The addition of inspiratory resistance increases the amplitude of the slow component of O₂ uptake kinetics.

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Running title: VO₂ slow component and inspiratory resistance

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ABSTRACT

The contribution of respiratory muscle work to the development of the \( \dot{\text{VO}}_2 \) slow component is a point of controversy since it has been shown that the increased ventilation in hypoxia is not associated with a concomitant increase in \( \dot{\text{VO}}_2 \) slow component. The first purpose of this study was thus to test the hypothesis of a direct relationship between respiratory muscle work and \( \dot{\text{VO}}_2 \) slow component by manipulating inspiratory resistance. Since the conditions for a \( \dot{\text{VO}}_2 \) slow component specific to respiratory muscle can be reached during intense exercise, the second purpose was to determine whether the respiratory muscles behave like limb muscles during heavy exercise. Ten trained subjects performed two 8-min constant-load heavy cycling exercises with and without a threshold valve in random order. \( \dot{\text{VO}}_2 \) was measured breath-by-breath using a fast gas exchange analyzer, and the \( \text{O}_2 \) uptake response was modeled after removal of the cardiodynamic phase by using two mono-exponential functions. As anticipated, when total work was slightly increased with loaded inspiratory resistance, slight increases in \( \dot{\text{VO}}_2 \) base, the primary phase amplitude and \( \dot{\text{VO}}_2 \) peak were noted (14.2%, \( P < 0.01 \); 3.5%, \( P > 0.05 \); and 8.3%, \( P < 0.01 \), respectively). The bootstrap method revealed small coefficients of variation for the model parameter including the slow component amplitude and delay (15% and 19% respectively), indicating an accurate determination for this critical parameter. The amplitude of the \( \dot{\text{VO}}_2 \) slow component displayed a 27% increase from 8.1 \( \pm \) 3.6 to 10.3 \( \pm \) 3.4 ml\( \cdot \)min\(^{-1}\)\( \cdot \)kg\(^{-1}\) (\( P < 0.01 \)) with the addition of inspiratory resistance. Taken together, this increase and the lack of any differences in \( \dot{\text{V}}_E \) and ventilatory parameters between the two experimental conditions suggest the occurrence of a \( \dot{\text{VO}}_2 \) slow component specific to the respiratory muscles in loaded condition.
Key words: $O_2$ uptake slow component, oxygen uptake kinetics, respiratory muscles, work of breathing.
INTRODUCTION

The characteristics of oxygen uptake (\(\dot{V}O_2\)) kinetics in constant-load exercise have been well documented (3, 4, 6, 8, 14, 21, 38, 39, 46). During the transition from rest or unloaded cycling to constant-load exercise of moderate intensity [i.e., below the ventilatory threshold (VT)], \(\dot{V}O_2\) rises after the cardiodynamic phase (phase I) in an approximately mono-exponential fashion (phase II) to attain steady state (phase III) within two to three minutes. However, the \(\dot{V}O_2\) response to constant-load exercise of heavy intensity (i.e., above the VT) is more complex: the fundamental exponential response of pulmonary oxygen uptake is supplemented by the development of a slow component phase (phase III) (6, 21).

Although the existence of the slow component has been demonstrated, the putative mechanisms have not been clearly established. Several hypotheses, including peripheral and central factors, have been proposed to explain the excess of \(\dot{V}O_2\). Of the peripheral factors, the recruitment of type II muscle fibers seems the most plausible explanation (4, 7, 12, 42, 43). Type II muscle fibers are currently reported to be less efficient than type I because the ADP/O ratio is 18% lower, partly because of the greater reliance on the \(\alpha\)-glycerophosphate shuttle over the malate-aspartate shuttle (17, 44). Simultaneous measurement of pulmonary and leg \(\dot{V}O_2\) suggested that about 86% of the excess \(\dot{V}O_2\) observed with high-intensity exercise originates in the exercising limbs (38). This result further suggests that the coupling between chemical and mechanical energy is altered during the slow component phase.

Central factors such as the \(O_2\) cost of ventilatory muscles and/or cardiac muscle may also explain a part of the \(\dot{V}O_2\) slow component. Gaesser and Poole (21) noted that ventilation
increased to a great extent during the slow component of \( \dot{VO}_2 \). Since increases in ventilation are closely associated with increases in both mechanical work and the specific \( O_2 \) uptake of the respiratory muscles, these authors naturally suggested that ventilation contributes to the development of the \( \dot{VO}_2 \) slow component. In a preliminary study (13), we assessed the role of increased ventilation during phase III. Based on the equations proposed by Coast et al. (16), the rise in ventilatory flow explained about 24% of the slow component amplitude for an exercise intensity corresponding to 95% of maximum aerobic power (MAP). We further suggested that the part explained by respiratory \( O_2 \) uptake varies with exercise intensity. The results of Engelen et al. (20), however, introduced controversy regarding the direct relationship between respiratory muscle work and the development of the \( \dot{VO}_2 \) slow component. These authors showed that ventilation increased by a greater proportion during phase III in hypoxia than in normoxia, although the slow component amplitude was not significantly different. To our knowledge, no study has shown the effects of systematic modification of respiratory muscle work on the \( \dot{VO}_2 \) slow component. The first aim of the present study was thus to test whether increased respiratory muscle work induced by the addition of inspiratory resistance leads to a concomitant increase in \( \dot{VO}_2 \) throughout the exercise.

The main mechanism currently advanced to explain the contribution of peripheral factors to the \( \dot{VO}_2 \) slow component, i.e., a progressive recruitment of fast twitch fibers, can not be ruled out for the respiratory muscles since the conditions for the occurrence of a such phenomenon could be reached: (i) the respiratory muscles sustain a severe work rate during heavy constant-load exercise, associated with high ventilation levels (23, 24, 25), and during such intense exercise 14 to 16% of cardiac output is directed toward these muscles (24) and (ii) the composition in myosin heavy chain isoforms is mixed in respiratory muscle, as it is in lower limb
muscles (34, 41). The diaphragm and the abdominal muscles include 50% slow twitch fibers. The intercostals and the scalena muscle display a similar proportion, with 60% slow twitch fibers. The respiratory muscles have a similar composition in IIa and IIb myosin heavy chain isoforms, except for the intercostals, which present the smallest proportion of the IIb type. The second purpose was thus to determine whether the respiratory muscles behave like the limb muscles during heavy exercise. We anticipated an increase in the amplitude of the \( \text{VO}_2 \) slow component with the addition of inspiratory loading.
METHODS

Subjects

Ten trained young males participated in the study after being informed of its purpose and requirements, as well as their rights as subjects. The Local Review Board for Research on Human Subjects approved the protocol. All subjects were free of cardiac and pulmonary disease and fully familiar with laboratory exercise testing procedures. The criteria of study inclusion were the following: age between 20 and 30 years, non-smoking, and training volume between seven to ten hours per week, mainly in aerobic sports. Plethysmography was performed for each subject to assess respiratory function. The subject characteristics including age, weight, and maximal oxygen uptake (\( \dot{V}O_2 \text{max} \)) are given on Table 1 and the plethysmographic results are shown on Table 2.

Preliminary test

Each subject performed an incremental cycling exercise to volitional exhaustion to determine VT and \( \dot{V}O_2 \text{max} \), which was defined as the highest 30-s averaged \( \dot{V}O_2 \) attained. Pedaling frequency was fixed at 70 rpm. The incremental exercise test began with 5 min of warm-up at 60 W. The work rate then increased by 30 W every minute until the subjects reached volitional exhaustion. MAP was determined as the minimal power eliciting \( \dot{V}O_2 \) max.

A friction-loaded cycle ergometer (Monark 818 E, Stockholm, Sweden) fitted with a strain gauge and an incremental encoder ensured accurate measurement of power output. The ergometer was calibrated immediately before the start of the test with a known mass hung on the friction belt, and in an unloaded condition to give a 0 value (2). The saddle height and position of
the hands on the handlebar were fixed for each subject. In addition, the subjects were required to maintain the position of their shoulder and elbow joints positions steady. Experimenters checked these points and gave verbal feedback.

*Constant-load exercise*

The subjects performed two cycling exercises with and without an added inspiratory load in a balanced random order. The constant power output exercises consisted of 4 min of unloaded cycling, 8 min at 80% MAP, and then 10 min of recovery with unloaded cycling. The 4 min of unloaded cycling allowed subjects to begin the test with stable ventilatory parameters and respiratory exchange ratio (\(\dot{\text{VCO}}_2/\dot{\text{VO}}_2\)). The power output was adjusted over a period shorter than 2 s. A metronome and visual feedback from a speed transducer linked to a computer were used to maintain constant pedaling frequency at 70 rpm. The delay between the two tests ranged from 48 h to 6 days.

*\(\dot{\text{VO}}_2\) measurement*

Breath-by-breath \(\dot{\text{VO}}_2\) measurement was performed using an automatic gas exchange system (CPX Medical Graphics, St Paul, MN, USA), including a cell of zirconium for O\(_2\) analysis, an infrared cell for CO\(_2\) analysis, and a heated pneumotachograph, type Fleish (n°3, Godart Statham, Holland). The CO\(_2\) and O\(_2\) analyzers were calibrated before each test with two gases of known composition (12% of O\(_2\) and 5% of CO\(_2\)). The calibration of the pneumotachograph was carried out using a 3-liter syringe. For the constant-load exercise with added inspiratory load, a system of threshold valves (threshold IMT 730 EU-respirronics, Health scan asthma lergy produc tor, NJ, USA) was inserted on the inspiratory circuit of the valve. This
type of threshold valve maintains a constant resistance whatever the ventilation level (18); in other words, the increase in the work rate of breathing due to the addition of inspiratory resistance is independent of ventilation. The level of resistance can be adjusted with a screw pitch operating as a spring. After several tests with different resistances (10, 15, 20, 25 cm H₂O) to ensure that the added loads were compatible with high intensity exercise, the inspiratory resistance was fixed at 15 cm H₂O. The two-way valve of the open circuit specific to gas exchange was reinforced by a mica part to prevent gas from escaping during inspiratory loading. The total dead space was 100 ml. Breath-by-breath data for \( \dot{V}O_2 \) (ml min\(^{-1}\) kg\(^{-1}\)), ventilation (\( \dot{V}E \), l min\(^{-1}\)), tidal volume (VT, l), respiratory frequency (\( F_R \), br min\(^{-1}\)), VT/inspiratory time (VT/Ti, l s\(^{-1}\)), total time (Ti/Ttot, s) and heart rate (HR, bpm min\(^{-1}\)) were collected continuously throughout testing. HR was measured with an electrocardiogram including standard bipolar electrode placement.

Data analysis

Non-linear regression techniques were used to fit \( \dot{V}O_2 \) data after exercise onset using a two mono-exponential functions to describe the two main characteristics of the \( \dot{V}O_2 \) response: primary phase (phase II) and slow component phase (phase III). The two mono-exponential functions started after independent time delays (4). Since the primary phase was not distorted by any early cardiodynamic influence (36, 45), the cardiodynamic phase was not modeled (12).

\[
\dot{V}O_2(t) = \dot{V}O_{2\text{ base}} + A_1 \left(1 - e^{-\left(t-td_1\right)/\tau_1}\right) U_1 \text{ phase II (primary component)}
+ A_2 \left(1 - e^{-\left(t-td_2\right)/\tau_2}\right) U_2 \text{ phase III (slow component)}
\]

where \( U_1 = 0 \) for \( t \leq td_1 \) or \( U_1 = 1 \) for \( t \geq td_1 \) and \( U_2 = 0 \) for \( t \leq td_2 \) or \( U_2 = 1 \) for \( t \geq td_2 \);
\( \dot{V}O_2 \) \text{base} is the unloaded cycling baseline value; \( A_1 \) and \( A_2 \) are the asymptotic values for the two exponential terms; \( \tau_1 \) and \( \tau_2 \) are the time constants; and \( \text{td}_1 \) and \( \text{td}_2 \) are the delays for phase II and phase III. The phase II term was terminated at the start of phase III (\( i.e. \), at \( \text{td}_2 \)). The slow component amplitude was assigned the value \( A'_2 \).

\[
A'_2 = A_2 \left(1 - e^{-\left(\frac{t_e - \text{td}_2}{\text{W}_2}\right)}\right)
\]

where \( t_e \) is the time at the end of exercise. \( \dot{V}O_2 \text{peak} \) corresponds to the \( \dot{V}O_2 \) achieved at the end of the submaximal constant load exercise. The slow component began only when the preceding function reached its asymptote. A constraint was thus imposed in the model, ensuring that at least 98% of the amplitude of phase II was reached before the beginning of the slow component. The values of measured \( \dot{V}O_2 \) that were greater than three standard deviations from modeled \( \dot{V}O_2 \) were considered outliers and removed. These outlier values were assumed to be due to abnormal breaths during exercise such as shallow breathing or breath-holding. These values represented less than 1% of the total data collected.

Model parameters were determined with an iterative process by minimizing the sum of the squared errors between modeled \( \dot{V}O_2 \) and actual \( \dot{V}O_2 \). Iterations continued until successive repetitions reduced both the sum of the residuals by \( <10^{-6} \) and the correlation coefficient of the relationship between residuals and time by \( <10^{-4} \). To assess the validity of the model parameters, coefficients of variation (CV) were computed using the bootstrap method (12, 19). Briefly, this consisted of resampling the original data set with replacements to create a number of “bootstrap replicate” data sets of the same size as the original data set. For each replicate set, model parameters were estimated following the same procedures as for original data. This operation was repeated 1000 times, and the estimated parameters were retained. The CV was computed to normalize the range of the confidence interval.
Contribution of ventilation to the development of the $\dot{V}O_2$ slow component

Based on the equations proposed by Coast et al. (16), the additional $\dot{V}O_2$ due to increased ventilation during the slow component phase was estimated in the unloaded condition. Briefly, the procedure consisted of computing the work of breathing ($W_B$, kg.m$^{-1}$.min$^{-1}$) from ventilation ($\dot{V}_E$, l.min$^{-1}$):

$$W_B = -0.251 + 0.0382 \dot{V}_E + 0.00176 \dot{V}_E^2$$

The $\dot{V}O_2$ used by the respiratory muscles ($VRMO_2$, ml.min$^{-1}$) was then inferred by:

$$VRMO_2 = 34.9 + 7.45 W_B$$

Finally, the additional $\dot{V}O_2$ of respiratory muscles ($\Delta VRMO_2$) due to increased ventilation during the slow component was calculated as:

$$\Delta VRMO_2 = VRMO_2e - VRMO_2b$$

where $VRMO_2b$ and $VRMO_2e$ were the $VRMO_2$ at the beginning and end of the slow component, respectively. Since $W_B$ was altered by the added inspiratory resistance, Coast’s equations could not be used in this condition.

Statistical analysis

The Fisher test was used to determine the model’s degree of significance. The quality of the adjusted model was assessed by the coefficient of determination ($r^2$) obtained between modeled $\dot{V}O_2$ and actual $\dot{V}O_2$. The random distribution of model residuals according to time was checked with linear and non-linear regressions. The conditions of application for the parametric tests were checked using the Shapiro-Wilk test for normality of distributions and the Fisher test for equality of variance. Paired t tests compared the model parameters between the
two experimental conditions. The relationship between slow component amplitude and ventilation was assessed by Pearson correlation coefficients in the two experimental conditions.

A two-way analysis of variance with repeated measures was used to identify any differences in ventilatory flow parameters (averaged over 20 s) at the beginning and end of phase III under the two experimental conditions. Differences were declared to be significant for $P < 0.05$. 
RESULTS

No significant relationships were identified between residuals and time in either experimental condition, suggesting random distribution and an appropriate model to describe the \( \dot{V}O_2 \) kinetics in both conditions. Model adjustment to the \( \dot{V}O_2 \) kinetics led to coefficients of determination ranging between 0.83 and 0.96 (mean value of 0.92 ± 0.04). The Fisher test indicated a high degree of significance of the model for all subjects and conditions (\( P < 0.001 \)). The mean \( \dot{V}O_2 \) response pattern for all subjects with and without inspiratory resistance and the associated fit curves obtained with the two mono-exponential functions are presented in Figure 1A. The distribution of residual errors as a function of time is shown in Figure 1B for the condition without added inspiratory load. It is of interest to note that the same pattern of distribution was found for the condition with added inspiratory load.

An increase in \( \dot{V}O_2 \) was noted throughout the constant power output exercise. \( \dot{V}O_2 \) base increased (14.2\%) significantly with the added inspiratory load (9.1 ± 1.1 vs. 10.4 ± 1.6 ml·min\(^{-1}\)·kg\(^{-1}\); \( P < 0.01 \)), as did \( \dot{V}O_2 \) peak, i.e., 8.3\% (49.1 ± 7.2 vs. 53.2 ± 7.2 ml·min\(^{-1}\)·kg\(^{-1}\); \( P < 0.01 \)) (Fig. 2). A slight (3.5\%) but non-significant increase in the amplitude of the primary phase (A'\(_{1}\)) was noted. The values for the model parameters and for \( \dot{V}O_2 \) base and \( \dot{V}O_2 \) peak in the two conditions are listed on Table 3. The coefficients of variation are also presented on Table 3; it should be noted that the critical parameters in the present study, \( td_2 \) and A'\(_{2}\), were 19\% and 15\% respectively. The time delay (\( td_1 \)) and time-constant of phase II (\( \tau_1 \)) were not significantly different between the two experimental conditions. The added inspiratory load also did not modify \( td_2 \) or \( \tau_2 \).
The most important result was the significant increase in slow component amplitude \((P < 0.01)\) when inspiratory resistance was added (Fig. 3). \(A'_{2}\) increased by 27\% from \(8.1 \pm 3.6\) ml.min\(^{-1}.kg\(^{-1}\)) without inspiratory resistance to \(10.3 \pm 3.4\) ml.min\(^{-1}.kg\(^{-1}\)) with resistance. \(\dot{V}_E\) increased significantly from beginning to end of phase III (\(\Delta \dot{V}_E\)) in each condition \((P < 0.01)\) and \(\dot{V}_E\) was not significantly different between the two conditions (Fig. 4). The correlation between \(\Delta \dot{V}_E\) and \(A'_{2}\) reached significance in neither condition. The ventilatory parameters during phase III in the two conditions are shown on Table 4.

In control condition, estimated \(W_B\) was \(17.2 \pm 5.4\) kg.m\(^{-1}.min\(^{-1}\)) and \(31.5 \pm 9.1\) ml.min\(^{-1}.kg\(^{-1}\)) at the beginning and end of phase III, respectively. Hence, VRMO\(_{2b}\) was \(163.4 \pm 40.5\) ml.min\(^{-1}\) and VRMO\(_{2e}\) was \(269.7 \pm 67.2\) ml.min\(^{-1}\). \(\Delta VRMO_2\) was \(106.3 \pm 61.4\) ml.min\(^{-1}\). The \(\dot{V}O_2\) of the respiratory muscles due to increased ventilation during the slow component was thus estimated at \(21 \pm 17\%\) of the total slow component.
DISCUSSION

The most important findings of the present study were (i) the increased $\dot{V}O_2$ throughout the exercise with the addition of inspiratory resistance and (ii) the marked increase in the amplitude of the $\dot{V}O_2$ slow component associated with a lack of any difference in $\dot{V}_E$ and ventilatory parameters between the two experimental conditions during phase III.

Limitations

Several authors (5, 28) have used a procedure consisting of two to three measurements of the individual $\dot{V}O_2$ kinetics to decrease the variability inherent to breath-by-breath measurement of gas exchange. In the present study, this method was not applied because it is not possible to exclude that cycle-to-cycle variability may have physiological meaning as it is the case for heart rate, a factor of the cardiac output and thus of the $O_2$ uptake (37). Several elements support the notion that the fits were of sufficient quality to determine the model parameters with only one transition: (i) the high degree of significance ($P < 0.001$, number of points > 400 during the slow component phase), (ii) the coefficients of determination (average = 0.92 ± 0.04) between modeled $\dot{V}O_2$ and actual $\dot{V}O_2$, (iii) the random distribution of the residuals, and (iv) the relatively small coefficients of variation (~17%) obtained on the model parameters with the bootstrap method. Other recent studies (9, 12, 32, 35, 40) also completed only one transition to describe the $\dot{V}O_2$ kinetics since enough measurements were obtained to fit a two mono-exponential functions.

The added respiratory load may have not only increased respiratory muscle work but also slightly modified cardiac work because this latter can be slightly altered by changes in intra-thoracic...
pressure (33). High intra-thoracic pressures—for instance, those developed during the Vasalva maneuver—decrease venous return (33) and increase heart work. In contrast, inspiratory loading is associated with a more negative esophageal pressure of -6 to -7 cm H$_2$O at peak inspiration compared with control, although it is unchanged at expiration (23, 24). This more negative esophageal pressure may facilitate venous return and slightly decreases cardiac work rate. Although cardiopulmonary interactions were not addressed in the present study, a slight underestimation of the increase in $\dot{V}O_2$ attributed to the respiratory muscle work with added inspiratory resistance may therefore have resulted, but not an overestimation.

Comparison with the literature

The amplitude of the $\dot{V}O_2$ slow component without inspiratory resistance agreed with that of previous studies. Barstow and Mole (4) observed amplitudes of 0.88 and 0.96 l.min$^{-1}$ at exercise intensities of 85% and 100% of $\dot{V}O_2$ max, respectively. Engelen et al. (20) found amplitudes of 0.22 l.min$^{-1}$ at an intensity of 75% of $\dot{V}O_2$ max. $\dot{V}O_2$ obtained during the present cycling exercise at 80% of $\dot{V}O_2$ max without added resistance was 0.67 l.min$^{-1}$. This value is in line with the assumption that the amplitude variation in the slow component is strongly dependent on exercise intensity (11, 29, 47). $\dot{V}O_2$base without added inspiratory load also agreed with the values of the literature (4, 20). In agreement with the present study, the addition of inspiratory resistance higher level of $\dot{V}O_2$ throughout the exercise was found compared to control (25). The difference reached significance from the 2nd min to the 5th min of exercise.

Does $\dot{V}_E$ contribute to the development of the slow component?
As anticipated, when total work (total work = work performed by exercising limbs + work by muscles indirectly involved) was increased in the loaded condition, a concomitant VO2 increase was noted throughout the exercise compared with the unloaded condition. The slight and significant increase ($P < 0.01$) in VO2base and VO2peak with added inspiratory resistance supports this notion, and the lack of significant increase (3.5%) in the primary phase amplitude may have been due to the greater variability found in transient phases compared with more stationary phases (31). We now emphasize that the only difference between the two conditions lies in the inspiratory resistance and that the additional work of breathing provokes a rise in VO2 throughout the exercise.

The present study provides direct evidence of the contribution of ventilatory work to the development of the slow component and, at first glance, it appears to contradict the study of Engelen et al. (20) on the role of the respiratory muscles. During the slow component phase, VO2 and VE—and thus the work of breathing and the O2 uptake of the respiratory muscles—increased significantly ($P < 0.01$) in both conditions. The subjects who presented the greatest increase in ventilation during phase III in the two conditions displayed the biggest change in VO2 slow component amplitude and vice versa, but the correlation did not reach statistical significance. The lack of a significant relationship is probably due to the relatively small contribution of ventilatory work to the slow component and to the small amplitude of the inter-individual variations in VE and VO2. Any increase in ventilation during the VO2 slow component necessarily corresponds to an increase in the mechanical work of the respiratory muscles and consequently leads to increased O2 demand in these muscles (1, 16). These variations between VE and VO2 must be regarded as causal relationships. Therefore, the
apparent contradiction with the results of Engelen et al. (20) is undoubtedly explained by two mechanisms that are mutually compensated in hypoxia: the increase in \( O_2 \) uptake of the respiratory muscles linked to increased ventilation during phase III is counterbalanced by lower \( O_2 \) uptake of the peripheral muscles in hypoxia in comparison with normoxia, or by lower \( O_2 \) delivery in hypoxia due to hemoglobin desaturation in arterial blood (10).

Based on the equations of Coast et al. (16), respiratory muscle \( \dot{V}O_2 \) due to increased ventilation can be evaluated as \( 21 \pm 17\% \) of the total slow component under normal conditions (at 80\% MAP), which is slightly lower than the 24\% observed at an intensity of 95\% \( \dot{V}O_2 \text{max} \) (13) and much higher than the 7\% observed at an intensity of 70\% \( \dot{V}O_2 \text{max} \) (22). The relative part explained by ventilation depends on the exercise intensity. It is interesting to note that the value of 21\% also falls within the range that Poole et al. (38) could not account for by measuring lower limb \( \dot{V}O_2 \).

*Can respiratory muscle display a slow component?*

From the unloaded cycling period to the end of the primary phase, the slight increase of \( \dot{V}O_2 \) in response to the added inspiratory resistance clearly reflects the direct relationship between the work of breathing and \( \dot{V}O_2 \). The subsequent increase in \( \dot{V}O_2 \) in the slow component period, associated with a 27\% increase in the slow component amplitude \( (P < 0.01) \), is probably more interesting. The question that should be addressed is why this additional work of breathing provokes a progressive rise in \( \dot{V}O_2 \). Based on the lack of difference in \( \dot{V}E \) and its factors between the two experimental conditions, one could argue that the increase in \( A'\dot{\dot{2}} \) with inspiratory resistance reflects a \( \dot{V}O_2 \) slow component specific to the respiratory muscles. The
type of threshold valves used in the present study is associated with an additional work independent of the ventilation level (18). The observation of no significant difference in $\dot{V}_E$ or the breathing pattern at the beginning and end of the $\dot{V}O_2$ slow component phase (Fig. 4) when compared with control suggests that the additional work imposed on the respiratory muscles by the load was constant with time and provoked a $\dot{V}O_2$ slow component. This information cannot be drawn from control studies during heavy exercise since ventilation typically increases with time (and thus the work of breathing). Based on the comparison between the two experimental conditions, it seems that the respiratory muscles behave just as the muscles directly concerned by the exercise: during a constant high-intensity work rate applied to the respiratory muscles, there is also a progressive decrease in muscular efficiency.

In agreement with this hypothesis, we can note that the main conditions for the occurrence of the $\dot{V}O_2$ slow component were reached for the respiratory muscles, at least in the loaded condition. First, there is little doubt that the subjects of the present study performed at a severe respiratory muscle work rate with the inspiratory resistance of 15 cm H$_2$O, since $\dot{V}_E$ reached 120 l.min$^{-1}$ (Fig. 4). Although the esophageal pressure was not measured directly to avoid invasive instrumentation, in similar conditions of heavy exercise and with an inspiratory resistance of 6-7 cm H$_2$O, the work rate of breathing measured directly from the esophageal pressure-volume loop increased to 128 - 157% of the control at peak inspiration (23, 24).

Second, as for the lower limb muscles, the myosin heavy chain isoform composition of the respiratory muscle is mixed (34, 41). The main mechanism currently advanced to explain the slow component of $O_2$ uptake (7, 8, 12) i.e, a progressive recruitment of fast twitch fibers, can not be ruled out for the respiratory muscles. In agreement with the Henneman et al. (27) law of motor unit recruitment, the slow twitch fibers of the respiratory muscles that are mainly engaged at the
beginning of exercise are likely to progressively reach a fatigued state and new motor units are recruited to maintain the constant power output. It is not necessary to assume that the newly recruited fibers, mainly in the fast twitch fiber pool, are less economic because (i) the great number of required active fibers implies substantial ATPase activity at least regarding the work of the sodium-potassium and calcium pumps against concentration gradients, and (ii) fast twitch fibers display a higher optimal shortening velocity than slow twitch fibers. On isolated human skeletal muscle fibers containing different myosin isoforms, He et al. (26) showed that the maximum efficiency was reached at a higher speed of shortening for the faster fibers. It follows that the newly recruited fast fibers and must work in unfavorable conditions.
CONCLUSION

As hypothesized, the addition of inspiratory resistance provoked a proportional increase in \( \dot{V}O_2 \) throughout exercise, supporting the role of the increase in \( \dot{V}E \) during phase III in the development of the \( \dot{V}O_2 \) slow component. The original finding of the present study was the marked increase (27\%, \( P < 0.01 \)) of the \( \dot{V}O_2 \) slow component amplitude with the addition of inspiratory resistance while no significant differences in \( \dot{V}E \) and ventilatory parameters were found between the two experimental conditions during phase III. It seems that the respiratory muscles behave like the limb muscles; they are likely to display a \( \dot{V}O_2 \) slow component.
REFERENCES


Figure Legends

Figure 1A. Average oxygen uptake (\(\dot{\text{VO}}_2\)) response for all subjects (n=10) showing the transition from unloaded cycling to heavy exercise in the two experimental conditions: with (L) and without (U) added inspiratory resistance.

Figure 1B. Distribution of the residual sum of squares in the condition without added inspiratory load. Note that the residuals were distributed randomly around zero.

Figure 2. \(\dot{\text{VO}}_2\) peak in the two experimental conditions: without added inspiratory load and with added inspiratory load. Note that the increase in \(\dot{\text{VO}}_2\) peak was 4.1 ml.min\(^{-1}\).kg\(^{-1}\) (\(P < 0.01\))

Figure 3. Amplitude of the \(\dot{\text{VO}}_2\) slow component in the two experimental conditions: without added inspiratory load and with added inspiratory load (\(P < 0.01\))

Figure 4. Change in ventilation (\(\dot{V}_E\)) between the beginning and end of phase III in the two experimental conditions (\(P > 0.05\)). Note the significant increase from the beginning to end of phase III in each condition (\(P < 0.01\)).

Figure 5. Mean lines of best fit of the dynamic response of \(\dot{\text{VO}}_2\) and VRMO\(_2\) in constant-load exercise obtained by plotting the response with mean parameter estimates during the condition without inspiratory resistance.
## Tables

### Table 1. Anthropometric characteristics of subjects and results of incremental tests

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>$\dot{V}O_2\max$ (ml·min$^{-1}$·kg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>22.2</td>
<td>181.5</td>
<td>76.2</td>
<td>53.8</td>
</tr>
<tr>
<td>S.D.</td>
<td>1.8</td>
<td>3.6</td>
<td>4.9</td>
<td>6.6</td>
</tr>
</tbody>
</table>

$\dot{V}O_2\max$ = maximal consumption oxygen; S.D. = standard deviation

### Table 2. Characteristics of respiratory function

<table>
<thead>
<tr>
<th>Subjects</th>
<th>PI max. (cm H$_2$O)</th>
<th>VC (l)</th>
<th>VC (%)</th>
<th>FEV$_1$ (l)</th>
<th>Tiffenau Ratio FEV$_1$ /FVC (%)</th>
<th>TLC (l)</th>
<th>TPC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>132</td>
<td>5.9</td>
<td>104</td>
<td>4.8</td>
<td>81</td>
<td>8.3</td>
<td>112</td>
</tr>
<tr>
<td>S.D.</td>
<td>23</td>
<td>0.6</td>
<td>10</td>
<td>0.5</td>
<td>5</td>
<td>0.9</td>
<td>15</td>
</tr>
</tbody>
</table>

PI max: Maximum inspiratory pressure in cm H$_2$O, VC: vital capacity in l and %, FEV$_1$: Force expired volume in one second, TLC: total lung capacity in l and %.
Table 3. Parameters estimated for model fitting of the oxygen uptake response during heavy exercise and $\dot{V}O_2$ peak in the two experimental conditions: with added inspiratory load (L) and without added inspiratory load (U)

<table>
<thead>
<tr>
<th></th>
<th>U Mean ± SD</th>
<th>L Mean ± SD</th>
<th>CV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A'_1$ (ml·min⁻¹·kg⁻¹)</td>
<td>31.2 ± 5.5</td>
<td>32.3 ± 5.5</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>$t_{d1}$ (s)</td>
<td>11.1 ± 5.6</td>
<td>12.1 ± 4.1</td>
<td>45</td>
<td>NS</td>
</tr>
<tr>
<td>$t_1$ (s)</td>
<td>36.3 ± 13.3</td>
<td>38.2 ± 9.1</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>$A'_2$ (ml·min⁻¹·kg⁻¹)</td>
<td>8.1 ± 3.6</td>
<td>10.3 ± 3.4</td>
<td>15</td>
<td>**</td>
</tr>
<tr>
<td>$t_{d2}$ (s)</td>
<td>174.9 ± 43.4</td>
<td>221.8 ± 135.6</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>$t_2$ (s)</td>
<td>110.1 ± 41.3</td>
<td>138.9 ± 54.7</td>
<td>484</td>
<td>NS</td>
</tr>
<tr>
<td>$\dot{V}O_2_{\text{base}}$ (ml·min⁻¹·kg⁻¹)</td>
<td>9.1 ± 1.1</td>
<td>10.4 ± 1.5</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>$\dot{V}O_2_{\text{peak}}$ (ml·min⁻¹·kg⁻¹)</td>
<td>49.1 ± 7.2</td>
<td>53.2 ± 7.2</td>
<td>**</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD, n = 10 subjects. $\dot{V}O_2_{\text{base}}$: baseline; $A_1$, $A_2$: amplitudes of response of phases II, III; $\tau_1$, $\tau_2$: time-constants of phases II, III; $t_{d1}$, $t_{d2}$: time delays of phases II, III. ** = P < 0.01 for differences with the condition ‘without inspiratory resistance’.
**Table 4. Ventilatory parameters during phase III in the two experimental conditions**

<table>
<thead>
<tr>
<th>parameters</th>
<th>beginning phase III</th>
<th>end phase III</th>
<th>beginning phase III</th>
<th>end phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}_E$ (l/min)</td>
<td>86.0 ± 15.4</td>
<td>122.6 ± 18.0**</td>
<td>87.9 ± 16.8</td>
<td>122.1 ± 17.1**</td>
</tr>
<tr>
<td>$V_T$ (l)</td>
<td>3.5 ± 0.4</td>
<td>3.5 ± 0.4**</td>
<td>3.3 ± 0.5</td>
<td>3.2 ± 0.5**</td>
</tr>
<tr>
<td>$F_R$ (br/min)</td>
<td>25.1 ± 4.6</td>
<td>36.8 ± 6.2**</td>
<td>26.6 ± 5.5</td>
<td>37.4 ± 7.2**</td>
</tr>
<tr>
<td>$T_i$ (s)</td>
<td>1.2 ± 0.2</td>
<td>0.7 ± 0.1**</td>
<td>1.2 ± 0.3</td>
<td>0.9 ± 0.2**</td>
</tr>
<tr>
<td>$T_e$ (s)</td>
<td>1.3 ± 0.3</td>
<td>0.9 ± 0.2**</td>
<td>1.2 ± 0.3</td>
<td>0.8 ± 0.2**</td>
</tr>
<tr>
<td>$T_{tot}$ (s)</td>
<td>2.5 ± 0.5</td>
<td>1.6 ± 0.3**</td>
<td>2.4 ± 0.5</td>
<td>1.7 ± 0.4**</td>
</tr>
</tbody>
</table>

Values are means ± SE; $\dot{V}_E$, ventilation; $V_T$, tidal volume; $F_R$, respiratory frequency; $T_i$, inspiratory time; $T_e$, expiratory time; $T_{tot}$, total time. Significantly different: ** $P < 0.01$ compared with beginning of phase III; there was no modification in these parameters when the experimental condition without added inspiratory load (U) was compared with the condition with inspiratory resistance (L) ($P > 0.05$).
Figure 1A.

Figure 1B.

\[ y = -2 \times 10^{-3}x + 9 \times 10^{-1} \]

\[ R^2 = 5 \times 10^{-2} \]
Figure 4.

![Graph showing VE (L.min⁻¹) without and with load.](image_url)

- ** without load
- ** with load
- NS without load
- NS with load

Figure 5.

![Graph showing VO2 and VRMO2 during unloaded cycling, phase II, and slow component.](image_url)