

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

Peer-reviewed author version

Buekers, Joren; Aerts, Jean-Marie; THEUNIS, Jan; Houben-Wilke, Sarah; Franssen, Frits M. E.; Uszko-Lencer, Nicole H. M. K.; Wouters, Emiel F. M.; Simons, Sami; DE BOEVER, Patrick & SPRUIT, Martijn A. (2020) Kinetic analyses as a tool to examine physiological exercise responses in a large sample of patients with COPD. In: JOURNAL OF APPLIED PHYSIOLOGY, 128 (4) , p. 813 -821.

DOI: 10.1152/jappphysiol.00851.2019

Handle: <http://hdl.handle.net/1942/31304>

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

3 Abbreviated title: Physiological exercise responses in COPD

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

7 <sup>1</sup> Health Unit, Flemish Institute for Technological Research (VITO), Mol, Belgium

8 <sup>2</sup> Measure, Model & Manage Bioresponses, Department of Biosystems, KU Leuven, Leuven,  
9 Belgium

10 <sup>3</sup> Department of Research and Development, CIRO, Horn, The Netherlands

11 <sup>4</sup> School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht  
12 University Medical Centre, Maastricht, The Netherlands

13 <sup>5</sup> Department of Respiratory Medicine, Maastricht University Medical Centre, Maastricht,  
14 The Netherlands.

15 <sup>6</sup> Department of Cardiology, Maastricht University Medical Centre, Maastricht, The  
16 Netherlands

17 <sup>7</sup> Centre for Environmental Sciences, Hasselt University, Diepenbeek, Belgium

18 <sup>8</sup> Rehabilitation Research Center (REVAL), Biomedical Research Institute (BIOMED),  
19 Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium

20

21 **Corresponding author:**

22 Joren Buekers, Kasteelpark Arenberg 30, 3000 Leuven, Belgium

23 joren.buekers@kuleuven.be

24 **Key words:** Oxygen uptake; minute ventilation; kinetics; mean response time; exercise  
25 physiology

## 26 Abstract

27 Kinetic features such as oxygen uptake ( $\dot{V}O_2$ ) mean response time (MRT) and gains of  
28  $\dot{V}O_2$ , carbon dioxide output ( $\dot{V}CO_2$ ) and minute ventilation ( $\dot{V}_E$ ) can describe physiological  
29 exercise responses during a constant work rate test of patients with chronic obstructive  
30 pulmonary disease (COPD). This study aimed to establish simple guidelines that can identify  
31 COPD patients for whom kinetic analyses are (un)likely to be reliable, and examined whether  
32 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,  
33 cardiovascular and/or physical impairments.

34 Kinetic features were examined for 265 COPD patients (FEV<sub>1</sub>: 54±19%predicted) that  
35 performed a constant work rate test (duration>180 s) with breath-by-breath measurements of  
36  $\dot{V}O_2$ ,  $\dot{V}CO_2$  and  $\dot{V}_E$ . Negative/positive predictive values were used to define cut-off values of  
37 relevant clinical variables below/above which kinetic analyses are (un)likely to be reliable.

38 Kinetic feature values were unreliable for 21% (=56/265) of the patients and for 79%  
39 (=19/24) of the patients with a peak work rate (WR<sub>peak</sub>)<45 W. Kinetic feature values were  
40 considered reliable for 94% (=133/142) of the patients with an FEV<sub>1</sub>>1.3 L. For patients  
41 exhibiting reliable kinetic feature values,  $\dot{V}O_2$  MRT was associated with ventilatory (e.g.  
42 FEV<sub>1</sub>%predicted: p<0.001; r=-0.35) and physical (e.g.  $\dot{V}O_{2,peak}$ %predicted: p=0.009; r=-0.18)  
43 impairments. Gains were mainly associated with cardiac function and ventilatory constraints,  
44 representing both response efficiency and limitation.

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

## 48 **New & Noteworthy**

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

## 55 **Introduction**

56 Dynamic responses of pulmonary oxygen uptake ( $\dot{V}O_2$ ), carbon dioxide output ( $\dot{V}CO_2$ )  
57 and minute ventilation ( $\dot{V}_E$ ) during a constant work rate cycling test (CWRT) depend on  
58 adequate pulmonary, cardiovascular and muscle functioning (29). During a CWRT,  $\dot{V}O_2$   
59 responses are characterized by a rapid cardio-dynamic phase (phase I; Figure 1), followed by  
60 an exponential  $\dot{V}O_2$  increase (phase II, the primary component of the response) towards an  
61 anticipated steady state (phase III) (36). An additional slow component, superimposed on the  
62 primary component of the response (Figure 1), can delay or prevent reaching this steady state  
63 (35, 37). Kinetic features such as mean response time (MRT) and gain describe the primary  
64 component of the  $\dot{V}O_2$  response (6).  $\dot{V}O_2$  mean response time (MRT) indicates the rate of the  
65  $\dot{V}O_2$  increase above unloaded cycling. It represents the time to reach 63% of the anticipated  
66 steady state while excluding the potential contribution of the slow component (Figure 1). A  
67 slow  $\dot{V}O_2$  response, indicated by a high MRT, leads to higher dependencies on anaerobic  
68 energy sources and contributes to exercise intolerance (29).  $\dot{V}O_2$  gain quantifies the  $\dot{V}O_2$   
69 increase (related to the primary component of the response) per unit increase in external work  
70 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.

## 93 **Materials and methods**

### 94 **Study design and participants**

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

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

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

## 127 **Kinetic analyses**

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

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

135 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  
136  $\dot{V}_E$  responses that were used for kinetic modelling (i.e. 150s to 180 s);  $Variable_{unloaded}$  as the  
137 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  
138 WR; and  $\Delta WR$  as the WR increase. The system model fit was assessed by the normalized  
139 root-mean-squared error value (NRMSE), calculated as the root-mean-square of the system

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

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

### 153 **Statistical analyses**

154 Results are presented as mean and standard deviation or median and interquartile range  
155 for respectively normally or non-normally distributed variables. Normality was tested using  
156 the Kolmogorov-Smirnov test. Patients with missing data were only excluded for statistical  
157 testing of the specific variable where data was missing. Patient characteristics were compared  
158 between patients exhibiting unreliable and reliable kinetic feature values, using Student's t-  
159 tests, Wilcoxon rank-sum tests and chi-squared tests, as appropriate.

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



164 were predicted to be unreliable (or reliable) for patients below (or above) the cut-off value.  
165 For each cut-off value, patients were then classified as a true negative (patients exhibiting  
166 unreliable kinetic feature values for whom kinetic feature values were also predicted to be  
167 unreliable), true positive (exhibiting reliable and predicted to be reliable), false negatives  
168 (exhibiting reliable, but predicted to be unreliable) or false positives (exhibiting unreliable,  
169 but predicted to be reliable). Negative predictive values (i.e. the amount of true negatives  
170 divided by the total amount of predicted negatives) were examined to determine cut-off  
171 values below which kinetic analyses are unlikely to be reliable. These negative predictive  
172 values indicated the percentage of patients below the selected cut-off values who indeed  
173 exhibited unreliable kinetic feature values. Equivalently, positive predictive values (i.e. the  
174 amount of true positives divided by the total amount of predicted positives, which indicated  
175 the percentage of patients above the selected cut-off value who indeed exhibited reliable  
176 kinetic feature values) were examined to determine cut-off values above which kinetic  
177 analyses are likely to be reliable. In addition, the group of patients that would be identified as  
178 “(un)likely to exhibit reliable kinetic feature values” should be sufficiently large. Therefore,  
179 the amount of patients with values below or above the selected cut-off values were  
180 simultaneously assessed.

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

## 188 **Results**

### 189 **Patient characteristics**

190 One hundred and forty-three of the 518 recruited COPD patients did not perform breath-  
191 by-breath measurements of  $\dot{V}O_2$ ,  $\dot{V}CO_2$  and  $\dot{V}_E$  during CWRT (Figure 2). For 70% of these  
192 patients (=100/143), this was because they received long-term oxygen therapy (Supplemental  
193 Material S2: <http://doi.org/10.5281/zenodo.3687069>). An additional 110 patients with severe  
194 ventilatory and physical impairments were excluded for analyses because of an insufficient  
195 (<180 s) CWRT endurance time (Figure 2; Supplemental Material S2:  
196 <http://doi.org/10.5281/zenodo.3687069>). The 265 remaining patients had an average age of  
197  $63 \pm 9$  years, suffered from moderate to very severe COPD, had an impaired diffusion capacity  
198 and experienced physical impairments (Table 1). There were slightly more men  
199 ( $156/265=59\%$ ) and 28 ( $28/265=11\%$ ) of the patients suffered from reduced LVEF (<50%).  
200 There were missing data points for fat-free mass index (n=12), transfer factor for carbon  
201 monoxide (TLCO; n=10), residual volume (RV; n=8), mMRC dyspnea grading (n=2),  
202 echocardiography (n=3), quadriceps isokinetic peak torque (n=23) and six-minute walking  
203 distance (n=1).

### 204 **Kinetic analyses**

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

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

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

228 Figure 5 illustrates representative  $\dot{V}O_2$ ,  $\dot{V}CO_2$  and  $\dot{V}_E$  responses of a patient that could be  
229 included for kinetic analyses. The Box-Jenkins transfer function system models of the 209  
230 patients that were included for kinetic analyses had a median NRMSE of  $11.6\pm 6.5\%$ . No  
231 differences in NRMSE values were observed when these patients were dichotomized  
232 according to age ( $\geq 60$  years:  $11.8\pm 6.8\%$ ;  $< 60$  years:  $11.3\pm 6.4\%$ ;  $p=0.63$ ), gender (male:  
233  $11.4\pm 6.4\%$ ; female:  $11.7\pm 6.1\%$ ;  $p=0.38$ ) or GOLD stage (GOLD stage I-II:  $11.3\pm 7.1\%$ ;  
234 GOLD stage III-IV:  $11.6\pm 5.3\%$ ;  $p=0.77$ ).

235 **Mean response time**

236 Patients exhibiting reliable kinetic feature values had a median  $\dot{V}O_2$  MRT of  $72 \pm 30$  s.  
237  $\dot{V}O_2$  MRT was negatively correlated with FEV<sub>1</sub>%predicted ( $p < 0.001$ ;  $r = -0.35$ ),  
238 TLCO%predicted ( $p = 0.01$ ;  $r = -0.18$ ) and partial pressure of oxygen ( $p = 0.02$ ;  $r = -0.16$ ), while  
239 being positively correlated with age ( $p = 0.004$ ;  $r = 0.20$ ), RV%predicted ( $p < 0.001$ ;  $r = 0.29$ ) and  
240  $V_E/MVV_{[150s-180s]}$  ( $p < 0.001$ ;  $r = 0.26$ ). Multiple regression analysis generated the following  
241 model:  $\dot{V}O_2$  MRT =  $-(0.47 \times \text{FEV}_1\% \text{predicted}) + (0.51 \times \text{age}) + 73.7$  ( $R^2 = 0.17$ ). In  
242 addition, slower  $\dot{V}O_2$  responses were linked with physical impairment as assessed by six-  
243 minute walking distance in meters ( $p = 0.01$ ;  $r = -0.18$ ) and as %predicted ( $p = 0.009$ ;  $r = -0.18$ ),  
244  $\dot{V}O_{2\text{peak}}$  in  $\text{ml} \cdot \text{min}^{-1}$  ( $p = 0.002$ ;  $r = -0.22$ ) and as %predicted ( $p < 0.001$ ;  $r = -0.24$ ). No significant  
245 correlations were observed between  $\dot{V}O_2$  MRT and gains of  $\dot{V}O_2$ ,  $\dot{V}CO_2$  or  $\dot{V}_E$ .

246 **Gains**

247 Patients exhibiting reliable kinetic feature values had a mean  $\dot{V}O_2$  gain of  $9.4 \pm 1.8$   $\text{ml} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$ .  
248  $\dot{V}O_2$  gain was negatively correlated with FEV<sub>1</sub>%predicted ( $p < 0.001$ ;  $r = -0.23$ ), left  
249 atrium diameter ( $p = 0.02$ ;  $r = -0.17$ ) and interventricular septum thickness ( $p = 0.03$ ;  $r = -0.15$ ),  
250 while being positively correlated with RV%predicted ( $p = 0.002$ ;  $r = 0.22$ ), partial pressure of  
251 carbon dioxide ( $p = 0.03$ ;  $r = 0.15$ ), LVEF ( $p = 0.001$ ;  $r = 0.23$ ) and  $\dot{V}_E/MVV_{[150s-180s]}$  ( $p < 0.001$ ;  
252  $r = 0.38$ ). Multiple regression analysis generated the following model:  $\dot{V}O_2$  gain =  $-(0.022 \times$   
253  $\text{FEV}_1\% \text{predicted}) + (0.044 \times \text{LVEF}) + 8.04$  ( $R^2 = 0.10$ )

254 Patients exhibiting reliable kinetic feature values had a mean  $\dot{V}CO_2$  gain of  $11.1 \pm 1.9$   
255  $\text{ml} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$ .  $\dot{V}CO_2$  gain was negatively correlated with age ( $p = 0.002$ ;  $r = -0.21$ ), BMI  
256 ( $p = 0.04$ ;  $r = -0.14$ ), fat-free mass index ( $p = 0.03$ ;  $r = -0.16$ ), left atrium diameter ( $p = 0.02$ ;  $r = -$   
257  $0.16$ ), right ventricle diameter ( $p = 0.02$ ;  $r = -0.16$ ) and interventricular septum thickness  
258 ( $p = 0.02$ ;  $r = -0.16$ ), while being positively correlated with TLCO%predicted ( $p = 0.03$ ;  $r = 0.15$ ),

259 partial pressure of oxygen ( $p < 0.001$ ;  $r = 0.23$ ), LVEF ( $p = 0.008$ ;  $r = 0.19$ ) and  $\dot{V}_E/MVV_{[150s-180s]}$   
260 ( $p < 0.001$ ;  $r = 0.22$ ). Multiple regression analysis generated the following model:  $\dot{V}CO_2$  gain =  
261  $-(0.032 \times \text{age}) - (0.17 \times \text{fat-free mass index}) + (0.028 \times \text{TLCO}\% \text{predicted}) + 14.56$  ( $R^2 =$   
262  $0.11$ ). In addition, a weak positive association was found between  $\dot{V}CO_2$  gain and  
263  $\dot{V}O_{2\text{peak}}\% \text{predicted}$  ( $p = 0.03$ ;  $r = 0.14$ ).

264 Patients exhibiting reliable kinetic feature values had a median  $\dot{V}_E$  gain of  $0.36 \pm 0.14$   
265  $L \cdot \text{min}^{-1} \cdot W^{-1}$ .  $\dot{V}_E$  gain was negatively correlated with  $\text{TLCO}\% \text{predicted}$  ( $p = 0.005$ ;  $r = -0.20$ ),  
266 BMI ( $p < 0.001$ ;  $r = -0.27$ ), fat-free mass index ( $p = 0.007$ ;  $r = -0.19$ ), partial pressure of carbon  
267 dioxide ( $p < 0.001$ ;  $r = -0.26$ ), left ventricular end-diastolic diameter ( $p = 0.02$ ;  $r = -0.16$ ), left  
268 atrium diameter ( $p = 0.04$ ;  $r = -0.14$ ), right ventricle diameter ( $p = 0.004$ ;  $r = -0.20$ ) and  
269 interventricular septum thickness ( $p = 0.04$ ;  $r = -0.15$ ), while being positively correlated with  
270  $FEV_1\% \text{predicted}$  ( $p = 0.04$ ;  $r = 0.14$ ) and  $\dot{V}_E/MVV_{[150s-180s]}$  ( $p = 0.004$ ;  $r = 0.20$ ). Multiple  
271 regression analysis generated the following model:  $\dot{V}_E$  gain =  $-(0.0017 \times \text{TLCO}\% \text{predicted})$   
272  $-(0.0051 \times \text{BMI}) + (0.0017 \times FEV_1\% \text{predicted}) + (0.0084 \times \text{left atrium diameter}) + 0.48$  ( $R^2$   
273  $= 0.20$ ). In addition,  $\dot{V}_E$  gain was negatively correlated with isokinetic peak torque as  
274  $\% \text{predicted}$  ( $p = 0.01$ ;  $r = -0.18$ ) and CWRT endurance time ( $p < 0.001$ ;  $r = -0.24$ ).

## 275 Discussion

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

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

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

295 When ventilatory restrictions did not result in unreliable kinetic feature values, they were  
296 still associated with higher  $\dot{V}O_2$  MRT values. Slow  $\dot{V}O_2$  responses in patients with COPD  
297 have mainly been attributed to slow central cardiovascular responses, resulting from  
298 increased intrathoracic pressure swings due to airflow obstruction and dynamic  
299 hyperinflation, ultimately impairing convective  $O_2$  transport to the working muscles (5, 9, 10,  
300 12, 15, 19). The observed associations between slow  $\dot{V}O_2$  responses and airflow limitation,  
301  $RV$  and  $V_E/MVV_{[150s-180s]}$  support this reasoning. Also impaired peripheral cardiovascular  
302 responses (9, 30) and slow muscle  $O_2$  utilization (22, 23, 32) have been suggested to slow  
303  $\dot{V}O_2$  responses of COPD patients. Most likely, the slow  $\dot{V}O_2$  responses observed in patients  
304 with COPD cannot be attributed to a single mechanism, but are the result of a combination of  
305 ventilatory, cardiovascular and/or muscular malfunctioning. Nevertheless, the results of the  
306 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

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

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

352 In addition, extracting kinetic features from a CWRT that is standardly performed during  
353 a pre-rehabilitation assessment does not require any additional testing, offering an easy  
354 approach to enhance clinical patient assessments. Whereas current clinical assessments are  
355 mainly based on outcomes that assess patients under 'steady-state' (resting) conditions,  
356 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

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

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

## 394 **Acknowledgements**

395 This research is part of a PhD research funded by Flemish Institute for Technological  
396 Research (VITO), Mol, Belgium. The original study (CHANCE study) was supported by the  
397 Lung Foundation Netherlands (3.4.10.015) and GlaxoSmithKline (SCO115406). These  
398 funding organizations provided only financial support not playing a role in the study design,  
399 data collection and analysis, decision to publish, or preparation of the manuscript. The  
400 authors would also like to express their gratitude to Miriam Groenen (CIRO, Horn, the  
401 Netherlands) for the meticulous data management.

## 402 **Conflicts of Interest**

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

- 404 1. **Aliverti A, Macklem PT.** How and why exercise is impaired in COPD. *Respiration*  
405 68: 229–239, 2001.
- 406 2. **Baarends EM, Schols AMWJ, Akkermans MA, Wouters EFM.** Decreased  
407 mechanical efficiency in clinically stable patients with COPD. *Thorax* 52: 981–986,  
408 1997.
- 409 3. **Barstow TJ.** Characterization of VO<sub>2</sub> kinetics during heavy exercise. *Med Sci Sports*  
410 *Exerc* 26: 1327–1334, 1994.
- 411 4. **Benson AP, Bowen TS, Ferguson C, Murgatroyd SR, Rossiter HB.** Data collection,  
412 handling, and fitting strategies to optimize accuracy and precision of oxygen uptake  
413 kinetics estimation from breath-by-breath measurements. *J Appl Physiol* 123: 227–  
414 242, 2017.
- 415 5. **Berton DC, Barbosa PB, Takara LS, Chiappa GR, Siqueira ACB, Bravo DM,**  
416 **Ferreira LF, Neder JA.** Bronchodilators accelerate the dynamics of muscle O<sub>2</sub>  
417 delivery and utilisation during exercise in COPD. *Thorax* 65: 588–593, 2010.
- 418 6. **Buekers J, Theunis J, Peña Fernández A, Wouters EF, Spruit MA, De Boever P,**  
419 **Aerts J-M.** Box-Jenkins Transfer Function Modelling for Reliable Determination of  
420 VO<sub>2</sub> Kinetics in Patients with COPD. *Appl Sci* 9: 1822, 2019.
- 421 7. **Casaburi R, Barstow TJ, Robinson T, Wasserman K.** Influence of work rate on  
422 ventilatory and gas exchange kinetics. *J Appl Physiol* 67: 547–555, 1989.
- 423 8. **Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RSY, Cooper CB.**  
424 Physiologic benefits of exercise training in rehabilitation of patients with severe  
425 chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 155: 1541–1551,  
426 1997.
- 427 9. **Chiappa GR, Borghi-Silva A, Ferreira LF, Carrascosa C, Oliveira CC, Maia J,**  
428 **Gimenes AC, Queiroga F, Berton D, Ferreira EM V., Nery LE, Neder JA.**  
429 Kinetics of muscle deoxygenation are accelerated at the onset of heavy-intensity  
430 exercise in patients with COPD: relationship to central cardiovascular dynamics. *J*  
431 *Appl Physiol* 104: 1341–1350, 2008.
- 432 10. **Chiappa GR, Queiroga F, Meda E, Ferreira LF, Diefenthaler F, Nunes M, Vaz**  
433 **MA, Machado MCL, Nery LE, Neder JA.** Heliox improves oxygen delivery and  
434 utilization during dynamic exercise in patients with chronic obstructive pulmonary  
435 disease. *Am J Respir Crit Care Med* 179: 1004–1010, 2009.
- 436 11. **Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR,**  
437 **Salem GJ, Skinner JS.** Exercise and physical activity for older adults. *Med Sci Sports*  
438 *Exerc* 41: 1510–1530, 2009.
- 439 12. **Faisal A, Zoumot Z, Shah PL, Neder JA, Polkey MI, Hopkinson NS.** Effective  
440 bronchoscopic lung volume reduction accelerates exercise oxygen uptake kinetics in  
441 emphysema. *Chest* 149: 435–446, 2016.
- 442 13. **Heijdra YF, Pinto-Plata V, Frants R, Rassulo J, Kenney L, Celli BR.** Muscle  
443 strength and exercise kinetics in COPD patients with a normal fat-free mass index are  
444 comparable to control subjects. *Chest* 124: 75–82, 2003.
- 445 14. **Lamarra N, Whipp BJ, Ward A, Wasserman K.** Effect of interbreath fluctuations  
446 on characterizing exercise gas exchange kinetics. *J Appl Physiol* 62: 2003–2012, 1987.
- 447 15. **Laveneziana P, Palange P, Ora J, Martolini D, O'Donnell DE.** Bronchodilator

- 448 effect on ventilatory, pulmonary gas exchange, and heart rate kinetics during high-  
449 intensity exercise in COPD. *Eur. J. Appl. Physiol.* 107: 633–643, 2009.
- 450 16. **Mannix ET, Manfredi F, Farber MO.** Elevated O<sub>2</sub> cost of ventilation contributes to  
451 tissue wasting in COPD. *Chest* 115: 708–713, 1999.
- 452 17. **Murgatroyd SR, Ferguson C, Ward SA, Whipp BJ, Rossiter HB.** Pulmonary O<sub>2</sub>  
453 uptake kinetics as a determinant of high-intensity exercise tolerance in humans. *J Appl*  
454 *Physiol* 110: 1598–1606, 2011.
- 455 18. **Neder JA, Berton DC, De Tarso Müller P, Elbehairy AF, Rocha A, Palange P,**  
456 **O'Donnell DE.** Ventilatory inefficiency and exertional dyspnea in early chronic  
457 obstructive pulmonary disease. *Ann Am Thorac Soc* 14: S22–S29, 2017.
- 458 19. **Nery LE, Wasserman K, Andrews JD, Huntsman DJ, Hansen JE, Whipp BJ.**  
459 Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction. *J*  
460 *Appl Physiol* 53: 1594–1602, 1982.
- 461 20. **O'Donnell DE, Travers J, Webb KA, He Z, Lam YM, Hamilton A, Kesten S,**  
462 **Maltais F, Magnussen H.** Reliability of ventilatory parameters during cycle  
463 ergometry in multicentre trials in COPD. *Eur Respir J* 34: 866–874, 2009.
- 464 21. **Otsuka T, Kurihara N, Fujii T, Fujimoto S, Yoshikawa J.** Effect of exercise  
465 training and detraining on gas exchange kinetics in patients with chronic obstructive  
466 pulmonary disease. *Clin Physiol* 17: 287–297, 1997.
- 467 22. **Palange P, Forte S, Onorati P, Paravati V, Manfredi F, Serra P, Carlone S.** Effect  
468 of reduced body weight on muscle aerobic capacity in patients with COPD. *Chest* 114:  
469 12–18, 1998.
- 470 23. **Palange P, Galassetti P, Mannix ET, Farber MO, Manfredi F, Serra P, Carlone S.**  
471 Oxygen effect on O<sub>2</sub> deficit and VO<sub>2</sub> kinetics during exercise in obstructive  
472 pulmonary disease. *J Appl Physiol* 78: 2228–2234, 1995.
- 473 24. **Pepi M, Agostoni P, Marenzi G, Doria E, Guazzi M, Lauri G, Maltagliati A,**  
474 **Guazzi M.** The influence of diastolic and systolic function on exercise performance in  
475 heart failure due to dilated cardiomyopathy or ischemic heart disease. *Eur J Heart Fail*  
476 1: 161–167, 1999.
- 477 25. **Puente-Maestu L, Buendía Abad MJ, Godoy R, Pérez-Parra JM, Cubillo JM,**  
478 **Whipp BJ.** Breath-by-breath fluctuations of pulmonary gas exchange and ventilation  
479 in COPD patients. *Eur J Appl Physiol* 87: 535–541, 2002.
- 480 26. **Puente-Maestu L, Sáenz ML, Sáenz P, De Oña JMR, Rodríguez-Hermosa JL,**  
481 **Whipp BJ.** Effects of two types of training on pulmonary and cardiac responses to  
482 moderate exercise in patients with COPD. *Eur Respir J* 15: 1026–1032, 2000.
- 483 27. **Puente-Maestu L, Sáenz ML, Sáenz P, Nuñez A, González F, Whipp BJ.**  
484 Reproducibility of the parameters of the on-transient cardiopulmonary responses  
485 during moderate exercise in patients with chronic obstructive pulmonary disease. *Eur J*  
486 *Appl Physiol* 85: 434–441, 2001.
- 487 28. **Rocha A, Arbex FF, Sperandio PA, Mancuso F, Marillier M, Bernard AC,**  
488 **Alencar MCN, O'Donnell DE, Neder JA.** Exercise intolerance in comorbid COPD  
489 and heart failure: the role of impaired aerobic function. *Eur Respir J* 53: 1802386,  
490 2019.
- 491 29. **Rossiter HB.** Exercise: Kinetic considerations for gas exchange. *Compr Physiol* 1:

- 492 203–244, 2011.
- 493 30. **Siqueira ACB, Borghi-Silva A, Bravo DM, Ferreira EMV, Chiappa GR, Neder**  
494 **JA.** Effects of hyperoxia on the dynamics of skeletal muscle oxygenation at the onset  
495 of heavy-intensity exercise in patients with COPD. *Respir Physiol Neurobiol* 172: 8–  
496 14, 2010.
- 497 31. **Smid DE, Wilke S, Jones PW, Muris JWM, Wouters EFM, Franssen FME,**  
498 **Spruit MA.** Impact of cardiovascular comorbidities on COPD assessment test (CAT)  
499 and its responsiveness to pulmonary rehabilitation in patients with moderate to very  
500 severe COPD: Protocol of the Chance study. *BMJ Open* 5: e007536, 2015.
- 501 32. **Somfay A, Porszasz J, Lee S-M, Casaburi R.** Effect of hyperoxia on gas exchange  
502 and lactate kinetics following exercise onset in nonhypoxemic COPD patients. *Chest*  
503 121: 393–400, 2002.
- 504 33. **Spruit MA, Singh SJ, Garvey C, Zu Wallack R, Nici L, Rochester C, Hill K,**  
505 **Holland AE, Lareau SC, Man WDC, Pitta F, Sewell L, Raskin J, Bourbeau J,**  
506 **Crouch R, Franssen FME, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R,**  
507 **Clini EM, Effing TW, Maltais F, Van Der Palen J, Troosters T, Janssen DJA,**  
508 **Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M,**  
509 **Garrod R, Schols AMWJ, Carlin B, Benzo R, Meek P, Morgan M, Rutten-Van**  
510 **Mölken MPMH, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL,**  
511 **Donner CF, Wouters EFM.** An official American thoracic society/European  
512 respiratory society statement: Key concepts and advances in pulmonary rehabilitation.  
513 *Am J Respir Crit Care Med* 188: e13–e64, 2013.
- 514 34. **Spruit MA, Vanderhoven-Augustin I, Janssen PP, Wouters EF.** Integration of  
515 pulmonary rehabilitation in COPD. *Lancet* 371: 12–13, 2008.
- 516 35. **Whipp BJ.** Dynamics of pulmonary gas exchange. *Circulation* 76: 18–28, 1987.
- 517 36. **Whipp BJ, Ward SA, Lamarra N, Davis JA, Wasserman K.** Parameters of  
518 ventilatory dynamics during exercise. *J Appl Physiol Respir Env Exerc Physiol* 52:  
519 1506–1513, 1982.
- 520 37. **Whipp BJ, Wasserman K.** Oxygen uptake kinetics for various intensities of constant-  
521 load work. *J Appl Physiol* 33: 351–356, 1972.
- 522 38. **Wolpat A, Lima F V., Silva FM, Tochetto M, de Freitas A, Grandi T, Rodrigues**  
523 **L, Paiva V, Cipriano G, Chiappa AM, Zago J, Chiappa GR.** Association between  
524 inspiratory muscle weakness and slowed oxygen uptake kinetics in patients with  
525 chronic obstructive pulmonary disease. *Appl Physiol Nutr Metab* 42: 1239–1246,  
526 2017.
- 527
- 528

529 **Figure captions**

530 **Figure 1:** Representation of a typical oxygen uptake ( $\dot{V}O_2$ ) response at the onset of a constant work rate test  
531 (blue line) and the specific phase II contribution (orange line). Both lines coincide during phase II. The black  
532 dashed line visualises the load increase at  $t = 0$  s. MRT = mean response time; TD = time delay; TC = time  
533 constant; WR = work rate; TD2 = time delay of phase III or the slow component, variable between 100-200 s  
534 (3).

535  
536 **Figure 2:** Overview of patients included for general and kinetic analyses. CWRT = constant work rate test;  $\dot{V}O_2$   
537 = oxygen uptake;  $\dot{V}CO_2$  = carbon dioxide output;  $\dot{V}_E$  = minute ventilation.

538  
539 **Figure 3:** Representative examples of  $\dot{V}O_2$  responses of patients exhibiting unreliable kinetic feature values due  
540 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  
541  $\dot{V}O_2$  response. The orange dashed lines represents the Box-Jenkins transfer function system model.  $\dot{V}O_2$  =  
542 oxygen uptake; NRMSE = normalized root-mean-squared error; MRT = mean response time.

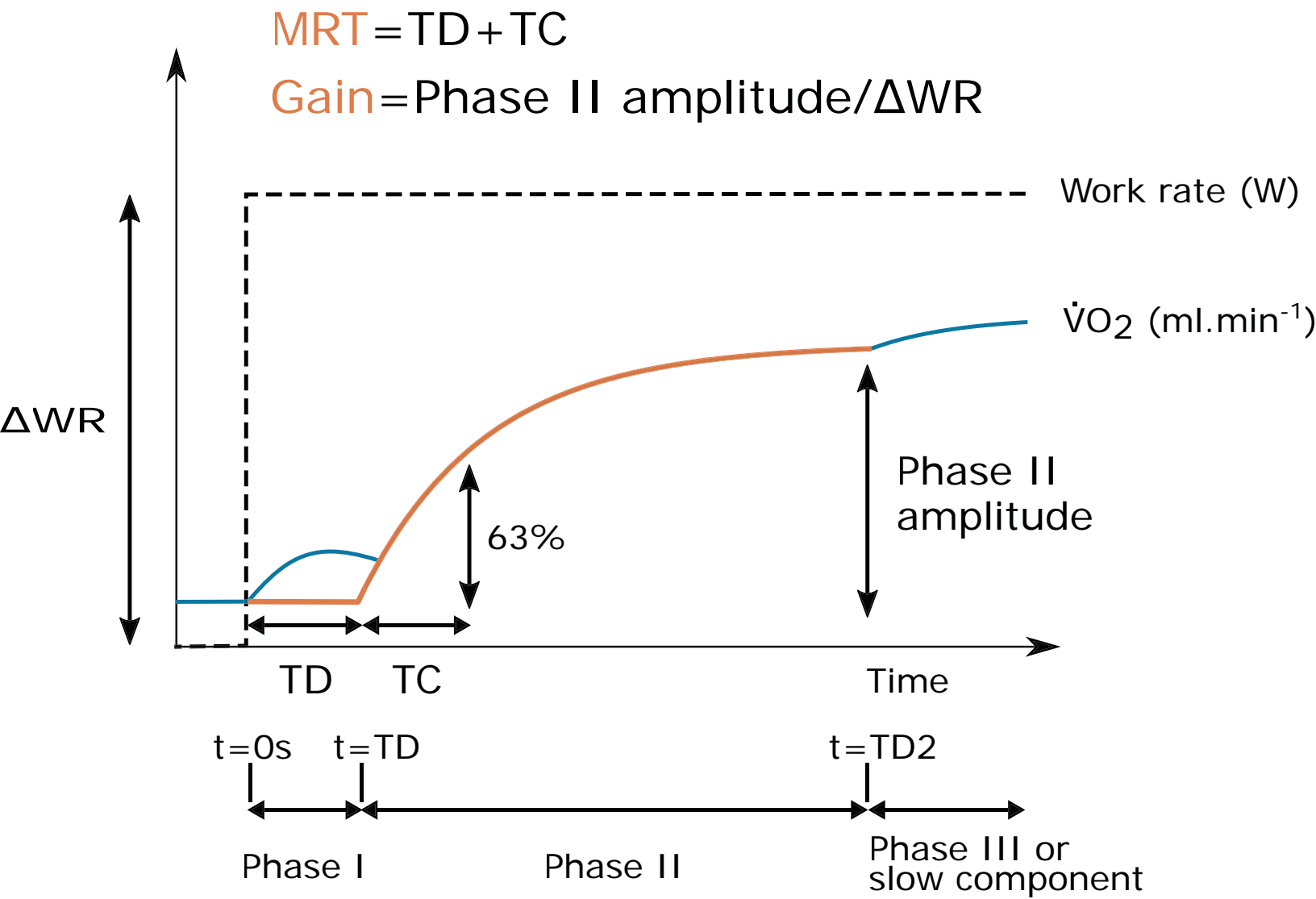
543  
544 **Figure 4:** A peak work rate ( $WR_{peak}$ ) cut-off value of 45 W corresponded to a negative predictive value of 79%  
545 for the prediction of patients who exhibited unreliable kinetic feature values. Twenty-four patients (24/265=9%)  
546 had a  $WR_{peak} < 45$  W. A forced expiratory volume in 1 s ( $FEV_1$ ) cut-off value of 1.3 L corresponded to a positive  
547 predictive value of 94% for the prediction of patients who exhibited reliable kinetic feature values. One hundred  
548 and forty-two patients (142/265=53%) had a  $FEV_1 > 1.3$  L.

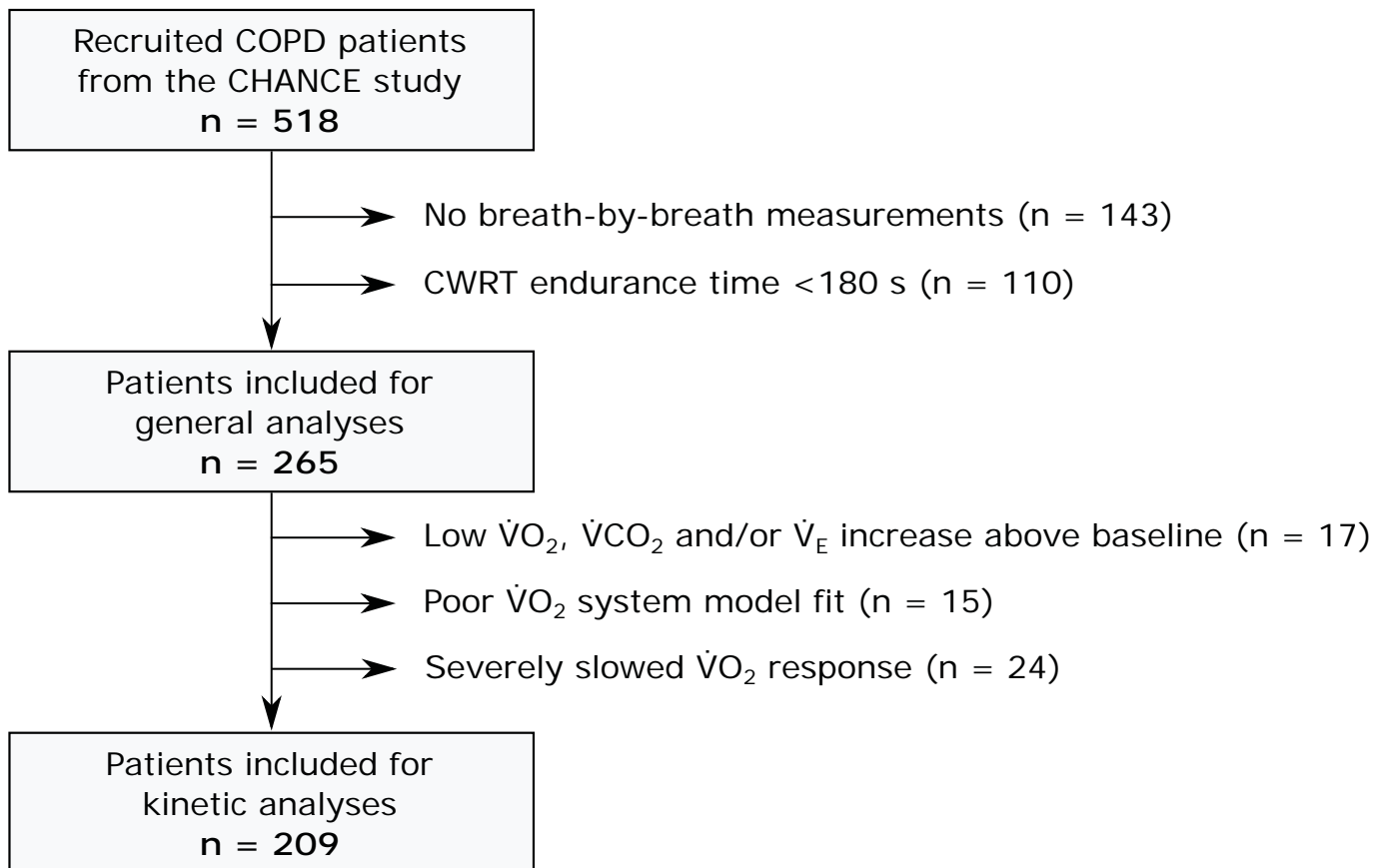
549  
550 **Figure 5:** Representative example of oxygen uptake ( $\dot{V}O_2$ ), carbon dioxide output ( $\dot{V}CO_2$ ) and minute  
551 ventilation ( $\dot{V}_E$ ) responses above unloaded cycling at exercise onset of a patient that was included for kinetic  
552 analyses. The work rate increased from 0 W to 67 W at Time = 0 s. The orange dashed lines represents the Box-  
553 Jenkins transfer function system model.

554

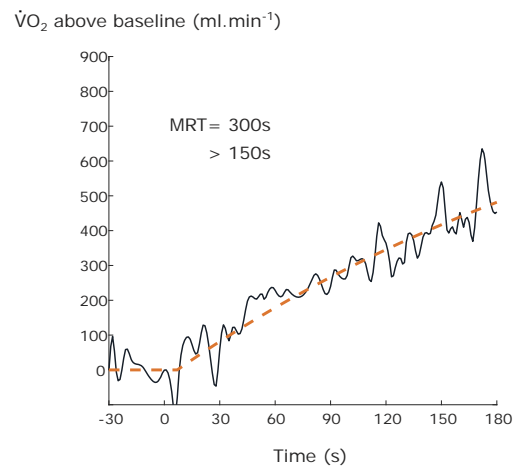
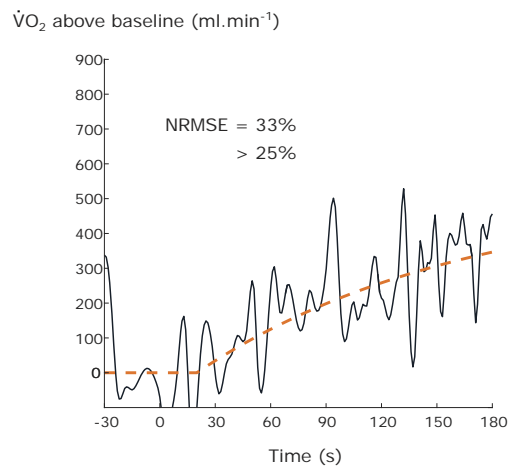
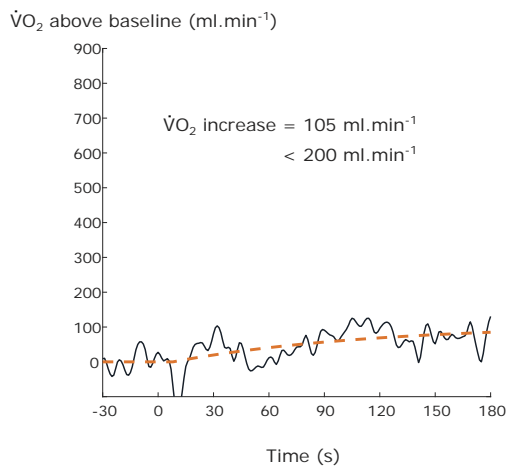
555

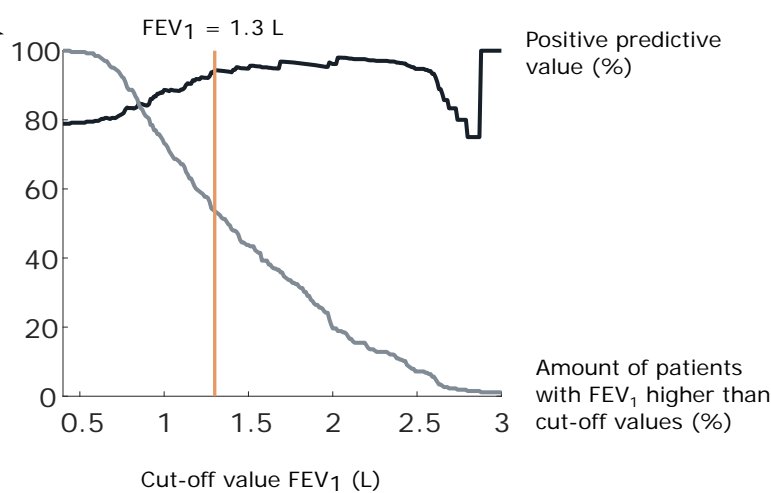
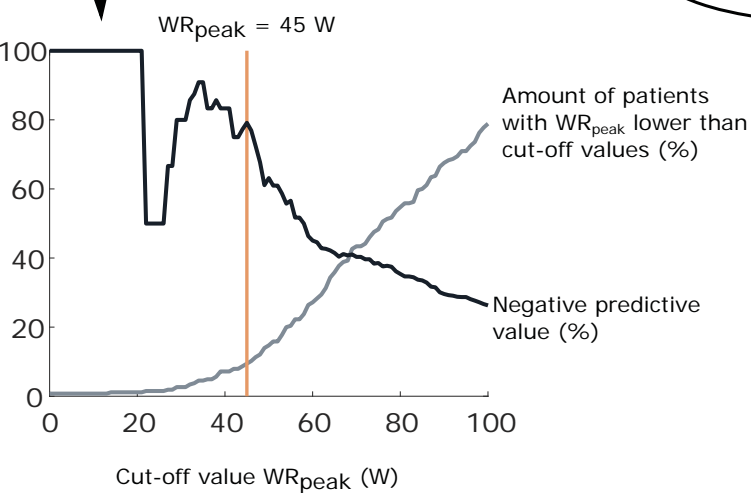
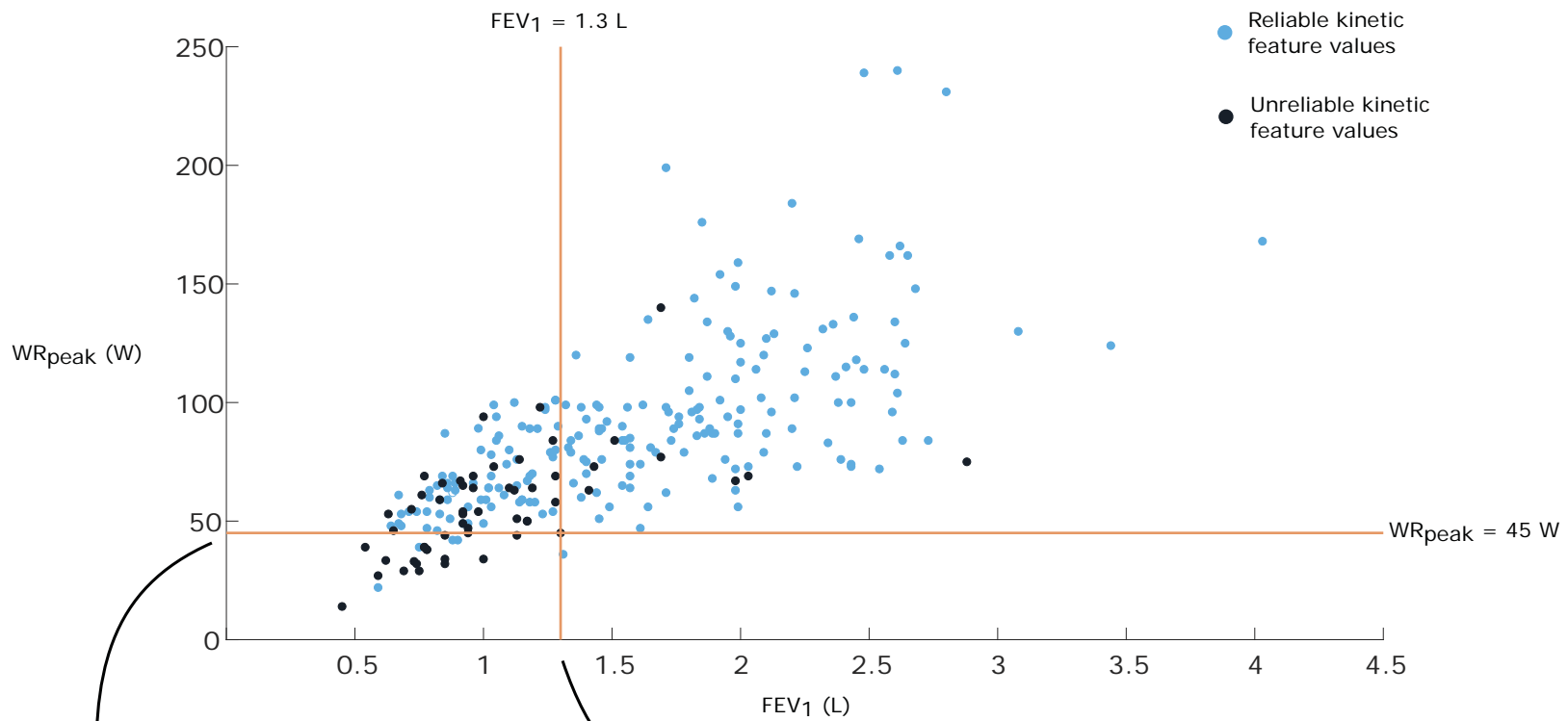
556



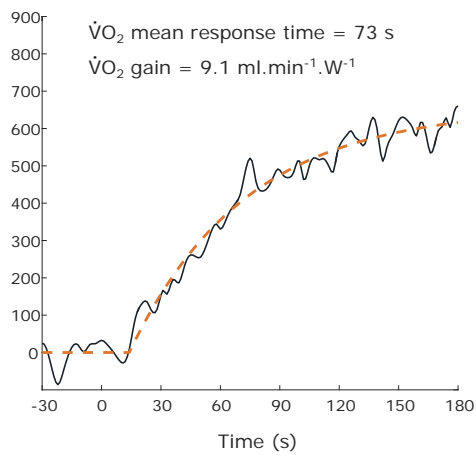




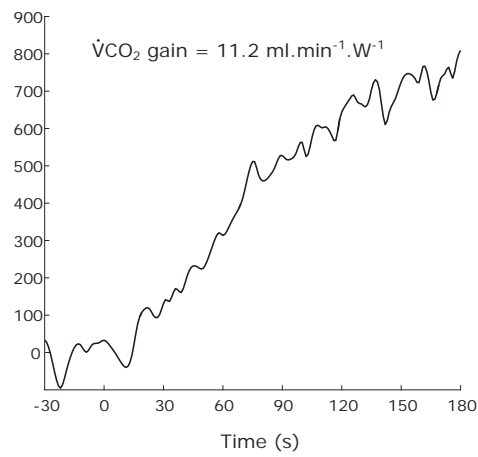




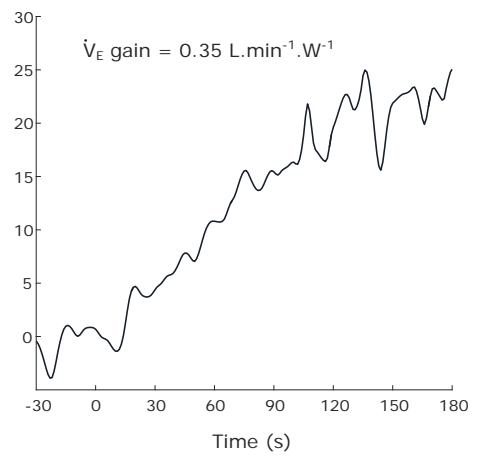
$\dot{V}O_2$  above baseline ( $\text{ml}\cdot\text{min}^{-1}$ )



$\dot{V}CO_2$  above baseline ( $\text{ml}\cdot\text{min}^{-1}$ )



$\dot{V}_E$  above baseline ( $\text{L}\cdot\text{min}^{-1}$ )



**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.

	<i>Patients included for general analyses (n=265)</i>	<i>Patients with unreliable kinetic feature values (n=56)</i>	<i>Patients with reliable kinetic feature values (n=209)</i>
<b>Demographics</b>			
Male – female	156 – 109	27 – 29	129 – 80
Age (years)	63 (9)	<b>68 (8)</b>	<b>62 (9)**</b>
Body Mass Index (kg/m <sup>2</sup> )	26.8 (6.0)	26.4 (5.4)	26.9 (6.2)
Fat-free mass index (kg/m <sup>2</sup> )	17.4 (2.5)	17.0 (2.3)	17.5 (2.6)
<b>Resting pulmonary function</b>			
Forced expiratory volume in 1 second (FEV <sub>1</sub> ; %predicted)	54 (19)	<b>43 (15)</b>	<b>57 (19)***</b>
Forced vital capacity (FVC; %predicted)	104 (18)	100 (20)	105 (17)
FEV <sub>1</sub> /FVC (%)	39 (12)	<b>33 (10)</b>	<b>42 (12)***</b>
Transfer factor for carbon monoxide (%predicted)	55 (16)	<b>47 (12)</b>	<b>56 (16)**</b>
Residual volume (%predicted)	151 (44)	<b>164 (36)</b>	<b>147 (45)*</b>
Modified Medical Research Council grading $\geq 2$ (% patients)	72	<b>88</b>	<b>68**</b>
<b>Resting arterial blood gases</b>			
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)
<b>Resting echocardiogram</b>			
Left ventricular ejection fraction (%) #	61 (7)	<b>59 (8)</b>	<b>62 (7)*</b>
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)
<b>Physical performance</b>			
Six-minute walking distance (m)	477 (105)	<b>401 (97)</b>	<b>497 (98)***</b>
Six-minute walking distance (%predicted)	74 (15)	<b>67 (15)</b>	<b>76 (14)**</b>
Peak work rate (W) #	76 (39)	<b>54 (29)</b>	<b>85 (37)***</b>
Peak work rate (%predicted) #	58 (31)	<b>46 (29)</b>	<b>60 (29)**</b>
Peak oxygen uptake (ml.min <sup>-1</sup> ) #	1105 (495)	<b>911 (287)</b>	<b>1178 (505)***</b>
Peak oxygen uptake (%predicted) #	63 (32)	60 (38)	64 (31)
Isokinetic peak torque (Nm)	104 (38)	<b>83 (30)</b>	<b>110 (38)***</b>
Isokinetic peak torque (%predicted)	71 (18)	<b>63 (14)</b>	<b>73 (19)**</b>
CWRT - Endurance time (s) #	294 (184)	<b>242 (119)</b>	<b>305 (199)**</b>
CWRT - Minute ventilation <sub>[150s-180s]</sub> (%MVV)	78 (24)	<b>84 (33)</b>	<b>76 (21)*</b>

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<sup>-5</sup>). CWRT = constant work rate test; MVV = maximal voluntary ventilation.