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Physiological responses to linear treadmill and cycle ergometer exercise in COPD

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ABSTRACT: Incremental cardiopulmonary exercise testing work rate ideally increases linearly to the subject's tolerance within approximately 10 min. Widely used treadmill protocols often yield shorter exercise times in debilitated patients. We compared a recently described treadmill protocol featuring linear work rate increase, weight adjustments and *a priori* exercise tolerance estimates with standard cycle and treadmill protocols. We also compared treadmill and cycle responses to examine mechanisms of oxyhaemoglobin desaturation differences.

In total, 16 subjects with chronic obstructive pulmonary disease (COPD; mean±SD forced expiratory volume in 1 s of 36.5±10.9% predicted) performed incremental exercise using cycle, linear treadmill and modified Bruce protocols.

Initial linear treadmill speed and grade yielded oxygen uptake ($V'O_2$) similar to cycle unloaded pedalling; Bruce protocol first stage elicited much higher $V'O_2$. Exercise duration was much shorter in Bruce than in cycle or linear treadmill protocols. At peak exercise, greater desaturation was noted in linear treadmill and Bruce protocols compared with cycle (-8.9±4.9 *versus* -8.5±4.7 *versus* -3.7±3.3%; $p<0.001$); at iso-$V'O_2$ values this difference widened as exercise proceeded. Iso-$V'O_2$ desaturation differences were largely related to higher ventilatory response to cycle than to treadmill exercise.

The linear incremental treadmill protocol generates responses similar to cycle ergometry in severe COPD. However, cycle ergometry elicits less desaturation than does ambulation, making the linear treadmill protocol advantageous when evaluating COPD patients.

KEYWORDS: Bruce protocol, cardiopulmonary exercise testing, chronic obstructive pulmonary disease, lactic acidosis threshold, oxyhaemoglobin desaturation

Clinical incremental cardiopulmonary exercise testing ideally incorporates a low initial work rate followed by short incremental steps leading to a maximally tolerated work rate within approximately 10 min [1]. Linear work rate increase better enables physiological exercise response discrimination necessary to evaluate exercise intolerance. Specifically, noninvasive detection of the lactic acidosis threshold (LAT) relies on linear work rate increase [2]. There is controversy regarding the exercise modality best suited for cardiopulmonary exercise testing [3]. Cycle ergometry is often utilised because it allows more convenient intratest procedures such as blood sampling and blood pressure monitoring, has potential safety advantages, and allows easier work rate quantification. Treadmill protocols have the advantage of better mimicking a routine daily activity [4].

Commonly used treadmill protocols, such as those used in cardiac stress testing, have characteristics that are not ideal for cardiopulmonary exercise testing. For severely impaired patients, initial work rate of most treadmill protocols often approaches maximal exercise capacity, resulting in a test too short to allow adequate physiological response evaluation. Furthermore, these protocols often employ non-uniform speed and grade increases, resulting in nonlinear metabolic rate increase.

In incremental treadmill exercise, most work is done against gravity. Work rate done against gravity is the product of body mass, the gravitational constant, treadmill velocity and the sine of treadmill angle. Patients of different mass perform different amounts of work when walking at a given grade and speed. Hence, a test that adjusts for variation in exercise tolerance and body mass is needed to create an exercise test of appropriate duration. A treadmill protocol utilising low initial work rate and adjustable rate of work rate increase, in which continuous speed and grade adjustment yields a linear increase in work rate done against gravity, was described by PORSZASZ *et al.* [5]. This initial report, however, described only the protocol's theoretical

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underpinnings and elicited only responses of healthy subjects. The present study's first aim was, therefore, to evaluate this protocol's utility in subjects with limited exercise tolerance: patients with chronic obstructive pulmonary disease (COPD). To do this, we compared responses to the linearised treadmill test with incremental cycle ergometry and also with a treadmill protocol commonly used in cardiac stress testing (Ball State University (BSU; Muncie, IN, USA)/Bruce protocol [6]).

The second aim was to examine a clinically important issue in exercise testing. Several authors have observed that COPD patients exhibit greater oxyhaemoglobin desaturation when walking than when cycling [7–9]; the mechanism of this difference is not understood. We reasoned that having the patient perform progressive exercise tests on treadmill and cycle with nearly identical work rate profiles would facilitate definition of responsible mechanism(s). These results suggest a novel mechanism that explains an appreciable portion of the difference in exercise desaturation in walking and cycling exercise.

METHODS

Subjects

The Institutional Review Board of Los Angeles Biomedical Research Institute (Torrance, CA, USA) approved this study. In total, 16 COPD patients gave written consent for participation. Subjects were included if their forced expiratory volume in 1 s (FEV_1) was $\leqslant$60% predicted [10]. Subjects were excluded if they had recent respiratory exacerbation, significant cardiac disease, resting pulse oximetry <88%, a diagnosis of cor pulmonale, orthopaedic exercise limitations or required chronic supplemental oxygen.

Experimental design

Subjects performed three incremental exercise tests at the same time of day on separate days within a 2-week period. Subjects continued prescribed medications and on each testing day they took two albuterol puffs (Warrick Pharmaceuticals, Reno, NV, USA) *via* metered dose inhaler prior to spirometry measurements (Vmax 229 and Autobox 6200; SensorMedics, Yorba Linda, CA, USA). On the initial visit, body plethysmography and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) were performed.

The initial test was a ramped electromagnetically braked cycle ergometer (Ergoline 800; SensorMedics) test. Periods of 3 min rest and 3 min unloaded cycling at 60 rpm were followed by ramp-wise work rate increase; slope was 5 $W \cdot min^{-1}$ if FEV_1 <1.0 L and 10 $W \cdot min^{-1}$ if FEV_1 $\geqslant$1.0 L. On two subsequent testing days, subjects performed incremental treadmill tests (Marquette 2000; SensorMedics) in randomised order. One was a modified Bruce protocol (BSU/Bruce). This protocol modified the original seven-step protocol, in which each nonlinear step was of 3 min duration, so that each stage was reached by gradual ''ramped'' changes in speed and grade [6]. Note that the BSU/Bruce protocol reaches a speed of 2.7 $km \cdot h^{-1}$ (1.7 mph) and 10% grade by 3 min of exercise, irrespective of the subject's weight, and does not individualise the incremental phase, as employed in most cycle tests [1] and some treadmill protocols [11]. The second treadmill test utilised a recently described linear ramped treadmill protocol [5]. The goal was to create an individualised work rate profile that matched the cycle ergometer test (*i.e.* would reach the same work rate at the targeted 10-min incremental test duration). After 3 min of walking at 0.8 $km \cdot h^{-1}$ (0.5 mph), the treadmill speed increased linearly by 0.27 $km \cdot h^{-1}$ (0.17 mph) each minute. After 3 min at 0.5% grade, the treadmill grade was adjusted curvilinearly to yield a linear work rate increase done against gravity. The algorithm for treadmill grade time-course was derived previously [5] and is based on the patient's body weight, the desired initial and targeted final treadmill speeds, the initial grade and the targeted peak work rate. Subjects walked upright and were not allowed to grasp the treadmill rails.

Measurements

During exercise, subjects were monitored by 12-lead ECG (Cardiosoft; SensorMedics) and pulse oximetry (Nellcor N-200, Pleasanton, CA, USA) and their blood pressure by sphygmomanometry (Welch-Allyn, Skaneateles Falls, NY, USA). Subjects respired through a mouthpiece with nose-clip in place. At rest, every 2 min during exercise and at peak exercise, subjects assessed Borg-perceived exertion ratings for both respiratory and leg discomfort. End-expiratory lung volume (EELV) was assessed from inspiratory capacity (IC) manoeuvres three times at rest, every 2 min during exercise and at peak exercise [12, 13]. In these manoeuvres, after EELV was observed to be stable over 3–4 breaths, subjects were instructed to inspire maximally to total lung capacity (TLC). For each measurement, EELV was calculated as resting TLC minus IC.

Oxygen uptake (V'_{O_2}), carbon dioxide output (V'_{CO_2}) and minute ventilation (V'_E) were measured breath by breath (Vmax Spectra; SensorMedics). Airflow and gas concentrations were calibrated prior to each test and system accuracy was checked periodically with a metabolic simulator [14]. Breath-by-breath data were used to calculate 10-s average response time-courses; the 10-s intervals including and following IC manoeuvres were deleted. Peak values were averaged over the last 30 s of exercise; LAT was defined by modified V-slope approach [15].

Statistical analysis

Excel 2003 (Microsoft, Seattle, WA, USA) calculated mean and SD. SigmaStat 3.5 and SigmaPlot 10 (SPSS Science, Chicago, IL, USA) produced graphical display and conducted one-way ANOVA with repeated measures; significant differences between measurement pairs were isolated by the Holm–Sidak procedure [16]. Variation about the mean was expressed as mean$\pm$SD in text and tables and mean$\pm$SE in figures. Differences were declared significant if $p<0.05$.

RESULTS

This study involved 16 subjects with severe COPD, as evidenced by low mean FEV_1 and $D_{L,CO}$ (table 1). Spirometric values obtained before each day's testing did not differ significantly among the three tests.

Comparison of responses to the three exercise tests

Figure 1 presents exercise profiles and V'_{O_2} responses to the three protocols for a representative subject. As intended, calculated linear treadmill work rate profile duplicated the cycle profile (fig. 1b) by utilising linear speed change and curvilinear grade change (fig. 1a and c). This yielded similar V'_{O_2} profiles (fig. 1d). In contrast, the BSU/Bruce protocol featured rapid grade and speed change (fig. 1a and c),

TABLE 1 Characteristics of subjects

Age yrs	64.4±9.9
Male/female n	9/7
BMI kg·m^{-2}	27.3±4.6
Tobacco use pack-yrs	40.6±23.7
FEV_1 L	1.04±0.44
FEV_1 % predicted[#]	36.5±10.9
VC L	2.69±1.00
VC % predicted[#]	75.1±17.5
IC L	2.28±1.01
IC % predicted[¶]	92.3±34.3
FRC L	4.71±1.52
FRC % predicted[¶]	148.0±22.2
RV L	3.92±1.39
RV % predicted[¶]	182.2±37.4
TLC L	6.99±2.13
TLC % predicted[¶]	123.0±20.9
$D_{L,CO}$ mL·min^{-1}·torr^{-1}	10.4±4.2
$D_{L,CO}$ % predicted[+]	42.9±14.3

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; VC: vital capacity; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; $D_{L,CO}$: single-breath diffusing capacity of the lung for carbon monoxide. [#]: predicted normal values according to reference [10]; [¶]: predicted normal values according to reference [17]; [+]: predicted normal values according to reference [18].

resulting in steep and nonlinear work rate increase (fig. 1b) and much shorter exercise duration. Note that the BSU/Bruce protocol grade and speed rose rapidly, leading to test termination after ~4 min. In contrast, linear rise in speed and curvilinear rise in grade in the linear treadmill protocol led to a linear rise in calculated work rate that closely matched the cycle ergometer protocol work rate and led to exercise termination after ~13 min (10 min incremental exercise). Figure 2 shows responses of $V'CO_2$, ventilatory equivalent for carbon dioxide ($V'E/V'CO_2$) and end-tidal gas tensions as a function of $V'O_2$ for the three tests of the same subject presented in figure 1. Note that LAT and peak $V'O_2$ are lower in the cycle protocol than in either of the two treadmill protocols. Also note that, because the BSU/Bruce protocol increments work rates much more rapidly, data points (10-s averages) are much sparser and have more variation in the middle range of $V'O_2$ where the LAT occurs, thus tending to decrease LAT detection reliability.

Table 2 presents physiological responses to the three exercise protocols for all subjects. Exercise duration for the BSU/Bruce protocol was less than half of that for either of the other two tests. The low initial work rate of the linear treadmill protocol produced a $V'O_2$ at 3 min of exercise comparable to that elicited by cycle ergometer unloaded pedalling. This contrasts with the much higher $V'O_2$ seen at 3 min in the BSU/Bruce protocol, which averaged 81% of peak $V'O_2$. Nevertheless, the two treadmill protocols resulted in similar peak $V'O_2$ values that average 14% higher than cycle ergometer values. We could determine the LAT in all three tests by the V-slope method in 12 subjects. In the remaining four, LAT was indeterminate in one or more tests. In these 12 subjects, LAT was, on average, 35% higher in both linear and BSU/Bruce treadmill protocols compared with cycle ergometry. Peak $V'E$ and heart rate were not significantly different among protocols. At peak exercise, cycle exercise yielded higher leg fatigue ratings and tended to elicit less dyspnoea than treadmill exercise.

There were appreciable differences between treadmill and cycle ergometer tests in the time-course of oxygen saturation decrease as assessed by pulse oximetry (table 2). While oxygen saturation levels were similar at the start of all three protocols, decreases from resting levels were significantly greater for both linear and BSU/Bruce treadmill protocols compared with cycle at the LAT (for the 12 subjects who consistently manifested an LAT), at peak exercise and at the nadir of oxygen saturation, which typically occurred early in recovery. As seen in figure 3a, difference in oxygen saturation with different exercise modalities was observed early in exercise; this difference increased as a function of the percentage of the peak work rate tolerated. Figure 3b displays this relationship as a function of $V'O_2$. Because peak $V'O_2$ differs among subjects, this plot displays values only up to 0.9 L·min^{-1} (the highest $V'O_2$ at which most patients were represented). It is clear that, at a given $V'O_2$, oxygen saturation was lower in treadmill tests than in the cycle test. These differences have clinical implications. Patients are often considered eligible to receive supplemental oxygen for ambulation if exercise saturation falls below 88%. By this criterion, based on the cycle test, three out of 16 subjects would qualify for ambulatory oxygen; based on either treadmill test, 11 out of 16 subjects would qualify.

Physiological correlates of differences in exercise desaturation

We sought physiological correlates of this difference in oxygen saturation between treadmill and cycle tests. Average $V'E$ was progressively higher for a given $V'O_2$ in cycle compared with treadmill exercise (fig. 4a). The increased $V'E$ for a given $V'O_2$ on the cycle compared with both treadmill protocols became statistically significant at a $V'O_2$ of 0.7 L·min^{-1} and remained significant at subsequent values ($p<0.001$). There was no significant difference in peak $V'E$ values, however. Respiratory frequency and tidal volume progression were similarly examined. Tidal volume, but not respiratory frequency, tended to be higher in the cycle test (data not shown). Figure 4b shows EELV measurements as a function of $V'O_2$ and at peak exercise. Progressive dynamic hyperinflation was seen as exercise proceeded, but significant differences in EELV increases were not seen among exercise protocols.

Figure 5 plots six physiological variables as a function of $V'O_2$. Overall, this figure demonstrates that differences in responses to cycle compared with treadmill exercise were consistent with hyperventilation with respect to oxygen-, but not carbon dioxide-related variables. Figure 5a shows that, as for $V'E$ (fig. 4a), $V'CO_2$ was higher at a given $V'O_2$ at higher exercise intensities. This similarity in $V'E$ and $V'CO_2$ profiles was confirmed in that neither the time-course of the $V'E/V'CO_2$ (fig. 5c) nor the end-tidal carbon dioxide tension (P_{ET,CO_2}; fig. 5e) differed among tests. In contrast, the ventilatory equivalent for oxygen ($V'E/V'O_2$; fig. 5d) and end-tidal oxygen tension (P_{ET,O_2}; fig. 5f) were distinctly higher during the cycle test at a given $V'O_2$. This difference is confirmed in that the

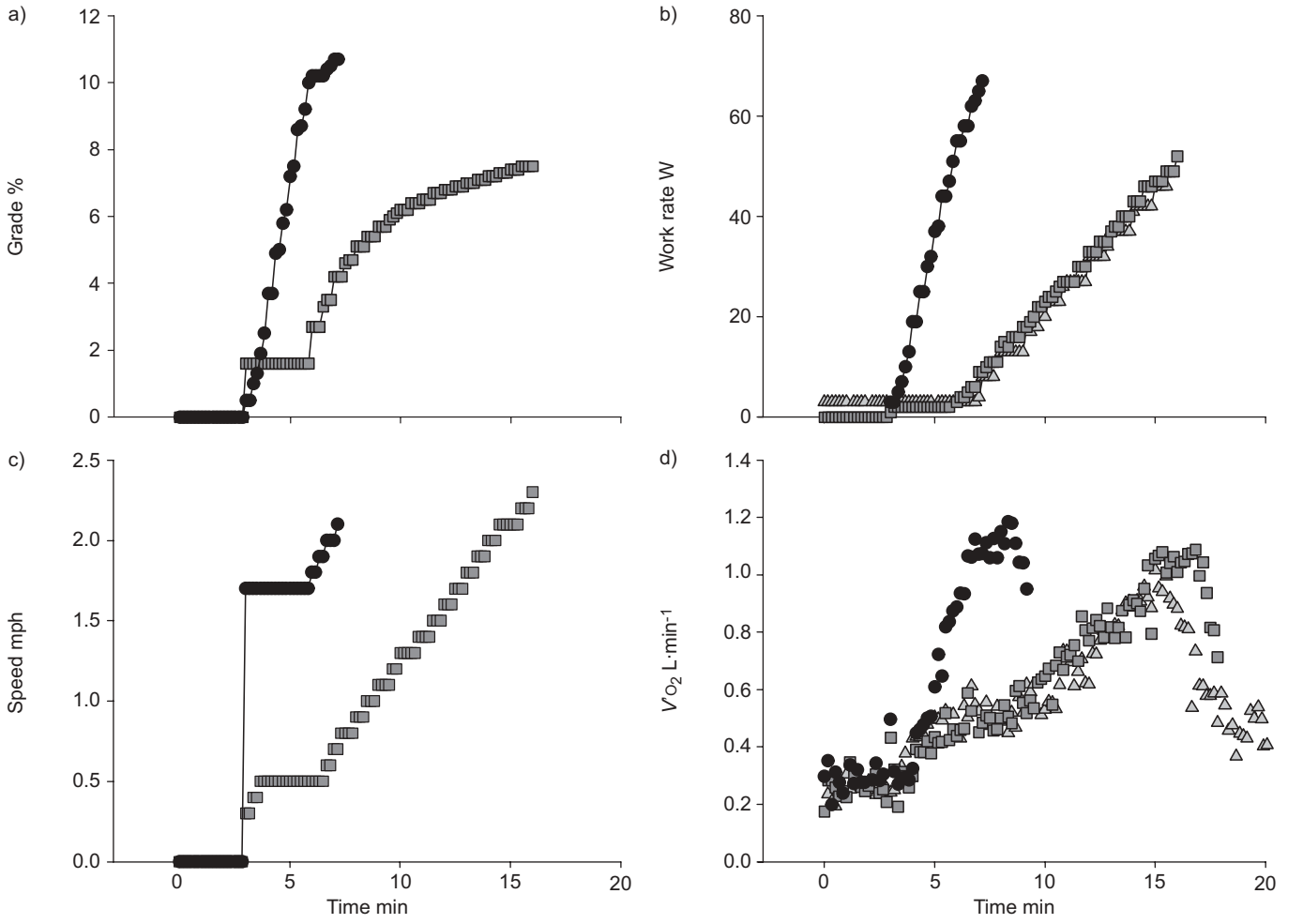

FIGURE 1. Comparison of linear treadmill (■), Ball State University (Muncie, IN, USA)/Bruce treadmill (●) and cycle ergometer (▲) protocol time-courses in a representative subject with chronic obstructive pulmonary disease. a) Treadmill grade; b) work rate performed against gravity for the treadmill protocols and done on the ergometer flywheel for the cycle ergometer; c) treadmill speed (1 mph=1.609 km·h^{-1}); d) oxygen uptake (V'_{O_2}). The first 3 min were a rest period in each protocol.

respiratory exchange ratio (R; V'_{CO_2}/V'_{O_2}) was distinctly higher for cycle than for treadmill exercise (fig. 5b). This suggests that cycle ergometer exercise elicits excess V'_{CO_2} out of proportion to V'_{O_2} and that V'_E tracks V'_{CO_2}, not V'_{O_2}. This difference seems likely to be related to greater lactic acidosis at a given V'_{O_2} with cycle compared with treadmill exercise, due to the lower LAT in the cycle test (see Discussion).

While P_{ET,O_2} would be expected to be a poor reflection of arterial oxygen tension (P_{a,O_2}), especially in patients with lung disease, differences in P_{ET,O_2} change between treadmill and cycle protocols should reflect differences in P_{a,O_2} change if lung gas exchange properties at a given exercise level are hypothesised not to differ. Figure 6 shows that, in fact, changes in P_{ET,O_2} and oxygen saturation in treadmill and cycle tests paralleled each other; P_{ET,O_2} and oxygen saturation falls were much more modest in cycle ergometer than in either treadmill test.

Analysis of the mechanisms of differences in exercise desaturation

The higher ventilatory response at a given V'_{O_2} for cycle, compared with treadmill, should result in higher alveolar ventilation and, therefore, higher P_{a,O_2} and oxygen saturation, assuming that lung gas exchange characteristics do not differ. A key question is whether observed differences in ventilatory response are sufficient to account for observed P_{ET,O_2} and oxygen saturation differences. This evaluation was facilitated by examining iso-V'_{O_2} responses to linearised treadmill and cycle exercise for relevant physiological responses at 0.1-L·min^{-1} intervals for the 16 subjects studied (122 data-points) and making the plausible assumption that lung gas exchange properties did not differ at a given V'_{O_2} between cycle and treadmill tests. The alveolar gas equation dictates that:

$$P_{A,O_2}=F_{I,O_2}(P_B-47)-P_{a,CO_2}/R$$

where P_{A,O_2} is ideal alveolar oxygen tension, F_{I,O_2} is the inspiratory oxygen fraction, P_B is the barometric pressure, P_{a,CO_2} is arterial carbon dioxide tension and R is respiratory exchange ratio (V'_{CO_2}/V'_{O_2}). As F_{I,O_2} and P_B do not differ between cycle (C) and treadmill (T) tests, and if it is assumed that P_{a,CO_2} does not differ between cycle and treadmill (note that P_{ET,CO_2} does not differ (fig. 5e)), then:

$$\Delta P_{A,O_2}=P_{a,CO_2}(1/R_T-1/R_C)$$

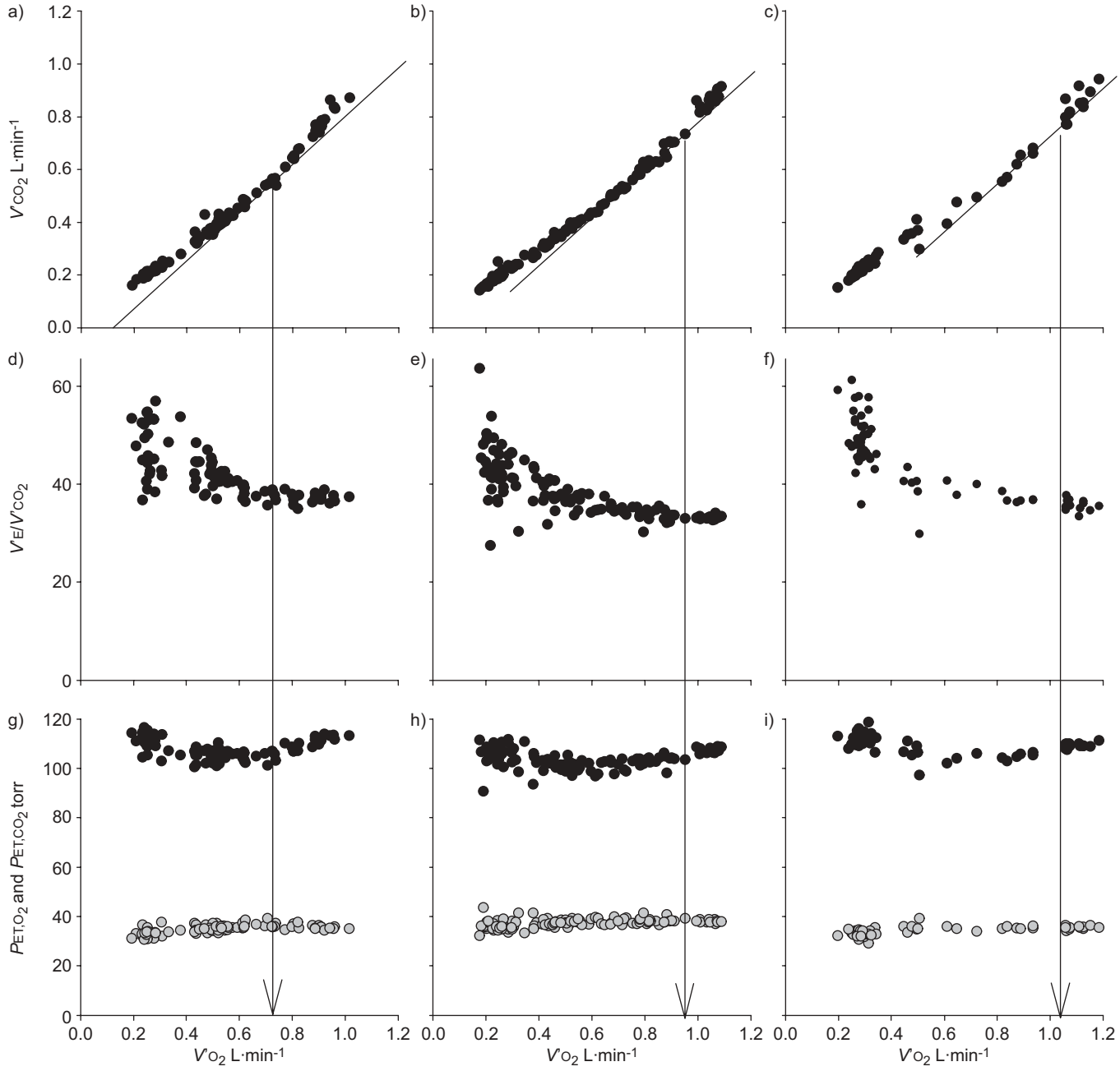

FIGURE 2. Responses of a–c) carbon dioxide output (V'_{CO_2}), d–f) ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2}) and g–i) end-tidal carbon dioxide tension (P_{ET,CO_2}; ■) and end-tidal oxygen tension (P_{ET,O_2}; ●) as a function of oxygen uptake (V'_{O_2}) in response to a, d and g) cycle ergometer, b, e and h) linear treadmill and c, f and i) Ball State University (Muncie, IN, USA)/Bruce incremental exercise tests in a representative subject with chronic obstructive pulmonary disease. Data are plotted at 10-s intervals. This montage is commonly used to estimate the lactic acidosis threshold; the diagonal lines in the upper plots have a slope of unity and are used to determine the point at which V'_{CO_2} increases out of proportion to V'_{O_2}. Arrows denote the lactic acidosis threshold.

Since the alveolar mass balance equation for carbon dioxide dictates that:

$$P_{a,CO_2}=kV'_{CO_2}/(V'_E(1-V_D/V_T))$$

where V_D/V_T is dead space fraction and k is a constant, it can be seen that, at iso-V'_{O_2} points,

$$\Delta P_{A,O_2}=(kV'_{O_2}/(1-V_D/V_T))(1/V'_{E,T}-1/V'_{E,C})$$

If V_D/V_T does not differ between exercise modes, this equation shows that iso-V'_{O_2} differences in P_{A,O_2} result directly from differences in ventilatory response. If it is further assumed that the difference between P_{A,O_2} and P_{ET,O_2} does not differ between exercise modes and that P_{a,CO_2} is 40 torr in both exercise modes, then calculated P_{A,O_2} differences based on observed differences in R can be compared with observed P_{ET,O_2} differences between cycle and treadmill. Figure 7a

TABLE 2 Physiological responses to incremental exercise

	Cycle ergometer	Linear treadmill	BSU/Bruce treadmill	p-value
Total exercise time min	12.0±2.1	11.5±2.8	5.1±1.8***	<0.001
Peak work rate W	71.9±39.4	70.1±52.2	89.6±44.2*	0.003
V'_{O_2} at 3 min L·min^{-1}	0.49±0.10	0.53±0.15	1.04±0.24***	<0.001
Peak V'_{O_2} L·min^{-1}	1.10±0.40***	1.28±0.55	1.29±0.43	<0.001
V'_{O_2}/WR slope mL·min^{-1}·W^{-1}	11.4±2.3	12.2±2.6	8.5±1.8*	<0.001
LAT$^{\#}$ L·min^{-1}	0.80±0.23***	1.08±0.42	1.08±0.32	<0.001
LAT/peak V'_{O_2} %	71.3±9.6*	80.5±11.1	81.9±11.1	0.007
Peak *f*C beats·min^{-1}	122±12	130±16	129±14	0.179
Peak V'_E L·min^{-1}	39.1±16.8	38.6±16.0	38.8±11.9	0.922
Peak V'_{CO_2} L·min^{-1}	1.16±0.51*	1.27±0.66	1.28±0.51	0.043
Peak V'_E/V'_{CO_2}	34.0±3.2***	31.4±4.4	31.4±4.7	<0.001
V'_E/V'_{CO_2} at LAT$^{\#}$	35.3±3.7	33.3±3.9	34.3±3.5	0.078
Peak P_{ET,CO_2} mmHg	37.5±3.7***	40.6±4.8	40.0±4.3	<0.001
Peak P_{ET,O_2} mmHg	113.5±5.8***	108.6±5.3	109.7±4.5	<0.001
Peak IC L	1.57±0.62	1.54±0.48	1.55±0.57	0.814
ΔIC peak-rest L	-0.57±0.37	-0.54±0.19	-0.54±0.31	0.860
Peak EELV¶	76.6±9.0	77.2±6.8	76.9±8.3	0.771
ΔEELV peak-rest¶	8.5±5.8	8.1±3.2	8.1±5.1	0.814
Resting S_{p,O_2} %	95.6±1.8	95.5±2.1	95.2±2.2	0.475
ΔS_{p,O_2} at LAT$^{\#}$ %	-0.9±1.2***	-4.3±3.0	-5.3±3.7	<0.001
ΔS_{p,O_2} at peak %	-2.7±2.9***	-7.3±4.4	-7.4±4.8	<0.001
Maximum ΔS_{p,O_2} %	-3.7±3.3***	-8.9±4.9	-8.5±4.7	<0.001
Peak Borg breathlessness	6.0±2.1*	6.5±2.1	6.6±2.2	0.046
Peak Borg leg discomfort	6.2±2.3	5.8±2.0	6.0±2.0	0.733

Data are presented as mean±SD, unless otherwise stated. BSU: Ball State University (Muncie, IN, USA); V'_{O_2}: oxygen uptake; WR: work rate; LAT: lactic acidosis threshold; *f*C: cardiac frequency; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide output; V'_E/V'_{CO_2}: ventilatory equivalent for carbon dioxide; P_{ET,CO_2}: end-tidal carbon dioxide tension; P_{ET,O_2}: end-tidal oxygen tension; IC: inspiratory capacity; EELV: end-expiratory lung volume; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetry. $^{\#}$: for 12 subjects who had determinate LAT values in all three tests; ¶: as a percentage of total lung capacity. *: $p<0.05$ compared with the other two protocols; ***: $p<0.001$ compared with the other two protocols.

shows that, at a given V'_{O_2}, both average calculated $\Delta P_{A,O_2}$ and measured $\Delta P_{ET,O_2}$ rose with V'_{O_2} and were of similar magnitude. Figure 7c shows that the correlation between these two variables was good ($r=0.73$, $p<0.001$).

To determine whether oxygen saturation differences could be similarly accounted for by ventilatory response differences, we assumed a normal oxyhaemoglobin desaturation curve (with P_{a,CO_2} of 40 torr and pH 7.4) [19]. For each data-point, we determined to what extent difference in P_{A,O_2} (assumed to reflect an equal difference in P_{a,O_2}) resulted from the difference between measured ventilatory response and whether this could predict the observed treadmill oxygen saturation decrease. Operationally, for each of 122 iso-V'_{O_2} data-points, we started with treadmill oxygen saturation, utilised the dissociation curve to estimate treadmill P_{a,O_2}, added to this the calculated $\Delta P_{A,O_2}$, and then again utilised the dissociation curve to determine oxygen saturation ''corrected'' for the ventilation difference. Finally, the difference between ''corrected'' treadmill saturation and observed treadmill saturation was compared with the difference between observed cycle saturation and observed treadmill saturation. Figure 7b shows that both these differences rose with V'_{O_2} and were of similar magnitude; calculated oxygen saturation difference averaged ~70% of the measured difference. Figure 7d shows that calculated difference between oxygen saturation based on ventilatory response differences was significantly correlated with observed oxygen saturation differences ($r=0.65$, $p<0.001$).

DISCUSSION

This study has two main focuses. First, we demonstrated that a newly described treadmill protocol yields a linear increase in work rate (and metabolic rate) and results in a test of sufficient duration to allow good physiological response characterisation in severe COPD. Secondly, a major determination made during exercise testing in COPD (and other diseases) is whether exercise-induced oxygen desaturation occurs, as supplemental oxygen prescription is often based on such evaluations. We observed clinically important oxygen desaturation blunting during cycling compared with treadmill exercise. Furthermore, we defined a mechanism likely to be responsible for a substantial portion of this blunting.

Several treadmill exercise protocols have been found clinically useful [5, 20]. Although treadmill protocols with linear work rate profiles have been recommended [11], the Bruce protocol is widely used, especially in cardiac exercise testing. However, the Bruce protocol's nonlinear physiological responses make it difficult to evaluate V'_{O_2} responses and cardiovascular exercise

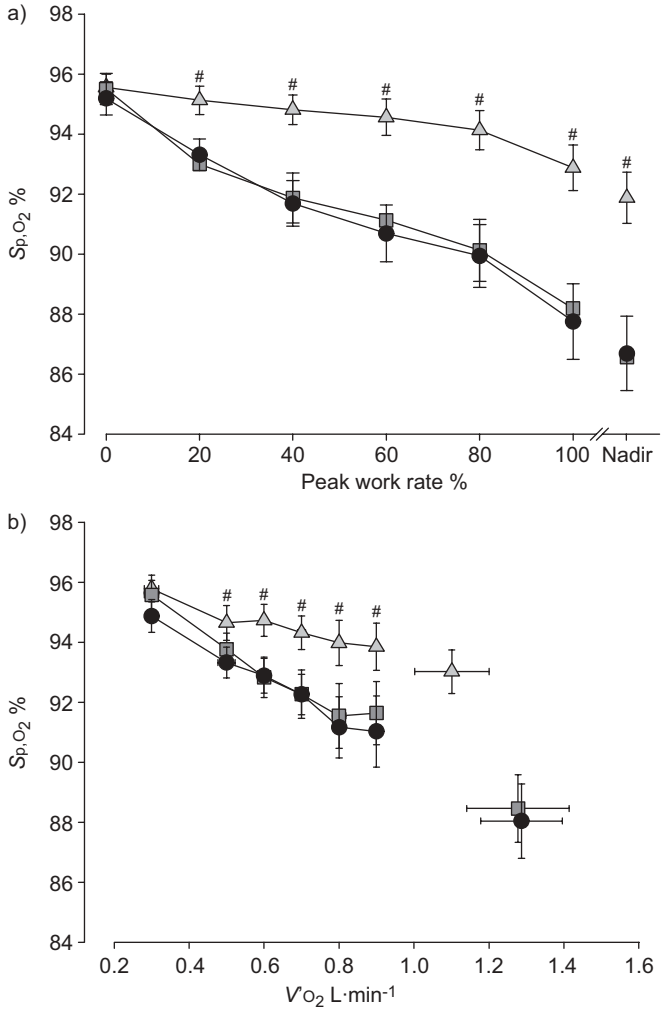

FIGURE 3. Mean±SE arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) during cycle ergometer (▲), linear treadmill (■) and Ball State University (Muncie, IN, USA)/Bruce (●) incremental exercise tests in 16 chronic obstructive pulmonary disease patients. a) S_{p,O_2} plotted as the percentage of the peak work rate tolerated by the subject. Nadir: average of the lowest 10-s value recorded. b) S_{p,O_2} plotted as a function of oxygen uptake ($V'O_2$). Data-points are plotted at rest and at 0.1-L·min^{-1} intervals through the incremental exercise, and are the average of 16 subjects' responses except for $V'O_2$ of 0.8 and 0.9 L·min^{-1}, which had 14 and 13 subjects, respectively. Data-points on the right are peak responses. #: p<0.003.

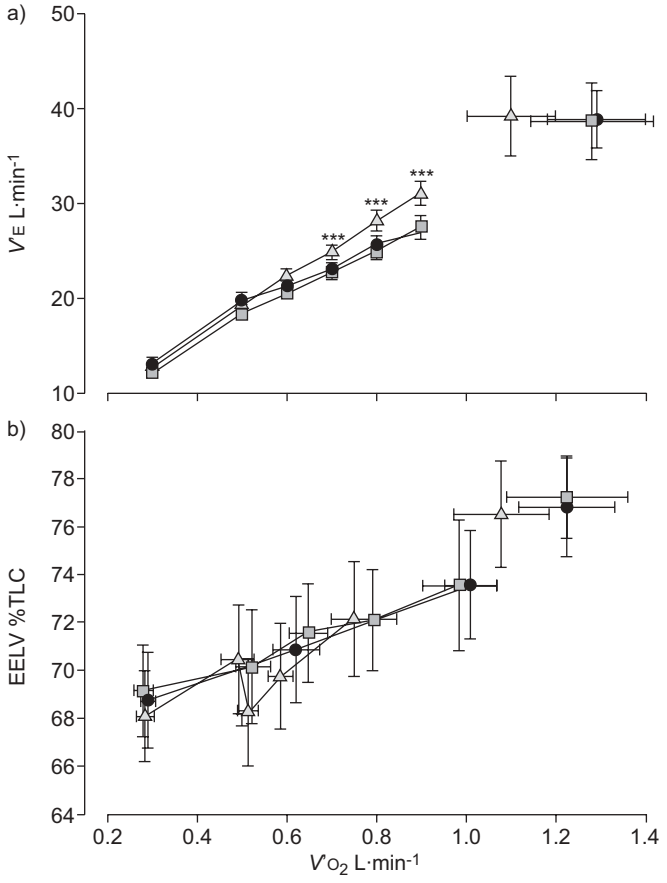

FIGURE 4. Mean±SE a) minute ventilation (V'_E) and b) end-expiratory lung volume (EELV) as a percentage of total lung capacity (TLC), as a function of oxygen uptake ($V'O_2$) during cycle ergometer (▲), linear treadmill (■) and Ball State University (Muncie, IN, USA)/Bruce (●) incremental exercise tests in chronic obstructive pulmonary disease patients. Data-points on the right are peak responses. a) Data-points are the average of 16 subjects' responses except for $V'O_2$ of 0.8 and 0.9 L·min^{-1}, which had 14 and 13 subjects, respectively. b) The increase in EELV did not differ significantly among protocols. ***: p<0.001.

limitations [4, 21–24]. Other tests, such as Balke or Astrand tests, achieve linear work rate increase while maintaining a high constant speed (5.3 and 8.0 km·h^{-1} (3.3 and 5.0 mph), respectively). However, their set grade increments yield different work rates for patients of varying mass. In these protocols, high speed and large grade changes yield short test durations in impaired patients. These tests cannot be adjusted for body weight and functionality [3, 21, 25].

Recently, a treadmill protocol was described that utilises linear speed changes and nonlinear inclination changes that result in a linear ramp-like change in work performed against gravity [5]. This protocol was previously evaluated in 22 healthy subjects but not in impaired patients. Similar to this study in healthy subjects, we found that the linear treadmill protocol yielded test durations near the target of 10 min. In contrast, the BSU/Bruce protocol yielded a much shorter test duration. Figure 2 shows consequences of this, *i.e.* sparse data in the mid-ranges of metabolic rate response. Furthermore, figure 1 shows a distinctly nonlinear $V'O_2$ response for the BSU/Bruce protocol. The linear treadmill protocol yielded similar response time-courses to cycle ergometer testing, but close examination reveals important differences that highlight physiological distinctions. Similarities include similar $V'O_2$ response to the initial exercise stage and similar peak V'_E, cardiac frequency and work rate. Peak $V'O_2$ for treadmill exercise averaged 14% higher than cycle exercise, consistent with previous studies, and probably reflects the larger muscle mass involved in treadmill exercise [1, 5, 11, 26, 27]. LAT was lower in cycle compared with treadmill testing in subjects who manifested an LAT. This, again, may be ascribed to the smaller muscle mass used with cycling [1, 5, 8, 28]. It should be noted that, when it can be detected, LAT determination from gas exchange has been shown to result in mild overestimates in COPD patients [29].

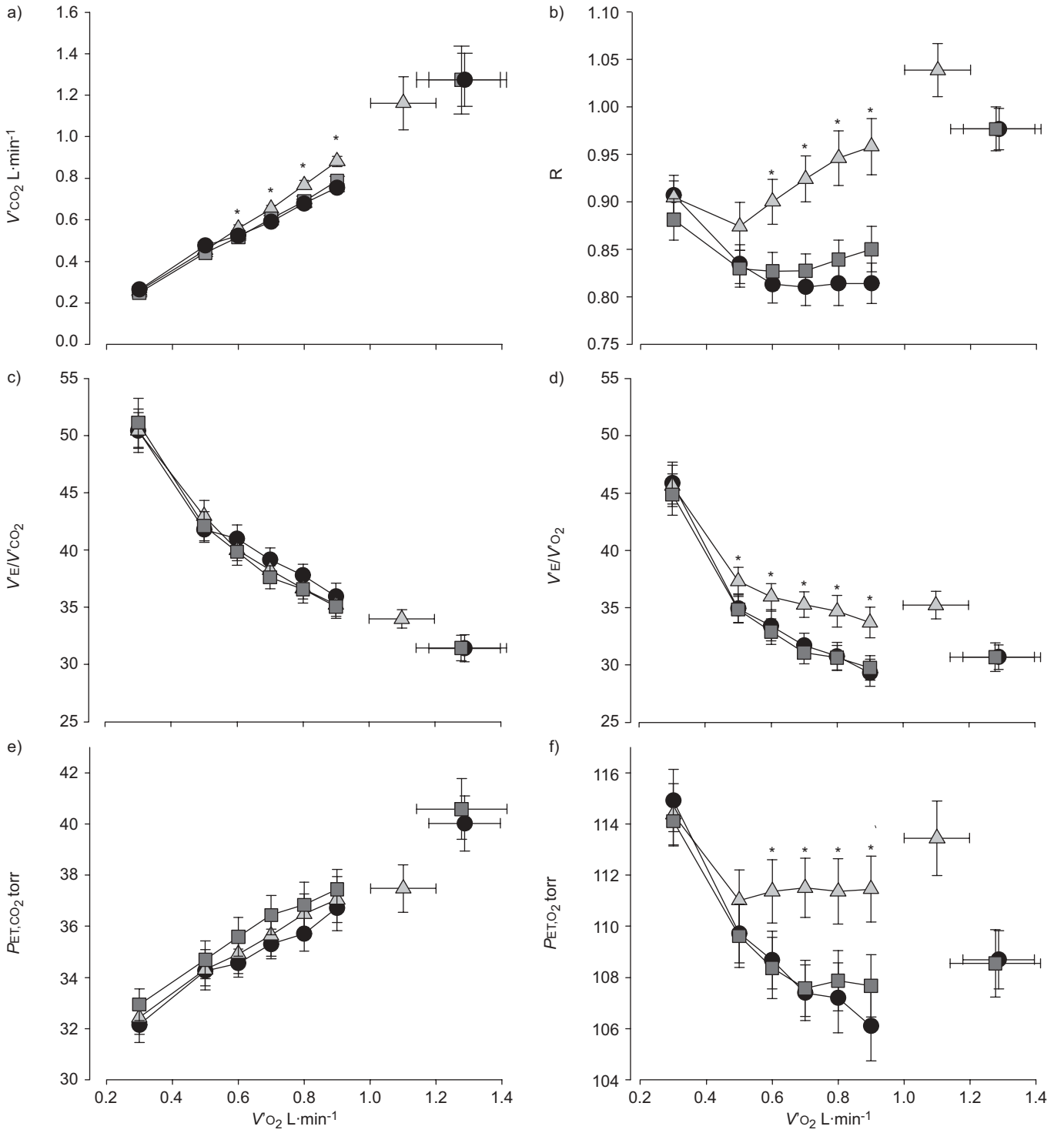

FIGURE 5. Mean±SE responses as a function of oxygen uptake (V'_{O_2}) to cycle ergometer (▲), linear treadmill (■) and Ball State University (Muncie, IN, USA)/Bruce (●) incremental exercise tests in chronic obstructive pulmonary disease patients. a) Carbon dioxide output (V'_{CO_2}); b) respiratory exchange ratio (R; V'_{CO_2}/V'_{O_2}); c) ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2}); d) ventilatory equivalent for oxygen (V'_E/V'_{O_2}); e) end-tidal carbon dioxide tension (P_{ET,CO_2}); f) end-tidal oxygen tension (P_{ET,O_2}). Data-points are the average of 16 subjects' responses except for V'_{O_2} of 0.8 and 0.9 L·min^{-1}, which had 14 and 13 subjects, respectively. Data-points on the right of each panel are peak responses. *: $p<0.05$ between cycle and either treadmill response.

Of greatest interest is the marked difference in oxygen saturation time-courses for the two treadmill protocols compared with cycle ergometry (fig. 3). Others have also noted greater oxygen desaturation with ambulatory modalities compared with cycle ergometry [7–9]. However, to our knowledge, this is the first oxygen saturation evaluation at equivalent metabolic rates while utilising similar work rate profiles in the two exercise modalities. The two treadmill

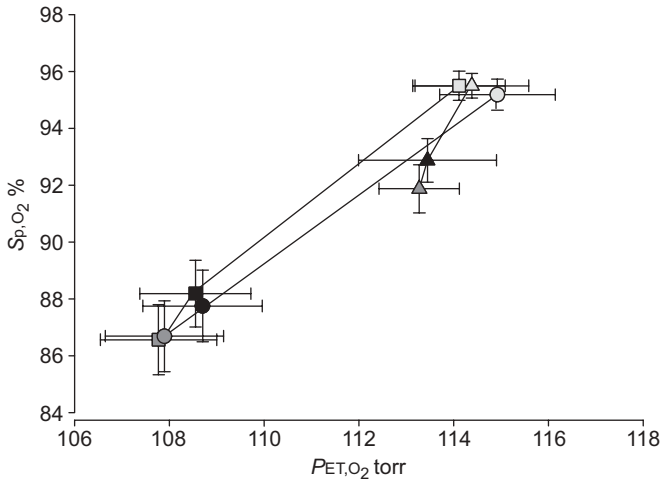

FIGURE 6. Mean±SE arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) and corresponding end-tidal oxygen tension (P_{ET,O_2}) values for cycle ergometer (△), linear treadmill (□) and Ball State University (Muncie, IN, USA)/Bruce (○) incremental exercise tests in 16 chronic obstructive pulmonary disease patients. Light shaded symbols represent values during rest, dark shaded symbols represent peak exercise, and medium shaded symbols represent values occurring at the lowest point of oxygen saturation (during or after exercise). Note that P_{ET,O_2} and S_{p,O_2} changes were closely related among exercise protocols.

protocols resulted in similar profiles of oxygen saturation change at iso-V'_{O_2} values. In contrast, cycle ergometer responses demonstrated a substantially blunted oxygen saturation fall. This is clinically important as 11 out of 16 patients would have been considered for supplemental oxygen treatment during exertion based on treadmill testing, but only three out of 16 based on cycle testing.

This oxygen saturation difference measured by pulse oximetry seems likely to reflect true differences in arterial oxygen saturation and P_{a,O_2}. First, a study comparing cycle with ambulation tests in which arterial blood gas samples were drawn (although only at peak exercise) confirms these differences [8]. Secondly, the present study shows parallel changes in P_{ET,O_2} and arterial oxygen saturation estimated by pulse oximetry (fig. 6). If it is allowed that, at a given V'_{O_2}, substantial differences in alveolar–end-tidal and alveolar–arterial oxygen tension difference are unlikely between cycle and treadmill exercise, then differences between P_{ET,O_2} profiles probably truly reflect P_{a,O_2} profile differences.

Several theories as to the mechanism of these differences in desaturation have been proposed. Lung gas exchange differences between sitting on the cycle ergometer and walking upright have been hypothesised. Other investigators noted decreased peak V'_{CO_2} and increased V'_E/V'_{CO_2} ratio in walking tests and surmised that this could correspond to worsened V_D/V_T resulting in less efficient gas exchange and consequent hypoxaemia [8]. Our study did not corroborate this finding; on the contrary, we found significantly higher peak V'_{CO_2} and V'_E/V'_{CO_2} with cycle compared with either treadmill protocols. Unlike prior shuttle and self-paced walking tests, our study utilised a linear treadmill and cycle protocol, which yielded identical calculated work rate profiles and similar test durations. We found no difference in V'_E/V'_{CO_2} when examined at iso-V'_{O_2} (fig. 5c). However, V'_E/V'_{CO_2} can only be used as a surrogate for V_D/V_T, and serial blood gas analysis (allowing P_{a,CO_2} measurement) would be helpful in evaluating this further. Another possibility is that better ventilation/perfusion matching or better oxygen diffusion is present during cycle than in treadmill exercise; however, no plausible mechanism for such a difference has been proposed.

It seems unlikely that there is a significant advantage in ventilatory mechanics while cycling. Theoretically, patients can use handlebars to brace their upper thorax on a cycle ergometer. However, patients in this study were ventilatorily limited (as documented by low breathing reserve; table 2) and we, and others [8, 28], have not found peak V'_E differences between cycle and treadmill tests. Furthermore, we did not find iso-V'_{O_2} differences in dynamic hyperinflation between cycle and treadmill tests (fig. 4b).

We propose a novel explanation for oxygen saturation differences. Figures 4 and 5 show that V'_E and V'_{CO_2} are similar at rest and at low exercise levels but, at higher V'_{O_2}, progressively greater V'_E and V'_{CO_2} are seen during cycle exercise. Figure 5 shows that this translates into higher V'_E/V'_{O_2} and R. The mechanism for higher V'_{CO_2} at a given V'_{O_2} seems likely to be related to earlier lactic acidosis onset in the cycle ergometer test. Lactic acid is predominantly buffered by bicarbonate, generating carbon dioxide that is exhaled in the breath. The higher V'_E is probably related to higher V'_{CO_2}; exercise ventilation has been shown to be tightly coupled to V'_{CO_2} (and not to V'_{O_2}) [30].

Can these differences be invoked to explain at least part of the observed differences in arterial oxygen saturation? We have performed calculations based on reasonable assumptions to show that they can. Figure 7a and b shows that the excess cycle V'_E predicts a difference in ideal P_{A,O_2} roughly similar in magnitude to the observed P_{ET,O_2} difference between cycle and treadmill. Similarly, calculated ideal P_{A,O_2} difference was shown to be capable of predicting a substantial portion of the observed difference between treadmill and cycle oxygen saturation. It is specifically acknowledged that several of the assumptions used in these calculations are unlikely to be accurate (*e.g.* that P_{a,CO_2} is 40 torr), although we cannot see that any of the assumptions would substantially bias the relationships we observed. It would certainly be appropriate to confirm these findings in studies in which arterial blood was collected serially, to allow iso-V'_{O_2} comparison of P_{a,O_2}, P_{a,CO_2} and oxygen saturation with metabolic and gas exchange responses to the two exercise modes. However, devising a strategy to sample arterial blood at iso-V'_{O_2} points during incremental exercise and to approach the number of comparisons we achieved (fig. 7c and d) would be extremely challenging.

In conclusion, we demonstrated that the linear treadmill protocol is suitable for use in patients with severe COPD and has advantages over a commonly used treadmill protocol. Importantly, this new treadmill protocol has the advantage of individualising work rate increments to elicit optimal test duration while keeping walking speed within comfortable limits. It seems likely to have similar advantages in other

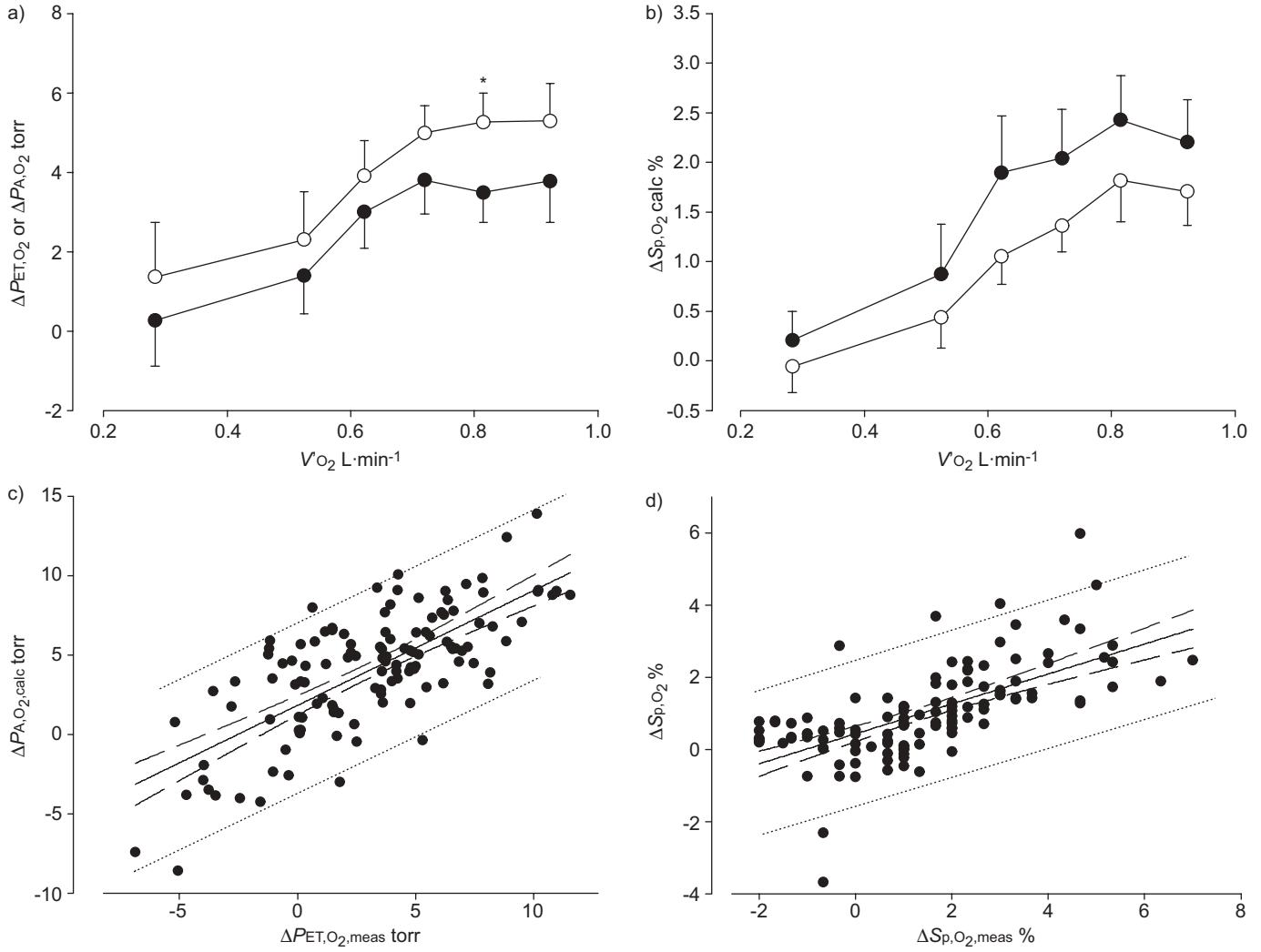

FIGURE 7. Calculations seeking to define the mechanism of differences in end-tidal oxygen tension (P_{ET,O_2}) and arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) in linear treadmill *versus* cycle exercise tests, utilising data from 16 chronic obstructive pulmonary disease patients. a) As a function of oxygen uptake (V'_{O_2}) during incremental exercise, calculated difference in alveolar oxygen tension ($\Delta P_{A,O_2,calc}$; ○) expected based on differences in ventilatory response to treadmill *versus* cycle ergometer exercise and measured differences in P_{ET,O_2} ($\Delta P_{ET,O_2,meas}$; ●) between cycle and treadmill. b) As a function of V'_{O_2}, calculated difference in S_{p,O_2} ($\Delta S_{p,O_2,calc}$; ○) expected based on the differences in ventilatory response to treadmill *versus* cycle ergometer exercise and measured difference in S_{p,O_2} ($\Delta S_{p,O_2,meas}$; ●) between cycle and linear treadmill tests. c and d) Iso-V'_{O_2} differences between cycle ergometer and linear treadmill responses measured at 0.1-L·min^{-1} intervals in all 16 patients (122 data-points). c) $\Delta P_{A,O_2,calc}$ expected based on the differences in ventilatory response to treadmill and cycle ergometer exercise *versus* $\Delta P_{ET,O_2,meas}$ between cycle and treadmill. Correlation coefficient 0.73, regression slope 0.72 and intercept 1.84 torr (all $p<0.001$). d) $\Delta S_{p,O_2,calc}$ expected based on differences in ventilatory response to treadmill and cycle ergometer exercise *versus* $\Delta S_{p,O_2,meas}$ between cycle and linear treadmill tests. Correlation coefficient 0.65, regression slope 0.42 and intercept 0.43% (all $p<0.001$). ——: regression line; – – – –: 95% regression confidence limits; ·····: 95% confidence limits of individual data-points. *: $p<0.05$.

debilitated patient groups, although studies in patients with milder COPD and in patients with other cardiopulmonary disorders would be of value. Many cardiopulmonary exercise tests are performed for the purpose of diagnosing mechanisms of exercise intolerance. Detecting oxygen desaturation that might occur in everyday activities is often an important part of this evaluation. It is clear that cycle ergometer testing is considerably less likely to elicit oxygen desaturation that might be encountered during ambulation. We therefore propose that the linear treadmill protocol we describe might be considered for adoption as the preferred methodology in diagnostic cardiopulmonary exercise testing.

SUPPORT STATEMENT

R. Casaburi occupies the Grancell/Burns Chair in the Rehabilitative Sciences (Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA, USA).

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Buchfuhrer MJ, Hansen JE, Robinson TE, *et al*. Optimizing the exercise protocol for cardiopulmonary assessment. *J Appl Physiol* 1983; 55: 1558–1564.

2 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; 60: 2020–2027.
3 Porszasz J, Stringer W, Casaburi R. Equipment, measurements and quality control in clinical exercise testing. *In*: Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 40: 108–128.
4 Wasserman K, Hansen JE, Sue DY, *et al.*, Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications. Philadelphia, Lippincott Williams and Wilkins, 2005.
5 Porszasz J, Casaburi R, Somfay A, *et al.* A treadmill ramp protocol using simultaneous changes in speed and grade. *Med Sci Sports Exerc* 2003; 35: 1596–1603.
6 Kaminsky LA, Whaley MH. Evaluation of a new standardized ramp protocol: the BSU/Bruce Ramp protocol. *J Cardiopulm Rehabil* 1998; 18: 438–444.
7 Cockcroft A, Beaumont A, Adams L, *et al.* Arterial oxygen desaturation during treadmill and bicycle exercise in patients with chronic obstructive airways disease. *Clin Sci (Lond)* 1985; 68: 327–332.
8 Palange P, Forte S, Onorati P, *et al.* Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. *J Appl Physiol* 2000; 88: 1715–1720.
9 Poulain M, Durand F, Palomba B, *et al.* 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. *Chest* 2003; 123: 1401–1407.
10 Knudson RJ, Lebowitz MD, Holberg CJ, *et al.* Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983; 127: 725–734.
11 Myers J, Buchanan N, Walsh D, *et al.* Comparison of the ramp *versus* standard exercise protocols. *J Am Coll Cardiol* 1991; 17: 1334–1342.
12 O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 770–777.
13 Porszasz J, Emtner M, Goto S, *et al.* Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. *Chest* 2005; 128: 2025–2034.
14 Huszczuk A, Whipp BJ, Wasserman K. A respiratory gas exchange simulator for routine calibration in metabolic studies. *Eur Respir J* 1990; 3: 465–468.
15 Sue DY, Wasserman K, Moricca RB, *et al.* Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. *Chest* 1988; 94: 931–938.
16 Glantz S. Primer of Biostatistics. 6th Edn. New York, McGraw-Hill, 2005.
17 Goldman HI, Becklake MR. Respiratory function tests; normal values at median altitudes and the prediction of normal results. *Am Rev Tuberc* 1959; 79: 457–467.
18 Burrows B, Kasik JE, Niden AH, *et al.* Clinical usefulness of the single-breath pulmonary diffusing capacity test. *Am Rev Respir Dis* 1961; 84: 789–806.
19 Kelman GR. Digital computer subroutine for the conversion of oxygen tension into saturation. *J Appl Physiol* 1966; 21: 1375–1376.
20 Naughton J, Patterson J, Fox SM 3rd. Exercise tests in patients with chronic disease. *J Chronic Dis* 1971; 24: 519–522.
21 American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
22 Ashley EA, Myers J, Froelicher V. Exercise testing in clinical medicine. *Lancet* 2000; 356: 1592–1597.
23 Hansen JE, Sue DY, Oren A, *et al.* Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. *Am J Cardiol* 1987; 59: 669–674.
24 Itoh H, Tajima A, Koike A, *et al.* Cardiopulmonary Exercise Testing and Cardiovascular Health. Armonk, Futura, 2002.
25 American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription (Exercise Protocols). Philadelphia, Lippincott Williams and Wilkins, 2000.
26 Hermansen L, Saltin B. Oxygen uptake during maximal treadmill and bicycle exercise. *J Appl Physiol* 1969; 26: 31–37.
27 Maeder M, Wolber T, Atefy R, *et al.* Impact of the exercise mode on exercise capacity: bicycle testing revisited. *Chest* 2005; 128: 2804–2811.
28 Mathur RS, Revill SM, Vara DD, *et al.* Comparison of peak oxygen consumption during cycle and treadmill exercise in severe chronic obstructive pulmonary disease. *Thorax* 1995; 50: 829–833.
29 Patessio A, Casaburi R, Carone M, *et al.* Comparison of gas exchange, lactate, and lactic acidosis thresholds in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993; 148: 622–626.
30 Casaburi R, Whipp BJ, Wasserman K, *et al.* Ventilatory and gas exchange dynamics in response to sinusoidal work. *J Appl Physiol* 1977; 42: 300–301.