

Physiologic Responses to Linear Treadmill and Cycle Ergometer Exercise in COPD

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**Short Title :** Linearized Treadmill Exercise Testing in COPD

## **ABSTRACT**

Incremental cardiopulmonary exercise testing work rate ideally increases linearly to the subject's tolerance within approximately 10 minutes. 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 to standard cycle and treadmill protocols. We also compared treadmill and cycle responses to examine mechanisms of oxyhemoglobin desaturation differences.

Sixteen COPD subjects ( $FEV_1\%predicted=36.5\pm 10.9(SD)$ ) 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 pedaling; 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 to cycle ( $-8.9\pm 4.9$  vs.  $-8.5\pm 4.7$  vs.  $-3.7\pm 3.3\%$ ,  $P<0.001$ ); 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.

**Abstract Word Count = 200**

**Key Words:** Bruce protocol, cardiopulmonary exercise testing, chronic obstructive pulmonary disease, lactic acidosis threshold, oxyhemoglobin desaturation

## **Introduction**

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 minutes[1]. Linear work rate increase better enables physiological exercise response discrimination necessary to evaluate exercise intolerance. Specifically, non-invasive detection of the lactic acidosis threshold 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 utilized because it allows more convenient intra-test 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 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 physiologic response evaluation. Further, these protocols often employ non-uniform speed and grade increases, resulting in non-linear 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 utilizing 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 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 COPD. To do this, we compared responses to the linearized treadmill test to incremental cycle ergometry and also to a treadmill protocol commonly used in cardiac stress testing (BSU-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 oxyhemoglobin 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 approved this study. Sixteen COPD patients gave written consent for participation. Subjects were included if forced expiratory volume in one second ( $FEV_1$ ) was  $\leq 60\%$  predicted[10]. Subjects were excluded if they had recent respiratory exacerbation,

significant cardiac disease, resting pulse oximetry <88%, a diagnosis of *cor pulmonale*, orthopedic exercise limitations or required chronic supplemental oxygen.

*Experimental Design.* Subjects performed 3 incremental exercise tests at the same time of day on separate days within a 2-week period. Subjects continued prescribed medications and each testing day took 2 albuterol puffs (Warrick Pharmaceuticals, Reno, NV) via metered dose inhaler prior to spirometry measurements (Vmax 229 and Autobox 6200, SensorMedics, Yorba Linda, CA). On the initial visit, body plethysmography and diffusing capacity for carbon monoxide were performed.

The initial test was a ramped electromagnetically-braked cycle ergometer (Ergoline 800, SensorMedics) test. Three minutes rest and 3 minutes unloaded cycling at 60rpm was followed by ramp-wise work rate increase; slope was  $5 \text{ W}\cdot\text{min}^{-1}$  if  $\text{FEV}_1 < 1.0\text{L}$  and  $10 \text{ W}\cdot\text{min}^{-1}$  if  $\text{FEV}_1 \geq 1.0\text{L}$ . On two subsequent testing days, subjects performed incremental treadmill tests (Marquette 2000, SensorMedics) in randomized order. One was a modified Bruce protocol (BSU/Bruce). This protocol modified the original 7, 3-minute non-linear steps 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 1.7 mph and 10% grade by three minutes of exercise, irrespective of subject’s weight and does not individualize the incremental phase, as employed in most cycle tests[1] and some treadmill protocols[11]. The second treadmill test utilized a recently-described linear ramped treadmill protocol[5]. The goal was to create an individualized work rate profile that matches the cycle ergometer test (i.e., would reach the same work rate at the targeted 10 minute incremental test duration). After three minutes of walking at 0.5 mph,

treadmill speed increased linearly by 0.17 mph each minute. After three minutes at 0.5% grade, 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 EKG (Cardiosoft, GE-Sensormedics), blood pressure by sphygmomanometry (Welch-Allyn, Skaneateles Falls, NY) and pulse oximetry (Nellcor N-200, Pleasanton, CA). Subjects respired through a mouthpiece with noseclip in place. At rest, every two minutes 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) maneuvers three times at rest, every two minutes during exercise and at peak exercise[12,13]. In these maneuvers, 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 total lung capacity 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-second average response time courses; the 10-second intervals including and

following IC maneuvers were deleted. Peak values were averaged over the last 30 seconds of exercise; lactic acidosis threshold (LAT) was defined by modified V-slope approach[15].

*Statistical Analysis.* Excel 2003 (Microsoft, Seattle, WA) calculated mean and SD. SigmaStat 3.5 and SigmaPlot 10 (SPSS Science, Chicago, IL) produced graphical display and conducted one-way analysis of variance 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<sub>1</sub> and D<sub>L</sub>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<sub>2</sub> responses to the three protocols for a representative subject. As intended, calculated linear treadmill work rate profile duplicated the cycle profile (panel B) by utilizing linear speed change and curvilinear grade change (Panels A and C). This yielded similar V'O<sub>2</sub> profiles (panel D). In contrast, the BSU/Bruce protocol featured rapid grade and speed change (panels A and C) resulting in steep and non-linear work rate increase (panel B) and much shorter exercise duration. Note that the BSU/Bruce



protocol grade and speed rise rapidly, leading to test termination after about 4 minutes. In contrast, linear rise in speed and curvilinear rise in grade in the linear treadmill protocol lead to a linear rise in calculated work rate that closely matched the cycle ergometer protocol work rate and led to exercise termination after about 13 minutes (10 minutes of incremental exercise). Figure 2 shows responses of  $\dot{V}'\text{CO}_2$ ,  $\dot{V}'_E/\dot{V}'\text{CO}_2$  and end-tidal gas tensions as a function of  $\dot{V}'\text{O}_2$  for the three tests of the same subject presented in Figure 1. Note that lactic acidosis threshold and peak  $\dot{V}'\text{O}_2$  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 second averages) are much sparser and have more variation in the middle range of  $\dot{V}'\text{O}_2$  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  $\dot{V}'\text{O}_2$  at 3 minutes of exercise was comparable to that elicited by cycle ergometer unloaded pedaling. This contrasts with the much higher  $\dot{V}'\text{O}_2$  seen at three minutes in the BSU/Bruce protocol, which averaged 81% of peak  $\dot{V}'\text{O}_2$ . Nevertheless, the two treadmill protocols resulted in similar peak  $\dot{V}'\text{O}_2$  values that average 14% higher than cycle ergometer values. We could determine the lactic acidosis threshold 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, LAT was, on average, 35% higher in both linear and BSU/Bruce treadmill protocols compared to cycle ergometry. Peak  $\dot{V}'_E$  and heart rate were not significantly different among protocols. At peak exercise, cycle

exercise yielded higher leg fatigue ratings and tended to elicit less dyspnea 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 to cycle at the LAT (for the 12 subjects who consistently manifested an LAT), 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 percent peak work rate tolerated. Figure 3B displays this relationship as a function of oxygen uptake. Because peak oxygen uptake differs among subjects, this plot displays values only through  $0.9\text{L}\cdot\text{min}^{-1}$  (the highest  $\dot{V}'\text{O}_2$  at which most patients were represented). It is clear that, at a given  $\dot{V}'\text{O}_2$ , oxygen saturation is 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 3 of 16 subjects would qualify for ambulatory oxygen; based on either treadmill test 11 of 16 subjects would qualify.

*Physiologic Correlates of Differences In Exercise Desaturation.* We sought physiologic correlates of this difference in oxygen saturation between treadmill and cycle tests.

Average  $\dot{V}'_E$  was progressively higher for a given oxygen uptake in cycle as compared to treadmill exercise (Figure 4A). The increased  $\dot{V}'_E$  for a given oxygen uptake on the cycle

compared to both treadmill protocols became statistically significant at a  $\dot{V}'O_2$  of 0.7  $L \cdot \text{min}^{-1}$  and remained significant at subsequent values ( $P < 0.001$ ). There is no significant difference in peak  $\dot{V}'_E$  values, however. Respiratory rate and tidal volume progression was similarly examined. Tidal volume, but not respiratory rate, tended to be higher in the cycle test (data not shown). Figure 4B shows end-expiratory lung volume measurements as a function of  $\dot{V}'O_2$  and at peak exercise. Progressive dynamic hyperinflation is seen as exercise proceeds, but significant differences in EELV increases were not seen among exercise protocols.

Figure 5 plots six physiologic variables as a function of  $\dot{V}'O_2$ . Overall, this figure demonstrates that differences in responses to cycle as compared to treadmill exercise are consistent with hyperventilation with respect to  $O_2$ , but not  $CO_2$ -related variables. Panel A shows that, as for  $\dot{V}'_E$  (Figure 4A),  $\dot{V}'CO_2$  is higher at a given  $\dot{V}'O_2$  at higher exercise intensities. This similarity in  $\dot{V}'_E$  and  $\dot{V}'CO_2$  profiles is confirmed in that the time course of ventilatory equivalent for  $CO_2$  ( $\dot{V}'_E/\dot{V}'CO_2$ ) does not differ among tests (panel C) nor does  $P_{ET}CO_2$  differ among tests (Panel E). In contrast, ventilatory equivalent for oxygen ( $\dot{V}'_E/\dot{V}'O_2$ ) (Panel D) and  $P_{ET}O_2$  (Panel F) are distinctly higher during the cycle test at a given  $\dot{V}'O_2$ . This difference is confirmed in that respiratory exchange ratio (R) is distinctly higher for cycle than for treadmill exercise (Panel B). This suggests that cycle ergometer exercise elicits excess  $\dot{V}'CO_2$  out of proportion to  $\dot{V}'O_2$  and that  $\dot{V}'_E$  tracks  $\dot{V}'CO_2$ , not  $\dot{V}'O_2$ . This difference seems likely to be related to greater lactic acidosis at a given  $\dot{V}'O_2$  with cycle, compared to 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  $PO_2$ , especially in patients with lung disease, differences in  $P_{ET}O_2$  change between treadmill and cycle protocols should reflect differences in arterial  $PO_2$  change if lung gas exchange properties at a given exercise level are hypothesized not to differ. Figure 6 shows that, in fact, changes in  $P_{ET}O_2$  and oxygen saturation in treadmill and cycle tests parallel each other;  $P_{ET}O_2$  and oxygen saturation falls are 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 to treadmill, should result in higher alveolar ventilation and, therefore, higher arterial  $PO_2$  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 linearized treadmill and cycle exercise for relevant physiologic responses at 0.1 L 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

$$P_AO_2 = F_{IO_2}(P_B - 47) - P_aCO_2/R$$

where  $P_AO_2$  is ideal alveolar  $PO_2$ ,  $F_{IO_2}$  is inspired oxygen fraction,  $P_aCO_2$  is arterial  $PCO_2$  and  $R$  is respiratory exchange ratio ( $V'CO_2/V'O_2$ ). As  $F_{IO_2}$  and  $P_B$  do not differ between cycle (C) and treadmill (T) tests, and if it is assumed that  $P_aCO_2$  does not differ between cycle and treadmill (note that  $P_{ET}CO_2$  does not differ (Figure 5E)), then

$$\Delta P_{A}O_2 = P_aCO_2(1/R_{(T)} - 1/R_{(C)})$$

Since the alveolar mass balance equation for CO<sub>2</sub> dictates that

$$P_aCO_2 = kV'CO_2 / (V'_E(1 - V_D/V_T))$$

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 dead space fraction does not differ between exercise modes, this equation shows that iso- $V'O_2$  differences in ideal alveolar  $PO_2$  result directly from differences in ventilatory response. If it is further assumed that the difference between ideal alveolar and end-tidal  $PO_2$  does not differ between exercise modes and that  $P_aCO_2$  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 shows that, at a given  $V'O_2$ , both average calculated  $\Delta P_{A}O_2$  and measured  $\Delta P_{ET}O_2$  rise with  $V'O_2$  and are of similar magnitude. Figure 7C shows that the correlation between these two variables is 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 oxyhemoglobin desaturation curve[17] (with  $P_aCO_2=40$  torr and  $pH=7.4$ ). For each data point, we determined to what extent difference in  $P_{A}O_2$  (assumed to reflect an equal difference in  $P_aO_2$ ) resulted from the difference between measured ventilatory response and if 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, utilized the dissociation curve to estimate treadmill  $P_aO_2$ , added to this the calculated  $\Delta P_{A}O_2$ , and then again utilized 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 to the difference between observed cycle saturation and observed treadmill saturation. Figure 7B shows that both these differences rise with  $V'O_2$  and are of similar magnitude; calculated oxygen saturation difference averages roughly 70% of the measured difference. Figure 7D shows that calculated difference between oxygen saturation based on ventilatory response differences is 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 physiologic response characterization in severe COPD. Second, a major determination made during exercise testing in COPD (and other diseases) is whether exercise-induced oxygen desaturation occurs; supplemental oxygen prescription is often based on such evaluations. We observed clinically important of oxygen desaturation blunting during cycling as compared to treadmill exercise. Further, we defined a mechanism likely responsible for a substantial portion of this blunting.

Several treadmill exercise protocols that have been found clinically useful [e.g., 5, 18]. 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 non-linear physiologic responses make it difficult to evaluate  $V'O_2$  responses and cardiovascular exercise limitations[4, 19-22]. Other tests,

such as Balke or Astrand tests, achieve linear work rate increase while maintaining a high constant speed (3.3 and 5.0mph, 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, 19, 23].

We recently described[5] a treadmill protocol that utilizes linear speed changes and non-linear inclination changes that result in a linear ramp-like change in work performed against gravity. This protocol was previously evaluated in 22 healthy subjects but not in impaired patients. Similar to our study in healthy subjects, we found that the linear treadmill protocol yielded test durations near the target 10 minutes. In contrast, the BSU/Bruce protocol yielded a much shorter test duration. Figure 2 shows consequences of this: sparse data in the mid-ranges of metabolic rate response. Further, Figure 1 shows a distinctly non-linear  $\dot{V}'O_2$  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 physiologic distinctions. Similarities include similar  $\dot{V}'O_2$  response to the initial exercise stage and similar peak  $\dot{V}'E$ , heart rate, and work rate. Peak  $\dot{V}'O_2$  for treadmill exercise averages 14% higher than cycle exercise, consistent with previous studies, and likely reflects the larger muscle mass involved in treadmill exercise [1, 5, 11, 24, 25]. LAT is lower in cycle compared to treadmill testing in subjects who manifested an LAT. This, again, may be ascribed to the smaller muscle mass used with cycling[1, 5, 8, 26]. 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[27].

Of greatest interest is the marked difference in oxygen saturation time courses for the two treadmill protocols as compared to cycle ergometry (Figure 3). Others have also noted greater oxygen desaturation with ambulatory modalities compared to cycle ergometry[7-9]. However, to our knowledge, this is the first oxygen saturation evaluation at equivalent metabolic rates while utilizing similar work rate profiles in the two exercise modalities. The two treadmill protocols resulted in similar profiles of oxygen saturation change at iso- $\dot{V}'O_2$  values. In contrast, cycle ergometer responses demonstrated a substantially blunted oxygen saturation fall. This is clinically important as 11 of 16 patients would have been considered for supplemental oxygen treatment during exertion based on treadmill testing, but only 3 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  $PO_2$ . First, a study comparing cycle to ambulation tests in which arterial blood gas samples were drawn (though only at peak exercise) confirms these differences[8]. Second, the present study shows parallel changes in  $P_{ET}O_2$  and arterial oxygen saturation estimated by pulse oximetry (Figure 6). If it is allowed that, at a given  $\dot{V}'O_2$ , substantial differences in alveolar-end tidal  $PO_2$  and in alveolar-arterial  $PO_2$  are unlikely between cycle and treadmill exercise, then differences between  $P_{ET}O_2$  profiles likely truly reflect  $PaO_2$  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 hypothesized. Other investigators noted decreased peak  $\dot{V}'CO_2$  and increased  $\dot{V}'_E/\dot{V}'CO_2$  ratio in walking tests and surmised that this could correspond to worsened  $V_D/V_T$  resulting in less efficient gas exchange and consequent



hypoxemia[8]. Our study did not corroborate this finding; to the contrary, we found significantly higher peak  $V'CO_2$  and  $V'_E/V'CO_2$  with cycle compared to either treadmill protocols. Unlike prior shuttle and self-paced walking tests, our study utilized 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- $V'O_2$  (Figure 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  $P_aCO_2$  measurement) would be helpful in evaluating this further. Another possibility is that better  $V_A/Q$  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. Yet, patients in this study were ventilatory limited (as documented by low breathing reserve, Table 2) and we, and others [8, 26], have not found peak  $V'_E$  differences between cycle and treadmill tests. Further, we did not find iso- $V'O_2$  differences in dynamic hyperinflation between cycle and treadmill tests (Figure 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 related to earlier lactic acidosis onset in the cycle ergometer test. Lactic acid is predominantly buffered by bicarbonate, generating  $CO_2$  that is

exhaled in the breath. The higher  $V'_E$  is likely related to higher  $V'CO_2$ ; exercise ventilation has been shown to be tightly coupled to  $V'CO_2$  (and not to  $V'O_2$ )[28].

Can these differences be invoked to explain at least part of observed differences in arterial oxygen saturation? We have performed calculations based on reasonable assumptions to show that they can. Figure 7A and 7B show that the excess cycle  $V'_E$  predicts a difference in ideal alveolar  $PO_2$  roughly similar in magnitude to the observed  $P_{ET}O_2$  difference between cycle and treadmill. Similarly, calculated ideal alveolar  $PO_2$  difference is shown 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 (for example, that  $PaCO_2$  is 40 torr), though 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 arterial  $PO_2$ ,  $PCO_2$  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 comparisons we achieved (Figures 7C and 7D) 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 individualizing work rate increments to elicit optimal test duration while keeping walking speed within comfortable limits. It seems likely to have similar advantages in other debilitated patient groups, though studies in patients with milder COPD and in patients with other cardio-

pulmonary 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 preferred methodology in diagnostic cardiopulmonary exercise testing.

#### **Acknowledgement**

R. Casaburi occupies the Grancell/Burns Chair in the Rehabilitative Sciences.

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## Figure Legends

Figure 1: Comparison of linear treadmill (shaded squares), BSU/Bruce treadmill (black circles) and cycle ergometer (shaded triangles) protocol time courses in a representative COPD subject. Panel A: treadmill grade. Panel B: work rate performed against gravity for the treadmill protocols and done on the ergometer flywheel for the cycle ergometer. Panel C: treadmill speed in miles per hour. Panel D: oxygen uptake ( $\dot{V}O_2$ ). The first 3 minutes are rest in each protocol.

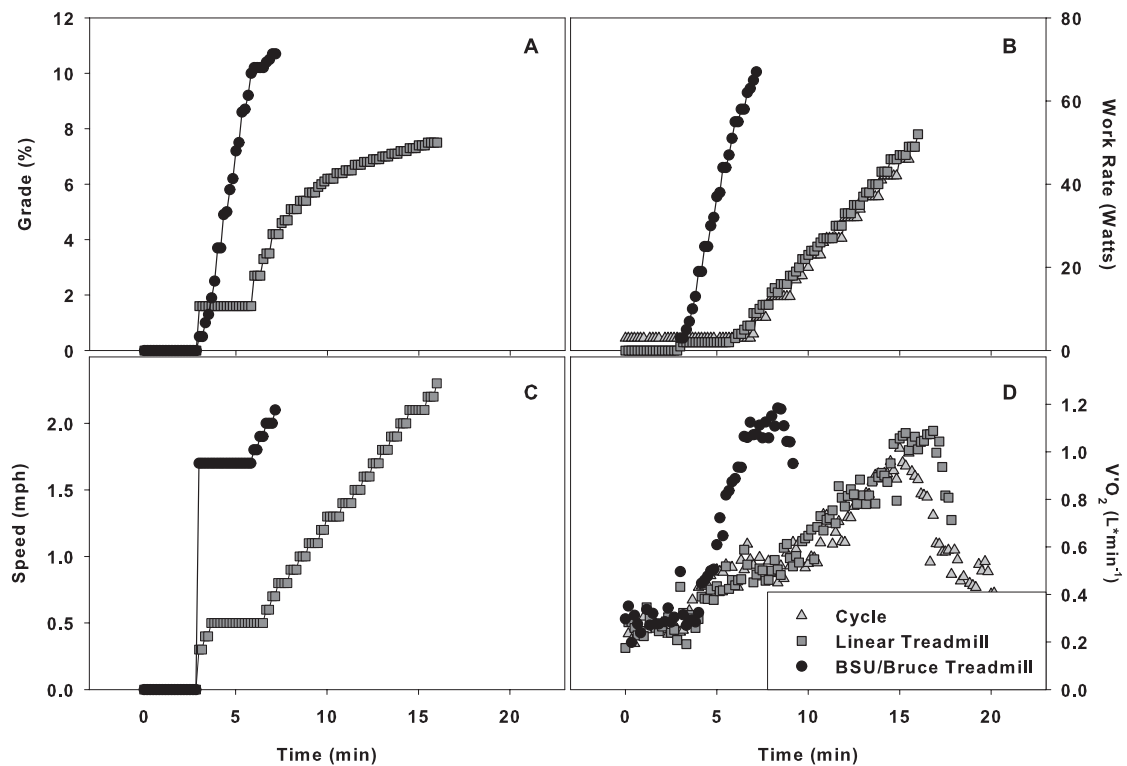


Figure 2: Responses of  $\dot{V}CO_2$ , ventilatory equivalent for  $\dot{V}CO_2$  ( $\dot{V}_E/\dot{V}CO_2$ ) and end-tidal gas tensions ( $P_{ET}CO_2$  and  $P_{ET}O_2$ ) as a function of oxygen uptake ( $\dot{V}O_2$ ) in response to cycle ergometer, linear treadmill and BSU/Bruce incremental exercise tests in



a representative COPD subject. Data are plotted at 10 second 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  $\dot{V}'\text{CO}_2$  increases out of proportion to  $\dot{V}'\text{O}_2$ . Arrows denote the lactic acidosis threshold.

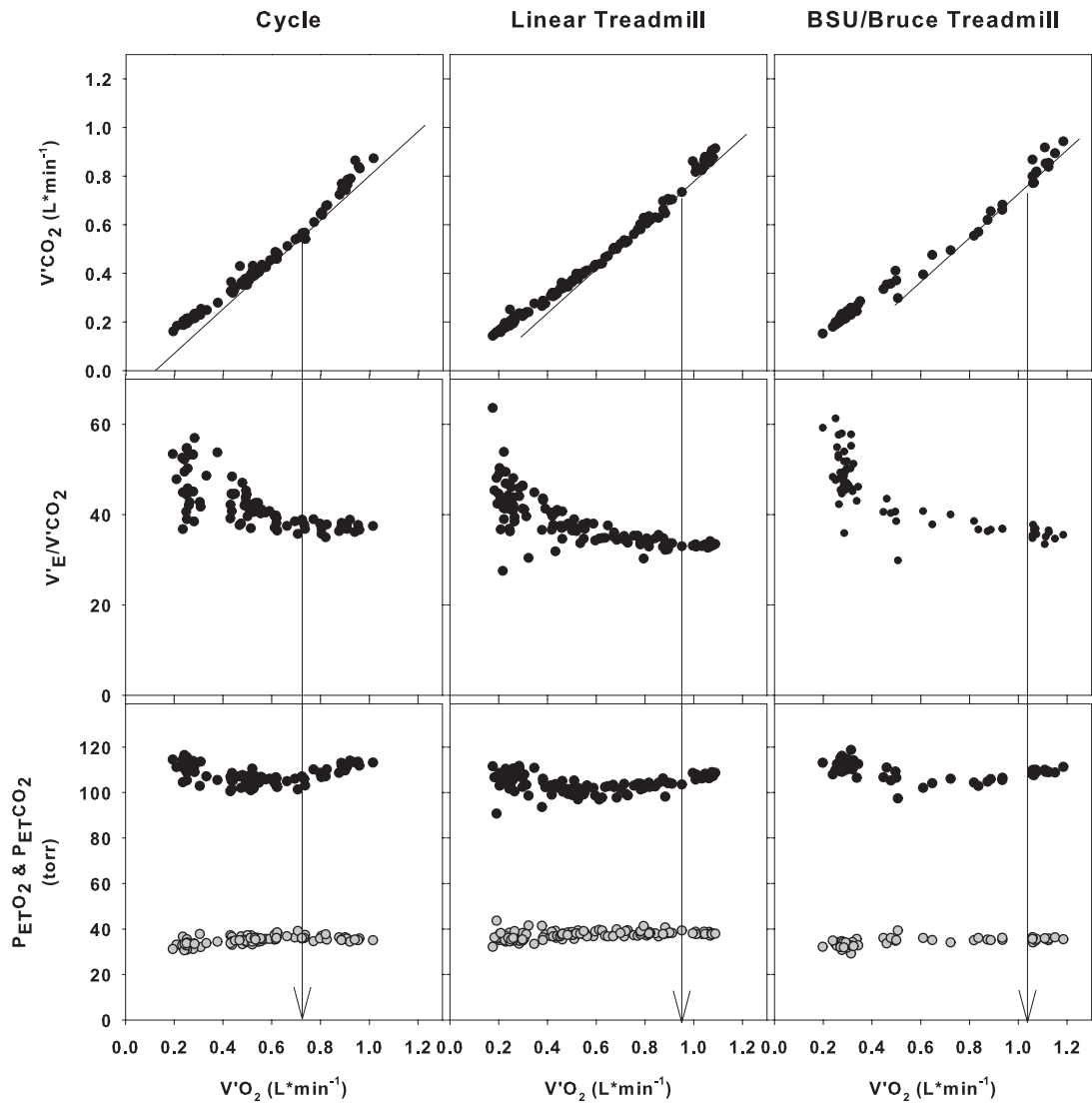


Figure 3: Mean ( $\pm$ SE) oxygen saturation (as assessed by pulse oximetry,  $\text{S}_p\text{O}_2$ ) during cycle ergometer (shaded triangle), linear treadmill (shaded square) and BSU/Bruce (black

circle) incremental exercise tests in 16 COPD patients. Panel A: oxygen saturation ( $\pm$ SE) plotted as percent of the peak work rate tolerated by the subject. The rightmost data points are the average of the lowest 10 second value recorded (nadir). Panel B: oxygen saturation ( $\pm$ SE) plotted as a function of oxygen uptake ( $V'O_2$ ). Data points are plotted at rest and at 0.1 liter intervals through the incremental exercise. Data points in panel B are the average of 16 subjects' responses except for  $V'O_2$  of 0.8 and 0.9 L $\cdot$ min $^{-1}$ : 14 and 13 subjects, respectively. Data points at the right are peak responses. \* denotes  $P < 0.003$ .

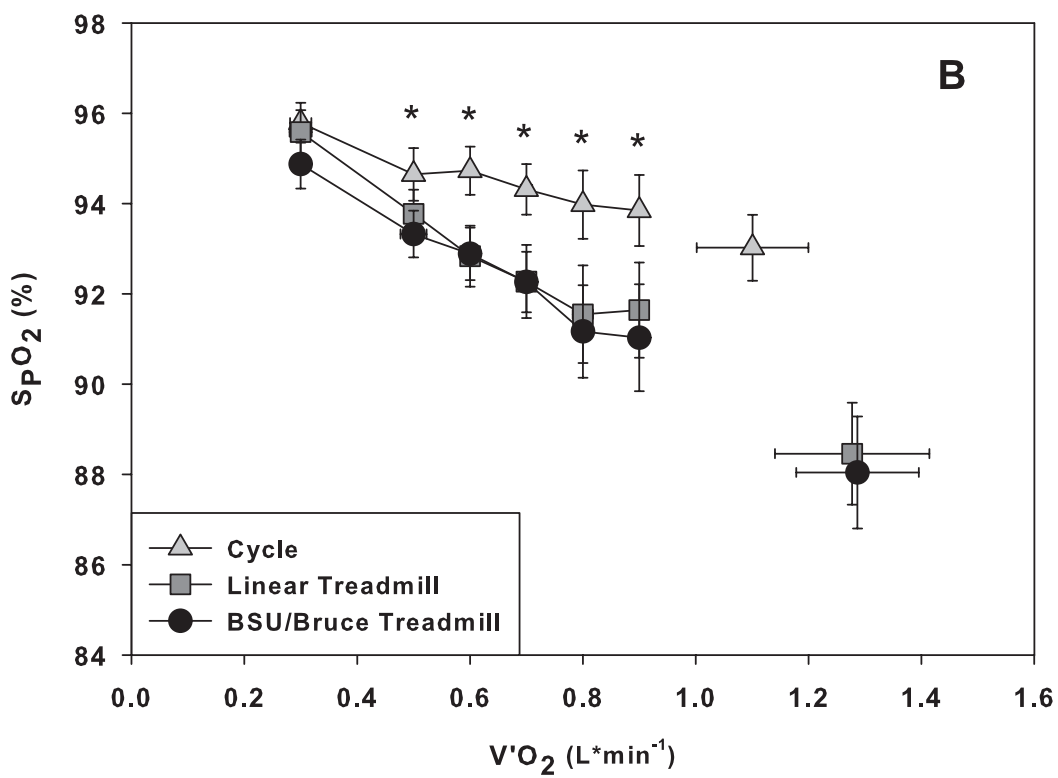
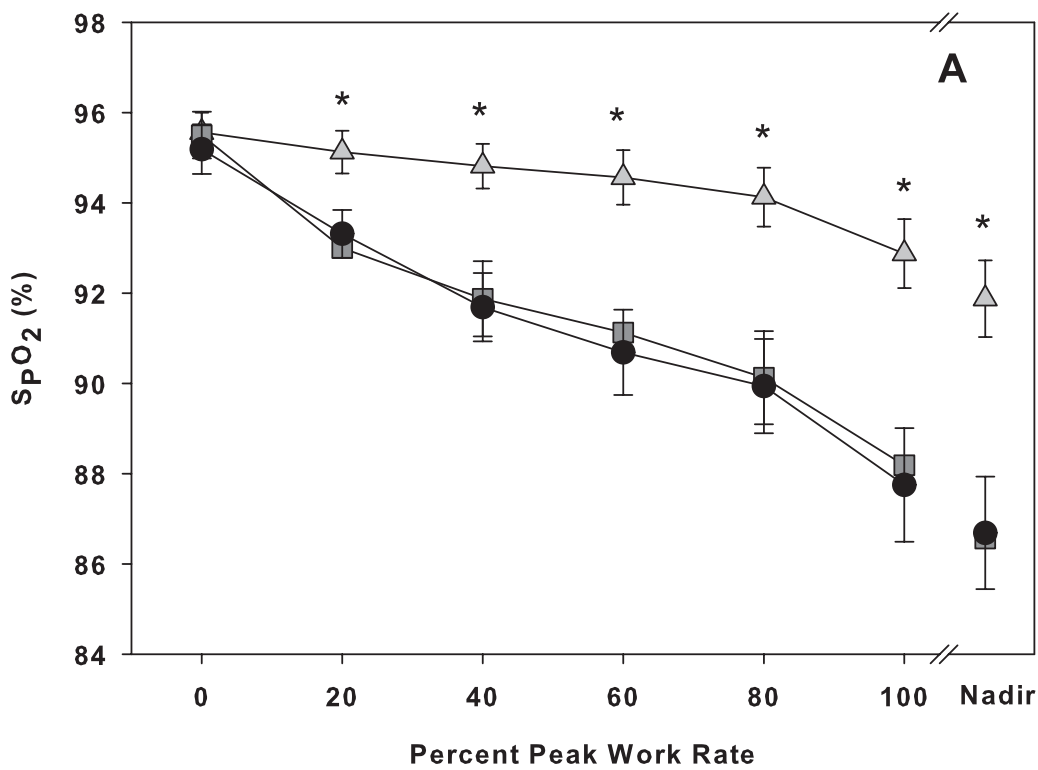


Figure 4: Mean ( $\pm$ SE) minute ventilation ( $V'_E$ ) (Panel A) and end-expiratory lung volume (EELV) as a percentage of total lung capacity (TLC) (Panel B) as a function of oxygen uptake ( $V'O_2$ ) during cycle ergometer (shaded triangle), linear treadmill (shaded square) and BSU/Bruce (black circle) incremental exercise tests in COPD patients. Data points in panel A are the average of 16 subject's responses except for  $V'O_2$  of 0.8 and 0.9  $L \cdot \text{min}^{-1}$ : 14 and 13 subjects, respectively. Data points on the right are peak responses. \* denotes  $P < 0.001$ . The increase in EELV does not differ significantly among protocols.

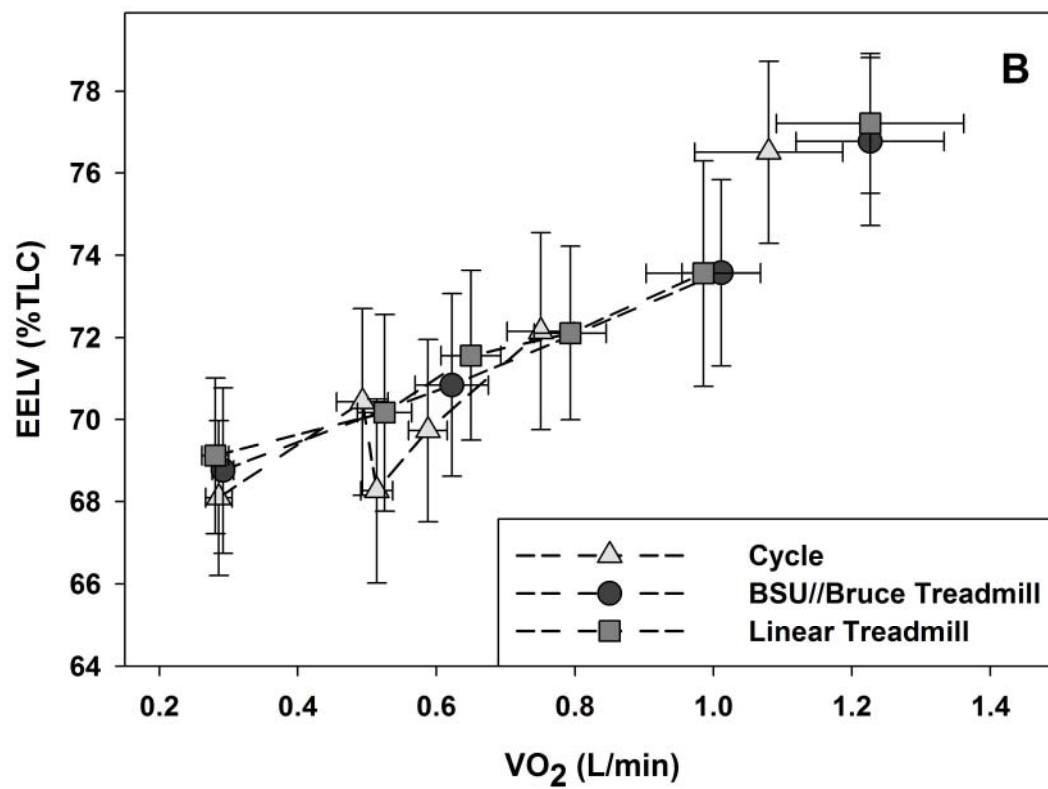
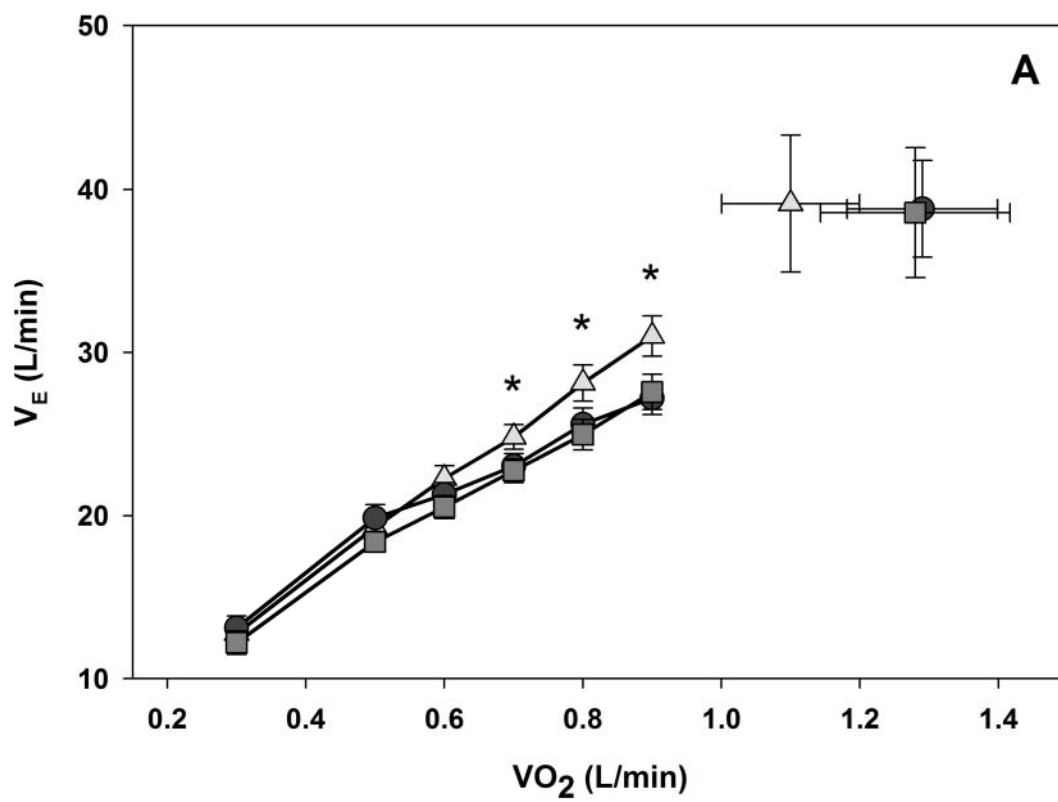


Figure 5: Mean ( $\pm$ SE) responses as a function of oxygen uptake ( $V'O_2$ ) to cycle ergometer (shaded triangle), linear treadmill (shaded square) and BSU/Bruce (black circle) incremental exercise tests in COPD patients. Data points are the average of 16 subject's responses except for  $V'O_2$  of 0.8 and 0.9 L $\cdot$ min $^{-1}$ : 14 and 13 subjects, respectively. Data points on the right of each panel are peak responses. Panel A: CO<sub>2</sub> output ( $V'CO_2$ ). Panel B: respiratory exchange ratio (R,  $V'CO_2/V'O_2$ ). Panel C: ventilatory equivalent for CO<sub>2</sub> ( $V'_E/V'CO_2$ ). Panel D: ventilatory equivalent for O<sub>2</sub> ( $V'_E/V'O_2$ ). Panel E: end-tidal carbon dioxide partial pressure ( $P_{ET}CO_2$ ). Panel F: end-tidal oxygen partial pressure ( $P_{ET}O_2$ ). \* denotes  $P < 0.05$  between cycle and either treadmill response. See text.

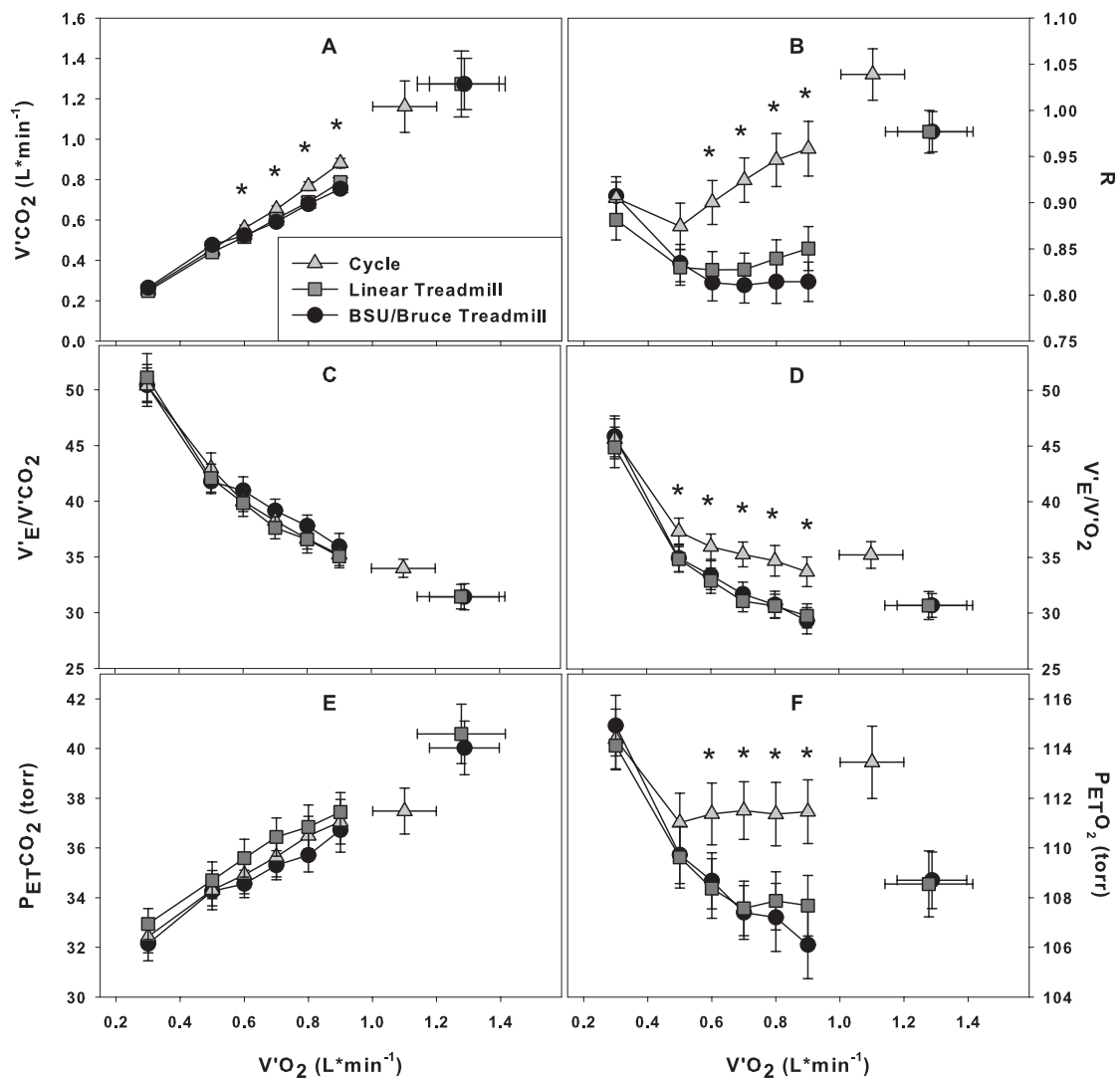
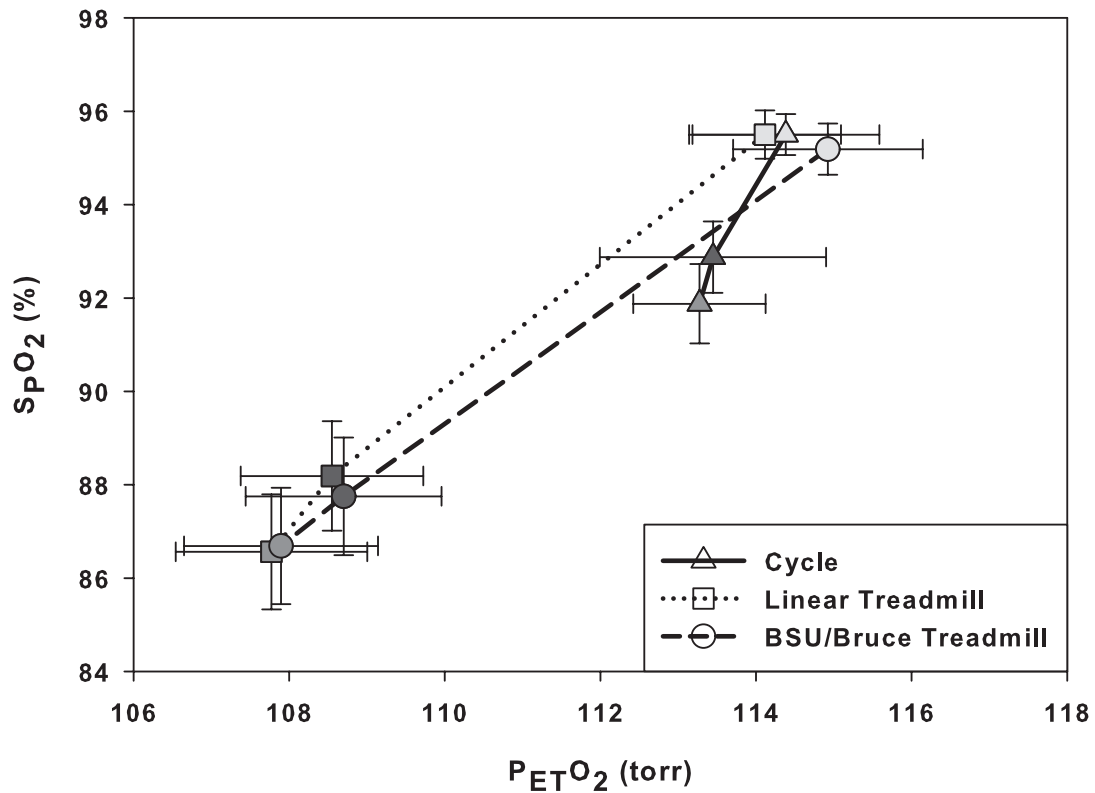


Figure 6: Mean ( $\pm$ SE) oxygen saturation ( $S_{PO_2}$ ) and corresponding end-tidal partial pressure of oxygen ( $P_{ET}O_2$ ) values for cycle ergometer (triangles), linear treadmill (squares) and BSU/Bruce (circles) incremental exercise tests in 16 COPD patients. Light shaded symbols represent values during rest, dark shaded symbols represent peak exercise, and medium shaded symbols represent values occurring at the lowest point of

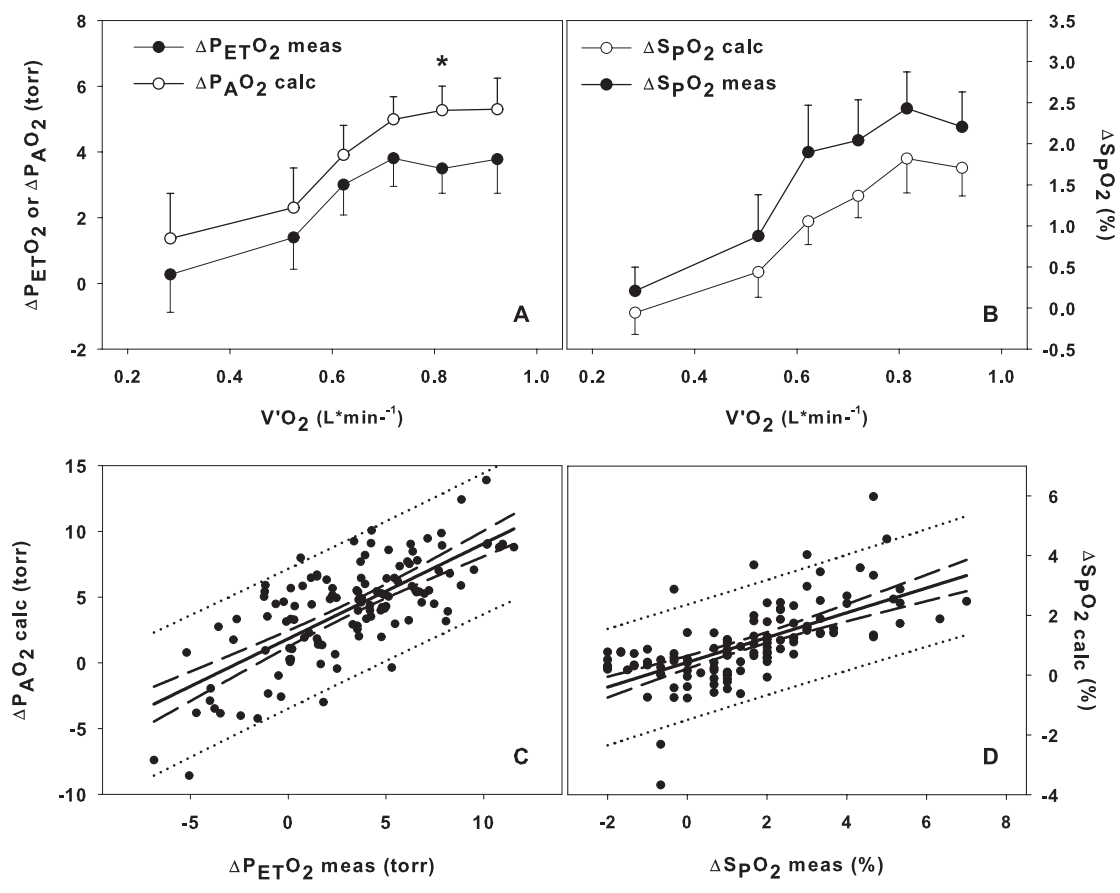
oxygen saturation (during or after exercise). Note that end-tidal  $PO_2$  and oxygen saturation changes are closely related among exercise protocols.



**Figure 7:** Calculations seeking to define the mechanism of differences in end-tidal oxygen partial pressure ( $PO_2$ ) and oxygen saturation ( $S_{PO_2}$ ) in linear treadmill vs. cycle exercise tests utilizing data from 16 COPD patients. Panel A: As a function of oxygen uptake ( $\dot{V}O_2$ ) during incremental exercise, calculated difference in alveolar  $PO_2$  ( $\Delta P_{A}O_2$  calc) expected based on differences in ventilatory response to treadmill vs. cycle ergometer exercise (see text) and measured differences in end-tidal  $PO_2$  ( $\Delta P_{ET}O_2$  meas) between cycle and treadmill. \* denotes  $P < 0.05$ . Panel B: As a function of oxygen uptake,



calculated difference in arterial oxygen saturation ( $\Delta S_{pO_2}$  calc) expected based on the differences in ventilatory response to treadmill vs. cycle ergometer exercise (see text) and measured difference in oxygen saturation assessed by pulse oximetry ( $\Delta S_{pO_2}$  meas) between cycle and linear treadmill tests. Panels C and D: iso- $\dot{V}'O_2$  differences between cycle ergometer and linear treadmill responses measured at 0.1 L intervals in all 16 patients (122 data points). Heavy lines are the regression line; dashed lines are the 95% regression confidence limits; dotted lines are 95% confidence limits of individual data points. Panel C: calculated difference in alveolar  $PO_2$  ( $\Delta P_{A}O_2$  calc) expected based on the differences in ventilatory response to treadmill and cycle ergometer exercise (see text) vs. measured differences in end-tidal  $PO_2$  ( $\Delta P_{ET}O_2$  meas) between cycle and treadmill. Correlation coefficient is 0.73 ( $P < 0.001$ ); regression slope is 0.72 and intercept is 1.84 torr (both  $P < 0.001$ ). Panel D: calculated difference in arterial oxygen saturation ( $\Delta S_{pO_2}$  calc) expected based on differences in ventilatory response to treadmill and cycle ergometer exercise (see text) vs. measured difference in oxygen saturation ( $\Delta S_{pO_2}$  meas) between cycle and linear treadmill tests. Correlation coefficient is 0.65; regression slope is 0.42 and intercept is 0.43% (all  $P < 0.001$ ).



## Tables

Table 1: Characteristics of Subjects

Age (yrs)	64.4±9.9
Male/Female	9/7
BMI (kg·m <sup>-2</sup> )	27.3±4.6
Pack-Years of Tobacco Use	40.6±23.7
FEV <sub>1</sub> (L), % Predicted [10]	1.04±0.44 (36.5±10.9)
VC (L), % Predicted [10]	2.69±1.00 (75.1±17.5)
IC (L), % Predicted [29]	2.28±1.01 (92.3±34.3)
FRC (L), % Predicted [29]	4.71±1.52 (148.0±22.2)
RV (L), % Predicted [29]	3.92±1.39 (182.2±37.4)
TLC (L), % Predicted [29]	6.99±2.13 (123.0±20.9)
D <sub>L</sub> CO (mL·min <sup>-1</sup> ·torr <sup>-1</sup> ), % Predicted [30]	10.4±4.2 (42.9±14.3)

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All values mean±SD; values in parentheses are % predicted. BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in one second; VC, vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; D<sub>L</sub>CO, single-breath diffusing capacity of the lungs for carbon monoxide.

Table 2: Physiologic Responses to Incremental Exercise

	<i>Cycle Ergometer</i>	<i>Linear Treadmill</i>	<i>BSU/Bruce Treadmill</i>	<i>P</i>
Total Exercise Time (min)	12.0 ± 2.1	11.5 ± 2.8	5.1 ± 1.8 <sup>†</sup>	<0.001
Peak Work Rate (W)	71.9 ± 39.4	70.1 ± 52.2	89.6 ± 44.2 <sup>‡</sup>	0.003
V'O <sub>2</sub> at 3 min (L·min <sup>-1</sup> )	0.49 ± 0.10	0.53 ± 0.15	1.04 ± 0.24 <sup>†</sup>	<0.001
Peak V'O <sub>2</sub> (L·min <sup>-1</sup> )	1.10 ± 0.40 <sup>†</sup>	1.28 ± 0.55	1.29 ± 0.43	<0.001
V'O <sub>2</sub> /WR Slope (L·min <sup>-1</sup> ·W <sup>-1</sup> )	11.4 ± 2.3	12.2 ± 2.6	8.5 ± 1.8 <sup>‡</sup>	<0.001
LAT (L·min <sup>-1</sup> )	0.80 ± 0.23 <sup>†</sup>	1.08 ± 0.42	1.08 ± 0.32	<0.001
LAT/Peak V'O <sub>2</sub> (%)	71.3 ± 9.6 <sup>‡</sup>	80.5 ± 11.1	81.9 ± 11.1	0.007
Peak HR (bpm)	122 ± 12	130 ± 16	129 ± 14	0.179
Peak V'E (L·min <sup>-1</sup> )	39.1 ± 16.8	38.6 ± 16.0	38.8 ± 11.9	0.922
Peak V'CO <sub>2</sub> (L·min <sup>-1</sup> )	1.16 ± 0.51 <sup>‡</sup>	1.27 ± 0.66	1.28 ± 0.51	0.043
Peak V'E/V'CO <sub>2</sub>	34.0 ± 3.2 <sup>†</sup>	31.4 ± 4.4	31.4 ± 4.7	<0.001
V'E/V'CO <sub>2</sub> at LAT	35.3 ± 3.7	33.3 ± 3.9	34.3 ± 3.5	0.078
Peak P <sub>ET</sub> CO <sub>2</sub> (mmHg)	37.5 ± 3.7 <sup>†</sup>	40.6 ± 4.8	40.0 ± 4.3	<0.001
Peak P <sub>ET</sub> O <sub>2</sub> (mmHg)	113.5 ± 5.8 <sup>†</sup>	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
Δ IC (L) (peak-rest)	-0.57 ± 0.37	-0.54 ± 0.19	-0.54 ± 0.31	0.860
Peak EELV (%TLC)	76.6 ± 9.0	77.2 ± 6.8	76.9 ± 8.3	0.771
ΔEELV (peak-rest) (%TLC)	8.5 ± 5.8	8.1 ± 3.2	8.1 ± 5.1	0.814

Resting O <sub>2</sub> Saturation (%)	95.6 ± 1.8	95.5 ± 2.1	95.2 ± 2.2	0.475
Change in O <sub>2</sub> Saturation (%) at LAT	-0.9 ± 1.2 <sup>†</sup>	-4.3 ± 3.0	-5.3 ± 3.7	<0.001
Change in O <sub>2</sub> Saturation (%) at Peak	-2.7 ± 2.9 <sup>†</sup>	-7.3 ± 4.4	-7.4 ± 4.8	<0.001
Maximum Change in O <sub>2</sub> Saturation (%)	-3.7 ± 3.3 <sup>†</sup>	-8.9 ± 4.9	-8.5 ± 4.7	<0.001
Peak Borg Breathlessness	6.0 ± 2.1 <sup>‡</sup>	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

<sup>†</sup> Statistically different from the other two protocols (P<0.001). <sup>‡</sup> Statistically different

from the other two protocols (P<0.05). All values mean±SD. V'O<sub>2</sub>, oxygen uptake; WR, work rate; LAT, lactic acidosis threshold; HR, heart rate; V'E, minute ventilation; V'CO<sub>2</sub>, carbon dioxide output, P<sub>ET</sub>CO<sub>2</sub>, end-tidal carbon dioxide partial pressure; P<sub>ET</sub>O<sub>2</sub>, end-tidal oxygen partial pressure; IC, inspiratory capacity; EELV, end expiratory lung volume; TLC, total lung capacity; O<sub>2</sub> Saturation, oxyhemoglobin saturation estimated by pulse oximetry. LAT, V'E/V'CO<sub>2</sub> at LAT and change in O<sub>2</sub> saturation at LAT values are for 12 subjects who had determinate LAT values in all three tests.