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# Critical Power and Respiratory Compensation Point Are Not Equivalent in Patients with COPD

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## ABSTRACT

**Introduction**: Several studies report that pulmonary oxygen uptake ($\dot{V}O_2$) at the respiratory compensation point (RCP) is equivalent to the $\dot{V}O_2$ at critical power (CP), suggesting that the variables can be used interchangeably to demarcate the threshold between heavy and severe intensity domains. But if RCP is a valid surrogate for CP, their values should correspond even when assessed in patients with chronic obstructive pulmonary disease (COPD) in whom the 'normal' mechanisms linking CP and RCP are impeded. The aim of this study was to compare $\dot{V}O_2$ at CP with $\dot{V}O_2$ at RCP in patients with COPD. **Methods**: Twenty-two COPD patients (14 male/8 female, $FEV_1$=46±17%pred) performed ramp-incremental cycle ergometry to intolerance (5-10 $W \cdot min^{-1}$) for the determination of gas exchange threshold (GET) and RCP. Critical power was calculated from the asymptote of the hyperbolic power-duration relationship from 3-5 constant-power exercise tests to intolerance. Critical power was validated with a 20-min constant-power ride. **Results**: Gas exchange threshold was identified in 20/22 patients at a $\dot{V}O_2$ of 0.93±0.18 $L \cdot min^{-1}$ (75±13% $\dot{V}O_{2peak}$) whereas RCP was identified in just 3/22 patients at a $\dot{V}O_2$ of 1.40±0.39 $L \cdot min^{-1}$ (85±2% $\dot{V}O_{2peak}$). All patients completed constant-power trials with no difference in peak physiological responses relative to ramp-incremental exercise ($p$>0.05). Critical power was 46±22 W which elicited a $\dot{V}O_2$ of 1.04±0.29 $L \cdot min^{-1}$ (90±9% $\dot{V}O_{2peak}$) during the validation ride. The difference in $\dot{V}O_2$ at 15 and 20 min of the validation ride was 0.00 ± 0.04 L which was not different to a hypothesized mean of 0 ($p$=0.856), thereby indicating a $\dot{V}O_2$ steady state. **Conclusions**: In COPD patients, who present with cardiopulmonary and/or respiratory-mechanical dysfunction, critical power can be determined in the absence of RCP. Accordingly, CP and RCP are not equivalent in this group.



**Key Words:** EXERCISE, EXERCISE LIMITATION, LUNG FUNCTION, LUNG DISEASE

## INTRODUCTION

The relationship between power output and time to the limit of tolerance ($T_{lim}$) during non-steady-state exercise is characterized by two variables. First is critical power (CP)—the asymptote of the hyperbolic power-$T_{lim}$ (P-$T_{lim}$) relationship—which demarcates the boundary between the heavy- and severe-intensity domain (1). Second is W′—the curvature constant of the P-$T_{lim}$ relationship—which characterizes the finite work that can be accomplished above CP before intolerance (1–4). Critical power is associated with endurance performance, is sensitive to endurance training (5–8), and is influenced by conditions that affect $O_2$ transport and/or utilization (such as hypoxia/hyperoxia [9–11] and cardiopulmonary disease [12, 13]).

The P-$T_{lim}$ relationship provides a framework with which to explore the mechanistic basis of exercise intolerance and fatigue (1). However, the gold-standard protocol for characterizing the P-$T_{lim}$ relationship, and thus obtaining estimates of CP and W', is both time-consuming and highly strenuous for the participant—requiring at least three exercise tests, performed at a severe intensity, to the limit of tolerance. As such, CP is not routinely measured during laboratory-based exercise testing. As possible alternatives to the gold-standard approach, researchers have studied a 3-minute "all-out" test (8,14), a combined "ramp-sprint" protocol (15), and whether the deoxyhemoglobin breakpoint ([HHb]BP) or the respiratory compensation point (RCP) during ramp-incremental exercise are valid surrogates for CP (16–20).

The scientific validity of RCP as a CP surrogate is an ongoing point of contention. In healthy adults, some studies show that CP and RCP occur at a similar $\dot{V}O_2$ (19,21) and power output (21,22), suggesting that the thresholds may be interchangeable. By contrast, Broxterman and colleagues concluded that treadmill speed and $\dot{V}O_2$ at critical speed and RCP were merely coincident (not equivalent) owing to the high degree of within-subject variability between

measures (18). Data from Leo and colleagues showed that power output at RCP, identified during ramp-incremental exercise, had poor agreement with CP (20), and others suggest that CP and RCP should not be used interchangeably because they respond differently to chronic exercise training (23). Lastly, because of the confounding effects of the kinetic dissociation between $\dot{V}O_2$ and power output during non-steady-state exercise, several studies are equivocal on whether an association between critical power/speed and RCP exists (18,24). Accordingly, there is no consensus on the equivalence of $\dot{V}O_2$ and/or power output at CP and RCP.

To date, the equivalence of CP and RCP has only been explored in healthy or athletic populations with normal cardiopulmonary function. However, the validity of the "equivalence hypothesis" depends on several assumptions, the most pertinent being that the signaling pathways connecting metabolic acidosis (originating in active muscles) and respiratory compensation (achieved by the ventilatory system) are unaffected by environment or pathophysiology.

Chronic obstructive pulmonary disease (COPD) is a progressive disorder underpinned by airway inflammation and remodeling, diminished airway caliber, and/or pulmonary emphysema (25). Patients with COPD exhibit deranged breathing mechanics characterized by expiratory flow limitation and dynamic hyperinflation which predispose to dyspnea and exercise intolerance (26). Many COPD patients also have altered chemoreceptor sensitivity which affects the ventilatory response to exercise (27). Based on the pathophysiology, it may be that few COPD patients have the respiratory-mechanical function and/or the signaling pathways necessary to exhibit respiratory compensation during incremental exercise. Yet, to our knowledge, this has not been empirically studied. Data from patients with respiratory dysregulation, in whom the 'normal' physiological cascade that connects CP and RCP is impeded, would provide a decisive answer as to the true "coincidence or equivalence" between these two measures. This exploratory study therefore

assessed the prevalence with which COPD patients exhibited respiratory compensation during ramp-incremental exercise and compared $\dot{V}O_2$ at the RCP to that measured at CP.

## METHODS

### Experimental Overview

This study used previously published ramp-incremental and constant-power exercise data from COPD patients (28,29) to address a novel research question. Participants attended the laboratory on four occasions (separated by >48 h) to complete the experimental protocol. At the first visit, they provided written, informed consent; had their vital signs and resting electrocardiogram assessed; and performed a pre- and post-bronchodilator pulmonary function test. Participants also completed a ramp-incremental exercise test on a cycle ergometer for the determination of gas exchange threshold (GET), RCP, and $\dot{V}O_{2peak}$. Visits 2 and 3 each comprised two constant-power exercise tests (separated by >2 h) to the limit of tolerance for the determination of CP and W′. During these visits, the test with the lowest power output was performed first to minimize carryover effects (30). At the final visit, participants performed a 20-min constant-power 'validation' trial at their calculated CP to assess for a physiological steady state.

### Participants

Participants were current or former smokers with COPD. Inclusion criteria were post-bronchodilator forced expiratory volume in one second ($FEV_1$) <80% predicted, age 40 - 80 y (inclusive), no exacerbations within 4 weeks, and no other known risk factors or comorbidities. The final sample comprised 22 patients in whom all required data were available (14 male/8 female; see Table 1 for patient characteristics and pulmonary function). The study was approved

by the Institutional Review Board at the Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center and was conducted in accordance with the Declaration of Helsinki except for principle 35 (public trial registration). All participants abstained from intense exercise for 48 h, alcohol and caffeine for 12 h, and food for 3 h prior to each visit.

**Pulmonary Function Tests**

Forced vital capacity (FVC) and $FEV_1$ were assessed via spirometry (Vmax 229; VIASYS SensorMedics, Yorba Linda, CA, USA). Values were expressed as percentages of predicted norms according to the National Health and Nutrition Examination Survey (NHANES)-III standards (31). Maximum voluntary ventilation (MVV) was estimated as $FEV_1 \times 40$ (32). Pulmonary function tests were carried out in accordance with recommended standards (33).

**Exercise Tests**

Exercise was performed on an electrically braked cycle ergometer (Ergoline 800; SensorMedics) at a pre-determined cadence of 60 $rev \cdot min^{-1}$ (actual cadence = 60 ± 3 $rev \cdot min^{-1}$). Exercise continued to the limit of tolerance, determined as the point at which the patient was unable to maintain a crank cadence >50 $rev \cdot min^{-1}$ despite verbal encouragement. The constant-power tests were also terminated if the patient exceeded the predetermined exercise duration of 20 minutes. Continuous breath-by-breath measures of pulmonary gas exchange ($\dot{V}O_2$, $\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) were made via metabolic cart (Vmax Spectra; SensorMedics), arterial $O_2$ saturation via pulse oximetry ($S_pO_2$), and heart rate ($f_C$) via 12-lead electrocardiogram.

***Ramp-incremental test.*** Ramp-incremental exercise was used to determine GET, RCP, and $\dot{V}O_{2peak}$, and to derive work rates for the constant power tests. Following 3-min seated rest, exercise

began with 3-min unloaded cycling (0 W) after which the power output increased continuously by 5 $W \cdot min^{-1}$ (for patients with $FEV_1 \leq 1.0$ L) or 10 $W \cdot min^{-1}$ (for patients with $FEV_1 > 1.0$ L). The breath-by-breath data were exported from the Vmax system as 10-s bin-averaged means, smoothed using a 3-point rolling average, and plotted in a 9-panel report (Sigma Plot version 13.0; Systat Software Inc., Chicago, IL). Two reviewers independently identified and verified GET and RCP using standard criteria (34). Specifically, GET was identified from the inflection point in the V-slope relationship and corroborated by inspection of the $\dot{V}_E/\dot{V}O_2$ and $P_{ET}O_2$ responses; RCP was identified using the $\dot{V}_E$ versus $\dot{V}CO_2$ relationship and corroborated by inspection of the $\dot{V}_E/\dot{V}CO_2$ and $P_{ET}CO_2$ responses. Peak variables were calculated as the highest 30 s average.

***Constant-power tests.*** Constant power tests were used to determine CP and W′ and to verify CP estimation. Following 3-min seated rest, exercise began with 3-min unloaded cycling (0 W) after which power output increased to a predetermined level and was maintained throughout the test. Power output for the four tests was calculated to elicit an even $T_{lim}$ distribution spanning ~2 - 20 min, and determined as follows: power output for test 1 was equivalent to maximal power output ($W_{max}$) achieved during the ramp-incremental test; power output for test 2 was between 110 and 120% $W_{max}$; power output for test 3 was 80% $W_{max}$; and power output for test 4 was calculated to elicit a $T_{lim}$ of 6-7 min based on mathematical interpolation from the first three constant-power tests. Power output and the corresponding $T_{lim}$ for each test were used to characterize the P-$T_{lim}$ relationship. Critical power (to the nearest 5 W) was calculated as the *y*-intercept of the regression line of power versus the inverse of endurance time ($1/T_{lim}$); W′ was calculated from the slope of the linearized expression of the hyperbolic P-$T_{lim}$ relationship ($P = [W'/(1/T_{lim})] + CP$) (35,36).

***CP validation*:** After CP and W′ had been determined, a subset of participants (n=18) completed a validation trial during which they exercised for 20 min at the estimated CP. The difference in $\dot{V}O_2$ at 15 and 20 min was calculated to assess for a physiological steady state.

**Statistical Analyses**

Statistical analyses were performed using IBM SPSS Statistics v24 (IBM; Illinois, USA). All physiological measures ($\dot{V}O_2$, $\dot{V}CO_2$, RER, $\dot{V}_E$, $\dot{V}_E$/MVV, $\dot{V}_E/\dot{V}CO_2$, $P_{ET}CO_2$, and $f_C$) were normally distributed according to Shapiro-Wilk tests. Physiological responses to ramp-incremental exercise and the constant-power trials that characterized the P-$T_{lim}$ relationship were compared using one-way repeated-measures ANOVA with Greenhouse-Geisser adjustment if data were non-spherical. A statistically significant ANOVA was followed by pairwise comparisons using a Tukey-adjusted *p*-value. For the CP validation trial, the mean difference in $\dot{V}O_2$ at 15 and 20 min was illustrated in a Bland-Altmann plot and compared to a hypothesized mean of 0 using a one-sample *t*-test. The independent relationships between $\dot{V}O_2$ at GET and CP expressed as a fraction of $\dot{V}O_{2peak}$ were assessed using Pearson's correlation coefficient. The magnitude of the difference between means (effect size) was assessed using Cohen's *d* (0.2 = small; 0.5 = medium; 0.8 = large) (37). Data are presented as mean ± SD and alpha level was specified *a priori* as 0.05.

**RESULTS**

**Pulmonary function tests (post-bronchodilator)**

Patients exhibited a moderate-to-very severe obstructive pattern (Table 1) and were classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) (38) spirometry stage 2 (n=11), 3 (n=7), and 4 (n=4).

**Ramp incremental test**

Peak physiological responses to the ramp-incremental test are shown in Table 2 and responses at GET and RCP are shown in Table 3. Individual plots of the $\dot{V}_E$-$\dot{V}CO_2$ relationship during ramp-incremental exercise are shown in Figure 1. All patients completed the ramp-incremental test, achieving a $\dot{V}O_{2peak}$ of 1.22 ± 0.37 L·min$^{-1}$. At exercise intolerance, RER was 1.04 ± 0.12, $\dot{V}_E$ was 86 ± 17%MVV, and $f_C$ was 74 ± 13% age-predicted maximum (39). Gas exchange threshold was identified in 20/22 patients at a $\dot{V}O_2$ of 0.93 ± 0.18 L·min$^{-1}$ (75 ± 13% $\dot{V}O_{2peak}$). Respiratory compensation point was identified in just 3/22 patients (Figure 1) at a $\dot{V}O_2$ of 1.40 ± 0.39 L·min$^{-1}$ (85 ± 2% $\dot{V}O_{2peak}$), $\dot{V}_E$ of 51.0 ± 17.1 L·min$^{-1}$, and power output of 84 ± 29 W.

**Constant-power tests**

Peak physiological responses to the constant-power tests are shown in Table 2 and responses at CP are shown in Table 3. All patients completed the constant-power trials, and the $T_{lim}$ relationship among tests was characterized by a hyperbolic function. The mean CP and W' were 46 ± 22 W and 6064 ± 2901 J, respectively. Modelling the relationship with $1/T_{lim}$ as the independent variable did not significantly alter CP (45 ± 22W, $p$ = 0.901) or W' (6263 ± 2926 J, $p$ = 0.822). Ramp-incremental and constant-power data for two patients, one with and one without an identifiable RCP, are shown in Figure 2. One-way repeated-measures ANOVA was used to compare peak physiological responses among ramp-incremental and each of the constant-power trials that characterized the P-$T_{lim}$ relationship. There was no difference in peak $\dot{V}O_2$ ($F[4, 105]$ = 0.09, $p$ = 0.986), indicating maximal capacities were attained in all trials. Similarly, there was no difference with respect to $\dot{V}CO_2$ ($F[4, 105)$ = 0.33, $p$ = 0.855), RER ($F[4, 105]$ = 1.58, $p$ = 0.186),

$\dot{V}_E$ (F[4, 105] = 0.10, $p$ = 0.983), $\dot{V}_E$/MVV (F[4, 105] = 0.32, $p$ = 0.861), $\dot{V}_E/\dot{V}CO_2$ (F[4, 105] = 0.39, $p$ = 0.819), $P_{ET}CO_2$ (F[4, 105] = 0.41, $p$ = 0.800), $f_C$ (F[4, 105] = 0.61, $p$ = 0.659), or $f_C\%f_{Cmax}$ (age-predicted) (F[4, 105] = 0.81, $p$ = 0.523) (Table 2).

Eighteen of 22 patients completed a 20-minute ride at CP. Oxygen uptake at 15 and 20 min was 1.04 ± 0.28 and 1.04 ± 0.29 $L{\cdot}min^{-1}$, respectively. The mean difference between time points was 0.00 ± 0.04 $L{\cdot}min^{-1}$ which was not different from a hypothesized mean of 0 ($p$ = 0.856, $d$ = 0.04; Figure 3). This steady-state (submaximal) $\dot{V}O_2$ helped corroborate the CP estimate.

**Comparison of thresholds**

The associations of $\dot{V}O_2$ at GET with ramp-incremental $\dot{V}O_{2peak}$, and $\dot{V}O_2$ at CP with ramp-incremental $\dot{V}O_{2peak}$, are shown in Figure 4. Peak oxygen uptake during ramp-incremental exercise was strongly correlated with $\dot{V}O_2$ at GET ($r^2$ = 0.507, $p$ < 0.001) and modestly correlated with $\dot{V}O_2$ at CP ($r^2$ = 0.340, $p$ = 0.011). Although, on average, $\dot{V}O_2$ at GET was less than $\dot{V}O_2$ at CP ($p$ < 0.001, $d$ = 1.32), the difference between these thresholds (the $\dot{V}O_2$ range of the heavy intensity domain, or 'H space') decreased congruent with $\dot{V}O_{2peak}$. Critical power was identified in all patients, but RCP was identified in just three patients. In those three, $\dot{V}O_2$ at CP was 1.39 ± 0.23 $L.min^{-1}$ (86 ± 11 $\%\dot{V}O_{2peak}$) and at RCP was 1.40 ± 0.39 $L.min^{-1}$ (85 ± 2 $\%\dot{V}O_{2peak}$) (percentage discrepancy due to rounding artefact).

**DISCUSSION**

This study assessed the prevalence with which COPD patients exhibited RCP during ramp-incremental exercise and compared $\dot{V}O_2$ at the RCP to $\dot{V}O_2$ at CP. We were able to determine CP from the P-$T_{lim}$ relationship in all COPD patients and corroborate the attainment of a steady-state

$\dot{V}O_2$ during a 20-min ride at CP. Nevertheless, only three of 22 patients (14%) exhibited steepening of the $\dot{V}_E$-$\dot{V}CO_2$ slope, increased $\dot{V}_E/\dot{V}CO_2$ ratio, and/or systematically decreased $P_{ET}CO_2$ that is consistent with respiratory compensation (34). These data confirm that any equivalence between CP and RCP in previous literature results from the sequential expression of disparate physiological mechanisms that are dissociated in patients with cardiopulmonary and/or respiratory-mechanical dysfunction. This fundamentally undermines the validity of RCP as a surrogate for CP.

**Technical Considerations**

Studies that show no equivalence between CP and RCP have been criticized for failing to validate that the calculated CP reflected the highest power output at which a steady state could be attained such that exercise was being performed using wholly oxidative metabolism (40,41). For instance, $\dot{V}O_2$ at CP was incorrectly derived from the $\dot{V}O_2$-power output relationship elicited by ramp-incremental exercise (18,23), thereby underestimating the $\dot{V}O_2$ associated with a given power output. To determine CP, we established the P-$T_{lim}$ relationship for each patient following 3-5 constant-power exercise tests. To corroborate CP, our patients performed a 20-min constant-power trial during which we observed a steady-state $\dot{V}O_2$—that is, the mean difference between $\dot{V}O_2$ at 15 and 20 min was 0.00 ± 0.04 $L \cdot min^{-1}$ which was not different from a hypothesized mean of 0 ($p$ = 0.856, $d$ = 0.04; Figure 3). Although this confirms that we did not overestimate CP, we cannot say with absolute certainty that our estimated CP was the highest steady-state power (i.e., that it was not underestimated). Nevertheless, of the 3-5 constant-power trials used in the characterization of the P-$T_{lim}$ relationship (and performed to intolerance), the test with the lowest power output was, on average, only 9 ± 8 W above the estimated CP. In addition, the power

accuracy of our electrically-braked cycle ergometer is ± 5 W. We are therefore confident that the calculated CP was a close approximation of the highest steady state power output.

Our data also highlight that the characteristically low $\dot{V}O_{2peak}$ of COPD patients reduces the available $\dot{V}O_2$ and power output range within each intensity domain (Figure 4). Indeed, when $\dot{V}O_{2peak}$ is less than 10 $mL \cdot min^{-1} \cdot kg^{-1}$, it becomes difficult to differentiate between $\dot{V}O_2$ at GET, CP, and $\dot{V}O_{2peak}$. These data—the first presentation of such in the literature—contribute to our understanding of why small changes in power output can have such profound effects on exercise tolerance in COPD, particularly in patients with very low $\dot{V}O_{2peak}$.

**Critical Power and Respiratory Compensation Point**

There is extensive literature on the relative proximity of CP to various metabolic/ventilatory thresholds (for review, see [41]). Although several studies show that CP (from "all-out" or constant-power exercise) and RCP (from ramp-incremental exercise) occur at equivalent power outputs in healthy subjects (21,22), the validity of this finding is dependent on (at least) three important assumptions: i) that CP is a power output; ii) that the kinetic dissociation between power output and physiological responses to ramp-incremental exercise (e.g., $\dot{V}O_2$, $\dot{V}_E$, $\dot{V}CO_2$) does not significantly influence the association between CP and RCP; and iii) that the signaling pathways connecting metabolic acidosis (originating in active muscles) and respiratory compensation (achieved by the ventilatory system) are unaffected by environment or pathophysiology.

Regarding the first assumption, although CP is typically measured in the power domain (e.g., quantified as watts during cycle ergometry), the absolute value recorded by the ergometer's external sensor assumes that the internal (unmeasured) power—that in the form of instrumental

friction or work required to move the locomotor muscles against the force of gravity—remains constant. Indeed, Barker *et al*. (2006) showed that external power on the flywheel was influenced by pedal cadence, but that total power measured as $\dot{V}O_2$ was independent of cadence and remained constant (43). In this sense, it may be more appropriate to consider CP in terms of $\dot{V}O_2$ which, through knowledge of exercise economy, can be coupled with a range of external powers. On examination, CP is actually an emergent property of muscle metabolism, depending partly on activity of oxidative enzymes, describing the highest rate of ATP utilization that can be met with intramuscular metabolic stability (40,41). Nevertheless, internal work can only be assumed to be constant under controlled laboratory conditions wherein factors like pedal cadence, that would normally confound the P-$T_{lim}$ model, can be tightly controlled. It may be reasonable therefore to explore an equivalence between power output at CP and RCP in laboratory studies when the other two assumptions are met.

The second assumption is that the relationship between CP and RCP is not influenced by the kinetic dissociation between power output and physiological responses to ramp-incremental exercise. Respiratory compensation point is determined during ramp-incremental exercise as an increase in the slope of the $\dot{V}_E$-$\dot{V}CO_2$ relationship; corroborated as a reduction in end-tidal, transcutaneous-capillary, or arterial $PCO_2$. However, following an increase in power output, a delay in the $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}_E$ response can be characterized via the respective mean response times (44). In healthy subjects, power output becomes dissociated from metabolic processes by a mean response time of ~45-60 s. During incremental exercise with a ramp-rate of 20 $W \cdot min^{-1}$, such a delay is equivalent to 15-20 W. It stands to reason that this dissociation would be exacerbated in patients with chronic diseases that are characterized by slowed $\dot{V}O_2$-kinetics (13). Leo *et al*. (2017) were able to mitigate the large differences between power output at CP and RCP by adjusting for

the kinetic dissociation, irrespective of the ramp rate (i.e., fast, medium, or slow). Although this is consistent with the finding that $\dot{V}O_2$ at CP and RCP, and the associated power outputs, are closely associated in healthy subjects (19,21), there remains a large root-mean-square error of ~30 W between thresholds, even after adjusting for kinetic effects (13). This suggests that CP and RCP may not be consistently interchangeable.

The third assumption on which an equivalence between CP and RCP depends is that the signaling pathway connecting metabolic acidosis originating in the muscle and respiratory compensation accomplished by the ventilatory system is not unduly influenced by factors external to the organism (such as test protocols or environmental stimuli) or subject pathophysiology. Broxterman and colleagues argued that in order for RCP to be a valid surrogate for CP, the variables should be "consistently and strongly related" (16). Under normal conditions, respiratory compensation attenuates the increase in arterial hydrogen ion concentration [$H^+$] that is partly responsible for decreasing arterial pH. Keir and colleagues proposed that lactate accumulation at work rates above CP causes a near immediate rise in [$H^+$] and a rapid, reflexively-driven compensatory increase in ventilation (i.e., the RCP), concluding that CP and RCP "are surrogates that are linked together by a common metabolic stimulus" (17). But environmental conditions like hypoxia can sensitize ventilatory control mechanisms such that, during ramp-incremental exercise at high altitude, RCP and GET occur simultaneously without an isocapnic buffering region (45). These data speak to the labile nature of RCP.

Pertinently, the equivalence of CP and RCP has so far only been explored in healthy and/or athletic individuals with intact biochemical and respiratory-mechanical signaling. Given that the equivalence between CP and RCP depends upon a tightly regulated cascade of physiological mechanisms—progressive muscle acidosis, chemosensory responses to arterial acidosis, neural-

mechanical coupling influencing increased alveolar ventilation—we tested the "equivalence hypothesis" in patients with respiratory-mechanical limitation in whom the physiological cascade is impeded. To our knowledge, this is the first study to do so. The main outcome, that all patients exhibited a valid CP while only three patients produced an identifiable RCP, demonstrates empirically that some pathologies disrupt the sequence of physiologic events on which the equivalence of CP and RCP depend.

In COPD, exercise intolerance during ramp-incremental exercise is rarely the result of neuromuscular fatigue (46). Instead, exercise cessation is usually attributable to intolerable dyspnea that results from the complex interplay among expiratory flow limitation, gas trapping, dynamic hyperinflation, and decreasing inspiratory reserve volume congruent with increasing neural respiratory drive (47). Even in mild COPD, the respiratory system may reach its physiologic limit at lower peak work rates and ventilations than in healthy populations (48). The low ventilatory reserve in our patients at exercise intolerance (11-16%) is evidence of a discernable ventilatory limitation. The degree of respiratory-mechanical constraint can also be visualized in some patients as an apparent negative/downward inflection in the $V_E$-$VCO_2$ relationship toward the end of ramp-incremental exercise (Figure 3), and this is distinct from the normal positive/upward inflection usually observed in individuals without respiratory-mechanical constraint. As such, while COPD patients exhibit P-$T_{lim}$ profiles that allow the characterization of CP, disease pathophysiology typically denies them the signaling and/or ventilatory mechanics necessary to exhibit respiratory compensation during incremental exercise. Collectively, our data reinforce the contention that CP and RCP are not consistently and strongly related.

## CONCLUSIONS

In COPD patients, who present with cardiopulmonary and/or respiratory-mechanical dysfunction, CP and RCP are not equivalent. These data undermine the validity of RCP as a surrogate for CP.

**Acknowledgements**

This study utilized data set originally published in 2013/14 (28,29).

**Conflict of Interest**

The authors declare no conflicts of interest. NBT is supported by a postdoctoral fellowship from the Tobacco-Related Disease Research Program (TRDRP; award no. T31FT1692). CF is involved in contracted clinical research with United Therapeutics, Genentech, and Regeneron. She is a visiting Associate Professor at the University of Leeds, UK. HR is supported by grants from NIH (R01HL151452, R01HL153460, P50HD098593, R01DK122767, P2CHD086851) and the Tobacco Related Disease Research Program (T31IP1666). He reports consulting fees from Omniox Inc., and is involved in contracted clinical research with Boehringer Ingelheim, GlaxoSmithKline, Novartis, AstraZeneca, Astellas, United Therapeutics, Genentech, and Regeneron. He is a visiting Professor at the University of Leeds, UK. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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**FIGURES LEGENDS**

**Figure 1.** Individual participant $\dot{V}_E$-$\dot{V}CO_2$ responses during ramp-incremental exercise. Only 3/22 patients (patients 4, 11, and 16) had an identifiable RCP.

**Figure 2.** Representative data (n=2) from ramp-incremental and constant-power exercise. Panels on the left show data from a patient without an identifiable RCP, and panels on the right show data from a patient with an identifiable RCP. Panels A1 and A2 illustrate the $\dot{V}O_2$-$\dot{V}CO_2$ relationship during ramp-incremental exercise on which the identified GET has been overlayed. Panels B1 and B2 illustrate RCP from the $\dot{V}_E$-$\dot{V}CO_2$ relationship during ramp-incremental exercise. Panels C1 and C2 illustrate the hyperbolic P-$T_{lim}$ relationship and the calculated critical power (66 vs. 73 W) during constant-power exercise. Panels D1 and D2 illustrate $\dot{V}O_2$ from a 20-min CP ride during which $\dot{V}O_2$ reached a steady state.

**Figure 3.** Bland-Altman plot showing the mean difference in $\dot{V}O_2$ between 15 and 20 min of the CP validation ride ($n$=18). The mean difference between time points was 0.00 ± 0.04 $L \cdot min^{-1}$ and was not different from 0 ($p$ = 0.856, $d$ = 0.04). Circles represent individual participants. The square data point represents the group mean with standard deviations. Shaded area shows the upper- and lower-limits of agreement (+1.96 SD and -1.96 SD, respectively).

**Figure 4.** The association of $\dot{V}O_2$ at GET with $\dot{V}O_{2peak}$ from ramp-incremental exercise, and $\dot{V}O_2$ at CP with $\dot{V}O_{2peak}$ from ramp-incremental exercise. Relative peak oxygen uptake during ramp-incremental exercise was strongly correlated with $\dot{V}O_2$ at GET (open circles/dashed line; $r^2$ =

0.507, $p < 0.001$) and modestly correlated with $\dot{V}O_2$ at CP (closed circles/thick line; $r^2 = 0.340$, $p = 0.011$). Data shown for patients who had an identifiable GET (n=20) and patients who completed a 20-min ride at CP (n=18). The difference between GET and CP (i.e., the $\dot{V}O_2$ range of the heavy intensity domain, or 'H space') is represented by grey shading and decreases congruent with $\dot{V}O_{2peak}$.

**Figure 1**

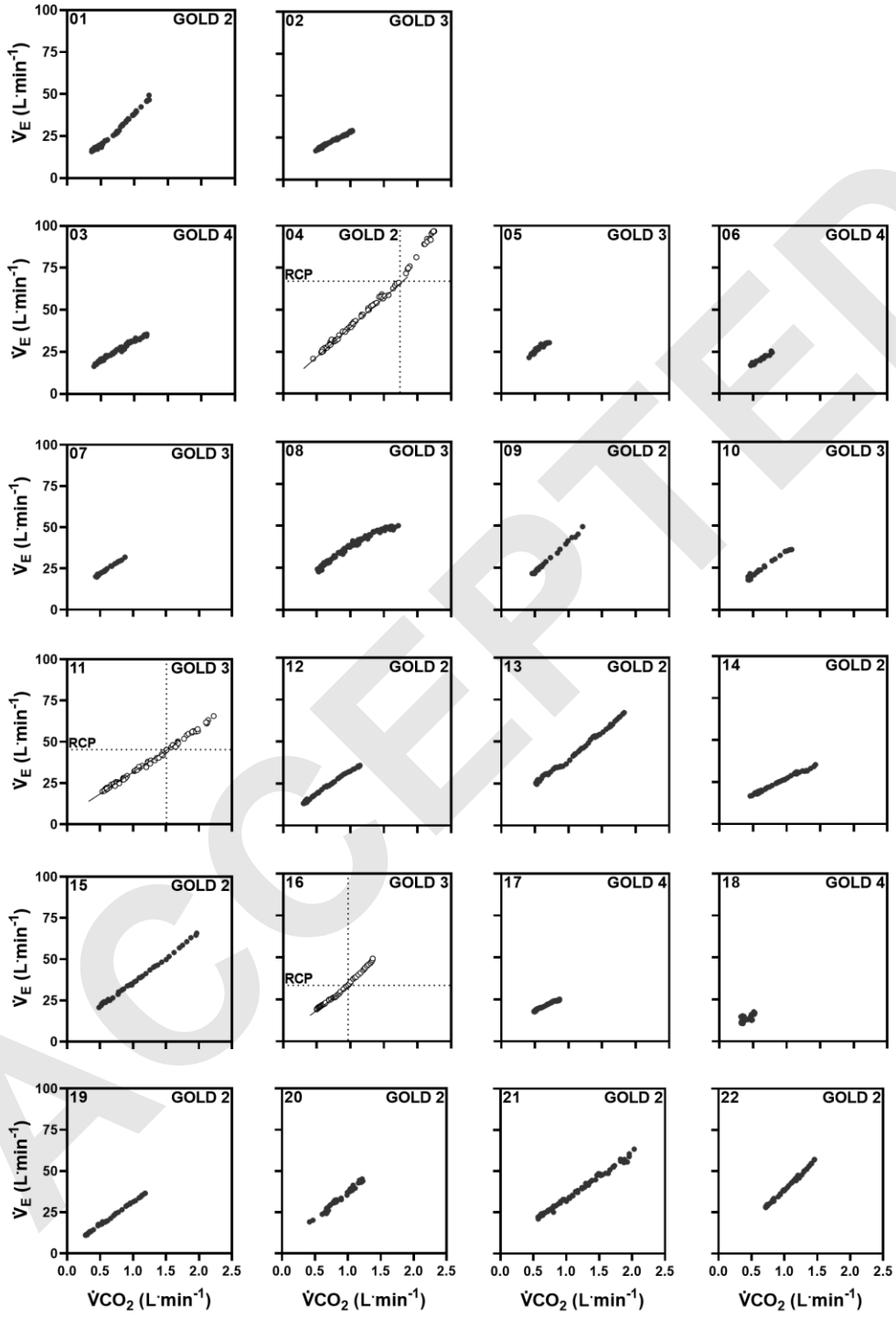

**Figure 2**

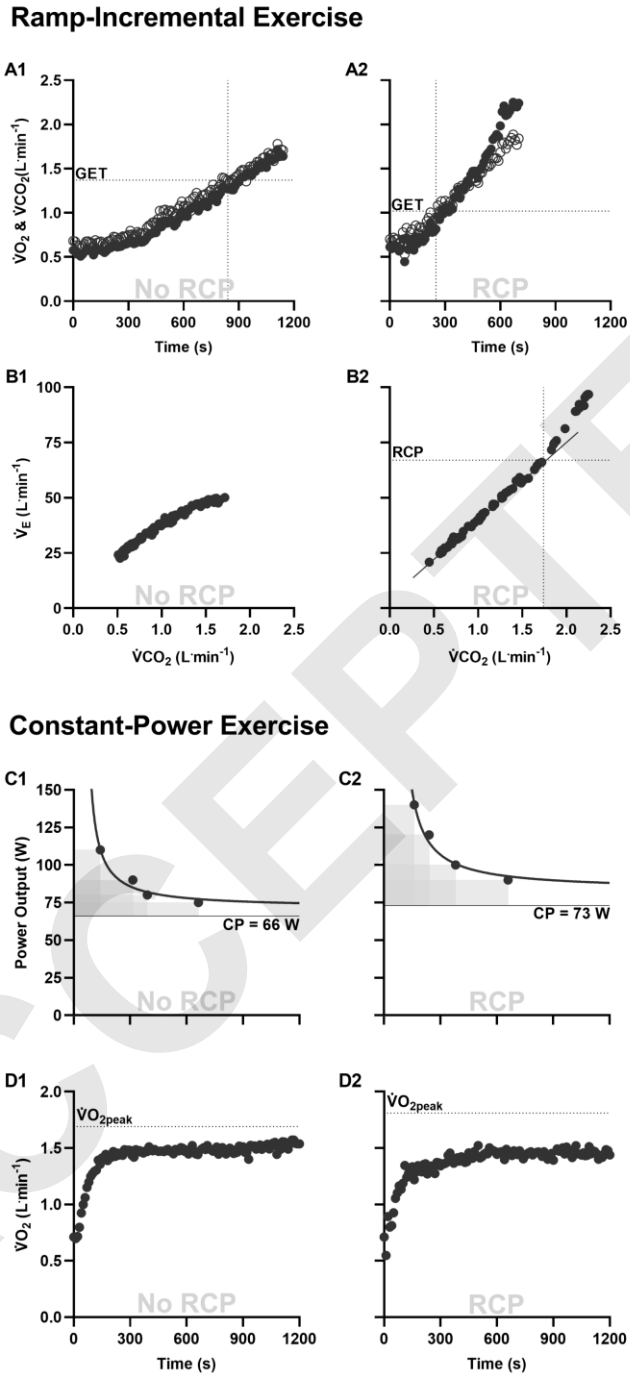

**Figure 3**

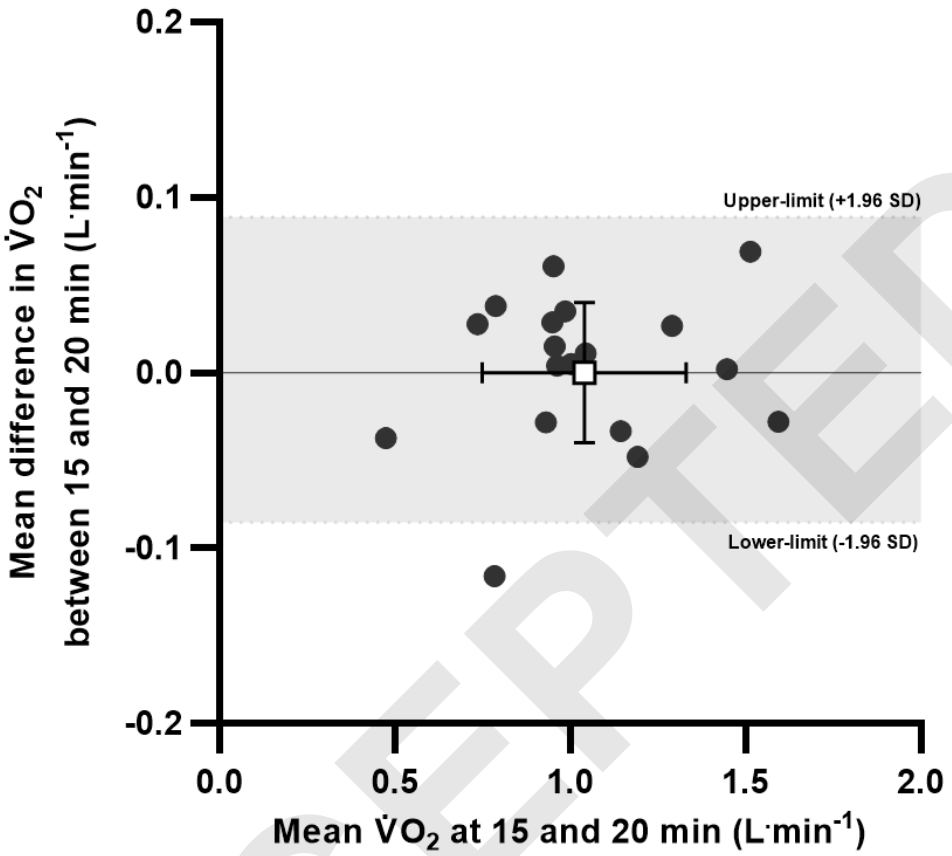

**Figure 4**

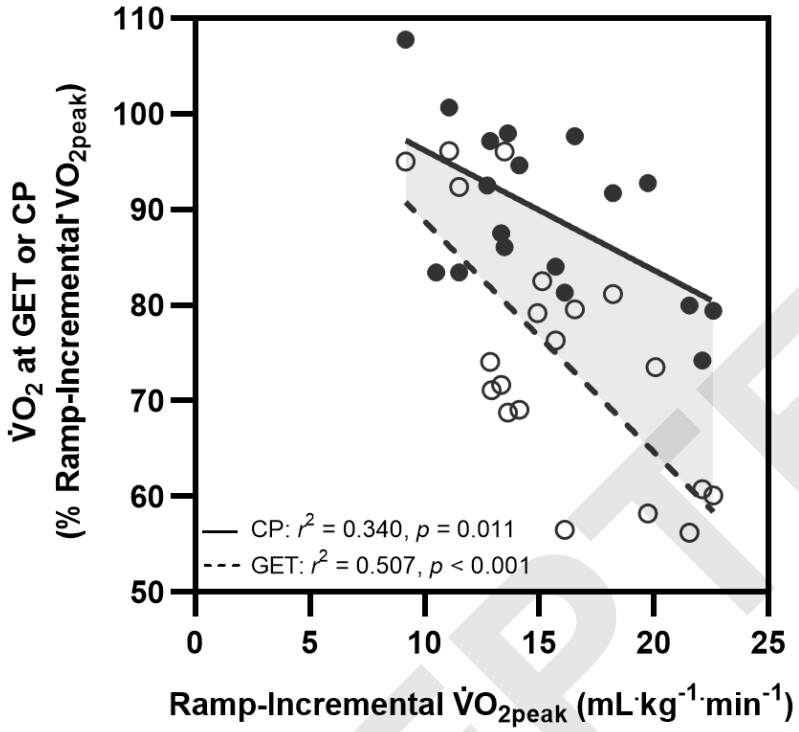

**Table 1.** Patient characteristics and post-bronchodilator pulmonary function.

| | **Overall (*n*=22)** |
|---|---|
| ***Demographics*** | |
| Male/Female (*n*) | 14/8 |
| GOLD Status = 1, 2, 3, 4 (*n*) | 0, 11, 7, 4 |
| Age (y) | 63 ± 9 |
| Mass (kg) | 79.4 ± 13.7 |
| Stature (cm) | 170.0 ± 7.0 |
| ***Pulmonary Function*** | |
| FVC (L) | 3.17 ± 1.03 |
| $FEV_1$ (L) | 1.30 ± 0.50 |
| $FEV_1$ (%Pred) | 46.8 ± 17.7 |
| $FEV_1$/FVC (%) | 41.8 ± 12.5 |
| MVV ($L \cdot min^{-1}$) | 51.9 ± 20.1 |

*Mean ± SD. Spirometry reference values taken from the NHANES III study (31).*

**Table 2.** Peak physiological responses to ramp-incremental and four constant-power exercise tests (ordered lowest to highest power output).

| | Ramp | Constant-Power 1 (n=22) | Constant-Power 2 (n=22) | Constant-Power 3 (n=22) | Constant-Power 4 (n=17) | *p* |
|---|---|---|---|---|---|---|
| **Power Output** (W) | 73 ± 28 | 55 ± 24 | 65 ± 28 | 78 ± 35 | 79 ± 29 | 0.038 |
| $\dot{V}O_2$ ($L \cdot min^{-1}$) | 1.22 ± 0.37 | 1.26 ± 0.35 | 1.26 ± 0.39 | 1.27 ± 0.37 | 1.22 ± 0.33 | 0.986 |
| $\dot{V}CO_2$ ($L \cdot min^{-1}$) | 1.30 ± 0.48 | 1.30 ± 0.45 | 1.38 ± 0.52 | 1.42 ± 0.52 | 1.29 ± 0.45 | 0.855 |
| **RER** | 1.04 ± 0.12 | 1.01 ± 0.11 | 1.07 ± 0.12 | 1.10 ± 0.14 | 1.04 ± 0.13 | 0.186 |
| $\dot{V}_E$ ($L \cdot min^{-1}$) | 44.1 ± 17.7 | 45.1 ± 18.0 | 46.2 ± 18.5 | 46.0 ± 18.3 | 43.5 ± 17.3 | 0.983 |
| $\dot{V}_E$ (%MVV) | 86 ± 17 | 88.3 ± 18.5 | 90.4 ± 17.9 | 89.4 ± 15.2 | 86.0 ± 17.6 | 0.861 |
| $\dot{V}_E/\dot{V}CO_2$ | 34.2 ± 5.2 | 34.7 ± 5.4 | 33.9 ± 6.2 | 32.7 ± 6.1 | 33.8 ± 5.2 | 0.819 |
| $P_{ET}CO_2$ (mmHg) | 38.2 ± 7.6 | 37.2 ± 8.1 | 38.4 ± 8.0 | 39.9 ± 7.5 | 39.1 ± 6.3 | 0.800 |
| $f_C$ ($beats \cdot min^{-1}$) | 121 ± 23 | 124 ± 17 | 123 ± 20 | 118 ± 16 | 116 ± 16 | 0.659 |
| $f_C$ (%$f_{Cmax}$)* | 74 ± 13 | 75 ± 10 | 75 ± 11 | 72 ± 9 | 70 ± 9 | 0.523 |

*Mean ± STDEV, n=22. $\dot{V}O_2$ = rate of pulmonary oxygen uptake; $\dot{V}CO_2$ = rate of pulmonary carbon dioxide output; RER = respiratory exchange ratio; $\dot{V}_E$ = minute ventilation; MVV = maximum voluntary ventilation; $P_{ET}CO_2$ = partial pressure of end-tidal $CO_2$; $f_C$ = cardiac frequency; p = ANOVA result. *Age-predicted $f_{Cmax}$ derived using 208 – (0.7 × age) (39).*

**Table 3.** Physiological responses at GET (*n*=20), CP (*n*=18), RCP (*n*=3), and $\dot{V}O_{2peak}$ (*n*=22).

| | **Ramp-Incremental Exercise** | | | | | | | | | **Validation Trial** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GET (*n*=20) | | | RCP (*n*=3) | | | $\dot{V}O_{2peak}$ (*n*=22) | | | CP (*n*=18) | | |
| $\dot{V}O_2$ ($L \cdot min^{-1}$) | 0.93 | ± | 0.18 | 1.40 | ± | 0.39 | 1.22 | ± | 0.37 | 1.04 | ± | 0.29 |
| $\dot{V}O_2$ (%$\dot{V}O_{2peak}$) | 75 | ± | 13 | 85 | ± | 2 | 100 | ± | 0 | 90 | ± | 9 |
| $\dot{V}CO_2$ ($L \cdot min^{-1}$) | 0.84 | ± | 0.18 | 1.49 | ± | 0.45 | 1.30 | ± | 0.48 | 1.00 | ± | 0.31 |
| **RER** | 0.90 | ± | 0.05 | 1.06 | ± | 0.05 | 1.04 | ± | 0.12 | 0.95 | ± | 0.05 |
| $\dot{V}_E$ ($L \cdot min^{-1}$) | 30.3 | ± | 6.6 | 51.0 | ± | 17.1 | 44.1 | ± | 17.7 | 36.6 | ± | 12.8 |
| $\dot{V}_E$ (%MVV) | 54 | ± | 25 | 81 | ± | 19 | 86 | ± | 17 | 78 | ± | 17 |
| $\dot{V}_E/\dot{V}CO_2$ | 36.1 | ± | 4.0 | 34.3 | ± | 4.7 | 34.2 | ± | 5.2 | 36.7 | ± | 5.7 |
| $f_C$ ($beats \cdot min^{-1}$) | 100 | ± | 17 | 116 | ± | 5 | 121 | ± | 23 | 117 | ± | 20 |
| $f_C$ (%$f_{Cmax}$)* | 61 | ± | 10 | 71 | ± | 8 | 74 | ± | 13 | 72 | ± | 12 |

*Mean ± STDEV. GET, RCP, and $\dot{V}O_{2peak}$ determined from ramp-incremental exercise; CP determined from 20-minute CP validation trial; $\dot{V}O_2$ = rate of pulmonary oxygen uptake; $\dot{V}CO_2$ = rate of pulmonary carbon dioxide output; RER = respiratory exchange ratio; $\dot{V}_E$ = minute ventilation; MVV = maximum voluntary ventilation; $f_C$ = cardiac frequency; *Age-predicted $f_{Cmax}$ derived using 208 – (0.7 × age) (39).*