Ventilatory and metabolic adaptations to walking and cycling in patients with COPD

PAOLO PALANGE,1 SILVIA FORTE,2 PAOLO ONORATI,1 FELICE MANFREDI,1 PIETRO SERRA,1 AND S. CARLONE1
1Dipartimento di Medicina Clinica, University of Rome “La Sapienza,” and 2Consiglio Nazionale delle Ricerche, 00185 Rome, Italy

Palange, Paolo, Silvia Forte, Paolo Onorati, Felice Manfredi, Pietro Serra, and S. Carlone. Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. J Appl Physiol 88: 1715–1720, 2000.—To test the hypothesis that in chronic obstructive pulmonary disease (COPD) patients the ventilatory and metabolic requirements during cycling and walking exercise are different, paralleling the level of breathlessness, we studied nine patients with moderate to severe, stable COPD. Each subject underwent two exercise protocols: a 1-min incremental cycle ergometer exercise (C) and a “shuttle” walking test (W). Oxygen uptake (V˙O2), CO2 output (V˙CO2), minute ventilation (V˙E), and heart rate (HR) were measured with a portable telemetric system. Venous blood lactates were monitored. Measurements of arterial blood gases and pH were obtained in seven patients. Physiological dead space-tidal volume ratio (VD/VT) was computed. At peak exercise, W vs. C V˙O2, V˙E, and HR values were similar, whereas V˙CO2 (848 ± 69 vs. 1,225 ± 45 ml/min; P < 0.001) and lactate (1.5 ± 0.2 vs. 4.1 ± 0.2 meq/l; P < 0.001) were lower, ∆V˙E/∆V˙CO2 (35.7 ± 1.7 vs. 25.9 ± 1.3; P < 0.001) and ∆HR/∆V˙O2 values (51 ± 3 vs. 40 ± 4; P < 0.05) were significantly higher. Analyses of arterial blood gases at peak exercise revealed higher V˙E/VT and lower arterial partial pressure of oxygen values for W compared with C. In COPD, reduced walking capacity is associated with an excessively high ventilatory demand. Decreased pulmonary gas exchange efficiency and arterial hypoxemia are likely to be responsible for the observed findings.

exercise; chronic obstructive pulmonary disease; pulmonary gas exchange; ventilatory demand

The mechanisms of reduced exercise tolerance in chronic obstructive pulmonary disease (COPD) have been investigated in several laboratories, mostly by analysis of pulmonary gas exchange during cycle ergometer testing. These studies have provided evidence that impairment of muscle energetics, with early onset of anaerobic glycolysis and consequent increase in ventilatory demands, is a major determinant in reducing the ability of these patients to tolerate a physical effort (3, 12). However, data obtained with this approach may not reflect adequately the physiological and metabolic events that come into play during routine daily activities. Patients with severe COPD often exhibit intolerable dyspnea during walking, a light form of exercise that involves both upper and lower extremities. It is likely that during walking the metabolic and ventilatory responses differ from those of cycling, primarily because of differences in recruitment of muscle groups and/or in hemodynamic adaptations. Previous studies (4, 6, 13, 17) have compared ventilatory responses to treadmill and bicycle exercise in COPD patients. To our knowledge, no data are available on the ventilatory and metabolic [e.g., CO2 output (V˙CO2), lactate production] adaptations to walking on flat ground in COPD. The question that remains to be answered is whether, even during walking, the ability of COPD patients to exercise is significantly influenced by poor muscle aerobic capacity.

Data from literature suggest that a reduction in muscle oxidative capacity, not necessarily due to inactivity per se, is present in animals with lung emphysema (14) and in patients with COPD (12). Poor muscle oxidative capacity may contribute significantly to exercise limitation in COPD. Because of central respiratory limitation, however, the full oxidative potential of leg muscle is difficult to assess, particularly during exercise that involves large muscle mass such as cycle ergometry (15).

In a group of patients with moderate to severe COPD, we measured pulmonary gas exchange parameters, blood lactate, and arterial blood gases during maximal walking (W) and cycling (C) exercise. By examining the adaptations to these two types of physical effort, we tested the hypothesis that in COPD patients, in contrast to cycling, in which exercise capacity may be significantly affected by metabolic factors, W ability is likely to be influenced by ventilatory demand, dyspnea sensation, and lung gas exchange efficiency.

MATERIALS AND METHODS

Nine male subjects with moderate to severe, stable chronic airway obstruction and mild hypoxemia were studied. Admission criteria included clinical diagnosis of COPD, forced expiratory volume in 1 s (FEV1) < 50% of predicted, and room air arterial partial pressure of oxygen (Pao₂) > 55 and < 75 Torr. The pertinent clinical and functional characteristics of the subjects are summarized in Table 1. At the time of the study, patients had no sacral or ankle edema and no evidence of cor pulmonale or metabolic, renal, hepatic, or neuromuscular disorders. None of them had received systemic steroids for at least 2 mo before the study. A stable regimen of bronchodilators with oral theophylline, inhaled β2-stimulants, and...
inhaled steroids was maintained throughout the study. The experimental protocol was approved by the Committee for Protection of Human Subjects, University of Rome, according to the Declaration of Helsinki; all subjects signed an informed consent before initiation of the study.

Equipment. Spirometry and arterial blood gases were obtained before each bout of exercise to confirm clinical stability. For C, each subject exercised on an electromagnetically braked cycle ergometer (Bosch, ERG-551), and pulmonary gas exchange indexes were determined breath by breath (Cosmed, Quark b2, Rome, Italy). Patients breathed through a face mask; ventilation was measured with a photoelectric turbine. Gas was drawn from the distal part of the turbine by the use of a special sample capillary of polymer Nafion (Perma Pure); O2 and CO2 concentrations were determined by rapid response analyzers (O2 zirconium, CO2 infrared). Electrocardiogram was monitored continuously at 6 V by a cardioscope heart rate (HR) was derived from R-R intervals; and arterial O2 saturation was monitored throughout the study by pulse oximetry (Biox 3740, Ohmeda). Oxygen uptake (V˙O2, STPD), CO2 output (V˙CO2, STPD), minute ventilation (Ve, BTPS), and respiratory rate were measured for each breath with the use of a computerized system. Corrections for the transport delay from the mouthpiece to the sensors and for the rise time of the analyzers were taken into account (1).

Data were displayed on-line and were also stored on disk for further analyses. During W, a telemetric portable system (Cosmed, K4, Rome, Italy) was utilized for V˙O2, V˙CO2, Ve, and HR measurements. The K4 system consisted of face mask, HR chest strip, battery and transmitting unit (containing the O2 and CO2 gas analyzers), and a receiving unit. The transmitting unit with battery pack and face mask with tubing (total weight 0.8 kg) was attached to the individual with a harness, and the receiving unit was connected to a personal computer anywhere within 700 m of the transmitting unit. The face mask contained a turbine for measurement of ventilation as well as a capillary gas sampling port within the turbine’s housing. The expired gas was sampled at a rate proportional to ventilation, by way of a dynamic sampling pump, through a special sample capillary of polymer Nafion (Perma Pure) and into a microchamber containing the O2 (polargraphic) and CO2 (infrared) electrodes. O2 and CO2 analyzers were thermostated and compensated for the variations of barometric pressure and humidity of the environment. Ve (BTPS), V˙O2 (STPD), and V˙CO2 (STPD) were calculated every 15 s. Calibration of the turbine by use of a 3-liter syringe and a two-point calibration of the gas analyzers by use of gas mixtures from tanks of standard gas were performed before each test.

Before the study, the agreement between the K4 and breath-by-breath systems in assessing pulmonary gas exchange indexes was verified in five healthy subjects at different levels of cycle-ergometer exercise: 1) 1-min incremental (30 W/min) test to exhaustion and 2) moderate constant work rate tests at 25% and 75% of maximal workload achieved during test 1. Subjects performed each protocol twice on both K4 and breath-by-breath systems; for data analysis, the mean value was used. The test order was randomized. Values of V˙O2, V˙CO2, and V˙E did not differ significantly between K4 and breath-by-breath, either at peak or at submaximal level of exercise. The slopes of increments in V˙O2/W (10.4 ± 0.3 vs. 10.5 ± 0.4 ml·W−1·min−1) and V˙E/V˙CO2 (20.2 ± 0.6 vs. 19.7 ± 0.5) during the incremental test were also similar. With the Bland-Altman test (2), the mean V˙O2 difference was −0.5 ml·kg−1·min−1, and the limits of agreement (means ± 2 SD) were +2.1 to −2.9 ml·min−1·kg−1; the biases in V˙CO2 and Ve were comparably small.

Exercise test. Before each test, a polyethylene venous catheter was inserted in a vein of the hand. For lactate measurements, venous blood samples, arterialized with the use of a warm pad, were obtained at rest and during the first 15 s of recovery from maximal W and C. Lactate was measured in duplicate immediately after sampling with an upgraded analyzer (2300, glucose-lactate analyzer, Yellow Springs Instruments, Yellow Springs, OH).

For W, after three practice sections performed within 10 days, a 1-min incremental modified "shuttle" walking test to volitional fatigue was performed. As originally described by Singh and co-workers (16), the modified shuttle test was performed in an enclosed corridor on a 10-m-long course identified by two cones inset 0.5 m from either end to avoid the need for abrupt changes in direction. The speed at which patients walked was dictated by an audiosignal played on a tape cassette originally generated from a microcomputer. The start of the test was indicated by a single beep. Thereafter the tape emitted a single beep at regular intervals at which point the subject attempted to be at the opposite end of the course, that is, by the time the patient heard the signal he should be turning round the cone to proceed back down the course. The initial walking speed was set at 0.50 m/s; subsequently the speed was increased each minute by 0.17 m/s. A change of speed to the next level was indicated by a single beep. The operator sat alongside the course and gave no encouragement; the only verbal contact was the advice given each minute to increase the walking speed slowly. The test was stopped when the patient was not able to maintain the required speed.

For C, a 1-min incremental exercise test was performed. After 3 min of rest and 2 min of unloaded pedaling, workload was increased (5 W/min) until exhaustion, i.e., the point when patients could no longer keep the pedaling frequency of 50 rpm. The interval between tests was 24–48 h and the order was randomized. Ve, HR, V˙O2, and V˙CO2 were calculated every 15 s. Other variables obtained were respiratory exchange ratio (RER) = V˙CO2/V˙O2; O2 pulse (in ml/beat) = V˙O2/HR; HR reserve (HRr, bpm) = (220 − age) − HRmax and breathing reserve (BR, in l/min) = (FEV1 × 40) − Ve max. At the end of the exercise, patients were asked to estimate the degree of breathlessness and leg fatigue by using a visual scale (10).

Seven of the nine patients agreed to be reevaluated with an identical exercise protocol; W and C tests were performed in random order. Spirometry and arterial blood gases were repeated before each bout of exercise to confirm clinical stability. Pulmonary gas exchange measurements were obtained by the telemetric system previously described. Arterial samples for measurement of lactate, PaO2, arterial partial pressure of CO2 (PaCO2), and pH were obtained at rest and during the last 15 s of exercise. Before each exercise test, a catheter was inserted into the brachial artery of the nondominant arm. The catheter was flushed with a heparinized saline solution. To avoid spuriously dilution, 2 ml of blood was
discarded before collection of arterial samples. Lactate, \( P_{O_2} \), and \( P_{CO_2} \) were measured in duplicate immediately after sampling with upgraded analyzers (2300 glucose-lactate analyzer, Yellow Springs Instruments; IL 1640, Lexington, MA). During the last 15 s of W, one investigator walked at the patient’s side; arterial sampling was obtained without interfering with arm movements. The physiological dead space/tidal volume ratio (\( V_{D}/V_{T} \)), an index of lung gas exchange efficiency, was calculated by using the formula (19)

\[
V_{D}/V_{T} = 1 - (V_{CO_2}/V_{E} \times 863/P_{ACO_2}, \text{Torr})
\]

Statistical analyses. Group data are presented as mean values ± SE. Differences among measured parameters were determined by paired t-test. Pearson’s product-moment correlation coefficient (R) was used to detect correlations between criterion variables. The level of statistical significance was set at *P* < 0.05.

**RESULTS**

Under the two experimental conditions, W and C, the duration of exercise was comparable (6.1 ± 0.4 vs. 6.4 ± 0.3 min). The maximal power output during C was 69 ± 3 W. During W, maximal speed achieved was 1.3 ± 0.1 m/s. HRR and BR were similar. Maximal aerobic capacity (Table 2) during W and C was uniformly reduced as shown by the low \( V_{O_2} \) peak values; \( V_{E} \), HR, and RER values were not statistically different. By contrast, during W the following variables were different vs. during C: 1) lactate, \( V_{CO_2} \), and RER levels were lower, suggesting a reduced contribution of nonaerobic metabolism to energy generation, i.e., anaerobic glycolysis; 2) the slopes of \( \Delta V_{E}/\Delta V_{CO_2} \) and \( \Delta H_{R}/\Delta V_{O_2} \) were higher; and 3) degree of breathlessness was greater, whereas level of leg discomfort was smaller.

Figure 1 shows the \( V_{E}/V_{CO_2} \) and the HR/\( V_{O_2} \) responses during exercise for a representative COPD patient. The rates of increase of \( V_{E}/V_{CO_2} \) and of HR/\( V_{O_2} \) were higher during W than during C. The mean values of \( V_{E}/V_{CO_2} \) and HR/\( V_{O_2} \) slopes, calculated in each individual patient by linear regression analysis, were significantly higher, W vs. C: \( V_{E}/V_{CO_2}, y = 5 + 36x \) vs. \( y = 7 + 26x \) (t = 4.72, P < 0.001); HR/\( V_{O_2} \), \( y = 70 + 51x \) vs. \( y = 71 + 40x \) (t = 2.16, P < 0.05).

\( V_{E}/V_{CO_2} \) values, arterial blood parameters, and \( V_{D}/V_{T} \) values, obtained at peak exercise in seven patients, are presented in Table 3. During W, higher \( V_{E}/V_{CO_2} \) values were observed. In addition, \( V_{D}/V_{T} \) and pH values were higher whereas \( P_{O_2} \), values were lower during W than during C. Mean \( V_{E}, V_{O_2}, V_{CO_2} \), and RER values, not shown in the table, were not different from those observed in the previous tests (Table 2).

**DISCUSSION**

The most important finding of this study on COPD patients is the more pronounced \( V_{E}/V_{CO_2} \) response during W compared with C; this difference could not be accounted for by a larger contribution of anaerobic glycolysis to energy production (i.e., lactate levels were lower with W), whereas it was associated with a worsening in lung gas exchange efficiency (i.e., higher \( V_{D}/V_{T} \) and lower \( P_{O_2} \) with W). During W, compared with during C, despite a lower power output estimated from speed and weight (52 ± 3 vs. 69 ± 3 W), lower \( V_{CO_2} \), and a much smaller lactate elevation, the \( V_{E} \) increment was similar. In addition, the \( \Delta V_{E}/\Delta V_{CO_2} \) slope for W was steeper than the slope for C.

Two alternative explanations for the observed increased ventilatory response during W in COPD, individually or in combination (with or without a cause-effect interrelationship), are to be considered. First, decreased lung gas exchange efficiency and hypoxemia lead to increased ventilatory response; this in turn may be due to a larger V/Q mismatch from...
differences in body posture (gravitational effects on respiratory muscle, primarily the diaphragm), functional residual capacity, and/or pulmonary hemodynamics. Our findings of higher VD/VT and lower PaO2 during W strongly support this hypothesis. Ventilation during exercise depends on an interaction among V˙CO2, PaCO2, W strongly support this hypothesis. Ventilation during COPD may show increased ventilation because of the degree of V˙/Q˙ mismatching and wasted ventilation, be hypothesized, including the hypoxic ventilatory drive. COPD patients to hyperventilate the presence of high arterial Pa CO2, may explain, at least in part, the increased ventilatory demand. What drives COPD patients to hyperventilate during exercise is not clear. Several mechanisms may be hypothesized, including the hypoxic ventilatory stimulus. In the present study, the increased ventilatory demand observed during W was related to a very low gas exchange efficiency, as reflected by high VD/VT values. Even at rest patients with COPD may show increased ventilation because of the presence of V/Q mismatching. An above-normal level of ventilation is required to maintain normal PaO2 levels. At peak exercise our patients experienced similar degrees of CO2 retention during both W and C, indicating that the increase in ventilation was not able to compensate for the V/Q mismatching; also, the lower VCO2 at peak W in the presence of a similar degree of CO2 retention and lower lactate levels, is consistent with a smaller contribution of nonaerobic CO2 production. What drives COPD patients to hyperventilate during exercise is not clear. Several mechanisms may be hypothesized, including the hypoxic ventilatory stimulus. In the present study, as the result of high degree of V/Q mismatching and wasted ventilation, during W patients showed lower PaO2 values that, in the presence of high arterial PaCO2, may explain, at least in part, the increased ventilatory demand. What can be reasonably excluded is a significant contribution of lactic acidosis.

Another explanation for the increased ventilatory response during W could be an increased neurogenic afferent to the respiratory centers, pulmonary vagal mechanoreceptors from the extremities (5), and neurogenic stimuli (9). During W the arm muscles are active and may be the source of reflex impulses to the respiratory centers; in about 50% of the COPD patients studied by Celli et al. (4) and Delgado et al. (6), breathing was dysynchronous (i.e., contraction of accessory muscles was not synchronous with diaphragmatic contraction) and dyspnea was the major factor limiting the effort duration. By contrast, during C the arms remain in a fixed position and are a less likely potential source of ventilatory stimulation via neurogenic reflexes, and limitation to effort is usually due to leg fatigue (10). In our study, we have no data on intensity of neurogenic afferent; thus any comment in this regard would be purely hypothetical. The only possible speculation, suggested by the higher ΔHR/ΔVO2, is that during W the component of neurogenic hyperpnea was larger.

The greater lactate and the higher VCO2 responses during C, compared with W, are likely to be due to differences in the muscle mass and types of fibers recruited during the two types of exercise. During C the external work is performed by a smaller muscle mass; this implies that each individual muscle fiber has to perform more work and that its oxidative machinery is overwhelmed with greater lactate production. Moreover, because contracting muscles may degrade lactate, it is also possible that more lactate was removed during W. The fact that VO2 levels were similar at peak W and C can be partially explained by the high O2 cost of ventilation experienced by COPD patients (11); it is likely that during W, because of the high ventilatory demand and greater involvement of the trunk, the O2 cost of each liter of ventilation was also increased.

Previous work on walking in patients with COPD is limited to simple physiological measurements. In most instances, the investigators were attempting to establish the optimal duration and type of ambulation, with and without the observer's encouragement. After an initial wave of enthusiasm for walking tests in assessing functional exercise capacity, interest in this methodology declined because several laboratories failed to establish significant correlations between distance covered and resting routine physiological indexes. There are few reports in the literature contrasting ventilatory and metabolic adaptations to W vs. C in COPD patients. Swinburn and co-workers (17) compared the cardiorespiratory responses to 12-min walking tests and to cycle ergometer exercise in a group of patients with severe COPD. Similarly to our study, they found no significant differences in peak Ve and peak VO2 for the two types of exercise. The device they used to measure pulmonary gas exchange, however, did not

### Table 3. Gas exchange and arterial blood gas parameters at peak exercise

<table>
<thead>
<tr>
<th>Subject</th>
<th>V˙E/V˙CO2</th>
<th>PaO2, Torr</th>
<th>PaCO2, Torr</th>
<th>pH</th>
<th>V˙O2/VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>W</td>
<td>C</td>
<td>W</td>
<td>C</td>
<td>W</td>
</tr>
<tr>
<td>1</td>
<td>33.0</td>
<td>38.7</td>
<td>61</td>
<td>56</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>31.5</td>
<td>35.3</td>
<td>68</td>
<td>60</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>31.1</td>
<td>39.4</td>
<td>69</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>28.4</td>
<td>32.6</td>
<td>69</td>
<td>60</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>29.3</td>
<td>47.5</td>
<td>65</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>32.0</td>
<td>35.1</td>
<td>58</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>34.2</td>
<td>40.1</td>
<td>65</td>
<td>60</td>
<td>42</td>
</tr>
</tbody>
</table>

Values are for individual subjects; n = 7. V˙E/V˙CO2, physiological deadspace-tidal volume ratio. *P < 0.05; †P < 0.01.
allow them to measure $\dot{V}CO_2$ and RER. Errors in $\dot{V}O_2$ calculations may also have been incurred because, with $\dot{V}CO_2$ not measured, the Haldane correction could not be applied. Di Prampero and co-workers (7) compared $\dot{V}O_2$ responses and changes in blood lactate ($\Delta$ lactate) in normal individuals during constant-load bouts of cycling exercise and square-wave stepping, which, to a slight extent, is similar to walking. With cycling, they observed that $\Delta$ lactate was greater than with stepping. The authors postulated that the larger $\Delta$ lactate was due to different specific patterns of muscle fiber recruitment, static vs. dynamic components of muscle contraction, and/or muscle perfusion. The relevance of these findings to our investigation is limited because the subjects were normal and walking was replaced by stepping. Guyatt and co-workers (8) reported a correlation of low magnitude between walking-test scores and data from maximal exercise on a cycle ergometer in patients with chronic lung disease and heart failure; they implied that lack of a close correlation should not be surprising because walking assesses a patient’s ability to undertake the activities of day-to-day life whereas cycling is not a common physical effort. In a recent paper (13), the effects of walking and cycling were investigated. The response patterns of $\dot{V}O_2$ peak and blood lactate were similar to ours; valid comparisons between the two reports cannot be made because that study contrasted cycling exercise with graded constant speed treadmill exercise, a physical effort that is functionally quite different from that of walking on level ground.

In the first part of our study, a breath-by-breath apparatus for $\dot{V}O_2$ and a telemetric system for $\dot{V}CO_2$ were used. This was done because we wanted to characterize pulmonary gas exchange responses precisely, and to this end the breath-by-breath approach is uniformly considered the gold standard. To eliminate the possible errors introduced by the use of two different techniques for measuring pulmonary gas exchange, a validation study was conducted. The validation experiments for the telemetric equipment demonstrated very small biases in gas exchange measurements. To minimize errors the following precautions were taken: the turbine was the same for the two sets of equipment, gas analyzers were calibrated with the same tanks before each test, and calibrations were verified at the end of each experiment. In the second part of experiments, when arterial blood measurements were obtained, only the telemetric system was used for both $\dot{V}O_2$ and $\dot{V}CO_2$.

In summary, our study showed that, in patients with moderate to severe COPD, maximal aerobic capacity is markedly reduced. More importantly, we were able to demonstrate that with $\dot{W}$ the ventilatory demand was greater than with $\dot{C}$; this finding can be explained, at least in part, by a larger degree of lung gas exchange inefficiency (i.e., higher $V_{D}/V_{T}$) likely to be due to differences in body posture, functional residual capacity, and/or hemodynamics. By contrast, metabolic differences as reflected by blood lactate concentration did not explain the observed findings; during $\dot{W}$, blood lactate levels were lower and pH values higher. The increased ventilatory demand during $\dot{W}$ may also be related to differences in muscle groups recruited and/or inequalities in neurogenic afferent from the lung or from the exercising limbs. Whatever the mechanisms of the increased ventilatory demand are, in COPD patients the ability to walk seems to be primarily affected by the ventilatory restraint. As a clinical corollary to our findings, it should be kept in mind that the information obtained in COPD patients during cycling may not reflect precisely their ventilatory and metabolic requirements for daily activities such as walking. Because the shuttle walking test evokes a maximal response in cardiopulmonary indexes, it also seems inappropriate for evaluating the level of daily activity in COPD patients.

Address for reprint requests and other correspondence: P. Palange, Dipartimento di Medicina Clinica, Viale dell’Università 37, 00185 Rome, Italy (E-mail: palange@uniroma1.it).

Received 26 June 1998; accepted in final form 10 January 2000.

REFERENCES


