COMPARING PEAK AND SUB-MAXIMAL CARDIORESPIRATORY RESPONSES DURING FIELD WALKING TESTS WITH INCREMENTAL CYCLE ERGOMETRY IN COPD

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Kylie Hill conceived the study, assisted with data collection and interpretation of the results and wrote the manuscript. She has full access to the data and can vouch for its integrity. Thomas E Dolmage assisted with data collection, interpretation of the results and editing of the manuscript. Lynda Woon assisted with data collection and interpretation of the results and editing of the manuscript. Debbie Coutts assisted with data collection and editing of the manuscript. Roger Goldstein assisted with interpretation of the results and editing of the manuscript. Dina Brooks assisted with interpretation of the results and editing of the manuscript.

Summary at a glance:

In patients with moderate COPD, the six-minute walk test, incremental shuttle walk test and endurance shuttle walk test elicited a similar peak rate of oxygen uptake and heart rate response as a ramp cycle ergometry test, demonstrating that both self- and externally-paced field tests progress to high intensities.

ABSTRACT

Background and objective: Field and laboratory-based tests are used to measure exercise capacity in people with COPD. A comparison of the cardiorespiratory responses to field tests, referenced to a laboratory test, is needed to appreciate the relative physiological demands. We sought to compare peak and sub-maximal cardiorespiratory responses to the six-minute walk test (6MWT), incremental shuttle walk test (ISWT) and endurance shuttle walk test (ESWT) with a ramp cycle ergometry test (CET) in patients with COPD.

Methods: 24 participants (FEV_1 50±14%; 66.5±7.7 years; 15 men) completed 4 sessions, separated by ≥ 24 hours. During an individual session, participants completed either two 6MWTs, ISWTs, ESWTs using standardised protocols, or a single CET, wearing a portable gas analysis unit (Cosmed™ $K4b^2$) which included measures of heart rate and arterial oxygen saturation (SpO_2).

Results: Between tests, no difference was observed in the peak rate of oxygen uptake ($F_{3,69}$ = 1.2; p=0.31), end-test heart rate ($F_{2,50}$ = 0.6; p=0.58) or tidal volume ($F_{3,69}$ = 1.5; p=0.21). Compared with all walking tests, the CET elicited a higher peak rate of carbon dioxide output (1173 ± 350 $ml\cdot min^{-1}$; $F_{3,62}$ = 4.8; p=0.006), minute ventilation (48 ± 17 $L\cdot min^{-1}$; $F_{3,69}$ = 10.2; p<0.001) and a higher end-test SpO_2 (95 ± 4%; $F_{3,63}$ = 24.9; p<0.001).

Conclusions: In patients with moderate COPD, field walking tests elicited a similar peak rate of oxygen uptake and heart rate as a CET, demonstrating that both self- and externally-paced walking tests progress to high intensities.

Key words: COPD, exercise tests, repeatability, six-minute walk test, oxygen uptake

Short title: A comparison of exercise tests in COPD

INTRODUCTION

In people with COPD, impaired lung[1] and peripheral muscle function compromise exercise capacity.[2] Accurate assessment of exercise capacity yields prognostic information[3] and has important implications for an individual's clinical management such as evaluating the response to an intervention and prescribing exercise training intensities capable of inducing adaptation.[4-6] Laboratory-based incremental cycle ergometer tests (CET) are generally accepted as the gold standard for quantifying exercise capacity.[7] Such tests are, however, costly and require sophisticated equipment and resources that are not available in all facilities or to all clinicians. Therefore, field walking tests are often used.[8,9] Such tests are reproducible after one practice walk[10,11] and responsive to exercise training.[12-14] However, it is unclear how the peak cardiorespiratory responses during walking tests compare with a CET. That is, although the incremental shuttle walk test (ISWT) consistently elicits a similar peak rate of oxygen uptake ($\dot{V}O_2$) and heart rate as a CET,[15-18] the 6-minute walk test (6MWT) elicits similar peak responses in some[16,18,19] but not all studies.[17,20-22] No study has compared response during the endurance shuttle walk test (ESWT)[10] with the ISWT, 6MWT and CET. Such information is needed to appreciate the physiologic demands of each test, relative to one another. Further, the pattern of sub-maximal cardiorespiratory responses is needed to explain previous findings of higher dyspnea at time points prior to test completion during the 6MWT relative to the ISWT and CET.[16]

The primary aim of this study was to compare peak and sub-maximal cardiorespiratory responses during the 6MWT, ISWT and ESWT with a CET in people with COPD. A secondary objective was to report the coefficient of repeatability of gas exchange and breathing pattern variables.

METHODS

Design

This cross-sectional study was approved by the relevant Human Research Ethics Committees. Written informed consent was obtained from every person before participation. Each participant attended four two-hour assessment sessions, each separated by at least 24 hours. During a session, participants completed either 6MWTs, ISWTs, ESWTs or a CET. To account for potential improvements resulting from familiarisation,[10,11] each walking test was performed twice, separated by a 20 to 30 minute rest. To eliminate day-to-day variability,[23] the same test protocol was performed twice on a given day. The order of sessions differed among participants.

Study criteria

Participants were eligible for the study if they had a diagnosis of COPD,[24] a smoking history > 10 pack years and were clinically stable (i.e. had not used oral corticosteroids or antibiotics within the preceding two week period). Exclusion criteria comprised evidence of a co-morbid condition that might adversely affect exercise performance, a history of lung surgery, the use of a rollator or long term oxygen therapy or evidence of marked desaturation during exercise (i.e. $SpO_2 < 80\%$) that would have necessitated premature cessation of the test.[7] Most participants were familiar with the 6MWT prior to participating in this study.

Measurements

Exercise capacity

All walking tests were overseen by two experienced physiotherapists on a quiet, level, enclosed, temperature-controlled corridor. Before and after each walk test, and every minute during the CET, measurements were obtained of dyspnea and leg fatigue using the modified Borg scale.[25] During all tests, breath-by-breath measurements of gas exchange and breathing pattern were collected using a calibrated portable gas analysis system (Cosmed™, $K4b^2$, Italy). Arterial oxygen saturation (Nellcor™ Max Fast, forehead sensor, Pleasanton, CA, USA) and heart rate (Polar a1 heart rate monitor, Polar Electro Oy, Kempele, Finland) were monitored continuously.

Walk tests

The ISWTs and ESWTs were performed according to standardised protocols,[10,20] modified to include one standardised warning to increase walking speed the first time each participant lagged behind the pace dictated by the audio-signal.[16] The speed selected for the ESWTs was equivalent to 85% of the peak $\dot{V}O_2$ estimated using the distance achieved during the best ISWT.[10] This test was preceded by a 90 second warm-up period during which the participant walked slowly. The ESWT was terminated by the tester at 20 minutes.[10] For patients who achieved 20 minutes during their first ESWT, the second test was conducted at a faster walking pace. Similarly, to reduce the likelihood of walking for 20 minutes during the second ESWT,[13,26] those who walked for more than 10 minutes with minimal progression in heart rate or change in arterial oxygen saturation (SpO_2) for three consecutive minutes during the first test, also completed their second test at a faster pace. The 6MWTs were performed according to the American Thoracic Society guidelines.[27]

Cycle-ergometry test

A symptom-limited ramp CET was performed on an electronically braked bicycle ergometer (Lode Excalibur™ 926851V3.00, Groningen, Netherlands). Peak exercise responses during CET are reproducible in people with COPD[28,29] and therefore the CET was performed once. Participants pedaled without a load for three minutes and thereafter the load increased by 5, 10 or 15 $W \cdot min^{-1}$ based on each participant's history of daily physical activity and symptoms, to induce symptom limitation within approximately 10 minutes.

<u>Anthropometric and resting lung function</u>

During the first assessment session, age, sex and Modified Medical Research Council (MRC) dyspnea grade[30] were recorded and measurements were made of height and weight. The most recent measurements of resting lung function were extracted from the medical notes.

Analyses

Breath-by-breath data were exported to Sigmaplot® (version 11.0) for analyses. To plot the sub-maximal responses, for every test, measures of $\dot{V}O_2$, rate of carbon dioxide output

($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$), tidal volume, heart rate and SpO_2 were grouped into epochs equivalent to 10% increments of the total test duration (i.e. deciles) using a two-dimensional data transformation. Data collected during the 90 second warm-up and three minutes of unloaded pedaling that preceded the ESWT and CET, respectively, were excluded from analyses. Data collected across both 6MWTs, ISWTs and ESWTs were averaged for analysis, with the exception of those participants who completed the ESWTs at different speeds. In this instance, only data performed at the faster walking speed were used in the analysis.

Before undertaking statistical analysis, a natural logarithmic transformation was applied to all cardiorespiratory variables to improve the extent to which they approached a normal distribution. Peak (end-test) responses were compared among tests using one-way repeated measures analysis of variance with paired t-tests for post-hoc comparisons (Statistical Package for Social Sciences; SPSS, version 17.0). For heart rate, $\dot{V}CO_2$ and leg fatigue, Mauchly's test indicated that the assumption of sphericity was violated, and therefore the degrees of freedom were corrected using Huynh-Feldt estimates. P-values ≤ 0.05 were considered significant.

Repeatability of variables collected on completion of the walk tests was assessed using methods of Bland and Altman.[31] We calculated the bias, defined as the mean difference between two 6MWTs, ISWTs and ESWTs as well as the coefficient of repeatability, defined as 1.96 times the standard deviation of the difference. Patients who performed ESWTs at different speeds were excluded from this analysis.

Sample size calculations

A prospective sample size calculation was based on detecting a 10% difference in the primary outcome, peak $\dot{V}O_2$, between any walking test and CET. Using data available in the literature that reported a peak $\dot{V}O_2$ during a CET of 1.41 L·min^{-1},[19] we estimated that 24 participants would yield 80% power ($\alpha = 0.05$) to detect a difference of 0.14 L·min^{-1} in the peak $\dot{V}O_2$ (i.e. 10% difference and the coefficient of repeatability for this measure)[29] with a standard deviation of 0.24 L·min^{-1} (average standard deviation of the two tests reported by Troosters et al)[19] using a paired t-test.

RESULTS

Of the 33 individuals who consented to participate in this study, 5 (15%) were unable to tolerate the mask for portable gas analysis equipment, 1 (3%) was withdrawn due to hypertension, and 1 (3%) withdrew. Data from 2 (6%) individuals was ineligible due to equipment failure. Characteristics of the 24 participants who completed the study are summarised in Table 1.

Incremental shuttle walk tests were performed before 6MWTs by 13 (54%) participants. Three (12%) participants rested during the 6MWT. The ESWT and ISWT were each performed only once by one participant (4%) due to an abnormally high end-test heart rate. A higher walking speed was selected for the second ESWT in 5 (21%) participants.

Performance during each test is summarised in Table 2. Average speed during the 6MWT was 76.5 $m \cdot min^{-1}$ (95% CI, 71.8 to 81.1 $m \cdot min^{-1}$). Peak walking speed achieved during the ISWT was 85.9 $m \cdot min^{-1}$ (95% CI, 80.3 to 91.5 $m \cdot min^{-1}$). Average speed during the ESWT was 73.4 $m \cdot min^{-1}$ (95% CI, 68.3 to 78.4 $m \cdot min^{-1}$). Compared with each walking test, the CET elicited greater peak dyspnea ($F_{3,69} = 27.9$; $p < 0.001$) and leg fatigue ($F_{3,54} = 27.5$; $p < 0.001$). Patterns of response for cardiorespiratory variables are illustrated in Figures 1a to 1f. The sub-maximal pattern of change during the ESWT and 6MWT was curvilinear for all variables and the sub-maximal pattern of change during the ISWT and CET was linear for all variables.

Peak cardiorespiratory responses for each test are presented in Table 3. Compared with each walking test, the CET elicited a greater $\dot{V}CO_2$, respiratory exchange ratio and $\dot{V}_E$ as well as a smaller decrease in SpO_2. There was no difference in peak $\dot{V}O_2$, heart rate or tidal volume among the tests. The small variability between tests observed in resting measures in Figures 1a to 1f, reflects the metabolic load associated with the warm-up period and unloaded cycling that preceded the ESWT and CET, respectively.

The bias and coefficient of repeatability for gas exchange and breathing pattern variables collected during each walking test are presented in Table 4. Compared with data collected during the ISWT, the coefficients of repeatability tended to be narrower for data collected during the 6MWT and ESWT.

DISCUSSION

This is the first study to compare the peak and sub-maximal cardiorespiratory responses across three field walking tests with a laboratory-based CET in patients with COPD. The important findings of this study are; (i) all tests elicited similar peak $\dot{V}O_2$, heart rate and tidal volume, (ii) the CET elicited a greater peak $\dot{V}CO_2$, respiratory exchange ratio, $\dot{V}_E$ and smaller decrease in SpO_2 compared with all walking tests, (iii) the sub-maximal pattern of change during the ISWT and CET were similar, being linear for all variables and, (iv) the sub-maximal pattern of change during the 6MWT and ESWT were similar, being curvilinear for all variables. Further, this is the first study to report the bias and coefficient of repeatability for measures of gas exchange and breathing pattern variables measured during walking tests. Generally, the bias for each measure was small with variables measured on completion of the 6MWT and ESWT demonstrating narrower coefficients of repeatability compared to the ISWT.

The similar peak $\dot{V}O_2$ and heart rate during the ISWT and CET corroborates earlier reports.[15-18] It has been suggested that the 6MWT is most likely to elicit peak cardiorespiratory responses in people with COPD following an acute exacerbation,[32] or in those with profound functional limitation[33] or severe airflow obstruction.[16,19] However, our data reveal that among stable participants with, on average, moderate disease (FEV_1 = 50 ±

14 % predicted) and modest functional limitation (six-minute walk distance = 459 ± 66 m), the 6MWT elicited similar peak $\dot{V}O_2$ and cardiac demands as both the CET and ISWT. This relates, at least in part, to the utilisation of a 6MWT protocol that included standardised instructions, encouragement and consistent performance of two 6MWTs under identical conditions on the same day. Many of the participants had experience with the 6MWT; a factor likely to account for the modest learning effect and may have contributed to the magnitude of response elicited during the 6MWT. Although the CET elicited greater $\dot{V}CO_2$ and $\dot{V}_E$ than the 6MWT, exercise intensity is usually expressed in terms of $\dot{V}O_2$ or heart rate (as a surrogate for $\dot{V}O_2$) and therefore our data reveals that a standardised, encouraged 6MWT elicited a maximum exercise response in people with moderate COPD, with modest functional limitation, who were clinically stable.

Our data show remarkable similarity in the pattern of response and walking speeds used for the ESWT and 6MWT. This contrasts with the study by Pepin et al[34] who reported a greater $\dot{V}_E$, respiratory rate and heart rate on completion of the ESWT compared with the 6MWT, despite both tests being conducted at similar walking speeds. This disparity may be related to differences in lung function and exercise capacity between the study samples. Although FEV_1 (percent predicted) was similar between samples, the absolute FEV_1 and the forced expiratory ratio were lower in our participants (1.31 vs. 1.18 L and 46 vs. 40%). Further, the $\dot{V}O_2$ and distances achieved during the walking tests were considerably greater in the study by Pepin et al.[34] Taken together, it appears that the participants in this earlier study were characterised by less severe disease and better exercise capacity[34] and the capacity of the 6MWT and ESWT to elicit similar cardiorespiratory responses may be contingent on these factors.

In agreement with earlier reports, there was a smaller decrease in SpO_2[16,18,35] together with a higher $\dot{V}CO_2$, respiratory exchange ratio and $\dot{V}_E$ during the CET compared with the walking tests.[15,18] These differences have been demonstrated to persist when walking and cycling modalities were matched for $\dot{V}O_2$[36] and appear to relate to the greater specific load placed on the quadriceps during CET[37] eliciting a greater accumulation of lactate[15] which is buffered by bicarbonate, thereby increasing $\dot{V}_E$.[36] Regarding the pattern of response, cardiorespiratory variables during the ISWT and CET increased in a linear pattern reflecting the incremental increase in power[17] whereas the cardiorespiratory response to the 6MWT and ESWT was characterised by a similar magnitude of exponential increase over the first 50% of the test, followed by a relative plateau in response.[34] Figure 1c demonstrates that at time points before test completion, $\dot{V}_E$ was higher during the 6MWT and ESWT, compared with the ISWT and CET; data that support a previous finding of greater dyspnea during the 6MWT at time points before test completion, compared with incremental test protocols.[16] It appears that performance during the 6MWT and ESWT was influenced by the capacity of an individual to tolerate near maximum levels of $\dot{V}_E$.

The repeatability of cardiorespiratory measures collected at the end of the walking tests was similar to that previously reported for variables measured on completion of CET.[29] The somewhat wider coefficients for measures collected during the ISWT, relative to the 6MWT and ESWT, is likely to reflect that any increase in performance during the ISWTs resulting from familiarisation may have necessitated an increase in walking speed and considerable increase in cardiorespiratory demand. In contrast, the coefficients of repeatability calculated for data collected during the ESWT pertain only to tests during which the participants walked at identical speeds and there was a trivial difference in walking speeds during the two 6MWTs. A practical application of these data is that, following an intervention, to be 95% confident that any difference in cardiorespiratory response collected during the 6MWT, ISWT or ESWT was not simply due to normal variability inherent in these tests, the magnitude of change must exceed the coefficient of repeatability.

Limitations

As we excluded those who required long-term oxygen therapy or ambulatory aids, our results may not extend to these individuals. It is possible that the use of a treadmill rather than cycle ergometer would have allowed the participants to achieve greater a $\dot{V}O_2$ peak during the laboratory test.[36] Nevertheless, the CET was chosen as it is the most common laboratory-based cardiopulmonary exercise test in people referred to pulmonary rehabilitation.[12] We did not collect measures of inspiratory capacity and therefore cannot comment on differences in hyperinflation among the tests. Although a similar number of participants completed the 6MWT or ISWT during the first assessment session, practical issues (e.g. laboratory availability) prevented full compliance with the randomisation sequence, and it is possible that our results were affected by an order bias.

Conclusions

In clinically stable participants with moderate disease, field walking tests, when conducted according to a standardised protocol, elicited similar peak $\dot{V}O_2$ and heart rate responses as a CET. These data suggest that both self- and externally-paced walking tests progress to very high intensities and therefore appear to provide a basis on which to prescribe training intensities capable of inducing physiologic adaptation.[38,39]

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Table 1: Participant characteristics (n = 24; 15 men)

Variable	Mean ± SD	Range
Age (yr)	66.5 ± 7.7	48 to 83
Height (m)	1.64 ± 0.10	1.42 to 1.86
Weight (kg)	71.5 ± 14.1	46.7 to 91.6
BMI ($kg \cdot m^{-2}$)	26.8 ± 5.5	19.1 to 39.7
MRC dyspnea grade	2 ± 1*	0 to 2
FEV_1 (L)	1.18 ± 0.44	0.57 to 2.51
FEV_1 (% predicted)	50 ± 14	20 to 85
FEV_1/FVC (%)	40 ± 9	25 to 69
FRC (L)	5.19 ± 1.48	1.46 to 8.04
FRC (% predicted)	169 ± 37	98 to 213
D_LCO ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	12.6 ± 3.3	6.3 to 17.9
D_LCO (% predicted)	58 ± 18	26 to 95

*: data are median ± interquartile range; MRC: modified Medical Research Council (scores range from 0 to 4)

Table 2: Results of exercise tests

Six-minute walk test	Mean ± SD	Range
Learning effect (m)*	3 ± 11	-24 to 24
Distance (m)†	459 ± 66	355 to 631
End-test dyspnea†	3.6 ± 1.7	0.5 to 7.5
End-test leg fatigue†	2.3 ± 2.1	0 to 6
Incremental shuttle walk test		
Learning effect (m)*	25 ± 35	-20 to 100
Distance (m)†	338 ± 102	180 to 540
End-test dyspnea†	4.0 ± 1.1	1 to 6
End-test leg fatigue†	2.2 ± 2.2	0 to 6.5
Endurance shuttle walk test		
Learning effect (sec)‡	50 ± 83	-90 to 256
Time (sec)†	313 ± 160	123 to 765
Distance (m)†	384 ± 193	136 to 873
End-test dyspnea†	4.4 ± 1.7	1 to 8
End-test leg fatigue†	3.0 ± 2.4	0 to 8.5
Cycle ergometry test		
Peak power (W)	72 ± 28	27 to 129
End-test dyspnea	6.2 ± 2.0	0.5 to 9
End-test leg fatigue	5.7 ± 2.7	0.5 to 10

*: difference between second and first test; †: average of two tests (for ESWT, only tests performed the same walk speed were averaged, otherwise the test performed at the faster speed was included in the analysis); ‡: includes data from n = 18.

Table 3: Peak (end-test) cardiorespiratory responses

	6MWT	ISWT	ESWT	CET	ANOVA results
$\dot{V}O_2$ (ml·min^{-1})	1168 ± 344	1227 ± 310	1232 ± 368	1186 ± 314	$F_{3,69} = 1.2$; $p = 0.31$
$\dot{V}CO_2$ (ml·min^{-1})	1009 ± 270†	1036 ± 327†	1060 ± 342*	1173 ± 350	$F_{3,62} = 4.8$; $p = 0.006$
Respiratory exchange ratio	0.87 ± 0.11†	0.84 ± 0.10†	0.86 ± 0.12†	0.99 ± 0.17	$F_{3,69} = 18.7$; $p < 0.001$
$\dot{V}_E$ (L·min^{-1})	41 ± 17†	43 ± 15†	44 ± 16*	48 ± 17	$F_{3,69} = 10.2$; $p < 0.001$
Tidal volume (L)	1.39 ± 0.46	1.35 ± 0.42	1.36 ± 0.46	1.45 ± 0.46	$F_{3,69} = 1.5$; $p = 0.21$
Heart rate (beats·min^{-1})	128 ± 17	127 ± 14	130 ± 15	128 ± 19	$F_{2,50} = 0.6$; $p = 0.58$
SpO_2 (%)	88 ± 5†	88 ± 5†	88 ± 5†	95 ± 4	$F_{3,63} = 24.9$; $p < 0.001$

Data are mean ± SD; 6MWT: six-minute walk test; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; CET: cycle ergometry test; ANOVA: analysis of variance; $\dot{V}O_2$: rate of oxygen uptake; $\dot{V}CO_2$: rate of carbon dioxide output; $\dot{V}_E$: minute ventilation; SpO_2: arterial oxygen saturation measured via pulse oximetry. *: $p < 0.05$ vs. CET; †: $p < 0.01$ vs. CET. The subscripted numbers that accompany the F-statistics refer to the degrees of freedom available for the between and within-group comparisons.

Table 4: Mean difference (bias) and coefficient of repeatability for peak (end-test) cardiorespiratory responses

	6MWT		ISWT		ESWT†	
	Bias	Coefficient	Bias	Coefficient	Bias	Coefficient
$\dot{V}O_2$ (ml·min^{-1})	-33	322	-56	414	-138	287
$\dot{V}CO_2$ (ml·min^{-1})	-32	218	56	329	-76	218
Respiratory exchange ratio	-0.01	0.19	0.09	0.24	0.027	0.12
$\dot{V}_E$ (L·min^{-1})	-0.61	9.62	3.21	12.60	-1.30	10.84
Tidal volume (L)	-0.03	0.38	0.03	0.45	-0.05	0.27
Heart rate (beats·min^{-1})	2	10	4	13	2	9
SpO_2 (%)	-1	6	0	4	1	8

6MWT: six-minute walk test; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; $\dot{V}O_2$: rate of oxygen uptake; $\dot{V}CO_2$: rate of carbon dioxide output; $\dot{V}_E$: minute ventilation; SpO_2: arterial oxygen saturation measured via pulse oximetry; †: only tests performed the same walk speed were included in these analyses. Differences between tests were not systematic and therefore coefficients of repeatability could be calculated for all variables.

FIGURE LEGEND

Figures 1a-f: Data are mean and standard error. All participants contribute to each data point. Figures are patterns of response for; (a) rate of oxygen uptake ($\dot{V}O_2$), (b) rate of carbon dioxide output ($\dot{V}CO_2$), (c) minute ventilation ($\dot{V}_E$), (d) tidal volume (V_T), (e) heart rate (HR) and (f) arterial oxygen saturation measured via pulse oximetry (SpO_2) for each test.● : cycle ergometry test; ○ : six-minute walk test; ■ : incremental shuttle walk test; □ :endurance shuttle walk test; *: $p < 0.05$ for difference between cycle ergometry with all other tests.

Figure 1a

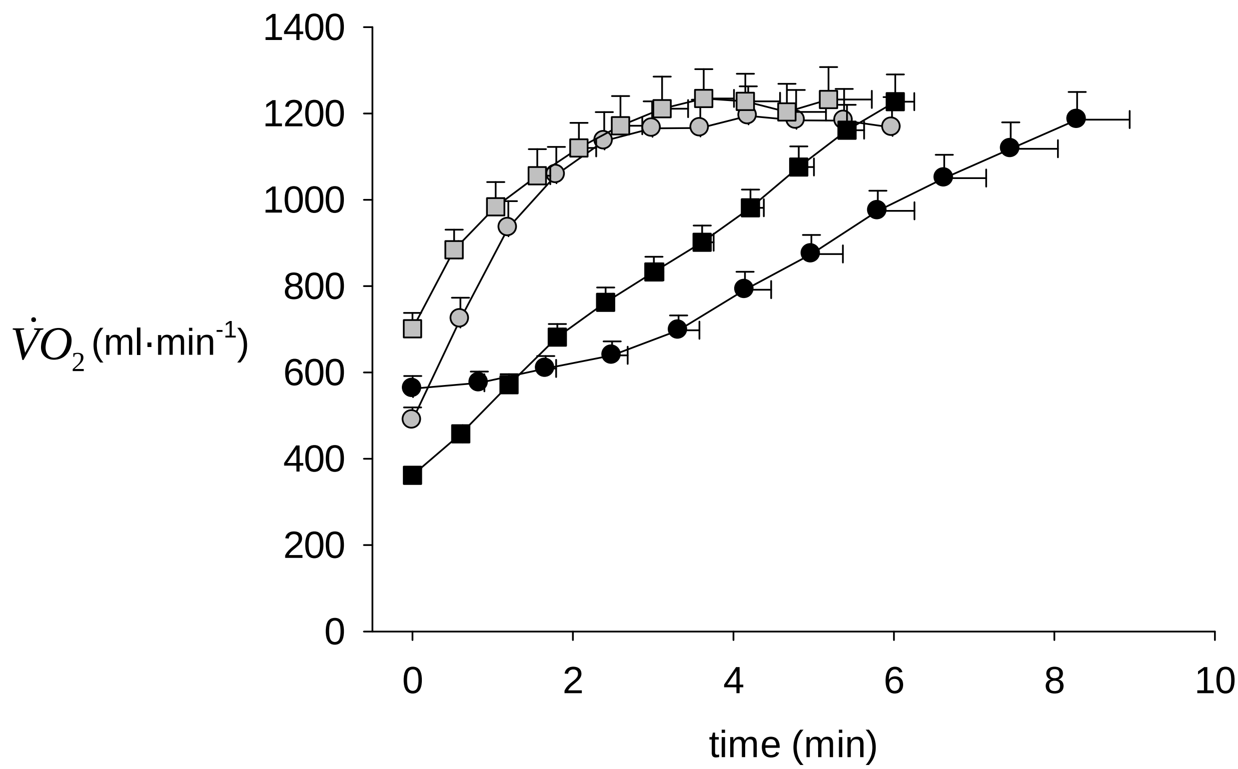

Figure 1b

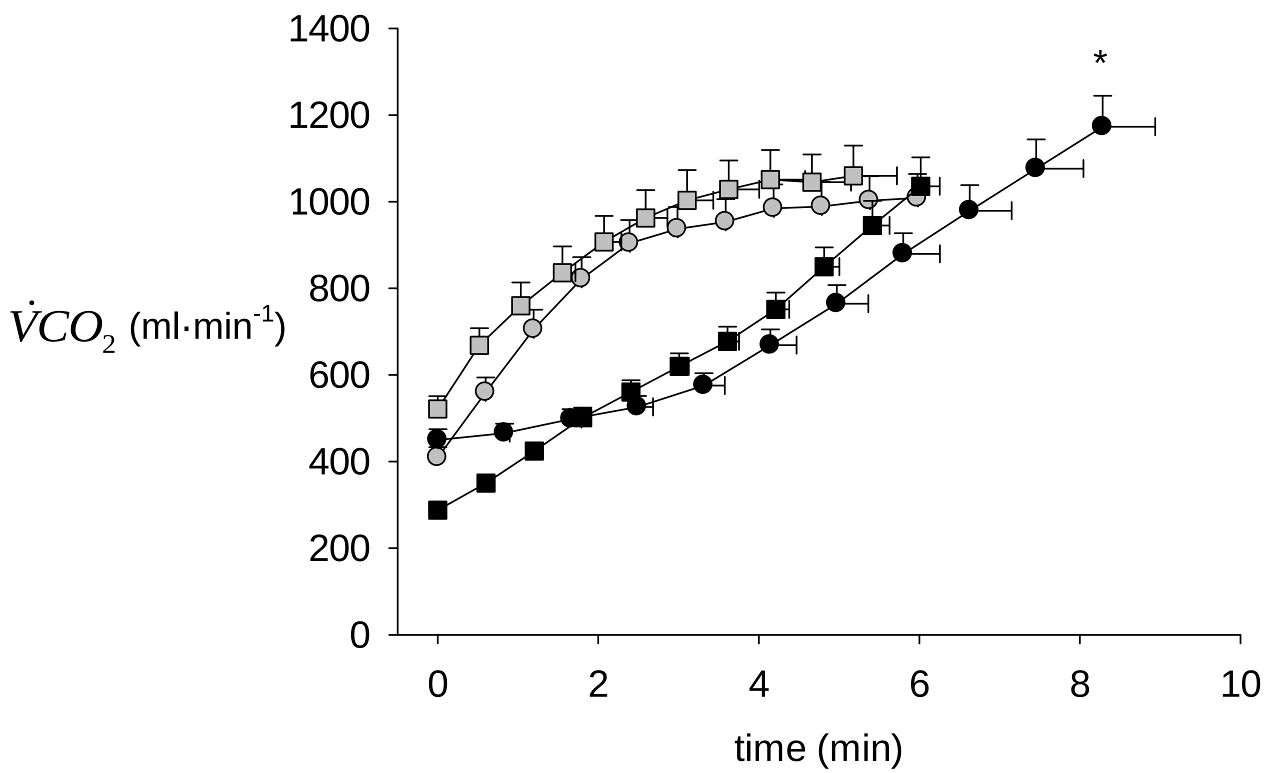

Figure 1c

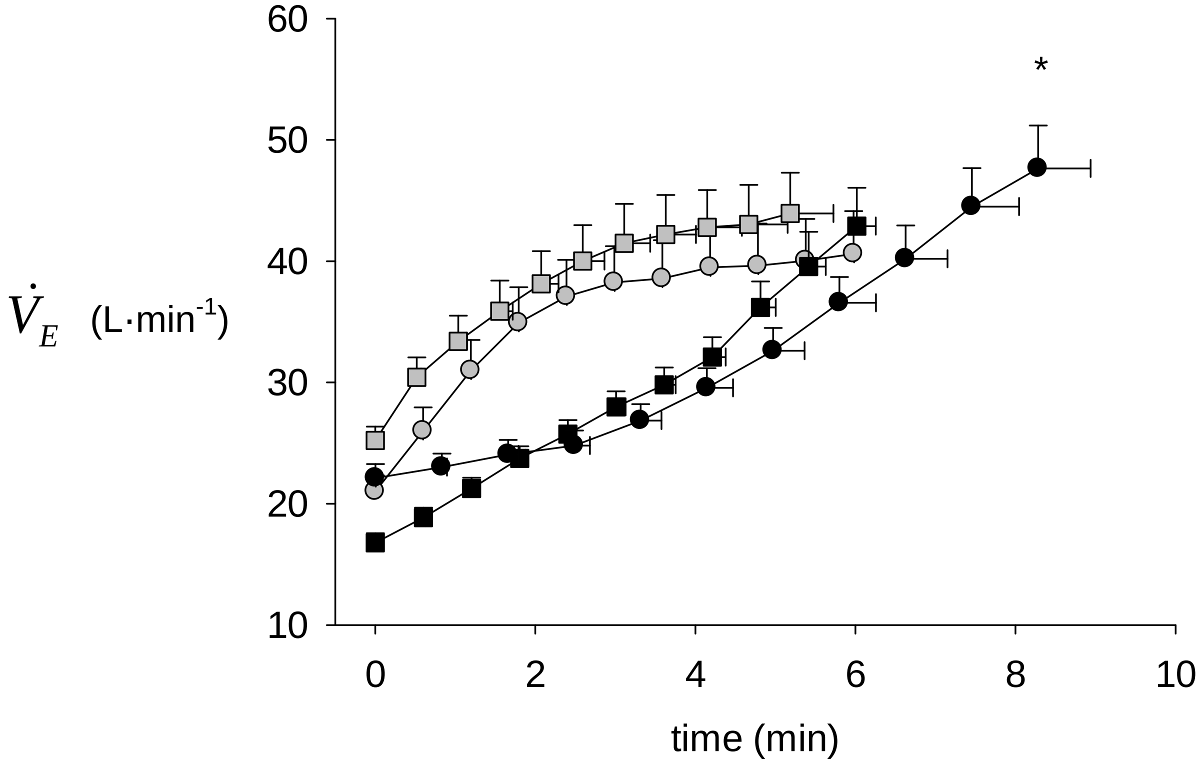

Figure 1d

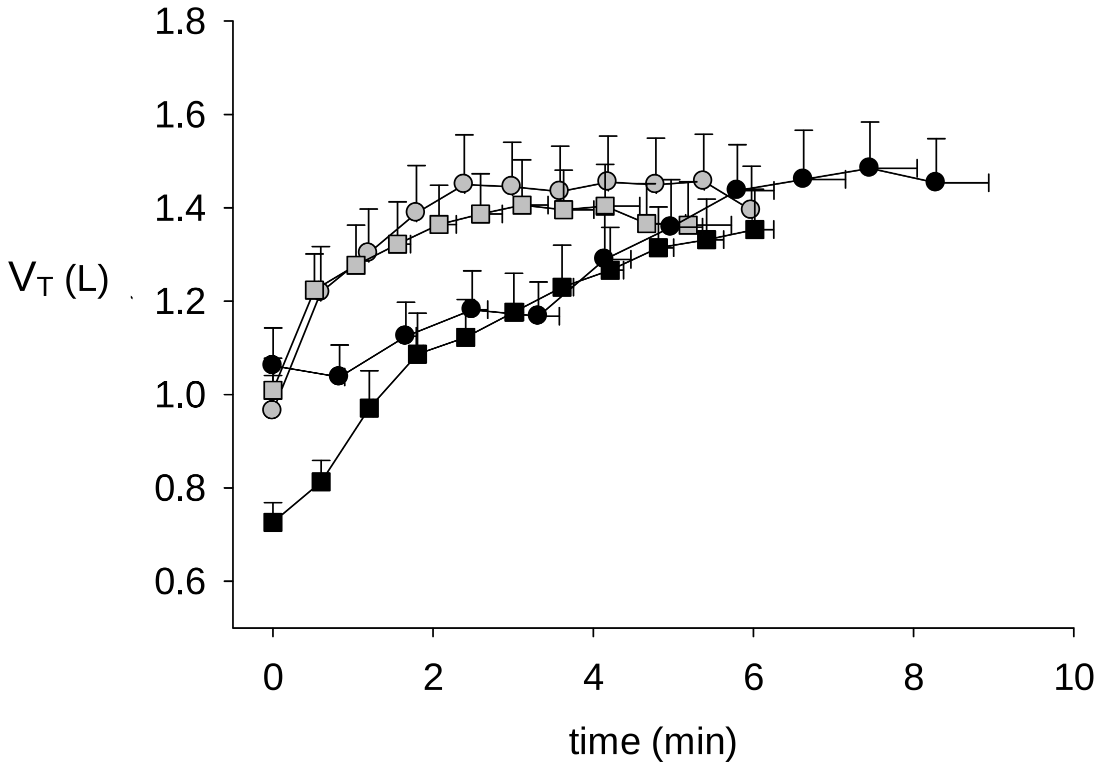

Figure 1e

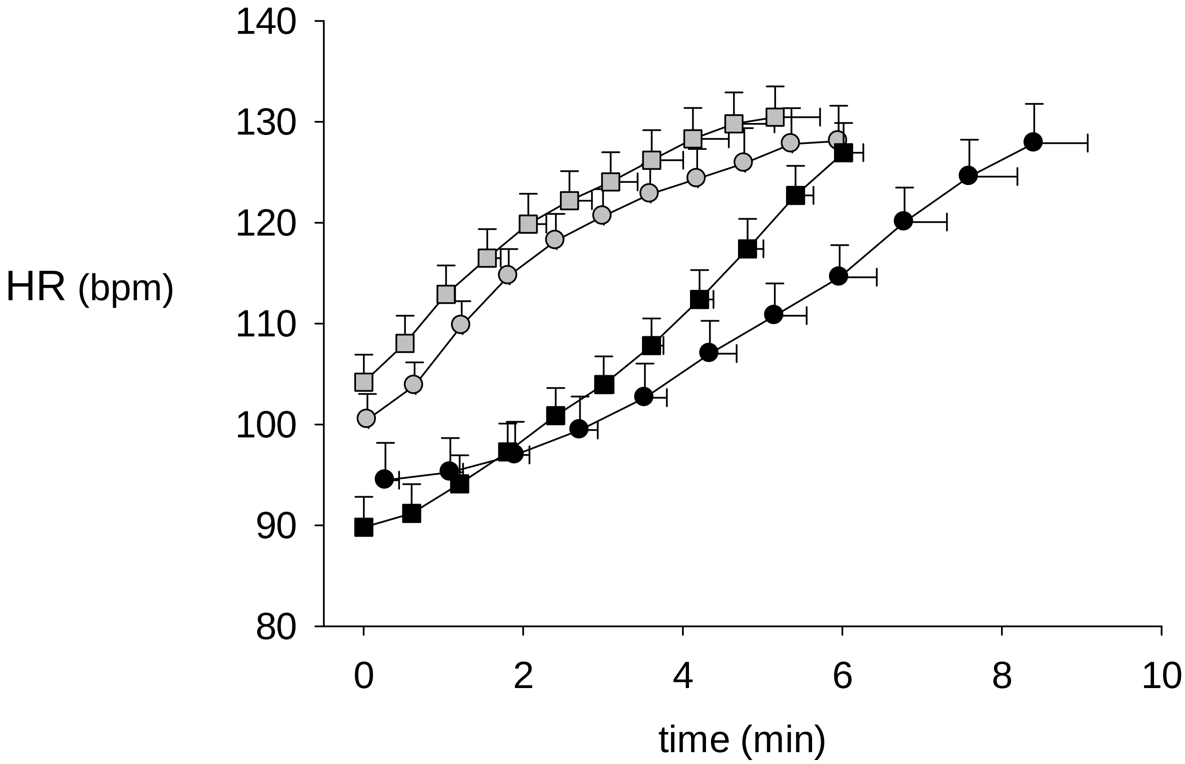

Figure 1f