Limitation of lower limb \( \dot{V}O_2 \) during cycling exercise in COPD patients

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Limitation of lower limb \( \dot{V}O_2 \) during cycling exercise in COPD patients. J Appl Physiol 90: 1013–1019, 2001.—Patients with chronic obstructive pulmonary disease (COPD) usually stop exercise before reaching physiological limits in terms of \( \dot{V}O_2 \) delivery and extraction. A plateau in lower limb \( \dot{O}_2 \) uptake (\( \dot{V}O_2 \)) and blood flow occurs despite progression of the imposed workload during cycling in some patients with COPD, suggesting that maximal capacity to transport \( \dot{O}_2 \) had been reached and that it had been extracted in the peripheral exercising muscles. This study addresses this observation. Symptom-limited incremental cycle exercise was performed by 14 men \([62 \pm 11 (SD) \text{ yr}] \) with severe COPD (forced expiratory volume in 1 s \( = 35 \pm 7\% \) of predicted value). Leg blood flow was measured at each exercise step with a thermodilution catheter inserted in the femoral vein. This value was multiplied by two to account for both working legs (\( Q_{\text{LEGS}} \)). Arterial and femoral venous blood was sampled at each exercise step to measure blood gases. Leg \( \dot{O}_2 \) consumption (\( \dot{V}O_{2\text{LEGS}} \)) was calculated from the Fick equation. Total body \( \dot{V}O_2 \) (\( \dot{V}O_{2\text{TOT}} \)) was measured from expired gas analysis, and tidal volume (\( V_T \)) and minute ventilation (\( V_E \)) were derived from the flow signal. In eight patients, \( \dot{V}O_{2\text{LEGS}} \) kept increasing in parallel with \( \dot{V}O_{2\text{TOT}} \) as external work rate was increasing. In six subjects, a plateau in \( \dot{V}O_{2\text{LEGS}} \) and \( Q_{\text{LEGS}} \) occurred during exercise (increment of \( <3\% \) between 2 consecutive increasing workloads) despite the increase in workload and \( \dot{V}O_{2\text{TOT}} \) [corresponding mean was \( 110 \pm 38 \text{ ml (11 \pm 4\%)} \)]. These six patients also exhibited a plateau in \( \dot{O}_2 \) extraction during exercise. Peak exercise work rate was higher in the eight patients without a plateau than in the six with a plateau (\( 51 \pm 10 \text{ vs. } 40 \pm 13 \text{ W, } P = 0.043 \)). \( V_T, V_E, \) and dyspnea were significantly greater at submaximal exercise in patients of the plateau group compared with those of the nonplateau group. These results show that, in some patients with COPD, blood flow directed to peripheral muscles and \( \dot{O}_2 \) extraction during exercise may be limited. We speculate that redistribution of cardiac output and \( \dot{O}_2 \) from the lower limb exercising muscles to the ventilatory muscles is a possible mechanism.

METHODS

Patient Populations

Fourteen men with severe COPD volunteered to participate in this study. Only one of these patients participated in our previous investigation of the hemodynamic response of the lower limb during exercise in COPD (16). The diagnosis of COPD was based on current or past smoking history, clinical evaluation, and pulmonary function tests (1). To improve the homogeneity of this group of patients, other inclusion criteria included resting arterial \( \dot{P}O_2 \) (\( \dot{P}A_2 \)) above 60 Torr and body weight between 90 and 110\% of ideal body weight. Subjects were stable at the time of the study, and none suffered from other significant medical conditions that could limit their performance.
capacity to perform an exercise test. No patients were taking systemic corticosteroids or were involved in a regular exercise training program. All but one patient were retired, and none reported heavy recreational activity. The research protocol was approved by the institutional ethics committee, and a written consent form was obtained from each patient.

Protocol

Catheter placements and leg blood flow measurements. Single-leg blood flow \( (Q_{\text{LEGS}}) \) was measured with a thermodilution catheter (model 93 A-105-5F, Edwards Laboratory, Santa Ana, CA) as previously described and used in this laboratory (16, 24, 25). After the right groin was shaved, disinfected, and anesthetized with lidocaine, the catheter was inserted in the femoral vein 2 cm below the inguinal ligament with the distal thermostip tip positioned 10–12 cm above the inguinal ligament in the external iliac vein. The catheter was interfaced with a Gould Statham SP 1435 cardic output computer (Oxnard, CA), and boluses of 1–5 ml of room temperature saline were injected to obtain two to four flow measurements at rest and during each exercise step. Thermodilution curves were displayed on the Gould recorder to ensure a monophasic curve with an exponential decay. The validity and reproducibility of the \( Q_{\text{LEGS}} \) measurements, using this equipment and methodology, have been previously evaluated by Sullivan et al. (24, 25). In these studies, a close relation \( (r = 0.98, P < 0.01) \) was found between thermodilution flow measured with this catheter system and simultaneous paired electromagnetic flow probe measurements in a perfused canine preparation (24). The variability of this measurement in healthy subjects and in patients with heart failure in whom duplicate submaximal exercise tests were performed was 16 ± 9% (25). To sample the femoral venous blood, an indwelling catheter was also inserted in the right femoral vein 1 cm below the thermodilution catheter. Finally, a cannula was placed in a radial artery.

Exercise test. Subjects were seated on an electrically braked ergocycle and connected to a gas-analysis system through a mouthpiece. This gas-analysis system consisted of a pneumotachograph, \( O_2 \) and \( CO_2 \) analyzers, and a mixing chamber (Quinton QMC, Quinton, Bothell, WA). After subjects rested for 5 min, a progressive and symptom-limited stepwise exercise test, with room air breathing and starting at a work rate of 10 W, was performed. Each exercise step lasted 3 min, and increments of 10 W were used. At rest and during exercise, five-breath averages of \( V_o_2 \) and minute ventilation \( (V_E) \) were obtained, and respiratory rate \( (R_R) \) and tidal volume \( (V_T) \) were derived from the flow signal. Dyspnea and leg fatigue perception were rated during the last minute of each exercise step using the Borg 10-point scale (3). \( Q_{\text{LEGS}} \) measurements were obtained during the second minute of each exercise step; the arterial and femoral blood were sampled during the last minute. Because \( Q_{\text{LEGS}} \) measurements were obtained before blood sampling and probably before a steady state was reached, a small error in leg \( V_o_2 \) calculation can be expected. Our laboratory has previously estimated that this may lead to an \( \approx 5\% \) underestimation in leg \( V_o_2 \) (16). Blood samples were placed in iced water until the end of the exercise test and processed within 30 min of withdrawal. Blood pressure was measured from the arm that was not cannulated during the last minute of each exercise step using an automated stress-testing blood pressure monitor (Quinton Q412).

Arterial and venous \( P_o_2, P_c_o_2, \) and \( pH \) were measured with a blood-gas machine (AVL 995, AVL Scientific, Roswell, GA), and \( O_2 \) saturation was measured with a CO-oximeter (OSM2 Hemoximeter, Radiometer, Copenhagen, Denmark). Blood-gas values were taken at 37°C. After blood was centrifuged at room temperature, plasmatic lactate concentrations were determined with an enzymatic technique (Kit lactate, Boehringer Mannheim, Mannheim, Germany).

Calculation. The alveolar-arterial \( P_o_2 \) difference (\( A-D_o_2 \)) was calculated with the following formula \( (P_a - P_h_o - F_i_o) - P_c_o_2 / RER, \) where \( P_a \) is barometric pressure, \( P_h_o \) is water vapor pressure, \( P_c_o_2 \) is arterial \( P_c_o_2, \) and \( RER \) is respiratory exchange ratio. Arterial and venous \( O_2 \) contents \( (C_{ao_2} \) and \( C_{f_v o_2} \) respectively) were calculated with the following formula: \( 1.39 \times H_b \times X_o_2 + 0.003 \times P_o_2, \) \( Q_{\text{LEGS}} \) measurements were multiplied by two to account for both exercising legs \( (Q_{\text{LEGS}}). \) Leg \( V_o_2 \) \( (V_o_2_{\text{LEGS}}) \) was calculated from the arterial-femoral venous \( O_2 \) content difference \( (C_{ao_2} - C_{f_v o_2}) \) multiplied by \( Q_{\text{LEGS}} \) (Pick principle). The leg \( O_2 \) extraction ratio was calculated from \( C_{ao_2} \) divided by the difference between \( C_{ao_2} \) and \( C_{f_v o_2}. \) Leg vascular resistance was calculated as the ratio of mean blood pressure to \( Q_{\text{LEGS}}. \)

Statistical Analysis

Results are expressed as means ± SD. The predicted values used for spirometry, lung volume, and lung CO-diffusing capacity are those of Knudson et al. (13), Goldman and Becklake (7), and Cotes and Hall (5), respectively. The maximal voluntary ventilation (MVV) was estimated by multiplying forced expiratory volume in 1 s (FEV) by 35 (4). A plateau in \( Q_{\text{LEGS}} \) and \( V_o_2_{\text{LEGS}} \) during exercise was defined a priori by an increment of <3% between two consecutive workloads (17). Changes in \( V_o_2_{\text{LEGS}}, Q_{\text{LEGS}} \), and \( C_{ao_2}-C_{f_v o_2} \) during the course of the exercise were compared between patients with and without a plateau in \( V_o_2_{\text{LEGS}} \) using profile analysis (23). Resting and exercise characteristics of patients with and without a plateau in their \( V_o_2_{\text{LEGS}} \) were compared using unpaired two-tailed Student’s t-tests.

RESULTS

Patient Characteristics

Patient characteristics are presented in Table 1. On average, they had a normal body mass index (20–25 kg/m²), severe airflow obstruction with an FEV1 of 35 ± 7% of predicted, slight reduction in \( P_a o_2, \) and normal resting \( P_c o_2. \) Each subject completed a symptom-limited incremental exercise test with peak power output ranging from 30 to 70 W. All subjects had classical evidence of ventilatory and gas-exchange limitation at peak exercise such as peak \( V_E/o_MVV \) ratio (peak \( V_E/MVV \) > 1 (1.04 ± 0.25)), arterial \( O_2 \) desaturation (change in arterial \( O_2 \) saturation from rest to peak exercise of −5 ± 4%), and \( CO_2 \) retention (\( \Delta P_a c_o_2 \) from rest to peak exercise of +6 ± 4 Torr).

\( V_o_2_{\text{LEGS}} \) and Total Body \( V_o_2 \)

In 6 of the 14 subjects, a plateau in \( V_o_2_{\text{LEGS}} \) was found (Fig. 1). In these subjects, the changes in \( V_o_2_{\text{LEGS}} \) between peak exercise and the immediately preceding workload was −9 ± 9%. The remaining eight patients demonstrated a 24 ± 10% increase in \( V_o_2_{\text{LEGS}} \) between peak exercise and the immediately preceding workload.
The average time courses of changes in total body \( \dot{V}O_2 (\dot{V}O_{2TOT}) \), \( \dot{V}O_2LEGS \), \( Q_{LEGS} \), and \( CaO_2-CrFvO_2 \) during exercise for patients with and without a plateau in \( \dot{V}O_{2LEGS} \) are provided in Fig. 2. As can be seen in the plateau group, \( \dot{V}O_{2TOT} \) was still increasing ([mean \( \Delta \dot{V}O_{2TOT} \) between the last two workloads = 110 \( \pm \) 38 ml (11 \( \pm \) 4\%)]) despite the occurrence of a plateau in \( \dot{V}O_{2LEGS} \). The time course of change in \( \dot{V}O_{2TOT} \) during exercise was similar between the two groups, with no evidence of a plateau. Peak \( \dot{V}O_{2TOT} \) achieved in both groups of patients was not statistically different (0.99 \( \pm \) 0.19 vs. 0.96 \( \pm \) 0.17 l/min in the plateau group and the nonplateau group, respectively). In contrast, the time courses of changes in \( \dot{V}O_{2LEGS}, Q_{LEGS} \), and \( CaO_2-CrFvO_2 \) during exercise were significantly different between the two groups as indicated by the profile analysis (\( P = 0.001 \)). As expected, the plateau in \( \dot{V}O_{2LEGS} \) (Fig. 2A) was accompanied by a corresponding phenomenon in \( Q_{LEGS} \) (Fig. 2C) and in \( CaO_2-CrFvO_2 \) (Fig. 2E). The \( O_2 \) extraction ratio also plateaued in the plateau group to reach 68 \( \pm \) 12\%, whereas it increased progressively throughout the exercise period in the nonplateau group up to a value of 75 \( \pm \) 9\% (\( P > 0.05 \)).

Comparison Between the Plateau and Nonplateau Group

Peak workload achieved was greater in the nonplateau group than in the plateau group (51 \( \pm \) 10 vs. 40 \( \pm \) 13 W, \( P = 0.043 \)) (Table 2). Work efficiency was significantly different between the two groups with a higher \( \Delta \dot{V}O_{2TOT} \)-to-\( \Delta \)work rate ratio in the plateau group (17.1 \( \pm \) 3.6 ml O\(_2\)/W) compared with the nonplateau group (12.9 \( \pm \) 2.7 ml O\(_2\)/W, \( P = 0.029 \)). At peak exercise, the \( \dot{V}O_{2LEGS} \)-to-\( \dot{V}O_{2TOT} \) ratio was significantly lower in the plateau group than in the nonplateau group, averaging 52 \( \pm \) 21\% and 72 \( \pm \) 10\%, respectively (\( P = 0.040 \)).

Patients of the two groups could not be differentiated on the basis of their pulmonary function, blood gases, and Hb concentration (Table 1). Body mass index and resting \( A-aD O_2 \) were smaller in patients of the nonplateau group compared with those of the plateau group (\( P = 0.037 \) and 0.033, respectively). \( Q_{LEGS} \) and \( CaO_2-CrFvO_2 \) tended to be greater at peak exercise in the nonplateau group (Table 2). As a result, peak \( \dot{V}O_{2LEGS} \) was significantly greater in the nonplateau group than in the plateau group (\( P = 0.036 \)). Leg vascular resistance at peak exercise was higher in the plateau group than in the nonplateau group (\( P = 0.044 \)). Both groups experienced similar degrees of exercise-induced arterial \( O_2 \) desaturation, \( CO_2 \) retention, and acidosis. The time courses of changes in breathing pattern, symptom scores, and heart rate during exercise for both groups are shown in Fig. 3. \( V_T, V_e \), and dyspnea were significantly greater at submaximal exercise in patients of the plateau group compared with those of the nonplateau group. These values were similar at peak exercise in both groups. The changes in RR and heart rate during exercise were similar for the two groups.

**DISCUSSION**

In this study, two behaviors of the \( \dot{V}O_{2LEGS} \)-work rate relationship were found during cycling exercise in patients with COPD. In one subgroup of patients, \( \dot{V}O_{2LEGS} \) kept progressing in a parallel fashion to \( \dot{V}O_{2TOT} \), whereas external work rate was increasing. In other patients, a plateau in \( \dot{V}O_{2LEGS} \) occurred despite the progression in \( \dot{V}O_{2TOT} \) and work rate. As expected from the Fick principle, this plateau in \( \dot{V}O_{2LEGS} \) was accompanied by a leveling off in \( Q_{LEGS} \) and in \( CaO_2-CrFvO_2 \). These results indicate that, despite evidences of ventilatory limitation, some patients with COPD exhaust their maximal ability to transport and extract \( O_2 \) in the peripheral muscles during whole body cycling exercise. Furthermore, these limitations may have detrimental effects on exercise tolerance, as indicated by the lower work capacity in the plateau group compared with the nonplateau group despite similar peak \( \dot{V}O_{2TOT} \) between the two groups. Thus, work efficiency was lower in patients of the plateau group.

In patients exhibiting a plateau in \( \dot{V}O_{2LEGS} \), the increase in \( \dot{V}O_{2TOT} \) toward end-exercise values could...
only be explained by an increase in metabolic activity outside the legs. If we assume that total cardiac output did not plateau, the only remaining physiological explanation for the plateau in \( \dot{V}O_2 \) and in \( \dot{Q}_{LEGS} \) relations obtained in the group demonstrating (left) or not demonstrating (right) a plateau in \( \dot{V}O_2 \). \( \dot{V}O_2 \) content difference (Ca\(_{O_2}\)-Cv\(_{O_2}\) )-work rate (E and F) relationships obtained in the group demonstrating (left) or not demonstrating (right) a plateau in \( \dot{V}O_2 \).

Such a redistribution of blood flow between the lower limb and respiratory muscles has been elegantly documented in elite athletes (\( \dot{V}O_2 \)TOT = 64 ± 6 ml·kg\(^{-1}\)·min\(^{-1}\)) by Harms and colleagues (8, 9). By manipulating the work of breathing during near maximal exercise, these authors provided strong evidence that, in elite athletes, cardiac output can be redistributed between the exercising peripheral muscles and the ventilatory muscles. Accordingly, we speculate that the most likely candidates for the possible blood flow redistribution in our patients are the respiratory muscles, with \( \dot{V}O_2 \) during exercise that might be sufficiently high in severe COPD to compete with the lower limb muscles for the available blood flow and \( O_2 \) (15). Because each patient had severe airflow obstruction, why then did only 6 of 14 patients exhibit a plateau in \( \dot{V}O_2 \)? A potential explanation is that there was a marked difference in work of breathing between the two groups as suggested by the greater VT, VE, and dyspnea at submaximal exercise intensity in patients of the plateau group compared with those of the non-plateau group. This supports the idea that work of breathing and presumably \( O_2 \) and blood flow requirements of the ventilatory muscles might have differed considerably between the two groups.

To provide a stronger conclusion on the concept of blood flow redistribution, it would have been necessary to measure and compare work of breathing between the two groups of patients and to evaluate the effects of changing work of breathing (with noninvasive ventilatory assistance for instance) on \( \dot{Q}_{LEGS} \) and the \( \dot{V}O_2 \) work rate relationship during exercise (8).
our data interpretation is correct, an increase in $Q_{LEGS}$ in patients of the plateau group should occur with respiratory muscle unloading. Richardson and colleagues (19) recently evaluated the effects of the respiratory muscle unloading in COPD patients who breathed a helium mixture during whole body cycling exercise (high ventilatory requirement) and single-knee extension exercise (low ventilatory requirement). Consistent with the concept of blood flow redistribution, they found that breathing the helium mixture was associated with higher peak $V\dot{O}_2$ only during whole body cycling exercise. Breathing a helium mixture during single-knee extension exercise did not improve peak $V\dot{O}_2$ presumably because the maximum ventilation and the demand placed on the respiratory muscles were lower during this exercise modality, therefore reducing the potential of blood flow redistribution from the respiratory to the knee-extensor muscles.

The mechanisms through which blood flow and $O_2$ could be distributed preferentially to respiratory muscles or other muscles and not to peripheral muscles were not explored in the present study. It has been suggested that the diaphragm and other respiratory muscles may have a greater potential for exercise-induced vasodilatation compared with peripheral muscles because of their higher oxidative capacity (14). It has also been shown that increased respiratory muscle activity may increase systemic sympathetic activity, causing peripheral vasoconstriction at peak exercise.

![Figure 3](image-url)

**Fig. 3.** Respiratory rate (RR; A), tidal volume (VT; B), minute ventilation (VE; C), dyspnea (D), leg fatigue scores (E), and heart rate (F) at rest (R) and during submaximal (open symbols) and peak (solid symbols) exercise in patients of the plateau group (open and solid circles) and those of the nonplateau group (open and solid squares). Peak exercise values for all these parameters were similar in both groups. VT, VE, and dyspnea were significantly greater at submaximal exercise in patients of the plateau group compared with those of the nonplateau group. The changes in RR and heart rate during exercise were similar for the 2 groups. The exact $P$ values of the comparisons that reached statistical significance are provided along the x-axes.
(8). Such a mechanism may have occurred in our patients of the plateau group, which had a leg vascular resistance that was higher than in patients of the nonplateau group.

In addition to the plateau in Q_{LEGS}, a limitation in leg O_2 extraction was necessary to obtain a plateau in VO_{2LEGS}. In the presence of a stable Q_{LEGS}, this suggests an impairment in O_2 transfer to the muscle may have contributed to the limitation in VO_{2LEGS} in patients of the plateau group (20). The analysis of the muscle structure was beyond the scope of this study, but a possible explanation for this is a reduction in muscle capillarization, which has previously been reported in patients with COPD (26). An alternative mechanism for the impairment in muscle O_2 conductance is a mismatch between the perfusion of the contracting muscle units and their metabolic activity (21). The limitation in O_2 extraction during exercise supports the concept of a peripheral component to exercise limitation, at least in some patients with COPD.

Measurement of leg blood flow is technically difficult, and a key question is whether the occurrence of a plateau in VO_{2LEGS} was a true physiological phenomenon or a technical artifact. The former interpretation is supported by two evidences. First, in one patient, the experimental procedure was performed on two separate occasions; in addition to being involved in the present study, this patient also participated in our previous investigation on leg blood flow measurements in COPD (16). In both circumstances, VO_{2LEGS} plateaued at 40 W. Second, the work efficiency was lower in the plateau group compared with the nonplateau group. This indicates, independently of VO_{2LEGS} measurements, that a greater proportion of VO_{2TOT} was devoted to other muscles rather than to the lower limb muscles, supporting our data interpretation that increased aerobic activity outside the lower limb exercising muscles was occurring in our patients.

In the present investigation, blood-gas values were reported at 37°C because changes in body temperature were modest at the level of exercise reached by our patients (change in rectal temperature measured with a thermocouple inserted 12–15 cm beyond the anal sphincter <0.5°C; Maltais, LeBlanc, and Johnson, unpublished observations). Assuming a similar change in arterial blood and rectal temperature and a change in femoral venous blood temperature 0.5°C greater than rectal temperature (22), we calculated that arterial and venous O_2 saturation values would be underestimated by ~2% and 6%, respectively (11). Because both errors are in the same direction and happened to be of similar absolute magnitude, they tend to cancel each other out. As a result, CaO_2-Cfo_2 and VO_{2LEGS} would be underestimated by only 1–2% by avoiding to correct blood-gas values for body temperature changes during exercise.

In summary, the present results indicate that some patients with COPD and severe airflow obstruction may reach their physiological limits in terms of lower limb VO_2, blood flow, and O_2 extraction during cycling exercise. Exercise tolerance was lower in patients exhibiting these limitations. The present results are consistent with the possibility of a blood flow redistribution between the respiratory and lower limb muscles in patients with COPD.

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