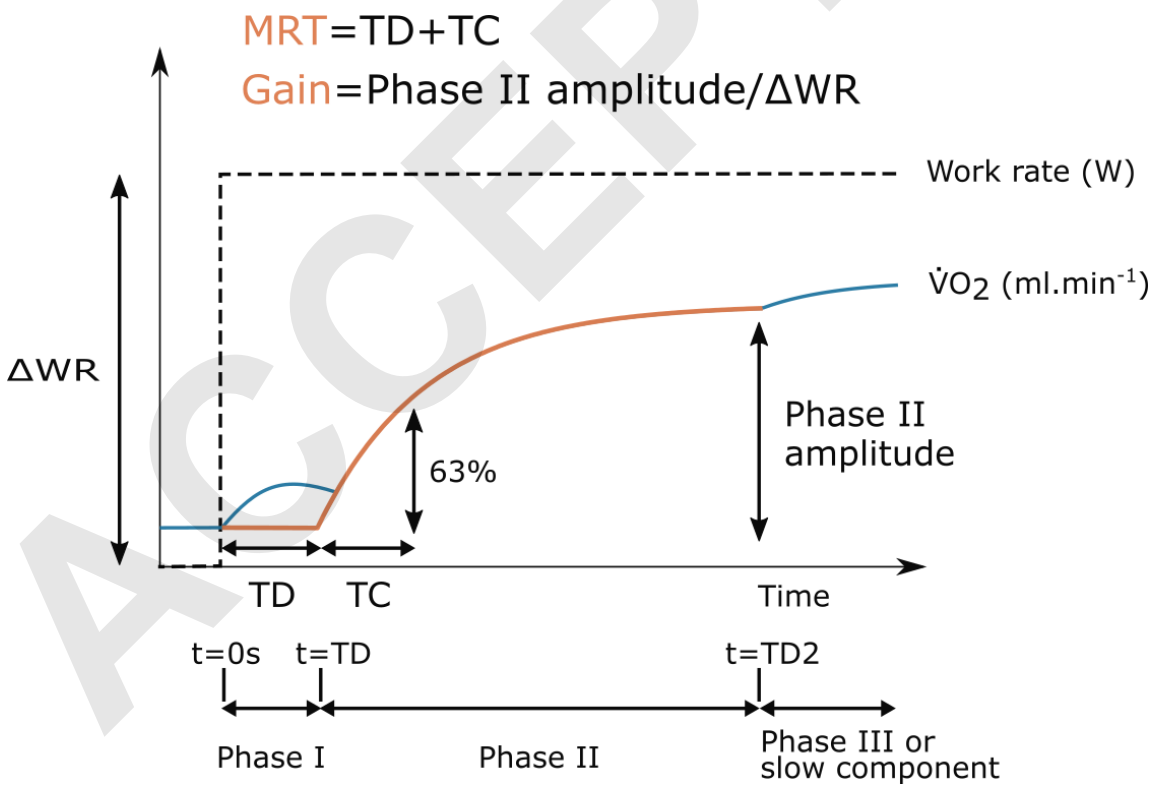
	Responders: Pre-PR	***Responders: Post-PR***	***Pre-post difference (P-value)***	***Non-responders: Pre-PR***	***Non-responders: Post-PR***	***Pre-post difference (P-value)***
$\dot{V}O_2$ mean response time (s)	75 (21)	70 (17)	**0.04**	78 (21)	83 (24)	0.11
$\dot{V}O_2$ gain ($ml \cdot min^{-1} \cdot W^{-1}$)	9.2 (1.7)	9.5 (1.5)	0.06	8.9 (1.6)	9.7 (1.7)	**0.01**
$\dot{V}CO_2$ gain ($ml \cdot min^{-1} \cdot W^{-1}$)	11.1 (1.8)	10.4 (1.5)	< **0.001**	10.6 (1.6)	11.0 (1.8)	0.15
$\dot{V}_E$ gain ($L \cdot min^{-1} \cdot W^{-1}$)	0.38 (0.11)	0.33 (0.09)	< **0.0001**	0.38 (0.11)	0.40 (0.11)	0.26

Patients are classified as responders (n=84) and non-responders (n=43). Displayed p-values indicate whether there were significant differences between pre- and post-PR values for responders (third column) and non-responders (sixth column).

Supplemental Digital Content 1

During a constant work rate test, oxygen uptake ($\dot{V}O_2$) responses are characterised by a rapid cardio-dynamic phase (phase I; see Figure below), followed by an exponential $\dot{V}O_2$ increase (phase II, the primary component of the response) towards an anticipated steady state (phase III). An additional slow component, superimposed on the primary component of the response (see Figure below), can delay or prevent reaching this steady state.

The Figure below provides a representation of a typical $\dot{V}O_2$ response at the onset of a constant work rate test (blue line) and the specific phase II contribution (orange line). Both lines coincide during phase II. The black dashed line visualises the load increase at t = 0 s. MRT = mean response time; TD = time delay; TC = time constant; WR = work rate; TD2 = time delay of phase III or the slow component, variable between 100-200 s.

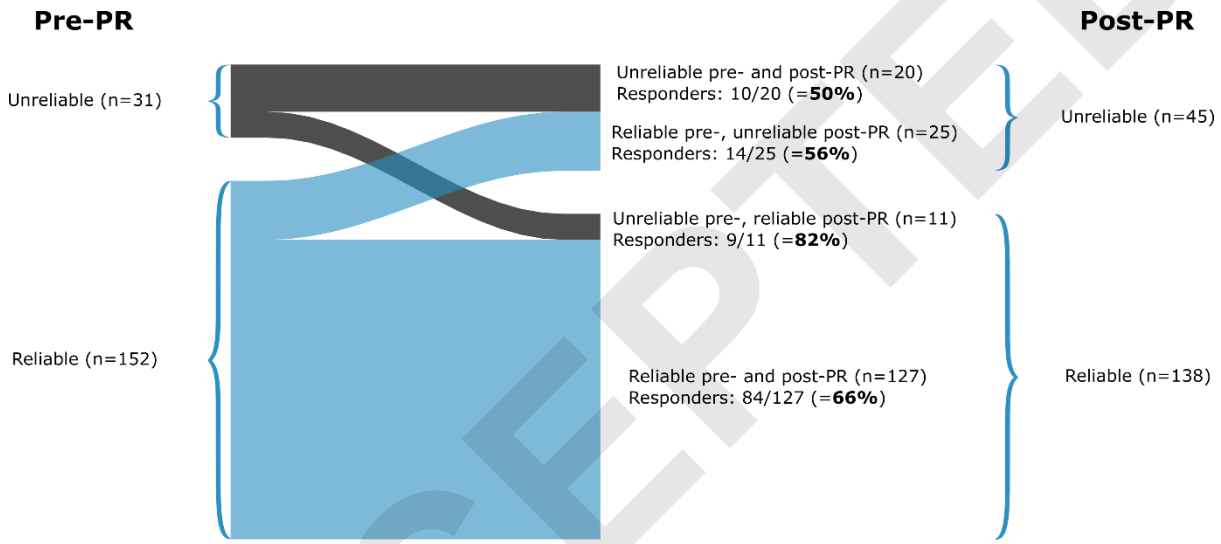


Supplemental Digital Content 2

Examples of breathing frequency and tidal volume responses that show the variable nature of these responses at the onset of a constant work rate cycling test. Neighbouring plots of breathing frequency and tidal volume responses originate from the same patient.

Supplemental Digital Content 3

The Figure below visualises the amount of patients with COPD that exhibited unreliable or reliable kinetic feature values both pre- and post-pulmonary rehabilitation (PR), and the amount of patients that changed group post-PR. Of note, most patients that changed from unreliable (pre-PR) to reliable kinetic feature values (post-PR) were responders to PR (9/11=82%). The group of patients with unreliable kinetic features values both pre- and post-PR had the lowest relative amount of responders to PR (10/20=50%).



The Table below compares patients exhibiting unreliable kinetic feature values pre- or post-PR (n=20+25+11=56; excluded for kinetic analyses) with patients exhibiting reliable kinetic feature values pre- and post-PR (n=127; included for kinetic analyses).

Table: Pre-rehabilitation characteristics, presented as mean (standard deviation) of patients with reliable and unreliable kinetic feature values pre- and/or post-pulmonary rehabilitation. Values in bold indicate significant differences between patients with reliable and unreliable kinetic feature values (*: $p<0.05$; *: $p<0.005$; ***: $p<0.0001$). # Variables are presented as median (interquartile range).

	Patients with reliable kinetic feature values (n=127)	Patients with unreliable kinetic feature values (n=56)
Demographics		
Male – female	73 – 54	31 – 25
Age (years)	**61 (10)**	**65 (3)****
Body Mass Index ($kg \cdot m^{-2}$)	26.7 (6.0)	26.4 (6.2)
Fat-free mass index ($kg \cdot m^{-2}$)	17.4 (2.5)	16.9 (2.5)
Resting pulmonary function		
Forced expiratory volume in 1 second (FEV_1; %predicted)	**60 (17)**	**44 (17)*****
Forced vital capacity (FVC; %predicted)	**107 (17)**	**97 (19)****
FEV_1/FVC (%)	**43 (11)**	**35 (11)*****
Transfer factor for carbon monoxide (%predicted)	**57 (17)**	**52 (15)***
Residual volume (%predicted)	145 (44)	158 (44)
Intrathoracic gas volume (%predicted)	138 (32)	148 (34)
Total lung capacity (%predicted)	116 (17)	116 (17)
Modified Medical Research Council grading ≥ 2 (% patients)	65	89
Resting arterial blood gases		
Arterial oxygen saturation (%)	94.4 (2.3)	94.2 (3.0)
Partial pressure of oxygen (kPa)	9.68 (1.34)	9.70 (1.31)
Partial pressure of carbon dioxide (kPa)	**5.00 (0.56)**	**5.19 (0.63)***
pH	7.43 (0.03)	7.42 (0.03)
Physical performance		
Six minute walking distance (m)	**518 (90)**	**419 (95)*****
Six minute walking distance (%predicted)	**79 (12)**	**68 (15)*****
Peak work rate (W)	**94 (34)**	**63 (22)*****
Peak work rate (%predicted)	**68 (25)**	**54 (24)****
Peak oxygen uptake ($ml \cdot min^{-1}$)	**1288 (415)**	**1008 (327)****
Peak oxygen uptake (%predicted)	70 (25)	65 (29)
Isokinetic peak torque (Nm)	**109 (37)**	**89 (34)****
Isokinetic peak torque (%predicted)	**74 (18)**	**63 (17)****
Constant work rate test – Endurance time (s) #	**311 (178)**	**241 (90)****
Constant work rate test – Borg dyspnoea score #	8 (3)	8 (3)
Constant work rate test – Borg fatigue score #	7 (4)	7 (4)

Supplemental Digital Content 4

Table: Pre-rehabilitation characteristics, presented as mean (standard deviation), of patients with COPD that performed a constant work rate test (CWRT) and had reliable kinetic feature values pre- and post-pulmonary rehabilitation, divided as patients with (responders) and without (non-responders) clinically relevant increase of CWRT endurance time following pulmonary rehabilitation (i.e. >105 s increase).

	All patients (n=127)	Responders (n=84)	Non-responders (n=43)
Demographics			
Male – female	73 – 54	49 – 35	24 – 19
Age (years)	61 (10)	**60 (10)**	**64 (9)***
Body Mass Index ($kg \cdot m^{-2}$)	26.7 (6.0)	**27.7 (6.4)**	**24.9 (4.6)***
Fat-free mass index ($kg \cdot m^{-2}$)	17.4 (2.5)	17.7 (2.7)	17.0 (2.1)
Resting pulmonary function			
Forced expiratory volume in 1 second (FEV_1; %predicted)	60 (17)	**63 (17)**	**56 (18)***
Forced vital capacity (FVC; %predicted)	107 (17)	108 (16)	106 (18)
FEV_1/FVC (%)	43 (11)	**45 (11)**	**40 (12)***
Transfer factor for carbon monoxide (%predicted)	57 (17)	**59 (17)**	**53 (16)***
Residual volume (%predicted)	145 (44)	142 (42)	151 (47)
Intrathoracic gas volume (%predicted)	138 (32)	**135 (32)**	**145 (31)***
Total lung capacity (%predicted)	116 (17)	115 (16)	118 (18)
Modified Medical Research Council grading ≥ 2 (% patients)	65	63	67
Resting arterial blood gases			
Arterial oxygen saturation (%) [#]	94.9 (2.5)	94.9 (2.5)	94.7 (2.7)
Partial pressure of oxygen (kPa)	9.68 (1.34)	9.62 (1.35)	9.80 (1.32)
Partial pressure of carbon dioxide (kPa)	5.00 (0.56)	5.00 (0.57)	5.01 (0.56)
pH [#]	7.43 (0.03)	7.43 (0.03)	7.42 (0.03)
Health and mood status			
COPD assessment test score [#]	21 (9)	21 (8)	22 (11)
Hospital Anxiety and Depression Scale - Anxiety score [#]	6 (7)	7 (7)	6 (7)
Hospital Anxiety and Depression Scale - Depression score [#]	6 (6)	7 (6)	6 (9)
Physical performance			
Six minute walking distance (m)	518 (90)	522 (88)	508 (94)
Six minute walking distance (%predicted)	79 (12)	79 (11)	79 (15)

Peak work rate (W) [#]	89 (45)	**91 (50.5)**	**84 (35)***
Peak work rate (%predicted)	68 (25)	70 (25)	64 (25)
Peak oxygen uptake ($ml \cdot min^{-1}$)	1288 (415)	**1361 (430)**	**1143 (343)****
Peak oxygen uptake (%predicted) [#]	65 (35)	67 (31)	59 (27)
Isokinetic peak torque (Nm)	109 (37)	**113 (36)**	**99 (37)***
Isokinetic peak torque (%predicted)	74 (18)	75 (17)	71 (20)
Constant work rate test – Endurance time (s) [#]	311 (178)	**337 (183)**	**295 (191)***
Constant work rate test – Borg dyspnoea score at exercise cessation [#]	8 (3)	8 (2)	8 (3)
Constant work rate test – Borg fatigue score at exercise cessation [#]	7 (4)	7 (5)	7 (5)

Values in bold indicate significant differences between responders and non-responders (*: $p<0.05$; **: $p<0.005$).

[#] Variables are presented as median (interquartile range).

Table: Changes in physical performance and constant work rate test (CWRT) isotime values following pulmonary rehabilitation (PR) for patients with reliable kinetic feature values (n=127), presented as mean (standard deviation).

	Responders: Pre-PR	***Responders: Post-PR***	***Pre-post difference (P-value)***	***Non-responders: Pre-PR***	***Non-responders: Post-PR***	***Pre-post difference (P-value)***
Health and mood status						
COPD assessment test score [#]	21 (8)	18 (10)	< **0.0001**	21 (11)	18 (11)	**0.0005**
Hospital Anxiety and Depression Scale - Anxiety score [#]	7 (7)	5 (5)	< **0.0001**	6 (7)	4 (4)	**0.03**
Hospital Anxiety and Depression Scale - Depression score [#]	7 (6)	4 (6)	< **0.0001**	6 (9)	3 (5)	**0.03**
Physical performance						
Six minute walking distance (m)	522 (88)	562 (90)	< **0.0001**	508 (94)	515 (87)	0.41
Isokinetic peak torque (Nm)	113 (36)	128 (41)	< **0.0001**	99 (37)	107 (39)	< **0.0001**
CWRT endurance time (s) [#]	337 (183)	952 (591)	< **0.0001**	295 (191)	309 (164)	0.31
CWRT isotime value						
Oxygen uptake ($ml \cdot min^{-1}$)	1231 (323)	1218 (335)	0.32	1070 (260)	1080 (269)	0.54
Carbon dioxide output ($ml \cdot min^{-1}$)	1326 (397)	1217 (365)	< **0.0001**	1126 (287)	1110 (313)	0.47
Minute ventilation ($L \cdot min^{-1}$)	48.0 (11.8)	42.7 (10.7)	< **0.0001**	44.5 (11.5)	43.8 (11.8)	0.47
Minute ventilation·Carbon dioxide output^{-1} ($L \cdot L^{-1}$)	37.2 (7.0)	35.9 (6.1)	< **0.001**	40.0 (6.1)	39.9 (5.6)	0.88
Breathing frequency ($breaths \cdot min^{-1}$)	29.0 (5.8)	25.5 (5.5)	< **0.0001**	29.6 (5.9)	29.0 (6.9)	0.34
Tidal volume ($L \cdot breath^{-1}$)	1.65 (0.46)	1.68 (0.47)	0.22	1.48 (0.41)	1.52 (0.48)	0.29

Heart rate (bpm)	125 (18)	113 (16)	< **0.0001**	119 (17)	114 (19)	**0.001**
Oxygen pulse (ml·beat^{-1})	10.0 (2.5)	10.9 (2.8)	< **0.0001**	9.1 (2.3)	9.6 (2.5)	**0.001**

Patients are classified as responders (n=84) and non-responders (n=43). Displayed p-values indicate whether there were significant differences between pre- and post-PR values for responders (third column) and non-responders (sixth column).

[#] Variables are presented as median (interquartile range).

Supplemental Digital Content 5

Examples of changes in physiological exercise responses following pulmonary rehabilitation for responders and non-responders. For clarity reasons, responses of different responders and non-responders are shown. Symbols in between the plotted responses indicate increased (upward arrow), decreased (downward arrow) or unchanged values (equality sign) for responders (symbols on the left side) and non-responders (symbols on the right side) following pulmonary rehabilitation. Framed symbols indicate differences between responders and non-responders for that specific variable.