Determinants of the Exercise Endurance Capacity in Patients with Chronic Obstructive Pulmonary Disease
The Power–Duration Relationship

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To characterize the determinants of the power–duration ($\dot{W}$–*t*) relationship in patients with chronic obstructive pulmonary disease (COPD), we evaluated 8 nonhypoxemic patients (FEV_1 = 1.27 ± 0.26 L) and 10 healthy controls. After an initial maximum-incremental exercise test on cycle ergometer (peak), the subjects underwent four high-intensity constant-load tests to the limit of tolerance (*t*), each on different days. The $\dot{W}$–*t* relationship was found to be hyperbolic in both groups. Absolute values of both the critical power asymptote (θ_F) and the curvature constant (W′) were lower in patients than in control subjects. However, when expressed as percentage of peak work rate θ_F was significantly higher in patients compared with control subjects (81.8 ± 3.3% versus 67.5 ± 3.7%, respectively, $p < 0.01$). There were severe reductions in *t* in the patients that were consistently associated with higher breathlessness scores and $\dot{V}_E$/MVV ratios. Interestingly, all patients were able to sustain exercise at θ_F for 20 min despite near-maximum physiological and subjective stresses. We conclude that the reductions of both parameters of the hyperbolic $\dot{W}$–*t* relationship (θ_F and W′) in patients with COPD were due to the ventilatory constraints and their sensory consequences. Importantly, θ_F separated a "sustainable" from a "nonsustainable" exercise-intensity domain: this parameter consistently occurred closer to peak work rate in patients than the healthy control subjects.

Chronic obstructive pulmonary disease (COPD) includes a group of nosologic entities characterized by constraint of expiratory airflow that is generally progressive but occasionally partially reversible (1). The multifactorial functional impairment in patients with COPD frequently reduces their tolerance to exertion (disablement): this in turn increases sedentarity, a process long recognized as representative of "dyspnea spiral" or, more properly, an "incapacity spiral." Exercise intolerance is therefore a hallmark of the disease and commonly associated with reduced quality of life, and even increased mortality (1–3).

There are, however, many unresolved issues concerning the mechanisms actually limiting (or constraining) the tolerance to dynamic exercise in COPD. Although many of the remaining controversies seem to be due to the heterogeneity of the physiopathology and/or the use of inappropriate control subjects, a very basic question in patients with COPD is how to assess "exercise capacity" and to identify the "exercise-intensity domains." For example, patients need both the capacity to achieve a high work-rate for brief periods (e.g., fast walking, climbing stairs) and the ability to produce sustained periods of moderate exercise (e.g., light housework, bathing): the main factor(s) limiting the ability to perform such activities may differ. Improved understanding of the exercise physiopathology or the interstudy comparability in patients with COPD may therefore depend on the identification of the time-related constraints of the activity progression, with specific reference to the exercise-intensity domains.

Tolerance to long-term exercise (endurance), however, is not a finite or single point consideration. In disease-free subjects, the relationship between the imposed work rate (power, $\dot{W}$) and the time to exhaustion (*t*) for high-intensity, constant-load exercise has been shown to be that of a rectangular hyperbola (4–6), of the form:

$$W' = (\dot{W} - \theta_F)t$$

where θ_F is the power asymptote (critical power or fatigue threshold) that has been considered to represent the maximum sustainable rate of aerobic ATP regeneration, and W′ is the curvature constant, equivalent to a constant amount of work that can be performed above θ_F. In this sense, W′ would represent components of an energy pool that is independent of the uptake of atmospheric O_2, that is, previously stored O_2, high-energy phosphates, and anaerobic glycolysis (5, 6).

To date, however, there are no data concerning either the shape or the determinants of the power–duration relationship for whole-body exercise in patients with COPD. For instance, if the $\dot{W}$–*t* relationship in these patients were not hyperbolic, this would suggest that there were different factors limiting the duration at different work rates (WRs). On the other hand, if the relationship were hyperbolic and consistently related to a given physiological response, this would suggest that there may be (*1*) a single (or possibly dominant) factor limiting the tolerance, and (*2*) a constant amount of suprathreshold work that a patient was prepared to endure. Furthermore, the existence of such an asymptote (critical power) would imply that a small improvement in this parameter might change a subject's endurance from being clearly limited to providing him or her with a level of exercise that could be maintained for prolonged periods. We felt that the analysis of the power–duration relationship in patients with COPD would produce new and possibly valuable insights into the determinants of the physical impairment and also the consequent rehabilitative strategies for the disease.

METHODS

Subjects

Eight males with established clinical and functional diagnosis of moderate-to-severe chronic obstructive pulmonary disease (COPD) comprised the study group. Chronic breathlessness (Medical Research Council dyspnea score > 2) (7) and a long history of cigarette smoking were present in all patients (Table 1). Inclusion criteria were ab-

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sence of physiologically significant deoxygenation at rest ($Pa_{O_2} > 55$ mm Hg, exercise $Sa_{O_2} > 90\%$), no locomotor or neurological diseases, and no change in medication dosage or symptom exacerbation in the preceding 4 wk. The control group consisted of 10 healthy nonsmoking males, aged above 60, who were recruited from the general population by advertisement (Table 1). All subjects were considered sedentary, that is, none was involved in regular physical activity programs at least for the past year. Before the tests, the procedures, including the known risks, were described in detail and written, informed consent (as approved by the Institutional Medical Ethics Committee) was obtained from all subjects.

Measurements

Anthropometry and body composition. Body height (cm) was measured with subjects standing barefoot and was determined to the nearest 0.5 cm. Total body mass (kg) was measured with subjects in light clothing and was established to the nearest 0.1 kg. Fat-free mass (FFM) was measured by the bioelectrical impedance method (Bodystat-500; Bodystat Ltd, Douglas, UK). Impedance measurements were performed on the right side, with subjects supine, and with their limbs slightly apart. FFM of the normal subjects was obtained by using the regression equation of Segal and coworkers (8), which is based on age, weight, height^2, and resistance. In the patient group, FFM was calculated using a validated patient-specific regression equation (9) from Ht^2/Res and total body mass. In both groups FFM values were expressed as a percentage of ideal body weight (10). Anthropometric and body composition characteristics did not differ between groups (Table 1).

Pulmonary function tests. Spirometric tests were performed using the 2130D SensorMedics Spirometer with flow measurement carried out with a calibrated pneumotachograph. The subjects completed at least three acceptable maximal forced expiratory maneuvers before and 5 min after 200 μg of inhaled salbutamol. Technical procedures, acceptability and reproducibility criteria were those recommended by the American Thoracic Society (11). The values were compared with those predicted from Knudson and coworkers (12) (Table 1). Maximum voluntary ventilation (MVV) was directly determined with the subjects using nose clips and breathing deeply (with a volume greater than the tidal volume preceding the maneuver but less than the vital capacity) and rapidly for a 12-s interval. The subjects were actively encouraged to maintain the same volume and frequency by following an on-line display of the maneuver on a computer screen, that is, the end-expiratory level remained relatively constant. At least two acceptable maneuvers were obtained with values differing by no more than 10% and, after flow integration, the highest value recorded by extrapolating the 12-s accumulated volume to 1 min (L/min, BTPS) (Table 1).

Exercise tests. The exercise tests were performed on an electromagnetically braked cycle ergometer (CardiO$_2$ Cycle; Medical Graphics Corp., St. Paul, MN) with the subjects maintaining a pedaling frequency of 60 ± 5 rpm. All tests were preceded by a 3-min baseline of "true" unloaded pedaling, that is, by means of motor-assisted pedaling during this phase. Pulmonary gas exchange and ventilatory variables were obtained from calibrated signals derived from rapidly responding gas analyzers and a pneumotachograph (CardiO$_2$ System; Medical Graphics Corp.). The following variables were recorded breath by breath and expressed as 5-s mean: pulmonary oxygen uptake ($\dot{V}O_2$, ml min^{-1} STPD), pulmonary carbon dioxide output ($\dot{V}CO_2$, ml min^{-1} STPD), respiratory exchange ratio (R), minute ventilation ($\dot{V}E$, L min^{-1} BTPS), tidal volume (VT, L), breathing frequency (f, rpm); ventilatory equivalent for O_2 and CO_2 ($\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$), end-tidal partial pressures of O_2 and CO_2 ($P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$, mm Hg), and inspiratory, expiratory, and total cycle times (TI, TE, and Ttot, s). Heart rate (HR, bpm) was determined using the R–R interval from a 12-lead on-line electrocardiogram and oxyhemoglobin saturation (Sa_{O_2}) by pulse oximetry. Subjects were also asked to rate "shortness of breath" or "leg effort" each minute in an alternated sequence using the 0 to 10 Borg's category-ratio scale. Each subject initially underwent a ramp-incremental exercise to the limit of tolerance. The power incrementation rate was selected such that the tolerance–duration (min) was 11.1 ± 1.7 and 11.8 ± 2.1 in patients and control subjects, respectively ($p > 0.05$). The peak $\dot{V}O_2$ values at the ramp-incremental

TABLE 1

SELECTED CHARACTERISTICS FOR PATIENTS WITH COPD AND AGE-MATCHED CONTROLS*

Variables	COPD (*n* = *8*)	Controls (*n* = *10*)
Age, yr	69.1 ± 8.5	65.6 ± 4.1
Height, cm	172.6 ± 4.1	176.5 ± 6.2
Weight, kg	75.3 ± 7.3	76.8 ± 9.6
Body mass index, kg/m^2	24.5 ± 2.1	25.2 ± 2.5
Fat-free mass, % ideal weight	69.6 ± 7.1	70.2 ± 7.4
FEV$_1$, L	1.27 ± 0.26†	3.31 ± 0.70
FEV$_1$, % predicted	46.2 ± 10.9†	107.0 ± 16.4
FVC, L	3.12 ± 0.34†	4.47 ± 0.85
FVC, % predicted	84.5 ± 11.2†	115.2 ± 15.4
FEV$_1$/FVC	0.44 ± 0.06†	0.74 ± 0.10
MVV, L/min	51.4 ± 9.8†	132.1 ± 11.9
Pa_{O_2}, mm Hg	73 ± 6	—

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; MVV = maximal voluntary ventilation.

* Values are mean ± 1 SD.

† $p < 0.05$.

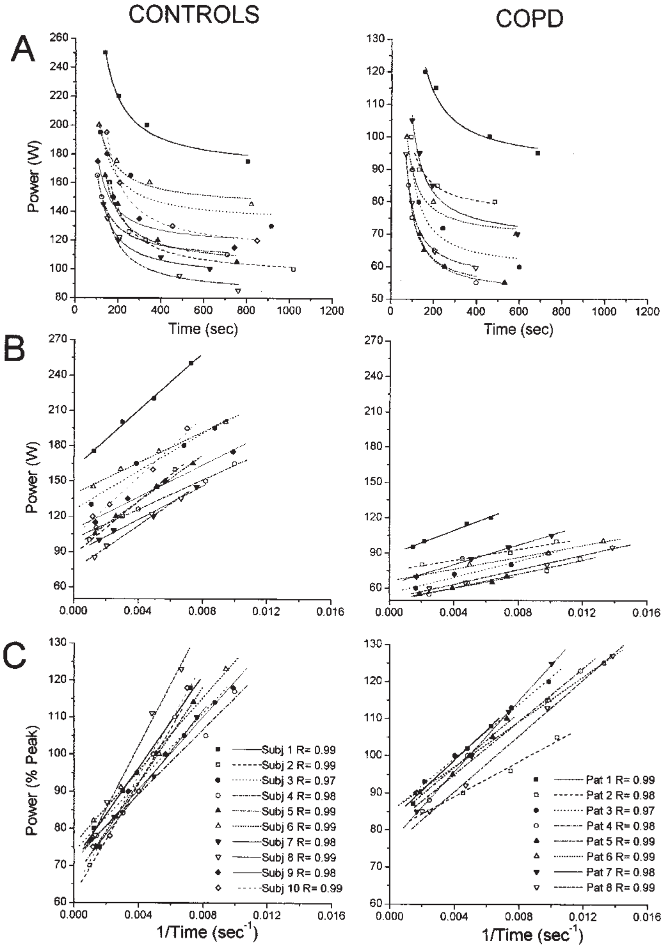

Figure 1. The power–duration ($\dot{W}$–*t*) relationship in response to high-intense exercise in patients with COPD (*right panels*) and age-matched healthy control subjects (*left panels*). (*A*) A hyperbolic relationship well described the $\dot{W}$–*t* relationship in all subjects. Note, however, the different range of values for the power axes in the two groups. (*B*) After linearization, significant reductions in intercept (critical power, θ_F) and slope (supra-θ_F work capacity, W′) were found in patients ($p < 0.01$). (*C*) The patients' linearized response as function of percentage peak WR, however, presented higher intercept (θ_F) but lower slope (W′) when compared with the control subjects ($p < 0.01$).

test (PEAK) were compared with those predicted by Neder and coworkers (13), considering sedentarity, sex, age, weight, and height. The lactate threshold (θ_L) was estimated using ventilatory and gas exchange indices, that is, from the inflection point of $\dot{V}CO_2$ as a function of $\dot{V}O_2$ (modified V-slope) (14) and from $\dot{V}E/\dot{V}O_2$ and $P_{ET_{CO_2}}$ increasing while $\dot{V}E/\dot{V}CO_2$ and $P_{ET_{CO_2}}$ remained stable (15).

On separate days (at least 2 d apart), each subject undertook a series of four different constant-load exercise tests to the limit of tolerance. The WRs were randomly applied in order to induce exhaustion in more than 1 and less than 20 min: these were individually chosen in an attempt to provide an even point distribution along the 1/time axis (*see below*). Relative to the peak values obtained at maximum-incremental exercise (% peak WR), these work loads corresponded in control subjects and patients to 70–82% and 85–90% (WR_1), 83–100% and 90–100% (WR_2), 94–113% and 96–119% (WR_3), and 110–127% and 105–129% (WR_4), respectively. In addition, a square-wave test was performed on a different day at the subsequently determined power output equivalent to θ_F with a target duration of 20 min: the subjects were not told that 20 min was the test's maximum duration. Time to fatigue (*t*) was taken as the interval between the sudden imposition of the work rate and the point at which the subject could no longer maintain the required pedaling rate (60 rpm) despite active encouragement from the same observer (4–6, 16). The subjects were not told how long or at what power they had exercised. Reproducibility and reliability of *t* in such high-intensity constant-load protocols in normal subjects were previously demonstrated by Poole and coworkers (5). In the patients group, we assessed reproducibility by repeat tests randomly assigned for different subjects. Values of *t* at a given power for a given subject showed only minor variation: median of 8 s (5–14) for tests < 3 min and median of 20 s (18–25) for tests > 6 min. To extract the parameters, the hyperbolic $\dot{W}$–*t* relationship was linearized by using the reciprocal of time and solved for W (Figure 1B):

$$\dot{W} = W'/t + \theta_F$$

where $\dot{W}$ (watts) is a linear function of 1/t (s^{-1}), and W' (kJ) and θ_F (watts) are the slope and intercept extracted by least-squares linear regression (5, 6).

To estimate the time course progression (kinetics) of the main exercise responses, we calculated the effective time constant (τ' or mean response time in seconds) at WR_4, a supramaximal work load for all subjects. We chose to determine this index of kinetics only at this particularly high-intensity WR, considering that at this "severe-intensity" domain there is insufficient time for the development of "excess" $\dot{V}O_2$ (17). One-second interpolated values were therefore fitted to a first-order exponential model, constrained to start at time zero, of the form:

$$y(t) = BL + A(1 - e^{(-t/\tau')}),$$

where BL is the average control value of the minute preceding exercise onset and A is the response amplitude.

Statistical Analysis

Means and standard deviations (SD) were obtained for values in subjects of both groups. Between-group differences in the variables expressed in absolute values and proportions were assessed by nonpaired Students' *t* and Mann–Whitney tests, respectively. One-way analysis of variance (ANOVA), with Scheffé post hoc test when appropriate, was used to evaluate differences between variables at different WRs within groups. Product–moment correlation (Pearson) was used to define association between variables. The probability of a type I error was established at 0.05 for all tests.

RESULTS

Maximum Exercise Capacity

The tolerance to ramp-incremental cycle ergometry (PEAK) was severely reduced in patients as compared to control sub-

TABLE 2

EXERCISE VARIABLES AT PEAK RAMP-INCREMENTAL (PEAK) AND AT THE LAST MINUTE OF THE TEST AT INDIVIDUAL'S CRITICAL POWER (θ_F) IN PATIENTS WITH COPD ($n = 8$) AND HEALTHY CONTROL SUBJECTS ($n = 10$)

			θ_F			
	PEAK		Patients		Control Subjects	
Variables	Patients	Control Subjects	Absolute	% Peak	Absolute	% Peak
Power, W	$79 \pm 14^{**,\dagger,\S}$	$162 \pm 33^{\dagger}$	$65 \pm 14^{**}$	$81.8 \pm 3.3^{*}$	110 ± 27	67.5 ± 3.7
$\dot{V}O_2$, ml/min	$1,223 \pm 167^{**,\dagger}$	$1,919 \pm 338^{\dagger}$	$1,108 \pm 168^{**}$	$92.2 \pm 6.9^{*}$	$1,641 \pm 324$	84.3 ± 5.9
$\dot{V}O_2$, % predicted	$58.1 \pm 8.4^{**,\dagger}$	$102.3 \pm 11.4^{\dagger}$	$50.4 \pm 3.6^{**}$	—	81.4 ± 5.6	—
$\dot{V}CO_2$, ml/min	$1,310 \pm 161^{**,\dagger}$	$2,245 \pm 446^{\dagger}$	$1,225 \pm 198^{**}$	$87.8 \pm 6.9^{*}$	$1,714 \pm 306$	76.3 ± 5.5
R	$1.07 \pm 0.02^{*}$	$1.19 \pm 0.06^{\dagger}$	1.05 ± 0.02	$95.3 \pm 2.6^{*}$	1.03 ± 0.03	85.8 ± 5.0
HR, bpm	$119 \pm 12^{**,\dagger}$	$155 \pm 14^{\dagger}$	$108 \pm 12^{*}$	$91.7 \pm 2.9^{*}$	128 ± 14	81.3 ± 4.2
HR, % predicted	$74.3 \pm 5.6^{**,\dagger}$	$98.5 \pm 6.5^{\dagger}$	$65.7 \pm 4.1^{**}$	—	81.2 ± 3.9	—
O_2 pul, ml/b/m	$10.3 \pm 2.2^{*,\dagger}$	12.2 ± 1.9	$8.9 \pm 1.9^{*}$	$78.2 \pm 8.9^{*}$	11.9 ± 5.8	99.1 ± 6.0
$\dot{V}E$, L/min	$48.7 \pm 7.1^{**,\dagger}$	$81.9 \pm 15.5^{\dagger}$	$40.2 \pm 4.4^{*}$	$82.1 \pm 8.5^{*}$	52.7 ± 11.2	65.2 ± 8.1
$\dot{V}E$/MVV, %	$95.9 \pm 11.4^{**,\dagger}$	$61.7 \pm 11.1^{\dagger}$	$80.1 \pm 6.5^{**}$	—	40.2 ± 5.8	—
f, bpm	$33 \pm 3^{\dagger}$	$34 \pm 4^{\dagger}$	27 ± 3	$84.4 \pm 5.2^{*}$	23 ± 7	71.5 ± 9.9
V_T/FVC	$57.9 \pm 9.9^{*}$	48.2 ± 7.8	$58.6 \pm 6.7^{*}$	102.3 ± 8.5	47.5 ± 9.9	100.8 ± 7.5
$\dot{V}E/\dot{V}O_2$	$39 \pm 4^{*}$	$42 \pm 4^{\dagger}$	$42 \pm 5^{*}$	$104.5 \pm 8.0^{*}$	36 ± 7	80.1 ± 7.9
$\dot{V}E/\dot{V}CO_2$	$36 \pm 3^{*}$	$43 \pm 4^{\dagger}$	$41 \pm 7^{*}$	$113.5 \pm 8.1^{*}$	34 ± 5	92.8 ± 9.4
$P_{ET_{O_2}}$, mg Hg	$113 \pm 5^{*}$	$120 \pm 6^{\dagger}$	112 ± 5	$99.7 \pm 2.9^{*}$	114 ± 6	94.7 ± 2.2
$P_{ET_{CO_2}}$, mg Hg	$40 \pm 4^{*}$	$31 \pm 5^{\dagger}$	36 ± 6	$91.0 \pm 8.2^{*}$	38 ± 6	107.1 ± 9.5
T_I/Ttot	$0.38 \pm 0.04^{*,\dagger}$	0.48 ± 0.04	$0.44 \pm 0.03^{*}$	$113.5 \pm 7.8^{*}$	0.48 ± 0.03	100.8 ± 7.3
T_I	$0.65 \pm 0.16^{**,\dagger}$	$0.92 \pm 0.24^{\dagger}$	$0.84 \pm 0.15^{*}$	$134.8 \pm 17.3^{*}$	1.09 ± 0.42	117.8 ± 13.3
Borg BL	6 (3–8)*	2 (0.5–4)	5 (4–6)*	—	2 (0.5–3)	—
Borg LE	3 (0–6)*	7 (6–10)	2 (0.5–5)*	—	6 (4–8)	—

Definition of abbreviations: BL = breathlessness; COPD = chronic obstructive pulmonary disease; ET = end-tidal partial pressure; f = respiratory rate; FVC = forced vital capacity; HR = heart rate; LE = leg effort; MVV = maximal voluntary ventilation; O_2 pul = oxygen pulse; R = respiratory exchange ratio; T_I = inspiratory time; Ttot = total respiratory cycle time; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen uptake; V_T = tidal volume.

* $p < 0.05$, **$p < 0.01$: patients versus control subjects within protocols.

† $p < 0.05$: PEAK versus θ_F within groups.

§ All values are means ± 1 SD with the exception of Borg scores, which are presented as median and range.

jects (Table 2). The PEAK responses were compatible with those of patients with moderate-to-severe disease: lower peak $\dot{V}O_2$ and oxygen pulse, large chronotropic reserve (HR $< 75\%$ predicted), and higher $\dot{V}E_{max}$/MVV ratio ($p < 0.01$). Breathlessness was the main limiting symptom in all patients but in none of the control subjects: patients' median (range) value for breathlessness was 6 (3–8) at the limit of tolerance but was only 2 in control subjects (0.5–4) (Table 2). The estimated lactate threshold (θ_L) was identified in all subjects of both groups: $\dot{V}O_2\theta_L$ absolute and relative (to percentage predicted peak $\dot{V}O_2$) values were also significantly lower in patients, but they did not differ between groups when expressed as percentage of the attained PEAK (75.6 ± 9.1 versus 73.7 ± 12.1% peak $\dot{V}O_2$).

The Power–Duration Relationship

The relationship between imposed power output ($\dot{W}$) and time to tolerance (*t*) in both groups was found to be well-characterized as a rectangular hyperbola (Figure 1A, control subjects on *left*, patients on *right*). The hyperbolic characteristic was confirmed by the excellent linear fit of $\dot{W}$ against the reciprocal of time (1/*t*): typical R values found in both groups were 0.99 and in no subject were these values below 0.97 (Figures 1B and 1C). Lower absolute values for both θ_F and W′ were

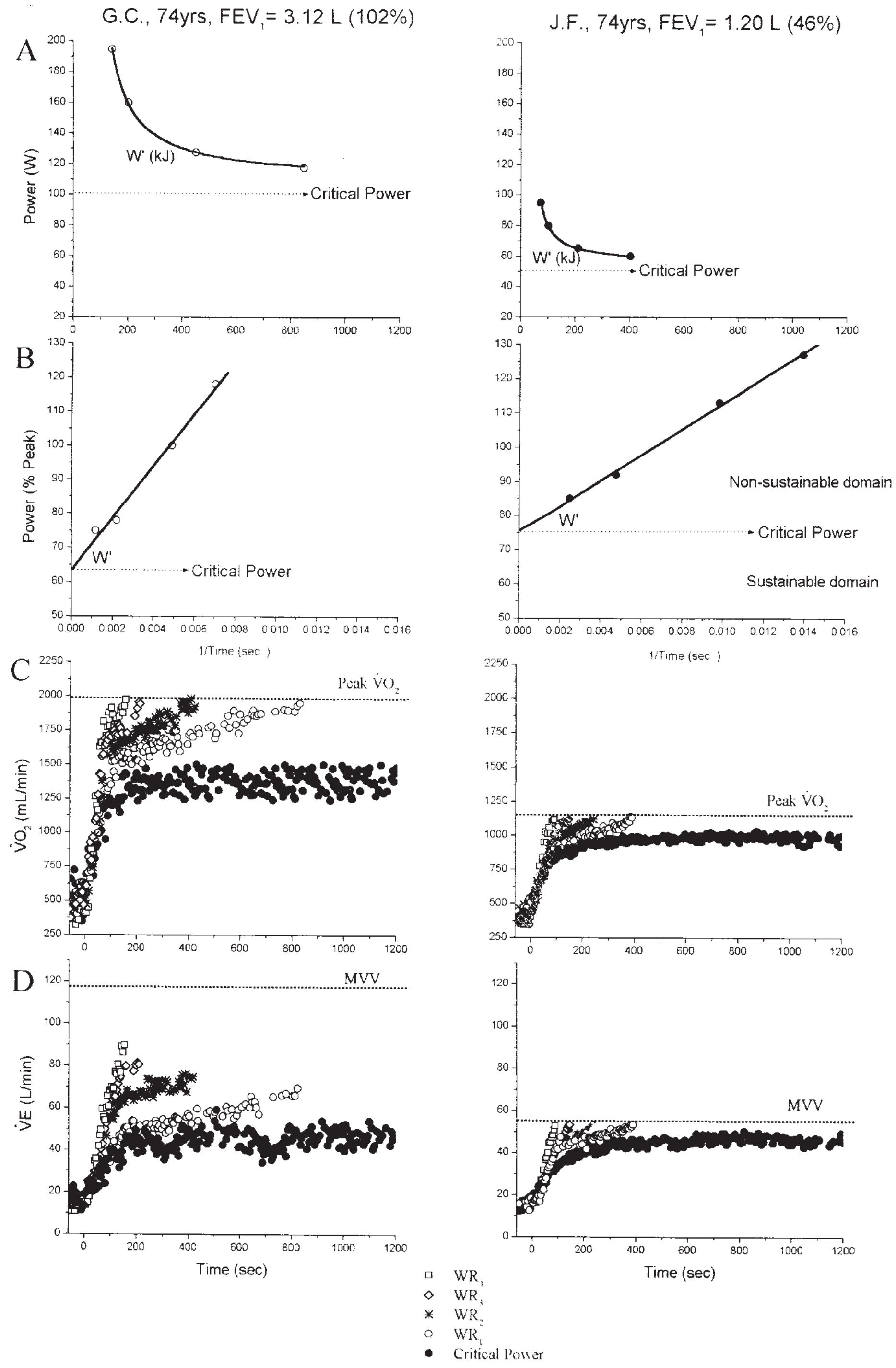

Figure 2. The $\dot{W}$–*t* relationship in response to four progressively intense (WR_1 to WR_4) exercise tests and its determinants in a healthy control (*left panels*) and a patient with COPD (*right panels*), matched by age. (*A*) A hyperbolic relationship was found in both subjects: reductions in the asymptote (critical power, θ_F) and the area under the curve (supra-θ_F work capacity, W′) were evident in the patient. (*B*) The patient's linearized response as a function of percentage peak WR, however, presented a higher intercept (θ_F) but still a lower slope (W′). (*C*) Oxygen uptake ($\dot{V}O_2$) at *t* in each power output did not differ from the $\dot{V}O_2$ at the maximum ramp-incremental test (peak) in both subjects. (*D*) Patients' $\dot{V}E$ at *t* ($\dot{V}E[t]$) was not significantly different from the maximum voluntary ventilation (MVV), whereas $\dot{V}E(t)$ was an inverse function of *t* in the control subject. Note that a 20-min test at the subject's critical power (*solid circles*, *panels C* and *D*) was successfully sustained at relatively higher metabolic and ventilatory stress in the patient.

found in patients as compared with control subjects (65 ± 14 versus 110 ± 27 $\dot{W}$ and 6.02 ± 1.64 versus 9.88 ± 2.39 kJ, respectively) ($p < 0.01$, Figure 1B and Table 2). Similarly, the slope W′ as a function of relative power intensity (percentage peak WR) was lower in patients than in control subjects (3,608 ± 707 versus 6,096 ± 1,334, $p < 0.01$, Figure 1C). On the other hand, the patients presented significantly *higher* values of θ_F as percentage of peak WR (81.8 ± 3.3% versus 67.5 ± 3.7%, $p < 0.01$, Figure 1C and Table 2).

Figure 2 shows a comparative evaluation between two representative subjects matched by age (control subject on *left*, patient on *right*): both a reduced curvature constant (W′) and a lower asymptote (θ_F) of the $\dot{W}$–*t* relationship are clearly evident in the patient (Figure 2A). On the other hand, θ_F as percentage of peak WR was higher in the patient as compared to the control subject (Figure 2B). Interestingly, in both groups $\dot{V}O_2$ at exhaustion (WR_1 to WR_4) did not differ from the peak $\dot{V}O_2$ obtained at the ramp-incremental test (Figure 2C and Table 3). However, the hyperbolic relationship in the patients developed as a result of the exponential-like ventilatory response reaching the maximum "ceiling" (MVV) (Figure 2D, *right* and Table 3). On the other hand, the ventilatory reserve was large and variable in the control group (Figure 2D, *left* and Table 3).

We also sought to investigate the relationship between the different exercise parameters. As expected, there was an effectively linear relationship between peak $\dot{V}O_2$ and θ_F in control subjects ($R = 0.77$, $p < 0.01$); in the patients, in contrast, a second-order curvilinear function better described this relationship (Figure 3A, $R = 0.68$, $p < 0.01$). These findings were also confirmed when peak $\dot{V}O_2$ was expressed as percentage predicted (data not shown). Furthermore, θ_F, as expected, was consistently higher than θ_L in both groups, and a linear relationship between them was found in the control subjects. Interestingly, however, we found no significant relationship between these parameters in the patients ($p > 0.05$) (Figure 3B).

Physiological Determinants of the W–*t* Relationship in Patients

Because a major thrust of this study was to investigate the physiological determinants of the hyperbolic $\dot{W}$–*t* relationship in patients, we therefore considered the variables of interest at the limit of tolerance (i.e., time *t*) at each WR intensity: a summary of these data is shown in Table 3. The individually selected WRs, when expressed as percentage of peak WR attained at the ramp test (*see* METHODS), were slightly higher in patients than in control subjects: this, however, was significant only for the less-intense WR (Table 3). A common finding for the two groups was the striking similarity between the within-group responses at different WRs and between WRs and PEAK. However, both $\dot{V}CO_2$ and R were lower in each group at the less intense WRs. Furthermore, $\dot{V}E$, $\dot{V}E/\dot{V}O_2$, and breathing frequency were an inverse function of *t* in control subjects: this was not the case in patients, however (Table 3). Interestingly, symptoms at *t*, particularly the breathlessness scores, were also remarkably similar at different WRs and between WRs and PEAK (Table 3). In summary, reduced *t* in patients was closely related to higher breathlessness scores, $\dot{V}E_{max}$/MVV ratios (at similar $\dot{V}E/\dot{V}CO_2$), VT/FVC, and PET_{CO_2} values. On the other hand, $\dot{V}E/\dot{V}O_2$, PET_{O_2}, TI and TI/Ttot were all significantly lower in patients ($p < 0.05$) (Table 3).

We also evaluated whether differences in the response kinetics influenced the observed differences in the $\dot{W}$–*t* determinants. The effective time constant values (τ′) for $\dot{V}O_2$ and HR were both larger in patients than in control subjects (76 ± 12 versus 44 ± 15 and 111 ± 26 versus 65 ± 18, respectively, p <

TABLE 3

VARIABLES AT PROGRESSIVELY INTENSE (WR_1 TO WR_4) CONSTANT-LOAD EXERCISE TESTS TO THE LIMIT OF TOLERANCE IN PATIENTS WITH COPD ($n = 8$) AND HEALTHY CONTROL SUBJECTS ($n = 10$)

	Patients				Control Subjects			
Variables	WR_1	WR_2	WR_3	WR_4	WR_1	WR_2	WR_3	WR_4
Power, W	$59 \pm 14^{*,\dagger,\ddagger,\S}$	$67 \pm 9^{\dagger,\ddagger}$	$84 \pm 11^{\ddagger}$	$101 \pm 16^{\dagger,\ddagger}$	$121 \pm 27^{*,\dagger}$	$136 \pm 27^{\dagger}$	156 ± 24	$182 \pm 32^{\dagger}$
Power, % peak	$87.5 \pm 2.3^{\ddagger}$	95.0 ± 7.4	109.3 ± 7.6	120.8 ± 8.8	76.5 ± 3.3	91.6 ± 9.8	102.8 ± 5.7	117.4 ± 5.6
Duration, min	$9.08 \pm 2.11^{\ddagger}$	$5.23 \pm 0.58^{\ddagger}$	$2.58 \pm 0.31^{\ddagger}$	$1.28 \pm 0.27^{\ddagger}$	13.50 ± 2.15	7.19 ± 0.41	4.02 ± 0.36	2.44 ± 0.31
$\dot{V}O_2$, ml/min	$1{,}181 \pm 170^{\ddagger}$	$1{,}178 \pm 161^{\ddagger}$	$1{,}216 \pm 165^{\ddagger}$	$1{,}222 \pm 167^{\ddagger}$	$1{,}854 \pm 323$	$1{,}830 \pm 299$	$1{,}848 \pm 323$	$1{,}859 \pm 315$
$\dot{V}CO_2$, ml/min	$1{,}201 \pm 187^{*,\dagger,\ddagger}$	$1{,}271 \pm 139^{\dagger,\ddagger}$	$1{,}341 \pm 152^{\ddagger}$	$1{,}369 \pm 128^{\ddagger}$	$1{,}877 \pm 334^{*,\dagger}$	$2{,}078 \pm 318^{\dagger}$	$2{,}327 \pm 402$	$2{,}444 \pm 478$
R	$1.03 \pm 0.05^{*}$	$1.08 \pm 0.05^{\ddagger}$	$1.11 \pm 0.06^{\ddagger}$	$1.13 \pm 0.03^{\dagger,\ddagger}$	$1.05 \pm 0.05^{*}$	1.16 ± 0.06	1.29 ± 0.05	$1.37 \pm 0.06^{\dagger}$
HR, bpm	$117 \pm 9^{\ddagger}$	$118 \pm 12^{\ddagger}$	$122 \pm 12^{\ddagger}$	$121 \pm 12^{\ddagger}$	151 ± 9	152 ± 12	151 ± 14	147 ± 13
O_2 pul, ml/b/m	$10.1 \pm 2.0^{\ddagger}$	$10.1 \pm 2.3^{\ddagger}$	$10.3 \pm 1.9^{\ddagger}$	$10.2 \pm 2.1^{\ddagger}$	12.3 ± 1.8	12.1 ± 2.1	12.0 ± 2.1	12.5 ± 2.0
$\dot{V}E$, L/min	$46.9 \pm 7.6^{\ddagger}$	$45.9 \pm 5.2^{\ddagger}$	$47.1 \pm 7.1^{\ddagger}$	$50.4 \pm 8.5^{\ddagger}$	$76.9 \pm 12.1^{*}$	85.1 ± 10.3	$93.1 \pm 11.0^{\dagger}$	$97.7 \pm 10.3^{\dagger}$
$\dot{V}E$/MVV, %	$91.5 \pm 12.6^{\ddagger}$	$91.1 \pm 13.2^{\ddagger}$	$93.3 \pm 14.2^{\ddagger}$	$99.6 \pm 15.2^{\ddagger}$	$57.7 \pm 8.9^{*}$	65.7 ± 11.3	$70.4 \pm 8.7^{\dagger}$	$73.9 \pm 9.5^{\dagger}$
f, bpm	32 ± 7	32 ± 8	34 ± 6	35 ± 7	$31 \pm 8^{*}$	34 ± 6	$37 \pm 7^{\dagger}$	$40 \pm 6^{\dagger}$
VT/FVC	$54.6 \pm 11.5^{\ddagger}$	$55.1 \pm 9.5^{\ddagger}$	$55.5 \pm 8.9^{\ddagger}$	$55.2 \pm 8.3^{\ddagger}$	47.4 ± 7.9	46.9 ± 6.6	46.2 ± 6.7	46.5 ± 8.6
$\dot{V}E/\dot{V}O_2$	$40 \pm 5^{\ddagger}$	$39 \pm 6^{\ddagger}$	$39 \pm 5^{\ddagger}$	$40 \pm 8^{\ddagger}$	$42 \pm 4^{*}$	45 ± 5	48 ± 6	52 ± 5
$\dot{V}E/\dot{V}CO_2$	38 ± 4	36 ± 5	38 ± 4	37 ± 5	40 ± 7	41 ± 9	40 ± 7	40 ± 6
PET_{O_2}, mg Hg	$113 \pm 3^{\ddagger}$	$114 \pm 5^{\ddagger}$	$113 \pm 5^{\ddagger}$	$113 \pm 7^{\ddagger}$	121 ± 6	123 ± 7	123 ± 6	123 ± 6
PET_{CO_2}, mg Hg	$40 \pm 4^{\ddagger}$	$40 \pm 4^{\ddagger}$	$41 \pm 4^{\ddagger}$	$40 \pm 5^{\ddagger}$	30 ± 9	32 ± 6	33 ± 5	32 ± 6
TI/Ttot	$0.37 \pm 0.04^{\ddagger}$	$0.38 \pm 0.03^{\ddagger}$	$0.37 \pm 0.02^{\ddagger}$	$0.37 \pm 0.03^{\ddagger}$	0.47 ± 0.02	0.48 ± 0.02	0.49 ± 0.03	0.49 ± 0.02
TI	$0.73 \pm 0.17^{\ddagger}$	$0.74 \pm 0.09^{\ddagger}$	$0.70 \pm 0.08^{\ddagger}$	$0.66 \pm 0.08^{\ddagger}$	0.88 ± 0.20	0.84 ± 0.09	0.83 ± 0.08	0.86 ± 0.08
Borg BL	$6\ (4–7)^{\ddagger}$	$5\ (3–6)^{\ddagger}$	$5\ (3–6)^{\ddagger}$	$6\ (4–8)^{\ddagger}$	2 (1–3)	3 (1–4)	2 (1–4)	3 (0.5–4)
Borg LE	$4\ (3–5)^{\ddagger}$	$3\ (2–4)^{\ddagger}$	$2\ (1–4)^{\ddagger}$	$2\ (1–3)^{\ddagger}$	7 (6–10)	7 (5–9)	7 (5–10)	8 (7–10)

Definition of abbreviations: BL = breathlessness; COPD = chronic obstructive pulmonary disease; ET = end-tidal partial pressure; f = respiratory rate; FVC = forced vital capacity; HR = heart rate; LE = leg effort; MVV = maximal voluntary ventilation; O_2 pul = oxygen pulse; R = respiratory exchange ratio; TI = inspiratory time; Ttot = total respiratory cycle time; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen uptake; VT = tidal volume; WR = work rate.

* $p < 0.05$: significant difference between work rates within groups.

† $p < 0.05$: significant difference between work rate and peak values (Table 2) within groups.

‡ $p < 0.05$: significant difference between groups within protocols.

§ All values are means ± 1 SD with the exception of Borg scores, which are presented as median and range.

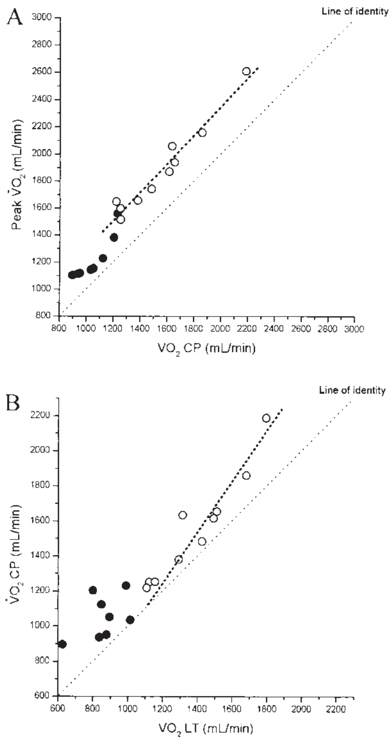

Figure 3. (*A*) An effectively curvilinear relationship was found between oxygen uptake at the critical power ($\dot{V}O_2$ CP) and peak $\dot{V}O_2$ in the patients (*closed circles*). Note that substantial changes in $\dot{V}O_2$ CP in the most severe patients were not reflected in appreciable increases on peak $\dot{V}O_2$. (*B*) $\dot{V}O_2$ CP was consistently higher than $\dot{V}O_2$ at the estimated lactate threshold (LT) in both patients and healthy control subjects (*open circles*). Although a significant linear relationship between these parameters was found in the controls ($r = 0.88$, $p < 0.01$), no relationship was evident in the patients ($r = 0.21$, $p > 0.05$).

0.01), that is, slower metabolic and cardiovascular kinetics in the patients. However, we were able to find no significant between-groups difference in the $\tau'\dot{V}CO_2$ and $\tau'\dot{V}E$ values (97 ± 34 versus 86 ± 25 and 104 ± 26 versus 95 ± 18, respectively, $p > 0.05$). As expected however, we found a very high correlation between $\tau'\dot{V}CO_2$ and $\tau'\dot{V}E$ in both groups ($R = 0.92$, $p < 0.01$). Interestingly, $\tau'\dot{V}O_2$ was significantly related to θ_F (in both absolute and relative values) but only in the control subjects ($R = 0.65$ and 0.71, respectively, $p < 0.05$). On the other hand, no significant relationship was found between $\tau'\dot{V}O_2$ and W′ in either patients or control subjects ($p > 0.05$).

Responses at the Critical Power

As expected from the large difference in the WRs, absolute values for most of the exercise responses at θ_F were typically lower in patients than in control subjects (Table 2). On the other hand, $\dot{V}E$/MVV, VT/FVC, $\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, and R (relative to the peak values) were significantly increased in patients. Interestingly, when the θ_F responses were expressed relative to PEAK, patients typically showed *higher* values compared with control subjects, that is, they were able to perform the 20-min θ_F bout at relatively more intense metabolic, ventilatory, and cardiovascular stresses (Table 2). Furthermore, breathlessness scores were significantly higher and leg effort scores lower in patients (Table 2). Interestingly, although the patients' breathlessness scores at θ_F were systematically below peak values, the peak–θ_F difference was consistently small: in no patient was this difference greater than 2.

DISCUSSION

We have investigated the determinants of endurance capacity to high-intensity, cycle ergometer exercise in a group of nonhypoxemic men with moderate-to-severe chronic obstructive pulmonary disease (COPD). The main original findings of the present study can be summarized as follows: (*1*) The time to the limit of exercise tolerance (*t*) decreased hyperbolically as a function of power output ($\dot{W}$), as shown previously in normal subjects. This was due to decrements in both intercept (critical power, θ_F) and slope (W′) of the linearized $\dot{W}$–*t* relationship. (*2*) The hyperbolic shape of the $\dot{W}$–*t* relationship appeared to be determined by the kinetics of the $\dot{V}E$ response toward a reduced and apparently fixed maximum $\dot{V}E$ ceiling. (*3*) The asymptote θ_F represented the highest power output in which the mechanical ventilatory constraints and the accompanying dyspnea did not limit sustained exercise. On the other hand, W′ (with the units of work) was related to a constant maximum limit of work-related symptoms that a patient was prepared to endure above θ_F, regardless the work rate. (*4*) These findings are consistent with a physiological and subjective threshold for the exercise endurance capacity in patients with COPD (θ_F): this parameter was shown to be unrelated to the estimated lactate threshold (Figure 3B) and typically to occur closer to peak $\dot{V}O_2$ in patients than in control subjects (Figure 1C).

Determinants of the $\dot{W}$–*t* Relationship in Patients with COPD

The most noticeable finding of this study was that ventilatory response dynamics constrained tolerance to long-term, high-intensity exercise in moderately severe, nonhypoxemic older patients with COPD. Endurance time was closely associated with both the ventilatory stress and the resulting sensory experiences. These findings contrast sharply with the large and variable ventilatory reserve at exhaustion time in the control subjects (Figure 2D, *left* and Table 3). In the patients, θ_F represented the highest work rate at which there was sufficient mechanical ventilatory reserve and the resulting dyspnea was still not limiting. However, as the power increased above θ_F, the $\dot{V}E$ ceiling/limiting dyspnea was attained at progressively shorter times, that is, with a faster $\dot{V}E$ response attaining the low ceiling (Figure 2D, *right*). On the other hand, we did not find significant relationships between two important aerobic parameters (θ_L and τ') and θ_F. These findings strongly suggest that cardiovascular and/or peripheral factors do not play a preponderant role in limiting exercise endurance in these patients with moderate-to-severe COPD, at least at higher exercise intensities—except with respect to possible indirect effect contributory to the ventilatory response. Additionally, the evidence for a work rate–endurance hyperbola demonstrated that each patient appeared to have a finite supra-θ_F work capacity whose boundaries were associated with a constant intensity of breathlessness (Table 3). This concept may prove to be useful as it is consistent with the notion that exercise work rate may be "traded" for endurance within the bounds of total capacity.

Responses at the Critical Power

Although all patients were able to sustain θ_F for 20 min, their near-maximum ventilatory stress was maintained at expenses of increased VT/FVC ratio with lower TI/Ttot (Table 2). This tachypneic response might be linked to the deleterious effects of the expiratory flow limitation during exercise and the consequent increase in end-expiratory lung volume (EELV). This leads to progressive dynamic hyperinflation (DH) and a less advantageous respiratory muscle length–tension relationship (18). Although increasing the respiratory rate seems to be the single available alternative, this strategy is disadvantageous in terms of effective alveolar ventilation and ventilatory muscle energetics (by increasing the ratio of transdiaphragmatic pressure to maximum trandisphragmatic pressure [Pdi/Pdi_{max}]). On the other hand, reducing T_I/T_{tot} would minimize the respiratory–muscle tension–time index, which could be theoretically useful in delaying fatigue. It is, however, of note that these altered mechanical responses during the θ_F tests in the patients were not associated with progressive increase in breathlessness (Table 2): evidence that the relationship between them is not linear.

The reduced level of O_2 pulse during the θ_F's test is consistent with lower peripheral O_2 extraction—skeletal muscle dysfunction—and/or reduced stroke volume. The latter might be related to a decrease in venous return and increases in the after load of both ventricles, secondary to progressive DH and consequent higher mean intracycle thoracic pressure (18). Indeed there is recent evidence from posttransplantation studies showing that O_2 pulse improves sooner than expected for possible changes in muscle oxidative capacity (19).

Clinical Significance and Practical Implications

Our results suggest that the critical power concept may have even greater significance for ventilatory-limited patients than for healthy subjects. The severely reduced area under the hyperbolic curve demonstrated that the tolerable duration of exercise fell dramatically above θ_F (Figures 1A and 1B). Importantly, θ_F values in percentage peak WR were higher in patients than controls: W′, however, remained lower in patients (Figure 1C). The peak work rate attained on a ramp-incremental exercise test, however, is an inverse function of work rate incrementation rate. We chose to use this value in our analysis not in the sense that it is a parameter of exercise tolerance (such as peak $\dot{V}O_2$) but that for a "reasonable" ramp rate it provides a sense of the tolerable duration that might be associated with this work rate during constant-load exercise. Interestingly, as shown in Figure 1, this was approximately 3–5 min in both groups. Therefore, patients were able to sustain a higher relative exercise intensity than control subjects although the endurance capacity declined abruptly above θ_F, that is, after the mechanical-ventilatory and subjective "threshold." It is also noteworthy that all patients could sustain for 20 min exercise at the level of critical power with stable $\dot{V}O_2$ and $\dot{V}E$ (Figure 2) without progressive discomfort (Table 2). This power output, therefore, did appear to separate a "sustainable" from a "nonsustainable" intensity with important significance for the patients' functioning.

Dynamic exercise training involving the locomotory muscles has been shown to have a central role in the efficacy of pulmonary rehabilitation programs (2, 20, 21). Casaburi and coworkers (22) and Maltais and coworkers (23), however, reported that the majority of their patients were not able to sustain high-intensity training (80% peak WR) at the start of a pulmonary rehabilitation program; we would interpret this as the subject's WR being supra-θ_F by some unknown amount. This further underscores the importance of siting WR demands within the appropriate intensity domain. In fact, in both studies (22, 23) the patients rapidly increased the tolerable WR throughout the program, that is, a predictable response for even small increases in θ_F.

Another aspect of practical importance concerns the remarkable consistency in the maximal attained dyspnea scores at the limit of tolerance (Table 3). These results suggest that both symptom-guided exercise training might be feasible in moderate-to-severe patients and that the attained degree of exertion is reproducible (24). Interestingly, this is likely to correspond to near-maximum values obtained at the incremental test (Tables 2 and 3).

Limitations of the Study

Although the present study has, we believe, shed light on certain underlying mechanisms of exercise intolerance in patients with COPD, it naturally has limitations. We have estimated the maximum limits of the ventilatory performance using the measured MVV, despite there being several shortcomings in this approach (25). We cannot also extrapolate our findings to all patients with COPD or make assumptions about the limiting factors at the sustainable, sub-θ_F exercise-intensity domain. It is also possible that we have underestimated the role of peripheral factors in limiting exercise tolerance as we did not assess objective evidence of, for example, muscular fatigue (26). We also tended to choose higher relative WRs for the patient' trials (Table 3), probably as an indirect consequence of their higher relative θ_F. These between-group differences, however, are unlikely to have influenced our results as we analyzed the individuals' four-point response, that is, we had a range of relative power outputs for each subject (Figure 1C). In addition, further studies using larger samples are needed to confirm our preliminary findings of a curvilinear peak $\dot{V}O_2$–θ_F relationship.

In conclusion, in nonhypoxemic, moderately severe patients with stable COPD, we have found that the power duration relationship ($\dot{W}$–t) could be characterized by a rectangular hyperbola. The $\dot{W}$–t parameters, the asymptote (θ_F), and the curvature constant (W′) were significantly reduced when compared to age-matched sedentary control subjects. These parameters were closely related to the subject's limiting breathlessness and the available ventilatory reserve. Based on the endurance capacity to a range of constant-load tests, we were able to characterize two important exercise-intensity domains in patients with COPD: "sustainable" and "nonsustainable." Our results warrant further research to evaluate the feasibility of simpler, clinically useful protocols, the behavior of the power–duration relationship in hypoxemic patients with different degrees of respiratory impairment, and the effects of different exercise training strategies on specific determinants of the endurance capacity.

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