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Kinetic analyses as a tool to examine physiological exercise responses in a large sample of patients with COPD

Abbreviated title: Physiological exercise responses in COPD

Joren Buekers[1,2], Jean-Marie Aerts[2], Jan Theunis[1], Sarah Houben-Wilke[3], Frits M.E. Franssen[3,4,5], Nicole H.M.K. Uszko-Lencer[3,6], Emiel F.M. Wouters[3,5], Sami Simons[5], Patrick De Boever[1,7], Martijn A. Spruit[3,4,5,8]

[1] Health Unit, Flemish Institute for Technological Research (VITO), Mol, Belgium
[2] Measure, Model & Manage Bioresponses, Department of Biosystems, KU Leuven, Leuven, Belgium
[3] Department of Research and Development, CIRO, Horn, The Netherlands
[4] School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Centre, Maastricht, The Netherlands
[5] Department of Respiratory Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands.
[6] Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands
[7] Centre for Environmental Sciences, Hasselt University, Diepenbeek, Belgium
[8] Rehabilitation Research Center (REVAL), Biomedical Research Institute (BIOMED), Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium

Corresponding author:

Joren Buekers, Kasteelpark Arenberg 30, 3000 Leuven, Belgium

joren.buekers@kuleuven.be

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Abstract

Kinetic features such as oxygen uptake ($\dot{V}O_2$) mean response time (MRT) and gains of $\dot{V}O_2$, carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) can describe physiological exercise responses during a constant work rate test of patients with chronic obstructive pulmonary disease (COPD). This study aimed to establish simple guidelines that can identify COPD patients for whom kinetic analyses are (un)likely to be reliable, and examined whether slow $\dot{V}O_2$ responses and gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ are associated with ventilatory, cardiovascular and/or physical impairments.

Kinetic features were examined for 265 COPD patients (FEV_1: 54±19%predicted) that performed a constant work rate test (duration>180 s) with breath-by-breath measurements of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$. Negative/positive predictive values were used to define cut-off values of relevant clinical variables below/above which kinetic analyses are (un)likely to be reliable.

Kinetic feature values were unreliable for 21% (=56/265) of the patients and for 79% (=19/24) of the patients with a peak work rate (WR_{peak})<45 W. Kinetic feature values were considered reliable for 94% (=133/142) of the patients with an FEV_1>1.3 L. For patients exhibiting reliable kinetic feature values, $\dot{V}O_2$ MRT was associated with ventilatory (e.g. FEV_1%predicted: $p<0.001$; $r=-0.35$) and physical (e.g. $VO_{2,peak}$%predicted: $p=0.009$; $r=-0.18$) impairments. Gains were mainly associated with cardiac function and ventilatory constraints, representing both response efficiency and limitation.

Kinetic analyses are likely to be unreliable for patients with a WR_{peak}<45 W. While gains enrich analyses of physiological exercise responses, $\dot{V}O_2$ MRT shows potential to serve as a motivation-independent, physiological indicator of physical performance.

New & Noteworthy

A constant work rate test that is standardly performed during a pre-rehabilitation assessment is unable to provide reliable kinetic feature values for COPD patients with a peak work rate below 45 W. For patients suffering from less severe impairments, kinetic analyses are a powerful tool to examine physiological exercise responses. Especially oxygen uptake mean response time can serve as a motivation-independent, physiological indicator of physical performance in patients with COPD.

Introduction

Dynamic responses of pulmonary oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) during a constant work rate cycling test (CWRT) depend on adequate pulmonary, cardiovascular and muscle functioning (29). During a CWRT, $\dot{V}O_2$ responses are characterized by a rapid cardio-dynamic phase (phase I; Figure 1), followed by an exponential $\dot{V}O_2$ increase (phase II, the primary component of the response) towards an anticipated steady state (phase III) (36). An additional slow component, superimposed on the primary component of the response (Figure 1), can delay or prevent reaching this steady state (35, 37). Kinetic features such as mean response time (MRT) and gain describe the primary component of the $\dot{V}O_2$ response (6). $\dot{V}O_2$ mean response time (MRT) indicates the rate of the $\dot{V}O_2$ increase above unloaded cycling. It represents the time to reach 63% of the anticipated steady state while excluding the potential contribution of the slow component (Figure 1). A slow $\dot{V}O_2$ response, indicated by a high MRT, leads to higher dependencies on anaerobic energy sources and contributes to exercise intolerance (29). $\dot{V}O_2$ gain quantifies the $\dot{V}O_2$ increase (related to the primary component of the response) per unit increase in external work rate (WR). Equivalent gains can be calculated for $\dot{V}CO_2$ and $\dot{V}_E$. These gains thus quantify

71 the magnitude of the primary component of the $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ responses above
72 unloaded cycling, corrected for external WR.

73 Patients with chronic obstructive pulmonary disease (COPD) suffer from decreased
74 exercise tolerance, characterized by slow $\dot{V}O_2$ responses, compared to healthy peers (9, 19,
75 22, 23, 32). These slow $\dot{V}O_2$ responses in patients with COPD have been attributed to slow
76 muscle O_2 utilization (22, 23, 32) and/or ventilatory and cardiovascular restrictions that
77 reduce oxygen delivery to the working muscles (5, 9, 10, 12, 15, 19). When a $\dot{V}O_2$ response
78 is severely slowed, the $\dot{V}O_2$ increase is rather linear in nature, making MRT calculations
79 unreliable (6). Low response amplitudes during CWRT can additionally lead to unreliable
80 kinetic feature values for patients with COPD (8). Nevertheless, the issue of unreliable
81 kinetic feature values has not yet been properly addressed. Additionally, $\dot{V}O_2$ kinetics of
82 patients with COPD have only been examined in small study samples including at most 45
83 patients (5, 8–10, 12, 13, 15, 19, 21–23, 25–27, 30, 32, 38). Lastly, the impact of COPD-
84 related ventilatory and cardiovascular impairments on gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ remains
85 unclear. We hypothesized that these gains could be an informative tool to examine
86 physiological exercise responses of patients with COPD.

87 To address these issues, this study used a large sample of patients with COPD (n=265): i)
88 to establish simple guidelines that can identify patients for whom kinetic analyses are
89 (un)likely to be reliable; ii) to determine whether slow $\dot{V}O_2$ responses during a standard
90 CWRT are associated with ventilatory, cardiovascular and/or physical impairment; and iii) to
91 determine whether gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ during a standard CWRT are associated with
92 ventilatory, cardiovascular and/or physical impairment.

Materials and methods

Study design and participants

The investigated dataset is part of the COPD, health status and comorbidities (CHANCE) study, an observational, cross-sectional, single-center study examining health status and comorbidities in patients with COPD (31). The CHANCE study was approved by the Medical Ethical Committee of the Maastricht University Medical Centre (METC 11-3-070) and registered at the Dutch Trial Register (NTR 3416). All patients provided written informed consent. The Medical Ethical Committee of the Maastricht University Medical Centre (METC 2018-0546) confirmed that the Medical Research Involving Human Subjects Act did not apply for additional analyses of physiological exercise responses, and thus additional official approval by the Committee was not required for the current study.

Patients with COPD, referred to CIRO (Horn, the Netherlands) for clinical assessment and pulmonary rehabilitation (34), were recruited during their pre-rehabilitation assessment (31). CIRO provides an interdisciplinary pulmonary rehabilitation program in accordance with the latest international American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation (33). Demographics, resting post-bronchodilator spirometry, whole-body plethysmography, lung diffusion capacity, the modified Medical Research Council (mMRC) dyspnea grading, resting arterial blood gas analyses (i.e. arterial oxygen saturation, pH and partial pressure of oxygen and carbon dioxide), fat-free mass index using dual-energy X-ray absorptiometry and physical performance (i.e. six-minute walking distance, $\dot{V}O_{2,peak}$, WR_{peak}, CWRT endurance time and quadriceps isokinetic peak torque) data were collected during the pre-rehabilitation assessment as described before (31, 34). Maximal voluntary ventilation (MVV) was estimated by multiplying FEV_1 by 40. Resting echocardiography was added to these standard tests to assess left ventricular ejection

fraction (LVEF), left ventricular end-diastolic diameter, left atrium diameter, right ventricle diameter and interventricular septum thickness (31). A symptom-limited incremental cardiopulmonary exercise test was performed on an electrically braked cycle ergometer (Oxycon Pro, Carefusion, Houten, the Netherlands) to assess peak $\dot{V}O_2$ and WR values. The day after, a symptom-limited CWRT was performed to assess CWRT endurance time. In accordance to standard practice, the CWRT started with a period of rest (3 minutes) and unloaded cycling (3 minutes), after which the WR increased instantaneously to 75% of the WR_{peak} achieved during the prior incremental cardiopulmonary exercise test (33). $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ responses were determined breath-by-breath (Oxycon Pro, Carefusion, Houten, the Netherlands).

Kinetic analyses

Breath-by-breath data during CWRT were pre-processed and resampled to a 1 Hz time series as explained by Buekers and colleagues (6). A Box-Jenkins transfer function with a first order system model and a second order noise model was fitted to the $\dot{V}O_2$ time series from 30 s before the increase in WR until 180 s after this step increase in WR to calculate $\dot{V}O_2$ MRT (= time delay + time constant; Figure 1) (6). This 180 s cut-off has generally been used to diminish the potential contribution of the slow component (35, 37). Gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ were estimated as follows:

$$Gain = \frac{Variable_{[150s-180s]} - Variable_{unloaded}}{\Delta WR}$$

where $Variable_{[150s-180s]}$ was calculated as the mean of the last 30 s of the $\dot{V}O_2$, $\dot{V}CO_2$ or $\dot{V}_E$ responses that were used for kinetic modelling (i.e. 150s to 180 s); $Variable_{unloaded}$ as the mean of the last 30 s of $\dot{V}O_2$, $\dot{V}CO_2$ or $\dot{V}_E$ during unloaded cycling before the increase in WR; and ΔWR as the WR increase. The system model fit was assessed by the normalized root-mean-squared error value (NRMSE), calculated as the root-mean-square of the system

model errors (i.e. difference between the modelled value and the pre-processed time series) divided by the difference between $Variable_{[150s-180s]}$ and $Variable_{unloaded}$.

Patients were excluded from analyses if they did not perform breath-by-breath measurements of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ during the CWRT or if they had a CWRT endurance time lower than 180 s. In addition, patients exhibiting unreliable kinetic feature values were excluded for kinetic analyses. Kinetic feature values could not reliably be calculated due to: 1) a low increase above unloaded cycling of $\dot{V}O_2$ (<200 $ml.min^{-1}$), $\dot{V}CO_2$ (<200 $ml.min^{-1}$) or $\dot{V}_E$ (<7 $L.min^{-1}$) after 180 s (being lower than 2.5 standard deviations of the breath-by-breath fluctuations (14, 25)); 2) a poor $\dot{V}O_2$ system model fit, defined as NRMSE >25%; 3) a severely slowed $\dot{V}O_2$ response ($\dot{V}O_2$ MRT >150 s; see Supplemental Material S1: http://doi.org/10.5281/zenodo.3638187). 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 (6).

Statistical analyses

Results are presented as mean and standard deviation or median and interquartile range for respectively normally or non-normally distributed variables. 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 were compared between patients exhibiting unreliable and reliable kinetic feature values, using Student's t-tests, Wilcoxon rank-sum tests and chi-squared tests, as appropriate.

In addition, this comparison between patients that exhibited unreliable and reliable kinetic feature values was used to highlight the variables of interest that could identify patients for whom kinetic analyses are (un)likely to be reliable. A range of cut-off values for these variables of interest were then tested as a prediction method, where kinetic feature values

were predicted to be unreliable (or reliable) for patients below (or above) the cut-off value. For each cut-off value, patients were then classified as a true negative (patients exhibiting unreliable kinetic feature values for whom kinetic feature values were also predicted to be unreliable), true positive (exhibiting reliable and predicted to be reliable), false negatives (exhibiting reliable, but predicted to be unreliable) or false positives (exhibiting unreliable, but predicted to be reliable). Negative predictive values (i.e. the amount of true negatives divided by the total amount of predicted negatives) were examined to determine cut-off values below which kinetic analyses are unlikely to be reliable. These negative predictive values indicated the percentage of patients below the selected cut-off values who indeed exhibited unreliable kinetic feature values. Equivalently, positive predictive values (i.e. the amount of true positives divided by the total amount of predicted positives, which indicated the percentage of patients above the selected cut-off value who indeed exhibited reliable kinetic feature values) were examined to determine cut-off values above which kinetic analyses are likely to be reliable. In addition, the group of patients that would be identified as "(un)likely to exhibit reliable kinetic feature values" should be sufficiently large. Therefore, the amount of patients with values below or above the selected cut-off values were simultaneously assessed.

For the patients that were included for kinetic analyses, correlations between kinetic feature values and patient demographics, resting pulmonary function, resting arterial blood gases, resting echocardiography and physical performances were assessed using Pearson and Spearman correlation coefficients, as appropriate. In addition, patient demographics, resting pulmonary function and resting echocardiography were used as independent variables in a multiple linear regression model to identify which patient characteristics were independently related to the kinetic feature values. Statistical significance was accepted at the $p<0.05$ level.

Results

Patient characteristics

One hundred and forty-three of the 518 recruited COPD patients did not perform breath-by-breath measurements of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ during CWRT (Figure 2). For 70% of these patients (=100/143), this was because they received long-term oxygen therapy (Supplemental Material S2: http://doi.org/10.5281/zenodo.3687069). An additional 110 patients with severe ventilatory and physical impairments were excluded for analyses because of an insufficient (<180 s) CWRT endurance time (Figure 2; Supplemental Material S2: http://doi.org/10.5281/zenodo.3687069). The 265 remaining patients had an average age of 63±9 years, suffered from moderate to very severe COPD, had an impaired diffusion capacity and experienced physical impairments (Table 1). There were slightly more men (156/265=59%) and 28 (28/265=11%) of the patients suffered from reduced LVEF (<50%). There were missing data points for fat-free mass index (n=12), transfer factor for carbon monoxide (TLCO; n=10), residual volume (RV; n=8), mMRC dyspnea grading (n=2), echocardiography (n=3), quadriceps isokinetic peak torque (n=23) and six-minute walking distance (n=1).

Kinetic analyses

Kinetic feature values were unreliable for 56 of the patients that were included for general analyses (17+15+24=56; 56/265=21%; Figure 2). These patients were thus excluded for kinetic analyses. Figure 3 provides representative examples of $\dot{V}O_2$ responses of patients that exhibited unreliable kinetic feature values due to a low $\dot{V}O_2$ response, a poor $\dot{V}O_2$ system model fit or a severely slowed $\dot{V}O_2$ response. These 56 patients were older and suffered from more severe ventilatory and physical impairments compared to the 209 patients with reliable

kinetic feature values (Table 1). Consequently, WR_{peak} and FEV_1 (in L) were considered as the variables of interest to identify patients for whom kinetic analyses are (un)likely to be reliable. As illustrated in Figure 4, kinetic feature values were unreliable for most patients with a low WR_{peak}, whereas kinetic feature values were reliable for most patients with a high FEV_1 value.

A WR_{peak} cut-off value of 45 W (corresponding to a negative predictive value of 79%) was selected to identify patients for whom kinetic analyses are unlikely to be reliable, as higher cut-off values would drastically increase the amount of patients for whom kinetic feature values would falsely be predicted to be unreliable (i.e. a drastic decrease of the negative predictive value, Figure 4). Twenty-four patients (24/265=9%) had a WR_{peak} value lower than this 45 W cut-off value (Figure 4). For FEV_1, a cut-off value of 1.3 L (corresponding to a positive predictive value of 94%) was selected to identify patients for whom kinetic analyses are likely to be reliable (Figure 4). One hundred and forty-two patients (142/265=53%) had a FEV_1 value higher than this 1.3 L cut-off value (Figure 4). Higher cut-off values could still increase the positive predictive value, however, this would drastically decrease the size of the patient group that could be identified as "likely to exhibit reliable kinetic feature values" (Figure 4).

Figure 5 illustrates representative $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ responses of a patient that could be included for kinetic analyses. The Box-Jenkins transfer function system models of the 209 patients that were included for kinetic analyses had a median NRMSE of 11.6±6.5%. No differences in NRMSE values were observed when these patients were dichotomized according to age (≥60 years: 11.8±6.8%; <60 years: 11.3±6.4%; p=0.63), gender (male: 11.4±6.4%; female: 11.7±6.1%; p=0.38) or GOLD stage (GOLD stage I-II: 11.3±7.1%; GOLD stage III-IV: 11.6±5.3%; p=0.77).

Mean response time

Patients exhibiting reliable kinetic feature values had a median $\dot{V}O_2$ MRT of 72±30 s. $\dot{V}O_2$ MRT was negatively correlated with FEV_1%predicted ($p<0.001$; $r=-0.35$), TLCO%predicted ($p=0.01$; $r=-0.18$) and partial pressure of oxygen ($p=0.02$; $r=-0.16$), while being positively correlated with age ($p=0.004$; $r=0.20$), RV%predicted ($p<0.001$; $r=0.29$) and $V_E/MVV_{[150s-180s]}$ ($p<0.001$; $r=0.26$). Multiple regression analysis generated the following model: $\dot{V}O_2$ MRT = – (0.47 × FEV_1%predicted) + (0.51 × age) + 73.7 ($R^2 = 0.17$). In addition, slower $\dot{V}O_2$ responses were linked with physical impairment as assessed by six-minute walking distance in meters ($p=0.01$; $r=-0.18$) and as %predicted ($p=0.009$; $r=-0.18$), $\dot{V}O_{2peak}$ in $ml.min^{-1}$ ($p=0.002$; $r=-0.22$) and as %predicted ($p<0.001$; $r=-0.24$). No significant correlations were observed between $\dot{V}O_2$ MRT and gains of $\dot{V}O_2$, $\dot{V}CO_2$ or $\dot{V}_E$.

Gains

Patients exhibiting reliable kinetic feature values had a mean $\dot{V}O_2$ gain of 9.4±1.8 $ml.min^{-1}.W^{-1}$. $\dot{V}O_2$ gain was negatively correlated with FEV_1%predicted ($p<0.001$; $r=-0.23$), left atrium diameter ($p=0.02$; $r=-0.17$) and interventricular septum thickness ($p=0.03$; $r=-0.15$), while being positively correlated with RV%predicted ($p=0.002$; $r=0.22$), partial pressure of carbon dioxide ($p=0.03$; $r=0.15$), LVEF ($p=0.001$; $r=0.23$) and $\dot{V}_E/MVV_{[150s-180s]}$ ($p<0.001$; $r=0.38$). Multiple regression analysis generated the following model: $\dot{V}O_2$ gain = – (0.022 × FEV1%predicted) + (0.044 × LVEF) + 8.04 ($R^2 = 0.10$)

Patients exhibiting reliable kinetic feature values had a mean $\dot{V}CO_2$ gain of 11.1±1.9 $ml.min^{-1}.W^{-1}$. $\dot{V}CO_2$ gain was negatively correlated with age ($p=0.002$; $r=-0.21$), BMI ($p=0.04$; $r=-0.14$), fat-free mass index ($p=0.03$; $r=-0.16$), left atrium diameter ($p=0.02$; $r=-0.16$), right ventricle diameter ($p=0.02$; $r=-0.16$) and interventricular septum thickness ($p=0.02$; $r=-0.16$), while being positively correlated with TLCO%predicted ($p=0.03$; $r=0.15$),

partial pressure of oxygen ($p<0.001$; $r=0.23$), LVEF ($p=0.008$; $r=0.19$) and $\dot{V}_E/MVV_{[150s-180s]}$ ($p<0.001$; $r=0.22$). Multiple regression analysis generated the following model: $\dot{V}CO_2$ gain = – (0.032 × age) – (0.17 × fat-free mass index) + (0.028 × TLCO%predicted) + 14.56 (R^2 = 0.11). In addition, a weak positive association was found between $\dot{V}CO_2$ gain and $\dot{V}O_{2peak}$%predicted ($p=0.03$; $r=0.14$).

Patients exhibiting reliable kinetic feature values had a median $\dot{V}_E$ gain of 0.36±0.14 $L.min^{-1}.W^{-1}$. $\dot{V}_E$ gain was negatively correlated with TLCO%predicted ($p=0.005$; $r=-0.20$), BMI ($p<0.001$; $r=-0.27$), fat-free mass index ($p=0.007$; $r=-0.19$), partial pressure of carbon dioxide ($p<0.001$; $r=-0.26$), left ventricular end-diastolic diameter ($p=0.02$; $r=-0.16$), left atrium diameter ($p=0.04$; $r=-0.14$), right ventricle diameter ($p=0.004$; $r=-0.20$) and interventricular septum thickness ($p=0.04$; $r=-0.15$), while being positively correlated with FEV_1%predicted ($p=0.04$; $r=0.14$) and $\dot{V}_E/MVV_{[150s-180s]}$ ($p=0.004$; $r=0.20$). Multiple regression analysis generated the following model: $\dot{V}_E$ gain = – (0.0017 × TLCO%predicted) – (0.0051 × BMI) + (0.0017 × FEV1%predicted) + (0.0084 × left atrium diameter) + 0.48 (R^2 = 0.20). In addition, V_E gain was negatively correlated with isokinetic peak torque as %predicted ($p=0.01$; $r=-0.18$) and CWRT endurance time ($p<0.001$; $r=-0.24$).

Discussion

This study examined kinetic feature values of physiological responses at the onset of a standard CWRT in a large sample of COPD patients with moderate to very severe COPD. Kinetic feature values were unreliable for 21% of the patients in the examined sample. The results showed that patients with a WR_{peak} value below 45 W can be expected to exhibit unreliable kinetic feature values, whereas patients with a FEV_1 value above 1.3 L can be expected to exhibit reliable kinetic feature values. For patients that exhibited reliable kinetic

feature values, slow $\dot{V}O_2$ responses were associated with ventilatory and physical impairments. Gains were mainly associated with cardiac function and ventilatory constraints.

Although 15% (6 out of 41) and 48% (12 out of 25) of COPD patients were excluded for kinetic analyses in previous studies (8, 27), this patient group has not yet been further examined. The current study showed that COPD patients with unreliable kinetic feature values during a standard CWRT represented a group of older patients with very severe ventilatory and physical impairments. More than three-quarters (79%) of patients with a WR_{peak} value below 45 W exhibited unreliable kinetic feature values. These severely reduced absolute WRs led to very low response amplitudes or reduced signal to noise ratios (6, 7), making kinetic feature values unreliable (4, 14). Consequently, kinetic analyses are likely to be unreliable for patients with a WR_{peak} lower than 45 W. In contrast, kinetic feature values can be expected to be reliable for patients with a FEV_1 value above 1.3 L, as 94% of the included patients with an FEV_1 value above 1.3 L exhibited reliable kinetic feature values.

When ventilatory restrictions did not result in unreliable kinetic feature values, they were still associated with higher $\dot{V}O_2$ MRT values. Slow $\dot{V}O_2$ responses in patients with COPD have mainly been attributed to slow central cardiovascular responses, resulting from increased intrathoracic pressure swings due to airflow obstruction and dynamic hyperinflation, ultimately impairing convective O_2 transport to the working muscles (5, 9, 10, 12, 15, 19). The observed associations between slow $\dot{V}O_2$ responses and airflow limitation, RV and $V_E/MVV_{[150s-180s]}$ support this reasoning. Also impaired peripheral cardiovascular responses (9, 30) and slow muscle O_2 utilization (22, 23, 32) have been suggested to slow $\dot{V}O_2$ responses of COPD patients. Most likely, the slow $\dot{V}O_2$ responses observed in patients with COPD cannot be attributed to a single mechanism, but are the result of a combination of ventilatory, cardiovascular and/or muscular malfunctioning. Nevertheless, the results of the current study are in line with the notion that ventilatory and associated cardiovascular

307 restrictions could be the main factor in slowing $\dot{V}O_2$ responses of COPD patients at higher
308 exercise intensities.

309 The associations between $\dot{V}O_2$ MRT and physical performances indicates that $\dot{V}O_2$ MRT,
310 extracted from a standard CWRT, could be an important physiological indicator of physical
311 performance. This has previously also been observed in healthy men (17). Slow $\dot{V}O_2$
312 responses at exercise onset introduce higher dependencies on anaerobic energy sources (29),
313 lead to faster muscle deoxygenation in patients with COPD (9) and are thus shown to be
314 related to impaired physical performances. Bronchodilator therapy or heliox breathing have
315 been reported to decrease $\dot{V}O_2$ MRT by improving breathing mechanics, subsequently
316 slowing muscle deoxygenation and ultimately leading to increased physical performances (5,
317 10). Strategies decreasing $\dot{V}O_2$ MRT, e.g. due to improved breathing mechanics related to
318 exercise training (8, 26), heliox breathing (10), bronchodilator therapy (5, 15) or
319 bronchoscopic lung volume reduction (12), are therefore likely to improve physical
320 performances.

321 Response gains have been considerably less examined than $\dot{V}O_2$ MRT. They are generally
322 assumed to be a measure of (in)efficiency (29). Therefore, the association of a higher $\dot{V}O_2$
323 gain with more severe airflow obstruction, a higher RV and a higher $\dot{V}_E/MVV_{[150s-180s]}$
324 suggests that these ventilatory impairments lead to $\dot{V}O_2$ inefficiency, which is most likely
325 related to the increased O_2 cost of breathing for COPD patients with more severe airflow
326 obstruction (2, 16). Aliverti and colleagues calculated that O_2 cost of breathing in COPD
327 patients might be as high as 48% of the total O_2 uptake (1). In a similar way, $\dot{V}_E$ gain can be
328 used as a measure of ventilatory (in)efficiency, for which generally the $\dot{V}_E/\dot{V}CO_2$ relationship
329 during incremental exercise testing has been used (18). The current study also confirmed that
330 $\dot{V}_E$ gain, similar to the $\dot{V}_E/\dot{V}CO_2$ relationship (18), was negatively correlated with diffusion
331 capacity and physical performance. Nevertheless, as a standard CWRT at 75% WR_{peak} can be

considered as a test of maximal physical performance for patients with COPD (20), response gains can also represent physiological limitations. In this regard, decreased cardiorespiratory functioning at older age could explain the limited $\dot{V}CO_2$ gain for older patients (11). Also a decreased diffusion capacity was associated with limited $\dot{V}CO_2$ gains, while increased airflow limitation was associated with limited $\dot{V}_E$ gains. Similarly, reduced LVEF and enlarged left atrium, right ventricle and interventricular septum were related to limited $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ increases per unit of WR, similar to the observed association between reduced $\dot{V}O_{2peak}$ and enlarged ventricular and atrial cavities in patients with heart failure (24). A recent study reported a similar association between a higher left ventricular end-diastolic diameter and a decreased $\dot{V}O_2$ response per unit of WR during an incremental exercise test of patients with coexisting COPD and systolic heart failure (28). Gains can therefore represent both response efficiency and limitation.

The kinetic features extracted from a standard CWRT ($\dot{V}O_2$ MRT and $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ gains) can thus shed light on physiological exercise responses, as discussed above. An important asset of these kinetic features is that they can be considered as motivation-independent, in contrast to generally accepted indicators of physical performance like WR_{peak}, $\dot{V}O_{2,peak}$ and CWRT endurance time (33). This also makes kinetic features insightful for quantifying physiological adaptations after interventions like exercise training or bronchoscopic lung volume reduction. Especially $\dot{V}O_2$ MRT shows potential to serve as a motivation-independent, physiological indicator of physical performance.

In addition, extracting kinetic features from a CWRT that is standardly performed during a pre-rehabilitation assessment does not require any additional testing, offering an easy approach to enhance clinical patient assessments. Whereas current clinical assessments are mainly based on outcomes that assess patients under ‘steady-state’ (resting) conditions, kinetic features quantify the dynamic, physiological responses during the ‘transition-state’

357 from unloaded cycling to cycling at 75% of WR_{peak}. This difference might also be one of the
358 main reasons why the 'steady-state' patients characteristics in this study could only explain a
359 relatively small proportion of the variance in kinetic feature values. Furthermore, including
360 intramuscular variables could still increase the explanatory power of 'steady-state' (resting)
361 patient characteristics.

362 Some limitations should be taken into account for proper interpretation of the results of
363 the current study. Firstly, kinetics analyses were based on a single transition from rest to
364 exercise, as the data were collected during a standard pre-rehabilitation CWRT (31). This
365 approach has been used before (8, 9, 12, 30), because performing multiple CWRTs during a
366 pre-rehabilitation assessment might not be practically feasible for this patient population.
367 Furthermore, a more complex type of models was used to account for breath-by-breath
368 fluctuations (6). Secondly, kinetic analyses of physiological responses during high intensity
369 exercise might be affected by the presence of a slow component that can delay or prevent
370 reaching a steady state (35, 37). The onset of this slow component can occur around 100s –
371 200s after exercise onset (3), which can add uncertainty to the extracted kinetic feature
372 values. The slowed physiological responses of patients with COPD might also prevent that a
373 steady state is fully reached at the 180 s cut-off value. Nevertheless, the applied 180 s cut-off
374 has often been used to account for the potential contribution of the slow component in
375 patients with COPD, as this slow component might not yet be discernible during the first 180
376 s of high-intensity exercise (5, 9, 10, 15, 30). Thirdly, gains were estimated using the
377 presented formula, as the very slow $\dot{V}CO_2$ and $\dot{V}_E$ responses did not allow for the
378 development of accurate models from which $\dot{V}CO_2$ and $\dot{V}_E$ gains could be extracted.
379 Therefore, gain values were approximations of the true underlying gains. Also the fact that
380 exercising at 75% WR_{peak} might not correspond to the same point on the power duration
381 curve for different patients, could add uncertainty to the estimated gains. Due to these sources

of uncertainty and the cross-sectional nature of the current study, future studies will still be needed to determine the exact clinical value of kinetic features that are extracted from a standard CWRT at 75% of WR_{peak}. Nevertheless, the results of the current study show that these features capture valuable information about physiological responses at exercise onset.

In conclusion, this study is the first to perform kinetic analyses on a large sample of COPD patients that were subjected to an elaborate clinical assessment. The results showed that patients with a WR_{peak} lower than 45 W are likely to exhibit unreliable kinetic feature values, while kinetic analyses can be considered reliable for most patients with an FEV_1 value above 1.3 L. For patients with reliable kinetic feature values, $\dot{V}O_2$ MRT during a standard CWRT could serve as a motivation-independent, physiological indicator of physical performance. Gains further enriched analyses of physiological exercise responses, representing both response efficiency and limitation.

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Conflicts of Interest

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

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Figure captions

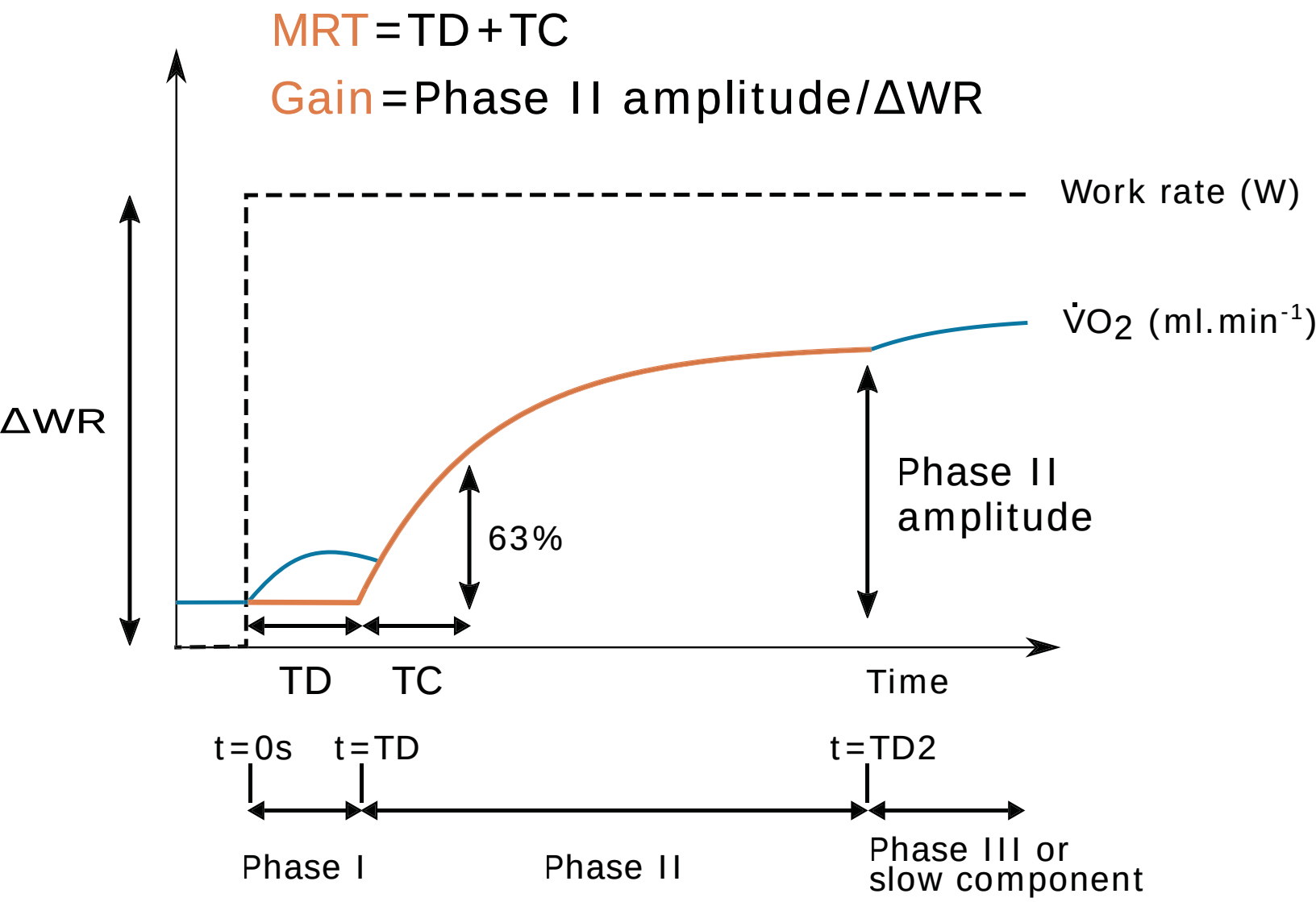
Figure 1: Representation of a typical oxygen uptake ($\dot{V}O_2$) response at the onset of a constant work rate test (blue line) and the specific phase II contribution (orange line). Both lines coincide during phase II. The black dashed line visualises the load increase at t = 0 s. MRT = mean response 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 (3).

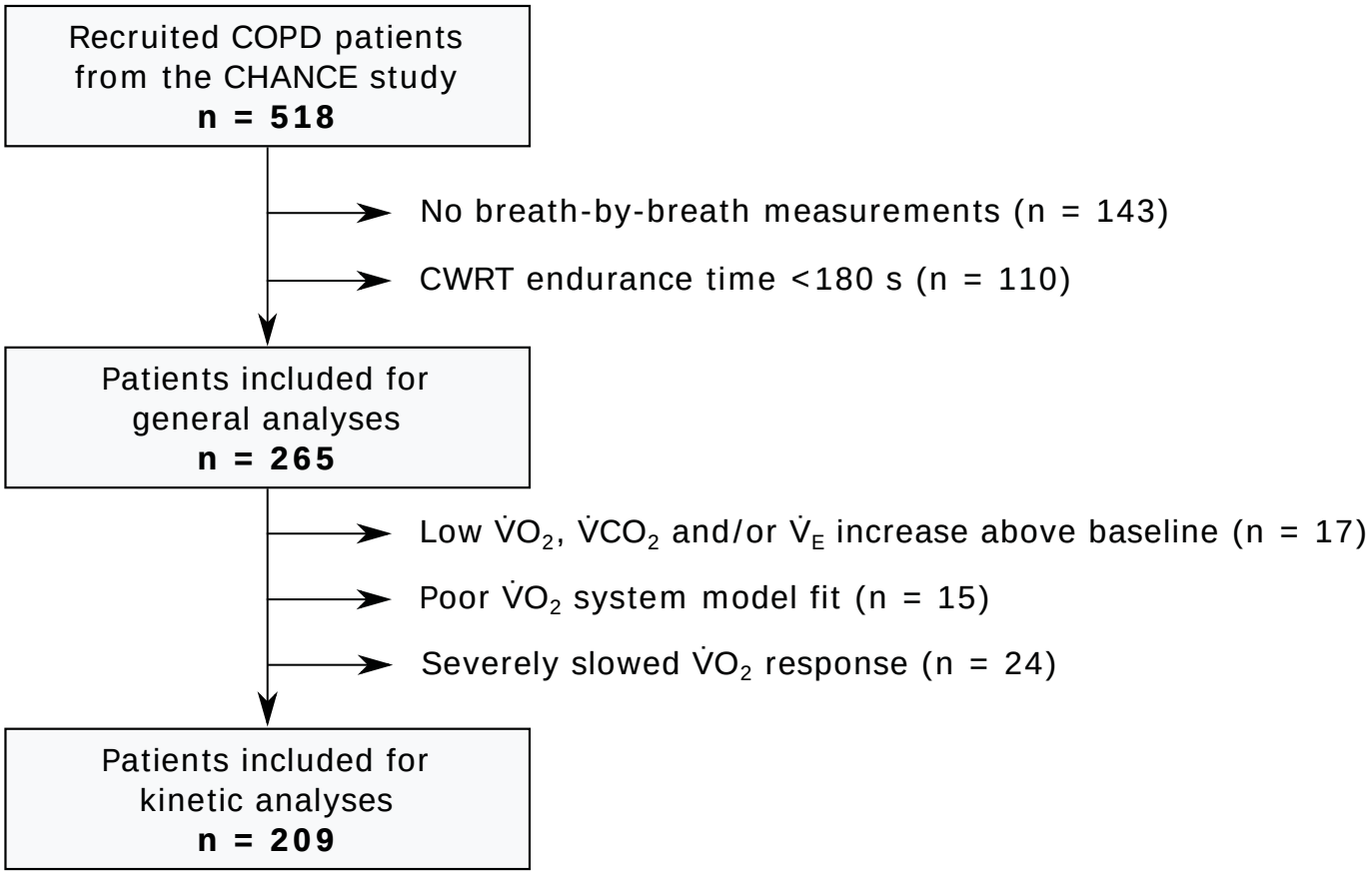
Figure 2: Overview of patients included for general and kinetic analyses. CWRT = constant work rate test; $\dot{V}O_2$ = oxygen uptake; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}_E$ = minute ventilation.

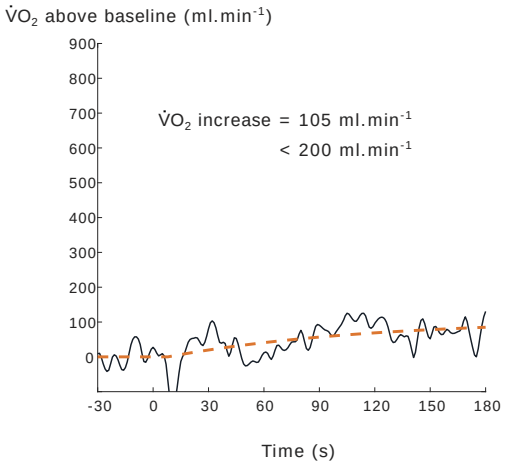
Figure 3: Representative examples of $\dot{V}O_2$ responses of patients exhibiting unreliable kinetic feature values due to a low $\dot{V}O_2$ increase above unloaded cycling (left), a poor $\dot{V}O_2$ system model fit (middle) or a severely slowed $\dot{V}O_2$ response. The orange dashed lines represents the Box-Jenkins transfer function system model. $\dot{V}O_2$ = oxygen uptake; NRMSE = normalized root-mean-squared error; MRT = mean response time.

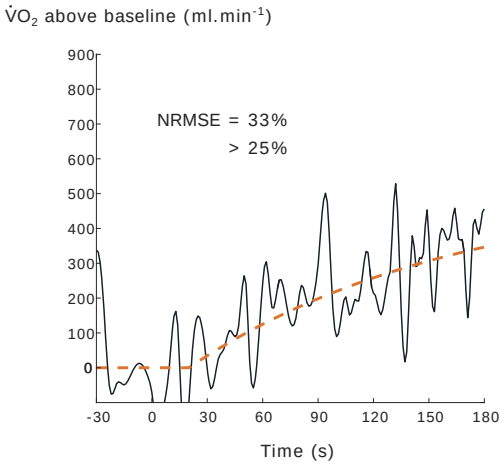
Figure 4: A peak work rate (WR_{peak}) cut-off value of 45 W corresponded to a negative predictive value of 79% for the prediction of patients who exhibited unreliable kinetic feature values. Twenty-four patients (24/265=9%) had a WR_{peak} <45 W. A forced expiratory volume in 1 s (FEV_1) cut-off value of 1.3 L corresponded to a positive predictive value of 94% for the prediction of patients who exhibited reliable kinetic feature values. One hundred and forty-two patients (142/265=53%) had a FEV_1 >1.3 L.

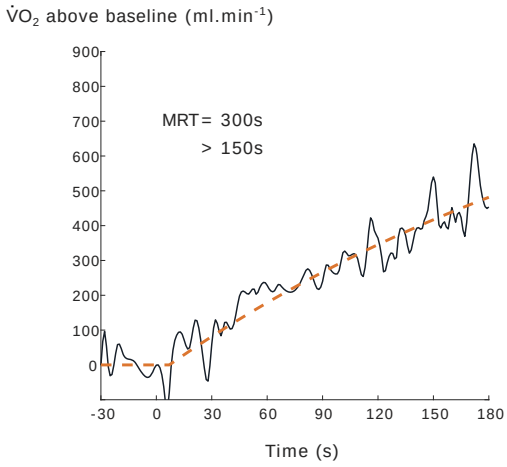
Figure 5: Representative example of oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) responses above unloaded cycling at exercise onset of a patient that was included for kinetic analyses. The work rate increased from 0 W to 67 W at Time = 0 s. The orange dashed lines represents the Box-Jenkins transfer function system model.

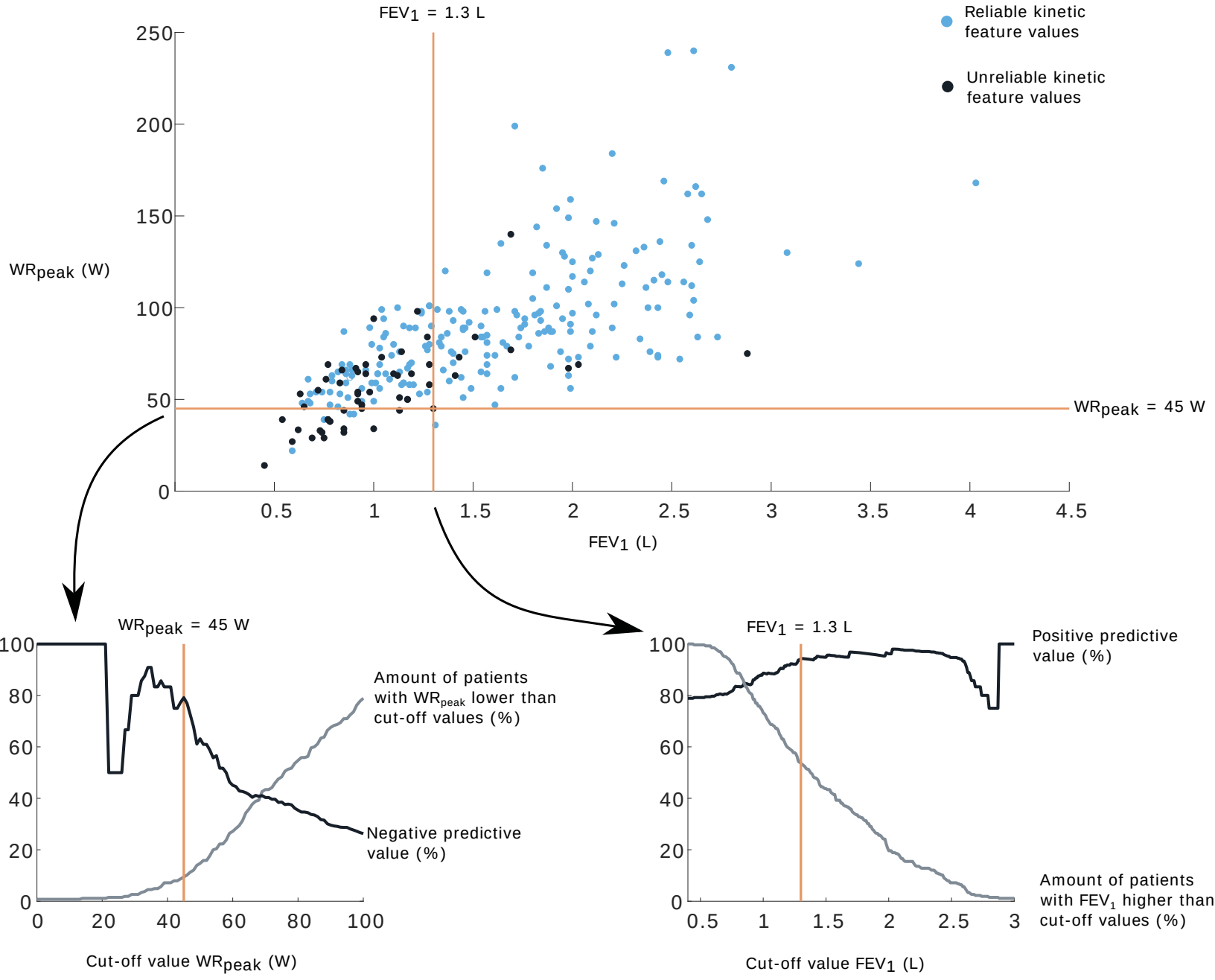

MRT = TD + TC
Gain = Phase II amplitude/ΔWR
Work rate (W)
V̇O2 (ml.min-1)
ΔWR
63%
Phase II amplitude
TD
TC
Time
t = 0s
t = TD
t = TD2
Phase I
Phase II
Phase III or slow component

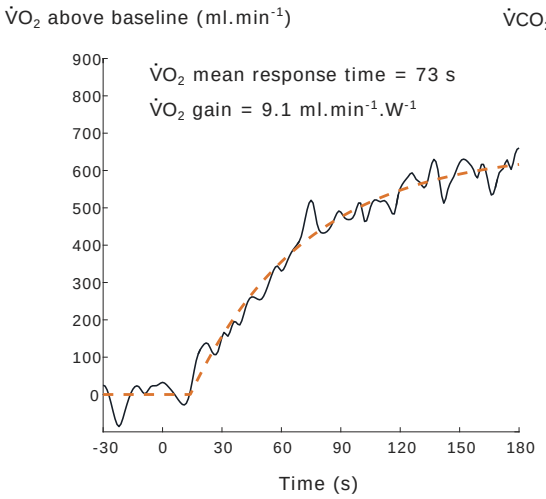

Recruited COPD patients from the CHANCE study
n = 518
No breath-by-breath measurements (n = 143)
CWRT endurance time <180 s (n = 110)
Patients included for general analyses
n = 265
Low $\dot{V}O_2$, $\dot{V}CO_2$ and/or $\dot{V}_E$ increase above baseline (n = 17)
Poor $\dot{V}O_2$ system model fit (n = 15)
Severely slowed $\dot{V}O_2$ response (n = 24)
Patients included for kinetic analyses
n = 209

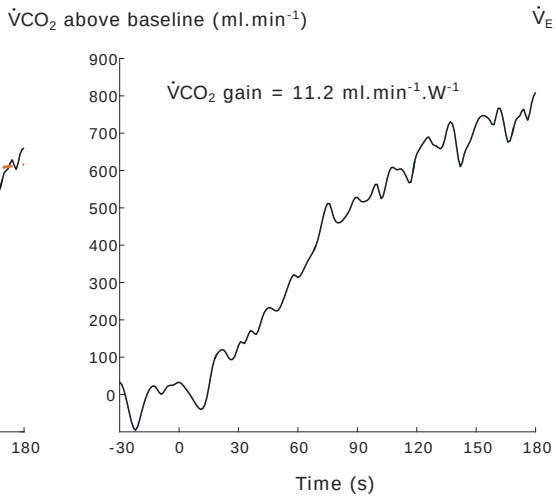

V̇O2 above baseline (ml.min-1)
V̇O2 increase = 105 ml.min-1
< 200 ml.min-1
900
800
700
600
500
400
300
200
100
0
-30
0
30
60
90
120
150
180
Time (s)


V̇O2 above baseline (ml.min-1)
NRMSE = 33%
> 25%
900
800
700
600
500
400
300
200
100
0
-30
0
30
60
90
120
150
180
Time (s)


V̇O2 above baseline (ml.min-1)
MRT= 300s
> 150s
900
800
700
600
500
400
300
200
100
0
-30
0
30
60
90
120
150
180
Time (s)


FEV1 = 1.3 L
Reliable kinetic feature values
Unreliable kinetic feature values
WRpeak (W)
WRpeak = 45 W
FEV1 (L)
250
200
150
100
50
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
WRpeak = 45 W
Amount of patients with WRpeak lower than cut-off values (%)
Negative predictive value (%)
Cut-off value WRpeak (W)
FEV1 = 1.3 L
Positive predictive value (%)
Amount of patients with FEV1 higher than cut-off values (%)
Cut-off value FEV1 (L)
100
80
60
40
20
0


V̇O2 above baseline (ml.min-1)
V̇O2 mean response time = 73 s
V̇O2 gain = 9.1 ml.min-1.W-1
900
800
700
600
500
400
300
200
100
0
-30
0
30
60
90
120
150
180
Time (s)


V̇CO2 above baseline (ml.min-1)
V̇CO2 gain = 11.2 ml.min-1.W-1
900
800
700
600
500
400
300
200
100
0
-30
0
30
60
90
120
150
180
Time (s)

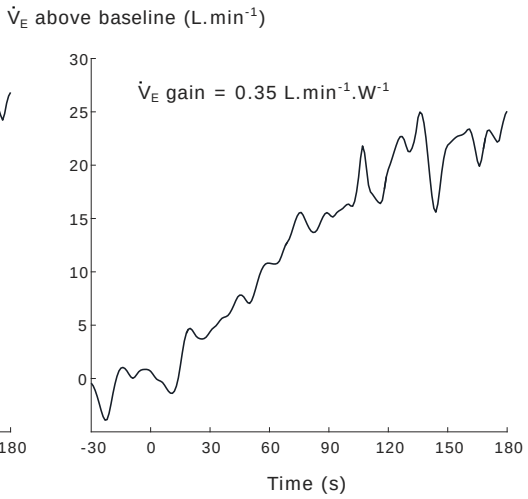

V̇E above baseline (L.min-1)
V̇E gain = 0.35 L.min-1.W-1
30
25
20
15
10
5
0
-30
0
30
60
90
120
150
180
Time (s)

Table 1: Characteristics of patients included for general analyses (first column), divided as patients exhibiting unreliable (second column; excluded for kinetic analyses) and reliable (third column; included for kinetic analyses) kinetic feature values.

	Patients included for general analyses (n=265)	*Patients with unreliable kinetic feature values (n=56)*	*Patients with reliable kinetic feature values (n=209)*
Demographics			
Male – female	156 – 109	27 – 29	129 – 80
Age (years)	63 (9)	**68 (8)**	**62 (9)****
Body Mass Index (kg/m²)	26.8 (6.0)	26.4 (5.4)	26.9 (6.2)
Fat-free mass index (kg/m²)	17.4 (2.5)	17.0 (2.3)	17.5 (2.6)
Resting pulmonary function			
Forced expiratory volume in 1 second (FEV_1; %predicted)	54 (19)	**43 (15)**	**57 (19)*****
Forced vital capacity (FVC; %predicted)	104 (18)	100 (20)	105 (17)
FEV_1/FVC (%)	39 (12)	**33 (10)**	**42 (12)*****
Transfer factor for carbon monoxide (%predicted)	55 (16)	**47 (12)**	**56 (16)****
Residual volume (%predicted)	151 (44)	**164 (36)**	**147 (45)***
Modified Medical Research Council grading ≥ 2 (% patients)	72	**88**	**68****
Resting arterial blood gases			
Arterial oxygen saturation (%) #	94.8 (2.7)	94.4 (3.3)	94.9 (2.6)
Partial pressure of oxygen (kPa)	9.66 (1.36)	9.53 (1.25)	9.69 (1.38)
Partial pressure of carbon dioxide (kPa) #	5.00 (0.70)	5.20 (0.90)	5.00 (0.70)
pH #	7.42 (0.03)	7.42 (0.05)	7.42 (0.03)
Resting echocardiogram			
Left ventricular ejection fraction (%) #	61 (7)	**59 (8)**	**62 (7)***
Left ventricular end-diastolic diameter (mm)	44 (6)	43 (6)	44 (6)
Left atrium diameter (mm)	36 (6)	35 (6)	36 (6)
Right ventricle diameter (mm)	35 (5)	35 (4)	34 (5)
Interventricular septum thickness (mm) #	9 (2)	9 (2)	9 (2)
Physical performance			
Six-minute walking distance (m)	477 (105)	**401 (97)**	**497 (98)*****
Six-minute walking distance (%predicted)	74 (15)	**67 (15)**	**76 (14)****
Peak work rate (W) #	76 (39)	**54 (29)**	**85 (37)*****
Peak work rate (%predicted) #	58 (31)	**46 (29)**	**60 (29)****
Peak oxygen uptake ($ml.min^{-1}$) #	1105 (495)	**911 (287)**	**1178 (505)*****
Peak oxygen uptake (%predicted) #	63 (32)	60 (38)	64 (31)
Isokinetic peak torque (Nm)	104 (38)	**83 (30)**	**110 (38)*****
Isokinetic peak torque (%predicted)	71 (18)	**63 (14)**	**73 (19)****
CWRT - Endurance time (s) #	294 (184)	**242 (119)**	**305 (199)****
CWRT - Minute ventilation$_{[150s-180s]}$ (%MVV)	78 (24)	**84 (33)**	**76 (21)***

Values are represented as mean (standard deviation). # Indicates when values are represented as median (interquartile range). Values in bold indicate significant differences between the two patient groups using Student's t-tests, Wilcoxon rank-sum tests or chi-squared tests, as appropriate (*: $p<0.05$; **: $p<0.001$; ***: $p<10^{-5}$). CWRT = constant work rate test; MVV = maximal voluntary ventilation.