ORIGINAL ARTICLE

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Alveolar oxygen uptake kinetics with step, impulse and ramp exercise in humans

Abstract The breath-by-breath $\dot{V}O_{2A}$ of five male subjects (21.2 years ± 3.2; 78.8 kg ± 5.9; 179.6 cm ± 5.8) was measured during a cycling exercise. Starting from a 10 W baseline, the subjects performed (i) ON and OFF step transitions (ST-ON; ST-OFF) to 50, 90, and 130 W; (ii) a ramp (R) exercise with work rate gradually increasing by 20 W min^{-1}; (iii) impulse transitions (I) to 250 and 410 W lasting 10 and 5 s, respectively. The $\dot{V}O_{2A}$ data was modelled using non-linear weighted least square regressions. The amplitudes of the $\dot{V}O_{2A}$ response turned out to be proportional to the input work rate intensities in all the modalities of exercise. Time constants (τ) and time delays (t_d) of ST-ON and R responses were not significantly different, whereas those of ST-OFF were characterised by longer τ values. τ and t_d of I responses turned out to be identical to those of ST-ON when the $\dot{V}O_{2A}$ responses were fitted using a five-component model. These results suggest that: (i) the system controlling alveolar gas exchange behaves linearly when it is forced by ST and R inputs (the ON and OFF phases being considered separate); (ii) the analysis of the I response depends strongly on the models selected to fit the $\dot{V}O_{2A}$ data. The asymmetry between the ON and OFF responses mirrors that found between the splitting and resynthesis rates of phosphocreatine, and these results support the notion that phosphocreatine could be the main controller of the skeletal muscle respiratory turnover in humans.

Keywords Step exercise · Gas-exchange kinetics · Linearity · Ramp exercise · Impulse exercise

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Introduction

Upon an exercise step transition, alveolar oxygen uptake ($\dot{V}O_{2A}$) lags behind the instantaneous change of muscular power output. Its kinetics is traditionally described by a bicomponent exponential time course (Whipp and Ward 1990), which attains a constant level proportional to the imposed external mechanical power.

The first component (phase I) of the $\dot{V}O_{2A}$ on-kinetics is related to the quick increase of pulmonary blood flow ($\dot{Q}_P$) (Loeppke et al. 1981) brought about by: (a) the withdrawal of the parasympathetic tone at the onset of the exercise and (b) the increase of venous return to the heart due to the effects of muscular and diaphragmatic pumps (Rowell et al. 1996). In this phase, the systemic arterio-venous O_2 concentration difference shows a rapid, yet small, increase caused by the blood effluent from the visceral vascular districts (Casaburi et al. 1989). The state of replenishment of the body's oxygen reserve may affect gas exchange in this phase and, if neglected, may also lead to an inaccurate estimate of the oxygen deficit, as was observed when body oxygen stores were manipulated on purpose (Prampero et al. 1970, 1983, 1989) and demonstrated by means of a modelling approach (Barstow et al. 1990).

The second component (phase II) occurs with a time delay, depending on $\dot{Q}_P$ and on the volume of the blood stored in the peripheral venous vessels before the onset of the exercise. It is characterised by a time course that is slower than that of phase I and dictated by an increase in cardiac output and a change of oxygen concentration in the mixed venous blood ($C\bar{v}O_2$) that is, in turn, induced by the progressive decrease of oxygen content in the blood draining from the contracting muscles. Phase II of the $\dot{V}O_{2A}$ on-kinetics has been evaluated in several types of subjects and conditions to obtain deeper insights on the activity of muscular oxidative metabolism during exercise in vivo, as it is considered to be mainly dictated by the $\dot{V}O_2$ increase occurring in the muscles at the onset of the exercise (Grassi et al. 1996).

The study of the oxygen uptake kinetics in humans has been boosted since equipment for the breath-by-breath (BB) determination of gas exchange was introduced (Linnarsson 1974). Nevertheless, the study of the $\dot{V}O_{2A}$ kinetics at the onset of the exercise has left partially unresolved the issue whether the system dictating alveolar gas exchange is dynamically linear. Proving that alveolar gas exchanges conform to dynamical linear system characteristics could provide important hints with respect to the physiological determinants of alveolar gas exchange regulation during exercise.

Physiological adaptations affecting the cardio-respiratory convective, O_2 transport and O_2 peripheral utilisation have been described to modify alveolar gas exchanges kinetics (for further details, see the review of Grassi 2000). For instance, experimental results suggested that $\dot{V}O_{2A}$ on-kinetics are affected by the inertia with which the cardiovascular oxygen transport adapts to the energetic requirements set at the beginning of the exercise (Hughson and Morissey 1982; Hughson et al. 1996; MacDonald et al. 1997; Tschakovsky and Hughson 1999). An alternative view proposed that $\dot{V}O_{2A}$ on-kinetics closely matched the rate of muscular oxidative metabolism, which, in turn, is linearly linked to the amount of free creatine (Cr) derived from phosphocreatine (PCr) splitting at the onset of the exercise (Binzoni et al. 1992; Prampero and Margaria 1968; Grassi 2000; Mahler 1985; Molé et al. 1985; Rossiter et al. 1999; Walsh et al. 2001; Whipp and Mahler 1980).

If $\dot{V}O_{2A}$ kinetics and peripheral oxidative metabolism are causally linked, we may also conclude that the input (i.e., the imposed external mechanical work rate) and the metabolic response (represented by oxygen uptake) are linearly related, provided the mechanical efficiency remains constant. On the contrary, if a limiting role of the cardiovascular oxygen transport is assumed, it follows that $\dot{V}O_{2A}$ kinetics may behave non-linearly in response to different forms of input functions.

To obtain deeper insights on the issue concerning the linear characteristics of the system dictating alveolar gas exchange, investigations were extended to the comparison of ON-OFF kinetics. While some studies showed symmetry between ON and OFF $\dot{V}O_{2A}$ kinetics (Griffiths et al. 1984; Paterson and Whipp 1994; Özyener et al. 2001), others found that the $\dot{V}O_{2A}$ responses during ON and OFF transients were markedly asymmetric in different exercise modalities (Brittain et al. 2001; Miyamoto and Niizeki 1992; Carter et al. 2000). These results have been taken as a disproof of the hypothesis that the system controlling alveolar gas exchange conforms to a dynamically linear system.

Recent data, obtained by simultaneously assessing alveolar oxygen uptake and PCr splitting-resynthesis rates, by means of P^{31} Nuclear Magnetic Resonance spectrometry at the onset-offset of a step exercise of moderate intensity (Rossiter at al. 2002), showed that $\dot{V}O_{2A}$ recovery kinetics are slower than that at the onset of the exercise. This is mirrored by a slower rate of PCr resynthesis in comparison with the time course of PCr splitting observed during the ON transient. The data concerning the asymmetry of the kinetics of PCr splitting and recovery, and hence of the ON and OFF $\dot{V}O_{2A}$ kinetics, have been explained as the consequence of alterations of forward and backward Cr kinase fluxes, as indicated by a theoretical model of the energy balance in muscle activity (Kushmerick 1998).

Deeper insights on this physiological issue might be obtained by studying the dynamic response of the alveolar gas exchange system when it is stressed by different inputs, namely different exercise modalities and intensities (Wigertz 1971; Fujihara et al. 1973a, 1973b; Hughson et al. 1988). This approach would make it possible to verify whether the system behaves linearly and satisfies the superposition principle. This means, in particular, that: (i) the response amplitude is proportional to the input (or forcing function) and (ii) the parameters describing the response kinetics (time constants and time delays) should be consistent for different inputs. To test the features of a dynamical system in the time domain, some standard inputs are usually utilised: impulse, step and ramp function. In fact, the response to each of these inputs fully characterises the dynamic features of the system and allows investigators to predict responses to the others. In particular, the integral of the impulse response, in a linear system, equals the response to the step; and the integral of the step input yields the output of the ramp forcing function.

If step and ramp inputs are relatively easy to impose on the alveolar gas exchange system, the same may not hold true for the impulse forcing function since, strictly speaking, its duration should ideally tend to zero, or at least be shorter than any of the time parameters of the system at stake (Fujihara et al. 1973a), and have an infinite amplitude. This may raise some practical problems, one of them being that a high intensity work rate must be imposed in order to obtain responses with a sufficient signal-to-noise ratio, which is likely to be low because of the short duration of the input.

Nevertheless, any impulse, regardless of its duration, may be considered as the sum of a ST-ON followed by an ST-OFF and, consequently, its response may be analysed as the composed kinetics of two step transitions.

On the basis of these premises and the still-open issues outlined above: (i) ON and OFF $\dot{V}O_{2A}$ kinetics were separately investigated, analysing the BB $\dot{V}O_{2A}$ data obtained in response to impulse, step and ramp exercises, and (ii) ON and OFF responses in the step and impulse exercises were compared.

Should the PCr splitting and resynthesis rates be linearly linked to ON and OFF $\dot{V}O_{2A}$ responses, we would expect to find consistent parameters describing the $\dot{V}O_{2A}$ ON and OFF kinetics in response to the different types of work rate forcing functions. Finally, the possible asymmetry between the $\dot{V}O_{2A}$ kinetics of the ON and OFF phases would further confirm the hypothesis that the muscular oxidative rate and the oxygen uptake at the whole body level are controlled by PCr resynthesis.

Methods

Subjects

Five adult healthy male subjects participated in the study (21.2 years ± 3.2), 76.8 kg ± 5.9), 179.6 cm ± 5.8) (mean $\pm$ SD). They were thoroughly informed about the aims and methods of the study as well as the risks implied by the measuring procedures, and were asked to sign a written informed consent. All subjects were involved in regular exercise training and were familiar with laboratory exercise testing procedures.

Experimental protocol

Subjects were instructed to avoid strenuous exercise in the 48 h preceding test sessions and to arrive at the laboratory in the morning after a light breakfast and in a rested and fully hydrated status. In a preliminary experimental session, individual maximal oxygen uptake and ventilatory threshold (AT_V, l min^{-1}) were assessed during a standard ramp exercise protocol (Wassermann et al. 1999).

Then, during the following weeks, the subjects came to the laboratory and performed step, ramp and impulse transitions (which were short lasting and of high intensity) that were proposed in a random order on a cycle-ergometer. The seat, handlebar height and frame angles were individually adjusted and maintained constant for each subject throughout the study. The subjects sat on the cycle-ergometer and started breathing through the mouthpiece; they then started pedalling at 60–70 rpm against an external load of 10 W that was maintained for 4 min. At the end of the fourth minute of exercise, the mechanical work rate was instantaneously imposed according to the selected work rate forcing functions.

Step exercises consisted of sudden transitions from 10 to 50, 90, or 130 W (ST-ON, Δ W: 40, 80, and 120 W). The selected work rates were lower than those corresponding to the individual ventilatory threshold assessed in the preliminary session. The constant work rates were maintained for 6 min. The subjects then suddenly returned to the initial 10 W work rate (ST-OFF), which was maintained for 6 min, before stopping the exercise. The work rate transitions were imposed by a computer that operated simultaneously with the cycle-ergometer and the metabolic cart.

During ramp protocol (R), the work rate kept increasing from a baseline of 10 W, by 20 W min^{-1} for 6 min, after which the so attained work rate of 130 W was maintained constant for 5 min.

Two impulse transitions (I) were performed starting from the same baseline of 10 W. In one occasion, the work rate increased to 250 W and was maintained for 10 s ($I_{\Delta\ 240\ W}$), and in the other it was set to 410 W ($I_{\Delta\ 400\ W}$) for 5 s. Afterwards, the subjects resumed the base line work rates of 10 W.

Each subject repeated the described protocols – three (step and ramp) or five (impulse) – at each work rate on different days. Each experimental run was separated by at least 1 h of rest.

Methods

To calculate $\dot{V}O_{2A}$ during the step, ramp and impulse exercises, oxygen and carbon dioxide fractions at the mouth and ventilatory flow were recorded throughout the tests, by means of a metabolic cart (Quark B^2, Cosmed, Italy). Subjects wore a nose clip and breathed through a mouthpiece mounted on a turbine flowmeter. Gases were sampled continuously through a capillary line inserted in the outer frame of the flowmeter and analysed by fast-response O_2 (chemical) and CO_2 (infra-red) sensors embedded in the metabolic cart. The software operating the metabolic cart allowed us to continuously record gas and flow signals (sampling frequency: 25 Hz) and save them as text files. The analysers and the propeller were calibrated before each experimental run: (i) with a gas mixture of known composition ($FO_2 = 0.16$; $FCO_2 = 0.04$; N_2 as balance) and ambient air; (ii) by means of a 3 l syringe (Hans Rudolph Inc., USA), following the procedures indicated by the manufacturer. Heart rate was recorded by means of a short-distance telemetry system (Polar Electro Oy, Kempele, Finland). The electromagnetically braked cycle-ergometer (SportExcalibur, Lode, D) was connected to and operated by a PC running the metabolic cart. The system made it possible to impose work rates according to pre-defined exercise protocols. The electromechanical characteristics of the ergometer permitted an almost instantaneous step change from one work rate to the next (the response time of the ergometer was around 80 ms, according to the operating manual and as measured in a preliminary session).

Single breath alveolar oxygen uptake was then calculated from the original gas and flow traces, by means of the algorithms of Grønlund, which takes into account variations of the lung's gas stores that occur from one breath to another (Grønlund 1984). In particular, the N_2 + Ar concentration was estimated as 100% minus the sum of measured O_2 and CO_2 concentrations, as also utilised by Clemensen et al. (1994). The algorithm was implemented by means of a computerised procedure written in the object-oriented G language, implemented in the developing environment Labview 5.0 (National Instruments, USA) and running on a Pentium CPU (Intel, USA).

To calculate AT_V, the BB values of oxygen uptake and carbon dioxide output, obtained from the metabolic cart during the incremental test, were preliminarily smoothed by applying a three-sample moving average procedure implemented to this aim by the manufacturer in the data analysis software. The AT_V was assessed individually by applying the V-slope method, as indicated by Wasserman et al. (1999). Maximal oxygen

uptake was calculated as the average of the oxygen uptake values measured in the last 30 s before the end of the exercise.

Data analysis

The $\dot{V}O_{2A}$ time series was aligned with the onset of work rate transitions and treated by subtracting the $\dot{V}O_{2A}$ values that were calculated by averaging the data obtained during the last minute of the phase preceding the work rate change. Then, the three to five series obtained in the different exercise protocols, and in each subject, were interpolated to 1 s interval, according to Lamarra et al. (1987). Finally, they were averaged to obtain a single data file for each exercise work rate forcing function in each subject.

ON-OFF step exercise

The $\dot{V}O_{2A}$ data of ST-ON was modelled as a bi-exponential function:

$$Y(t) = H(t - t_{d1}) \times G_1 \times (1 - e^{-(t - td_1/\tau_1)})$$
$$+ H(t - t_{d2}) \times G_2 \times (1 - e^{-(t - td_2/\tau_2)}) \qquad (1)$$

where $H(t - t_d)$ is the Heaviside function defined as

$$H(t - td) = \begin{cases} 0 & \text{if } t < t_d \\ 1 & \text{if } t \geqslant t_d \end{cases}$$

$Yt)$ represents the increase of $\dot{V}O_{2A}$ at the onset of the exercise above the value prevailing at 10 W, G_1 and G_2 indicate the gain terms, t_{d1} and t_{d2} are the time delays elapsed from the onset of the exercise and τ_1 and τ_2 represent the time constants of the two exponentials. The Heaviside functions inserted in Eq. 1, as well as in the following ones, account for the fact that each component does not come into play before an interval of time equal to the corresponding time delay.

The $\dot{V}O_{2A}$ data of ST-OFF was aligned with the offset of work rate transitions and treated by subtracting the $\dot{V}O_{2A}$ values calculated by averaging the data corresponding to the last minute of the 6-minute recovery phase. Afterwards, they were also modelled as a bi-exponential function:

$$Y(t) = \dot{V}O_{2ss} - H(t - t_{d3}) \times G_3 \times (1 - e^{-(t - t_{d3})/\tau_3})$$
$$- H(t - t_{d4}) \times G_4 \times (1 - e^{-(t - t_{d4})/\tau_4}) \qquad (2)$$

where $Yt)$ describes the decrease of $\dot{V}O_{2A}$ at the offset of the exercise, $\dot{V}O_{2SS}$ is the steady state oxygen uptake prevailing in the last minute of the exercise, G_3 and G_4 indicate the gain terms, t_{d3} and t_{d4} are the time delays measured from the end of the exercise, τ_3 and τ_4 represent the time constants of the two exponentials, and the other symbols maintain the same meaning as in Eq. 1. This model was derived as a modification of the model

proposed by Engelen et al. (1996) and was obtained by adding a new parameter describing the time delay between the end of the exercise and the beginning of the first component.

Ramp test

Since, in a linear system, the integral of the step response yields the response to the ramp data, single breath $\dot{V}O_{2A}$ data obtained during the ramp exercise was fitted by means of a model obtained by integrating Eq. 1:

$$Y(t) = \quad H(t - t_{d1}) \times G_1 \times [t - t_{d1} - \tau_1(1 - e^{-(t - t_{d1})/\tau_1})]$$
$$+ H(t - t_{d2}) \times G_2 \times [t - t_{d2} - \tau_2(1 - e^{-(t - t_{d2})/\tau_2})] \qquad (3)$$

where the symbols maintain the same meaning as in Eq. 1.

Impulse test

A given impulse input of width w was represented as a ST-ON followed by a ST-OFF. Therefore, the corresponding response may be treated according to the following equations:

$$Y(t) = [Y_1(ON) - Y_1(OFF)] + [Y_2(ON) - Y_2(OFF)] \qquad (4)$$

where $Y1$ (ON) and $Y2$ (ON) represent the two mono-exponential functions modelling phases I and II of the ST-ON response, respectively, and, in analogy, $Y1$ (OFF) and $Y2$ (OFF) are the corresponding components of ST-OFF.

Based on Eqs. 1 and 2, and considering the interposition of the time duration of the impulse (w), the single terms of Eq. 4 may be represented in their explicit form as:

$$Y_1(ON) = H(t - t_{d1}) \times G_1 \times (1 - e^{-(t - t_{d1})/\tau_1}) \qquad (4a)$$

$$Y_1(OFF) = H(t - t_{d3} - w) \times G_3 \times (1 - e^{-(t - t_{d3} - w)/\tau_3}) \qquad (4b)$$

$$Y_2(ON) = H(t - t_{d2}) \times G_2 \times (1 - e^{-(t - t_{d2})/\tau_2}) \qquad (4c)$$

$$Y_2(OFF) = H(t - t_{d4} - w) \times G4 \times (1 - e^{-(t - t_{d4} - w)/\tau_4}) \qquad (4d)$$

where w represents the duration (in seconds) of the impulse.

The $\dot{V}O_{2A}$ data of impulse response was also fitted using a second model to which a third ST-OFF component of amplitude G_5, time delay t_{d5} and time constant τ_5 was added. Therefore, the overall response to I was represented by means of the following equation:

$$Y(t) = [Y_1(ON) + Y_2(ON)] - [Y_1(OFF)]$$
$$+ Y_2(OFF) + Y_3(OFF)] \tag{5}$$

where

$$Y_3(OFF) = H(t - t_{d_5} - w) \times G_5 \times (1 - e^{-(t - t_{d5} - w)/\tau_5}) \tag{5a}$$

The parameters of the models were calculated using a weighted non-linear least squares estimating procedure, according to Carson et al. (1983), and implemented by means of the commercial software Labview 5.0 (National Instruments, USA). Initial guesses of the parameters of the model were entered after visual inspection of the data.

To judge the proportionality of the amplitude's terms of responses to different forms of forcing functions, their absolute values were normalised. To this aim, the estimated amplitudes of the responses to ST-ON, ST-OFF, and I were divided by the ratios between the corresponding network rate increments and 40 W, which corresponded to the net increment of the lowest step exercise. The normalising coefficients were:

- ST-ON/OFF: Δ 40 W = 1 (40/40 W); Δ 80 W = 2 (80/40 W); Δ 120 W = 3 (120/40 W);
- I: $I_{\Delta\ 240\ W}$ = 6 (240/40 W); and $I_{\Delta\ 400\ W}$ = 10 (400/40 W).

Normalised gains of the ramp fitting equations were obtained by multiplying the terms G_1 and G_2, of Eq. 3, by the exercise duration (6 min) and then divided by three, thus obtaining G_{1n} and G_{2n} terms, which are comparable to those referring to the lowest ST-ON.

Statistics

Mean values are presented in the text and in the tables with corresponding standard deviations. Comparisons of the parameter values (amplitudes, time constants, and time delays) between step transitions of different intensities, ramp and impulse ''were performed by means of a non-parametric Friedman test (Daniel 1991). In the case of a positive Friedman test, a non-parametric Wilcoxon test (Daniel 1991) was performed to single out paired differences. Asymmetry between ON and OFF phases was tested separately within each of the three step work rates, using a non-parametric Wilcoxon test for paired data. The test was applied to all the estimated parameters describing kinetics. The accepted critical level for statistical significance was set at $P < 0.05$.

To evaluate which of the two models (four or five components) more appropriately fitted impulse responses, an F-test was applied (Daniel and Wood 1980). The F-test assesses whether the reduction of the residual sum of squares was sufficient to compensate for the reduction of the degrees of freedom. Linear regression was calculated by means of the least-square method.

Results

The average $\dot{V}O_{2A}$ at steady state during the phase preceding the exercise transitions, while the subjects were pedalling at 10 W, amounted to 0.75 l min^{-1} (0.158). Oxygen uptake at steady state of the step exer-
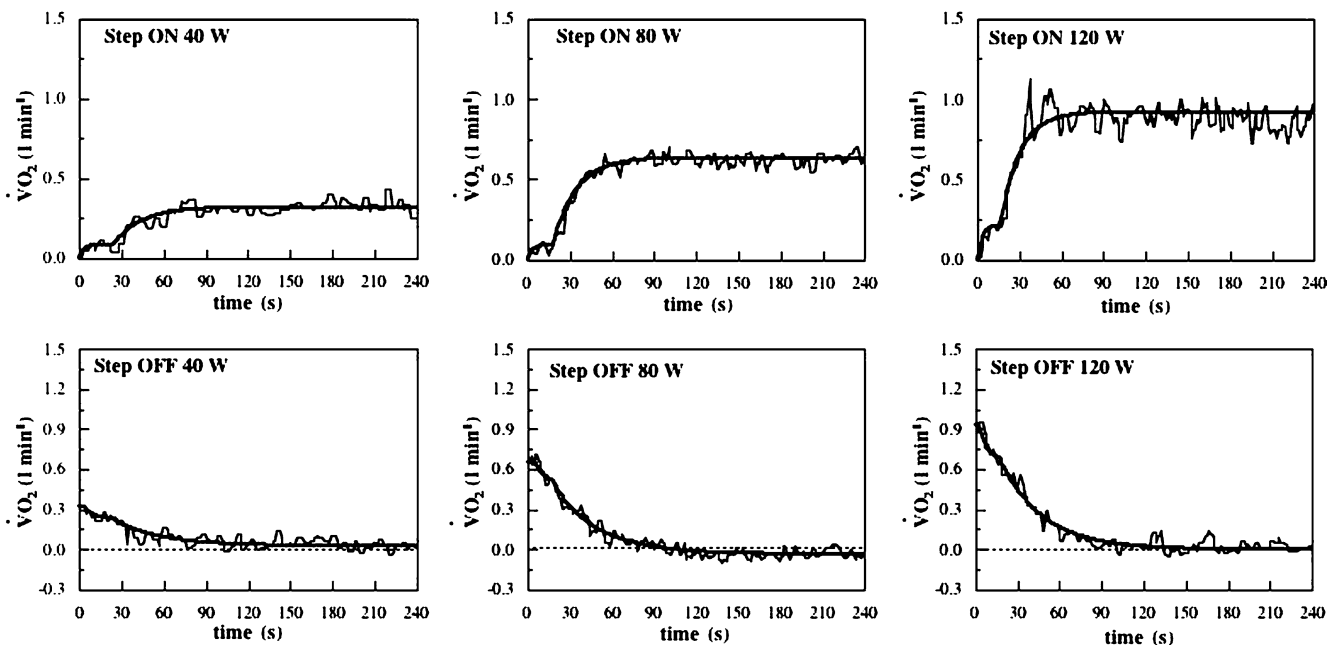

Fig. 1 Breath-by-breath alveolar oxygen uptake ($\dot{V}O_{2A}$) (*thin lines*) assessed in a typical subject during the three ST-ON (*upper row*) and ST-OFF (*lower row*) transitions and the corresponding fitting functions (*thick lines*) are represented as a function of the time elapsed from the beginning of exercise. The models fitting the experimental data are described by Eqs. 1 and 2 reported in the text. *Graphs* represent the $\dot{V}O_{2A}$ data above the baseline value and referring to the first 4 min of exercise and recovery, respectively

cise was 1.20 (0.131), 1.50 (0.060), and 1.84 1 min^{-1} (0.112) at 50, 90, and 130 W, respectively. The highest work rates imposed during the step exercise transition and attained at the plateau of the ramp amounted to on an average, 43.3% of the maximal metabolic power of the subjects [4.24 1 min^{-1} (0.67)] and to 71% of the $\dot{V}O_{2A}$ corresponding to the individual AT_V [2.60 1 min^{-1} (0.91)]. The maximal experimental amplitude of the $\dot{V}O_{2A}$ responses induced by the impulses amounted to, on an average, 1.24 and 1.17 1 min^{-1}, for the longest and shortest impulse, respectively, corresponding to 52 and 50% of the individual AT_V.

The $\dot{V}O_{2A}$ data of a typical subject during the three ST-ON and ST-OFF phases, along with their fitting functions, are presented in Fig. 1. The $\dot{V}O_{2A}$ data, observed during the two impulses and in the ramp tests, are shown in Fig. 2 along with the corresponding fitting curves. Diagrams A and B report the curves obtained by fitting the impulse data, by means of the four-component and five-component models, respectively.

Step and ramp responses

Average values, plus-minus their standard deviations, of: (i) the normalised gain terms (G_{1n} and G_{2n}), together with their sum ($G_{1n} + G_{2n}$), (ii) time delays (t_{d1} and t_{d2}) and; (iii) time constants (τ_1 and τ_2), of the functions describing phases I and II of $\dot{V}O_{2A}$ kinetics during ST-ON, ST-OFF and R, are presented in Tables 1 and 2, respectively. The absolute gain terms, in litres of oxygen per minute of the ON and OFF step exercise at the three intensities, are reported in Table 3.

A Friedman non-parametric test applied on the parameters of the models describing ST-ON and R did not show any significant differences.

The same analysis performed on the parameters of the ST-OFF kinetics did not demonstrate any significant difference among the intensities of the three work rates.

On the contrary, τ_1, τ_2, and t_{d1} of ST-ON were significantly lesser than their counterparts τ_3, τ_4, and t_{d3} of the corresponding ST-OFF phase, in all the three evaluated workloads.

Fig. 2 Breath-by-breath alveolar oxygen uptake ($\dot{V}O_{2A}$) (*thin lines*) assessed in a typical subject during the impulse and the ramp tests and the corresponding fitting functions (*thick lines*) are represented as a function of the time elapsed from the beginning of the exercise. The models fitting the experimental data are described by Eqs. 4 and 5 reported in the text. Impulse data are presented with the 4-component (diagram A) and 5-component (diagram B) models. As for Fig. 2, the graphs report the data above the value at rest and occurring in the 4 min after the onset of the exercise, with the exception of the Ramp diagram, which reports the $\dot{V}O_{2A}$ data measured during all the 6 min of the exercise
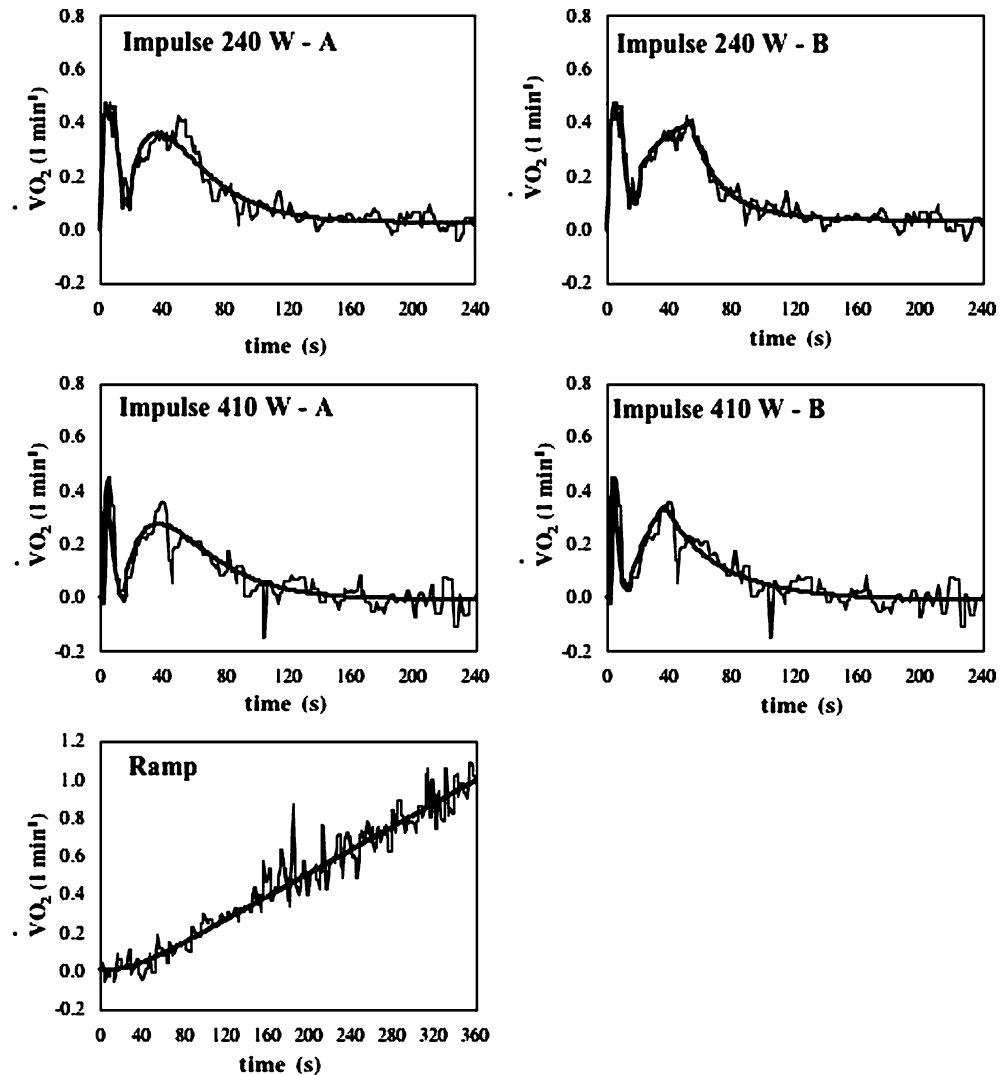
Impulse response

Normalised gain terms of the four-component and five-component models fitting the ON (G_{1n} and G_{2n}) and OFF (G_{3n}, G_{4n}, and G_{5n}) impulse responses are presented, together with their sums and the corresponding time delays and time constants, in Table 4. The corresponding absolute values of the gain terms are summarised in Table 5.

No significant differences were detected between the parameters of the four-component response to $I_{\Delta\ 240\ W}$ and $I_{\Delta\ 4000\ W}$, with the exception of G_{2n}, which was significantly smaller in the lowest intensity impulse.

As far as the five-component model is concerned, paired comparisons performed by means of a Wilcoxon test showed that G_{1n}, and G_{5n} were larger, and τ_1 longer, in $I_{\Delta\ 240\ W}$ than $I_{\Delta\ 400\ W}$, whereas G_{2n} and G_{4n} was smaller in $I_{\Delta\ 240\ W}$ than $I_{\Delta\ 400\ W}$.

The comparison of the parameters of the four-component impulse response with those of ST-ON, ST-OFF, and R showed that: (i) G_{2n} of $I_{\Delta\ 240\ W}$ was significantly smaller than that of ST-ON Δ 120 W; (ii) G_{2n} of $I_{\Delta\ 400\ W}$ was significantly larger than that of ST-ON Δ 40 W and; (iii) t_{d3} was significantly lesser in the two impulse transitions than in ST-OFF Δ 120 W.

Also the ON and OFF phases of the four-component impulse tests were characterised by significant asymmetry. τ_3, τ_4, t_{d3}, and t_{d4} were significantly longer than τ_1, τ_2, t_{d1}, and t_{d2}.

Finally, a Friedman non-parametric test, performed to compare the parameters of five-component impulse models with those of ST-ON and R, did not reveal any significant difference, with the exception of G_{1n} and G_{2n}

of $I_{\Delta\ 400\ W}$, which were smaller and larger than in the other cases, respectively.

Efficiency of the exercise

In Fig. 3, the absolute values ($n = 25$) of the total gain terms ($G_1 + G_2$) referring to ST-ON and I are plotted as a function of the corresponding network rate increments. The data was fitted ($r^2 = 0.975$) by means of a linear regression, without taking into consideration the y-intercept term. The reciprocal of the slope of the straight line corresponded to a value of delta efficiency ($\Delta\eta$), which amounted to 0.31. The latter was calculated assuming the consumption of 1 ml of oxygen yields 20.9 J of metabolic energy, a fact that is strictly true only if the respiratory quotient equals 0.96. $\Delta\eta$ in the case of the R exercise was calculated as the ratio between the linear work rate increment and the slope of BB $\dot{V}O_{2A}$ linear increase once the transient phase was completed, i.e. after the second minute of exercise. Its value amounted to, on an average, 0.33 ± 0.016.

Discussion

Steady state oxygen consumption during step exercises and at the end of the ramp exercise was well below the AT_V in each subject. Likewise, the amplitudes of the $\dot{V}O_{2A}$ response induced by the impulses were always below the ventilatory threshold of the subjects. Therefore, the imposed work rates were within the aerobic intensity of exercise and, as a consequence, early lactate

Table 1 Average values, with the corresponding standard deviations, of normalised gain terms (G_{1n} and G_{2n}), together with their sum ($G_{1n} + G_{2n}$), time delays (t_{d1} and t_{d2}) and time constants (τ_1 and τ_2) of the functions describing phases I and II of $\dot{V}O_{2A}$ kinetics at the onset of step (ST-ON) and during ramp (R) exercise

Exercise	G_{1n} (l min^{-1})	τ_1 (s)	t_{d1} (s)	G_{2n} (l min^{-1})	τ_2 (s)	t_{d2} (s)	$G_{1n} + G_{2n}$ (l min^{-1})	MSE
ST-ON	0.078	3.3	0.1	0.263	23.3	19.6	0.342	0.005
Δ 40 W	± 0.0233	± 0.51	± 0.15	± 0.0297	± 3.05	± 3.72	± 0.0173	± 0.0023
ST-ON	0.059	3.3	0.2	0.296	20.7	17.6	0.355	0.006
Δ 80 W	± 0.0169	± 0.39	± 0.39	± 0.0392	± 3.95	± 2.86	± 0.0347	± 0.0057
ST-ON	0.056	3.0	0.2	0.298	26.3	17.1	0.354	0.007
Δ 120 W	± 0.0183	± 0.63	± 0.27	± 0.0419	± 8.25	± 2.43	± 0.0292	± 0.0003
R	0.061	3.3	0.3	0.290	26.3	18.4	0.350	0.005
	± 0.0057	± 0.69	± 0.38	± 0.0256	± 6.74	± 3.59	± 0.0221	± 0.0023

Table 2 Average values, with the corresponding standard deviations, of normalised gain terms (G_{3n} and G_{4n}), time delays (t_{d3} and t_{d4}) and time constants (τ_3 and τ_4) of the functions describing $\dot{V}O_{2A}$ kinetics at the offset of step (ST-OFF) exercise

Exercise	G_{3n} (l min^{-1})	τ_3 (s)	t_{d3} (s)	G_{4n} (l min^{-1})	τ_4 (s)	t_{d4} (s)	$G_{3n} + G_{4n}$ (l min^{-1})	MSE
ST-OFF	0.070	4.5	2.1	0.283	34.1	17.6	0.353	0.006
Δ 40 W	± 0.0158	± 0.96	± 1.52	± 0.0487	± 7.39	± 5.85	± 0.0397	± 0.0039
ST-OFF	0.068	4.6	2.8	0.281	33.0	18.9	0.349	0.005
Δ 80 W	± 0.0150	± 0.93	± 2.77	± 0.0253	± 6.98	± 4.28	± 0.0155	± 0.0029
ST-OFF	0.072	4.6	3.0	0.271	32.5	16.9	0.343	0.004
Δ 120 W	± 0.0081	± 1.1	± 1.16	± 0.0308	± 3.79	± 0.67	± 0.0242	± 0.0019

Table 3 Average values, with the corresponding standard deviations, of the absolute gain terms (l min^{-1}), together with their sum, of the functions describing phases I and II of $\dot{V}O_{2A}$ kinetics at the onset (G_1, G_2, and $G_1 + G_2$) and offset (G_3, G_4, and $G_3 + G_4$) of step (ST) exercise at the three indicated work rates

Exercise	G_1 (l min^{-1})	G_2 (l min^{-1})	$G_1 + G_2$ (l min^{-1})	G_3 (l min^{-1})	G_4 (l min^{-1})	$G_3 + G_4$ (l min^{-1})
ST	0.078	0.263	0.342	0.070	0.283	0.353
Δ 40 W	± 0.0233	± 0.297	± 0.0173	± 0.0158	± 0.0487	± 0.0397
ST	0.119	0.591	0.710	0.137	0.562	0.698
Δ 80 W	± 0.0338	± 0.0784	± 0.0693	± 0.0300	± 0.0506	± 0.0309
ST	0.168	0.892	1.061	0.215	0.814	1.029
Δ 120 W	± 0.0549	± 0.1257	± 0.0875	± 0.0243	± 0.0924	± 0.0727

accumulation during the exercise transients (Cerretelli et al. 1979), and the appearance of a third phase of the $\dot{V}O_{2A}$ kinetics, characterised by a continuous increase in the oxygen uptake (Whipp and Wasserman 1972; Capelli et al. 1993), was avoided.

Linearity of the gas exchange system

This study investigated whether the system dictating alveolar gas exchanges in humans behaves linearly in response to different modalities of exercise performed below the ventilatory anaerobic threshold. First, the results obtained while investigating the gas exchange response to the step and ramp exercises are discussed. Then the $\dot{V}O_{2A}$ kinetics obtained by analysing impulse exercise inputs will be considered. Finally, the possible causes of the asymmetry between the ON and OFF response to the step and impulse, which was found in the present study, will be discussed.

Step and ramp exercise

Amplitudes, time delays, and time constants of the ST-ON and R exercises did not differ significantly. The same held true for the ST-OFF, when recovery was considered separate from the corresponding ST-ON. On the basis of these results, therefore, it can be concluded that, if the ON and OFF responses are considered separately, the system dictating alveolar gas exchanges in humans is linear, at least in these two exercise modalities. Indeed, in a linear dynamic system, the amplitude of the response i.e. increase in the $\dot{V}O_{2A}$ is proportional to the magnitude of the input function (increase in work rate) and the kinetic parameters (time constants and time delays) are equal for different input intensities and work rate forcing functions.

The finding of a linear behaviour of the gas exchange system, during the ST-ON and R exercises, is in contrast with the results reported by Hughson et al. (1988), who showed that the time constant of phase II of a small-amplitude, sub-maximal step exercise was significantly longer than any of the other higher amplitude step tests. More recently, Koppo et al. (2004) showed that the $\dot{V}O_{2A}$ phase II kinetics became slower at high power

outputs, than at moderate exercise intensities, both in trained and untrained subjects and that it was faster in trained athletes. This finding suggested that factors other than O_2 availability, such as type II muscle fibres recruitment, may affect the $\dot{V}O_{2A}$ phase II kinetics. Other studies, however, suggest that time constants are not affected by the amplitude of the inputs (Whipp and Wasserman 1972), and are in agreement with the findings reported in this study, which does not reject the hypothesis of a linear behaviour of the gas-exchange system.

A frank non-linearity of the system might suggest that the $\dot{V}O_{2A}$-kinetics are affected by the inertia of the cardiovascular oxygen transport in coping with the energetic requirements set at the beginning of the exercise (Hughson and Morissey 1982; Hughson et al. 1996; MacDonald et al. 1997; Tschakovsky and Hughson 1999), even though the role of peripheral factors, such as muscle fibres composition, may not be ruled out as a possible cause of the non-linear behaviour of the $\dot{V}O_{2A}$ response. On the contrary, if $\dot{V}O_{2A}$ kinetics is linearly linked to the amount of free Cr derived from PCr splitting at the onset of the exercise (Binzoni et al. 1992; Prampero and Margaria 1968; Grassi 2000; Mahler 1985, Molé et al. 1985; Rossiter et al. 1999; Walsh et al. 2001; Whipp and Mahler 1980), then one can expect the gas-exchange system to behave linearly.

This different conclusion, made on the linear characteristics of the system, might be also partially explained by the different methodologies applied in the various studies. In the present investigation, single breath $\dot{V}O_{2A}$ values were calculated by applying the algorithm of Grønlund (1984). We have previously suggested that the Grønlund algorithm has some advantages over traditional algorithms (Capelli et al. 2001; Cautero et al. 2002, 2003).

Impulse exercise

Testing a dynamic linear system, by imposing impulse inputs, would make it possible to characterise its response features. Other authors have also applied this procedure to investigate the features of the gas exchange system. For instance, Hughson et al. (1988) modelled the impulse response as an ON-OFF step response.

Table 4 Average values, plus−minus their standard deviations, of normalised gain terms, together with their sum, time delays and time constants of the functions describing phases ON and OFF of $\dot{V}O_{2A}$ kinetics during impulse response

Exercise	G_{1n} (1 min⁻¹)	τ_1 (s)	t_{d1} (s)	G_{2n}	τ_2 (s)	t_{d2} (s)	$G_{1n}+G_{2n}$ (1 min⁻¹)	G_{3n} (1 min⁻¹)	τ_3 (s)	t_{d3} (s)	G_{4n} (1 min⁻¹)	τ_4 (s)	t_{d4} (s)	G_{5n} (1 min⁻¹)	τ_5 (s)	t_{d5} (s)	$G_{3n}+G_{4n}+G_{5n}$ (1 min⁻¹)	MSE
$I_{\Delta\,240\,w}$ 4	0.065 ±0.0094	4.1 ±2.33	1.2 ±1.23	0.279 ±0.0268	27.4 ±6.78	16.7 ±2.95	0.343 ±0.0271	0.068 ±0.0196	6.9 ±2.34	0.0 ±0.28	0.282 ±0.0397	31.3 ±3.96	13.5 ±3.67				0.350 ±0.0189	0.0028 ±0.0018
$I_{\Delta\,240\,w}$ 5	0.062 ±0.0127	3.3 ±2.32	1.3 ±0.96	0.290 ±0.0325	26.5 ±6.78	16.6 ±0.38	0.349 ±0.0254	0.043 ±0.0179	2.3 ±0.92	−0.1 ±0.11	0.253 ±0.0346	28.9 ±3.74	10.4 ±2.76	0.061 ±0.0124	28.7 ±16.6	40.0 ±6.31	0.356 ±0.0220	0.0024 ±0.0021
$I_{\Delta\,400\,w}$ 4	0.048 ±0.0126	3.8 ±3.17	0.3 ±0.74	0.298 ±0.0305	26.5 ±5.97	13.4 ±0.19	0.346 ±0.0210	0.060 ±0.0149	7.3 ±4.33	0.0 ±0.24	0.291 ±0.0338	32.0 ±5.64	11.9 ±3.34				0.351 ±0.0196	0.0030 ±0.0020
$I_{\Delta\,400\,w}$ 5	0.036 ±0.0081	1.6 ±1.29	0.4 ±0.88	0.311 ±0.0267	26.5 ±6.74	13.6 ±3.12	0.348 ±0.0258	0.030 ±0.0083	3.9 ±1.95	0.3 ±0.32	0.293 ±0.025	28.7 ±7.08	9.8 ±2.79	0.029 ±0.0051	30.9 ±15.0	38.2 ±5.96	0.352 ±0.0248	0.0025 ±0.0021

First row shows, at each intensity, the values referring to the four-component model; in the *second row* the parameters of the five-component fitting equation are reported

Then, to test the superposition principle, they compared the integrated impulse response with that of the ST-ON. Since these did not match, the authors concluded that the system was non-linear. It should be pointed out, however, that the superposition test is a suitable procedure to evaluate the linearity of the system only if the duration of the impulse forcing function tends to zero or, from the practical standpoint, is very short when compared with any of the time parameters of the system at stake (Fujihara et al. 1973a).

Indeed, in the present study, the impulse has been considered as a short ST-ON transient that is immediately followed by an ST-OFF transient. The ON phase of the response to the impulse was then compared: (i) with the ST-ON and the R responses and; (ii) its OFF-response was compared with the ST-OFF. The superposition principle, by comparing the integrated impulse with the ST-ON, was not tested as the shortest time constants of the system were, at the best, of the same order of magnitude of the impulses' width.

Finally, the two impulses ($I_{\Delta\,240\,w}$ and $I_{\Delta\,400\,w}$) have been modelled by means of four-component and five-component models.

The comparison of the parameters, obtained by fitting the responses to the two impulse intensities by means of the four-component model, revealed that only G_{2n} of the lowest impulse was significantly smaller than in $I_{\Delta\,400\,w}$. This could be ascribed to various causes. A possible explanation could be a greater recruitment of accessory muscles of the upper limbs, by the subjects, during the more intense impulse. These muscles would have assisted the subject to hold himself better on the ergometer and would have thus led to a larger metabolic demand.

Moreover, at the highest work rate, a larger number of fast twitch fibres were likely to be recruited than at a lower intensity. The greater G_{2n} amplitude of the response observed in $I_{\Delta\,4000\,w}$ may be attributed to their lower efficiency (Kushmerick 1983).

The observation that the sum of G_{1n} and G_{2n} were not significantly different between the two impulses suggests another possibility. Indeed, this implies that in $I_{\Delta\,400W}$ the increase of G_{2n} compensates for the decrease of G_{1n}, although no statistically significant difference between the two G_{1n} was detected. The larger phase I amplitude of the lowest intensity impulse would suggest a greater role of the cardiodynamic phase in raising the whole body's oxygen uptake, and it may be justified by the longer duration of this impulse (10 s) in contrast to that of $I_{\Delta\,400\,w}$ (5 s). About 5 s may be too short an interval for permitting the pulmonary blood flow to attain a steady level, as is also shown by the average values of τ_1. Moreover, it is worth underlining the fact that the greater G_{2n} of $I_{\Delta\,400\,w}$ cannot account for lactic energy contribution. Rather, a larger contribution of anaerobic glycolysis at the highest impulse intensity would have decreased the amplitude of the $\dot{V}O_2$ response.

The comparison between the four-component impulse response and those of the other exercise modalities has failed to pass the criteria for linearity because G_{2n}

Table 5 Average values, with the corresponding standard deviations, of absolute gain terms, together with their sum, of the functions describing phases ON and OFF of $\dot{V}O_{2A}$ kinetics during impulse response

Exercise	G_1 (l min^{-1})	G_2 (l min^{-1})	$G_1 + G_2$ (l min^{-1})	G_3 (l min^{-1})	G_4 (l min^{-1})	G_5 (l min^{-1})	$G_3 + G_4 + G_5$ (l min^{-1})
$I_{\Delta\ 240\ W}$ 4	0.387 ±0.0561	1.673 ±0.1607	2.061 ±0.1623	0.407 ±0.1178	1.695 ±0.2379		2.102 ±0.1313
$I_{\Delta\ 240\ W}$ 5	0.372 ±0.0760	1.722 ±0.1736	2.095 ±0.1524	0.255 ±0.1072	0.363 ±0.0744	1.516 ±0.2077	2.134 ±0.1318
$I_{\Delta\ 400\ W}$ 4	0.478 ±0.1264	2.984 ±0.3051	3.461 ±0.2097	0.596 ±0.1490	2.910 ±0.3376		3.507 ±0.1961
$I_{\Delta\ 400\ W}$ 5	0.365 ±0.0806	3.114 ±0.2667	3.478 ±0.2582	0.302 ±0.0829	0.294 ±0.0509	2.926 ±0.2504	3.523 ±0.2475

First row shows, at each intensity, the values referring to the four-component model; in the *second row* the parameters of the five-component fitting equation are reported

and t_{d3} showed significant differences in the different exercise modalities. This finding might derive from the application of an inadequate model for fitting the $\dot{V}O_{2A}$ data in response to the impulses. In the present paper, the impulse responses were fitted by means of the five-component model (two components for the ON phase and three for the OFF phase). An *F*-test ($P < 0.05$) applied to the two models indicated that the five-component model better fitted the data of the input responses. The comparison between the parameters of the five-component impulse models with those of the ST-ON and R did not reveal any significant difference, with the exception of G_{1n} and G_{2n} of $I_{\Delta\ 400\ W}$, which turned out to be smaller and larger than in the other cases, respectively. These results extend the range of the linearity of the system to the lowest intensity impulse. They suggest that, when high intensity, short-width exercises are explored, additional causes come into play, which distort the gas exchange response.

The more complex model introduces a third OFF-component, appearing after about 40 s upon the return of the work rate to the baseline. The presence of a third

mono-exponential decay accounts for a slower decay of the $\dot{V}O_{2A}$ after the impulse. This finding may be tentatively described as follows. Although the $\dot{V}O_{2A}$ absolute response is lesser than the oxygen uptake corresponding to the AT_V, the high work rate suddenly imposed on the muscles may bring about a brisk acceleration of anaerobic glycolysis and lactate accumulation in the muscle. Indeed, Jacobs et al. (1983) found that the muscle's lactate concentration, after 10-s of supra-maximal cycling exercise, was approximately five times as high as the concentration when at rest. The increased hydrogen ion concentration (H^+) in the muscle, due to the abrupt rise of lactate, brings about a shift to the right of the equilibrium constant of the Lohmann reaction (Harris et al. 1977) and, hence, a parallel increase of Cr in the muscle. As already stated, the rate of oxidative metabolism is likely to be controlled by the level of muscular Cr. Therefore, the sustained concentration of Cr could account for the slower decay of the oxygen uptake, occurring in the recovery phase after ahigh intensity exercise. A similar hypothesis was previously proposed to explain the slow exponential $\dot{V}O_2$ decrease after heavy exercise (Cerretelli and di Prampero 1987), and was reappraised and discussed in a recent review (MacMahon and Jenkins 2002).
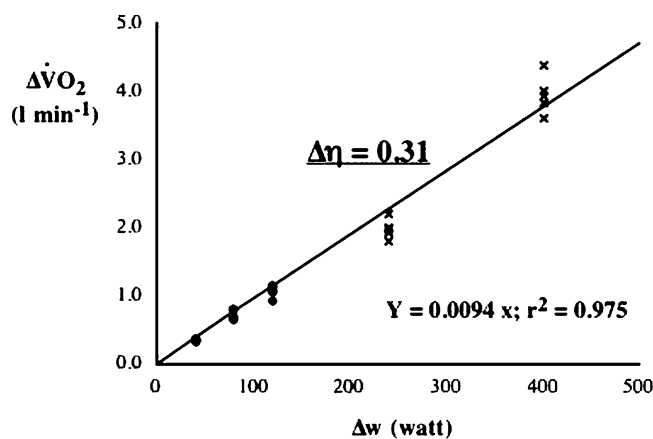
ON and OFF response asymmetry

Despite the deep interest in the study of gas exchange dynamics at the onset-offset of exercise, the symmetry between the ON and OFF phases has not yet been extensively investigated, nor its physiological determinants fully understood.

In the present study, a significant asymmetry was shown between the ON and OFF responses of the same work rate forcing functions (ST and *I*). This was in agreement with the results obtained by other investigators, who measured oxygen uptake at the mouth (Linnarsson 1974) or at the alveolar level, during different types of exercise (Brittain et al. 2001; Carter et al. 2000; Miyamoto and Niizeki 1992), but in disagreement with others (Griffiths et al. 1986; Paterson and Whipp 1994; Özyener et al. 2001).

Fig. 3 Absolute values of the total gain terms of the ST-ON (*filled circle*) and *I* (*crossed symbol*) exercise as a function of the corresponding network rate increments. Delta efficiency ($\Delta\eta$) was calculated as the reciprocal of the slope assuming an energy equivalent for oxygen equal to 20.9 J ml O$_2^1$ (see text for more details)

Although the determinant of the reported asymmetry of gas exchange kinetics between the ON and OFF phases is still unclear, one possible explanation may reside in the different kinetics of PCr splitting and resynthesis, which is measured by using direct bioptic sampling (Piiper and Spiller 1970) or P^{31} NMR (Rossiter et al. 2002). This non-symmetric rate has been explained as the consequence of the alterations of forward and backward Cr kinase fluxes, and justified by a theoretical dynamical model of the energy balance in muscle activity (Kushmerick 1998). This model, by means of differential equations, coupled the rates of ATPase and creatine kinase (CK) to oxidative phosphorylation and indicated that PCr breakdown at the onset of a step exercise is faster than its resynthesis during recovery. This is because different processes come into play in the two phases. At the onset of the exercise, the intervening processes are rapid and consist of the prompt onset of a high ATPase activity, the coexistence of CK forward and backward fluxes (forward flux faster than backward one) and an increasing oxidative turnover. During recovery, the ATPase goes back to its baseline and the remaining processes are now only the PCr fluxes and the declining oxidative rate (Kushmerick 1998). As a consequence of the faster breakdown rate of PCr, the time constant of the exponential Cr increase, during the ON transient, is shorter than that of its decrease during the OFF transient.

As the rate of oxidative metabolism is linearly controlled by free Cr concentration (or by some other compound whose concentration is proportional to that of Cr) (Mahler 1985; Connett and Honig 1989; Walsh et al. 2001), the slower $\dot{V}O_{2A}$ kinetics occurring at the OFF phase of the exercise would be a mirror image of the slower time course of PCr resynthesis. As such, the results obtained in this study would strengthen the hypothesis of a direct link between the muscular oxidative rate and the $\dot{V}O_{2A}$ kinetics at the level of the whole body, during both the ON and OFF phases, and are not against the view of a linear behaviour of the gas-exchange system.

Conclusions

The results of the present study showed that time delays and time constants of the ST-ON and ramp exercise did not differ and that the amplitudes were proportional to the input intensities. The same held true when ST-OFF was considered separately. These findings confirm the fact that the system controlling alveolar gas exchange in humans is linear and strengthens the hypothesis of a close link between it and the system that dictates metabolic respiratory rate in the muscular mitochondria, at least with these work rate forcing functions.

The same analysis applied to the impulse exercise revealed that the assumed model, utilised for fitting the $\dot{V}O_{2A}$ data, and the duration intensity of the exercise might substantially affect the results, leading to confounding conclusions regarding the linearity of the system.

Finally, a clear asymmetry was shown between the ON and OFF responses, in agreement with the results obtained by other investigators. This finding strengthens even more the hypothesis that gas exchange in humans behaves linearly and is in accordance with the reported asymmetry between the splitting and the resynthesis rates of PCr.

References

Barstow TJ, Lamarra N, Whipp BJ (1990) Modulation of muscle and pulmonary O_2 uptakes by circulatory dynamics during exercise. J Appl Physiol 68:979–986

Binzoni T, Ferretti G, Schenker K, Cerretelli P (1992) Phosphocreatine hydrolysis by 31P-NMR at the onset of constant-load exercise. J Appl Physiol 73:1644–1649

Brittain CJ, Rossiter HB, Kowalchuk JM, Whipp BJ (2001) The kinetics of O_2 uptake kinetics in different regions of the moderate intensity domain in humans. J Physiol (Lond) 531 P, 44P

Capelli C, Antonutto G, Zamparo P, Girardis M, di Prampero PE (1993) Effects of prolonged cycloergometric exercise on maximal power and oxygen uptake on humans. Eur J Appl Physiol 66:189–195

Capelli C, Cautero M, di Prampero PE (2001) New perspectives in breath-by-breath determination of alveolar trans-membrane gas exchange in humans. Pflügers Arch 44:566–577

Carson ER, Cobelli C, Finkelstein L (1983) The mathematical modelling of metabolic and endocrine systems. Wiley–Interscience, New York, pp 179–216

Carter H, Jones AM, Barstow TJ, Burnley M, Williams CA, Doust JH (2000) Oxygen uptake kinetics in treadmill running and cycle ergometry: a comparison. J Appl Physiol 89:899–907

Casaburi R, Daly J, Hensen JE, Effros RM (1989) Abrupt changes in mixed venous blood gas composition after the onset of exercise. J Appl Physiol 67:1106–1112

Cautero M, Beltrami AP, di Prampero PE, Capelli C (2002) Breath-by-breath alveolar oxygen transfer at the onset of step exercise in humans: methodological implications. Eur J Appl Physiol 88:203–213

Cautero M, di Prampero PE, Capelli C (2003) New acquisitions in the assessment of breath-by-breath alveolar gas transfer in humans. Eur J Appl Physiol 90:231–241

Cerretelli P, Prampero di PE (1987) Gas exchange in exercise. In: Fishman AP, Farhi LE, Tenney SM (eds) Handbook of physiology. Section 3: the respiratory system, vol IV. Gas Exchange, American Physiological Society, Bethesda, pp 297–339

Cerretelli P, Pendergast DR, Paganelli WC, Rennie DW (1979) Effects of specific muscle training on the $\dot{V}O_2$ on-response and early blood lactate. J Appl Physiol 47:761–769

Clemensen P, Christensen P, Norsk P, Grønlund (1994) A modified photo and magnetoacustic multigas analyzer applied in gas exchange measurements. J Appl Physiol 76:2832–2839

Connett RJ, Honig CR (1989) Regulation of $\dot{V}O_2$ in red muscle: do current biochemical hypothesis fit in vivo data? Am J Physiol 256:R898–R906

Daniel WW (1991) Biostatistics: a foundation for analysis in the health sciences. Wiley, New York, pp 576–630

Daniel C, Wood FS (1980) Fitting equations to data. Computer analysis of multifactorial data. Wiley, New York, pp 267–299

Engelen M, Porszasz, Riley M, Wasserman K, Maehara K, Barstow TJ (1996) Effects of hypoxic hypoxia on O2 uptake and heart rate kinetics during heavy exercise. J Appl Physiol 81:2500–2508

Fujihara Y, Hildebrandt JR, Hildebrandt J (1973a) Cardiorespiratory transients in exercising man. I. Test of superposition. J Appl Physiol 35:58–67

Fujihara Y, Hildebrandt J, Hildebrandt JR (1973b) Cardiorespiratory transients in exercising man. II. Linear models. J Appl Physiol 35:68–76

Grassi B (2000) Skeletal muscle $\dot{V}O_2$ on-kinetics: set by O_2 delivery or by O_2 utilization? New insight into an old issue. Med Sci Sports Exerc 32:108–116

Grassi B, Poole DC, Richardson RS, Knight DR, Erickson BK, Wagner PD (1996) Muscle O_2 uptake kinetics in humans: implications for metabolic control. J Appl Physiol 80:988–998

Griffiths TL, Henson LC, Whipp BJ (1984) Influence of inspired oxygen concentration on the dynamics of the exercise hyperpnoea in man. J Physiol (Lond) 380:387–403

Grønlund L (1984) A new method for breath-to-breath determination of oxygen flux across the alveolar membrane. Eur J Appl Physiol 52:167–172

Harris RC, Sahlin K, Hultman E (1977) Phosphagen and lactate contents of m. quadriceps femoris after exercise. J Appl Physiol 43:852–857

Hughson RL, Morrissey M (1982) Delayed kinetics of respiratory gas exchange in the transition from prior exercise. J Appl Physiol 52:921–929

Hughson RL, Sherrill DL, Swanson GD (1988) Kinetics of $\dot{V}O_2$ with impulse and step exercise in humans. J Appl Physiol 64:451–459

Hughson RL, Shoemaker JK, Tschakovski ME, Kowalchuck JM (1996) Dependence of muscle $\dot{V}O_2$ on blood flow dynamics at the onset of forearm exercise. J Appl Physiol 81:1619–1626

Jacobs I, Tesch PA, Bar-Or O, Karlsson J, Dotan R (1983) Lactate in human skeletal muscle after 10 and 30 s of supramaximal exercise. J Appl Physiol 55:365–367

Koppo K, Bouckaert J, Jones AM (2004) Effects of training status and exercise intensity on Phase II of $\dot{V}O_2$ kinetics. Med Sci Sports Exerc 36:225–232

Kushmerick MJ (1983) Energetics of muscle contraction. In: Peachy LE, Adrian RH, Geiger SR (eds) Handbook of physiology, Section 10, skeletal muscle: regulation and integration of multiple systems. American Physiological Society, Bethesda, pp 189–236

Kushmerick MJ (1998) Energy balance in muscle activity: Simulations of ATPase coupled to oxidative posporylation and to creatine kinase. Comp Biochem Physiol B Biochem Mol Biol 120:109–123

Lamarra N, Whipp BJ, Ward SA, Wasserman K (1987) Effect of interbreath fluctuations on characterising exercise gas exchange kinetics. J Appl Physiol 62:2003–2012

Linnarsson D (1974) Dynamics of pulmonary gas exchange and heart rate changes at start an end of exercise. Acta Physiol Scand (Suppl 415):41–68

Loeppke JA, Greene ER, Hoekenga DE, Caprihan A (1981) Beat-by-beat stroke volume assessment by pulsed Doppler in upright and supine exercise. J Appl Physiol 50:1173–1182

MacDonald M, Pedersen PK, Hughson RL (1997) Acceleration of $\dot{V}O_2$ kinetics in heavy submaximal exercise by hyperoxia and prior high-intensity exercise. J Appl Physiol 83:1318–1325

MacMahon S, Jenkins D (2002) Factors affecting the rate of phosphocreatine resynthesis following intense exercise. Sports Med 32:761–784

Mahler M (1985) First-order kinetics of muscle oxygen consumption and an equivalent proportionality between $\dot{Q}O_2$ and phosphorylcreatine level. J Gen Physiol 86:136–165

Miyamoto Y, Niizeki K (1992) Dynamics of ventilation, circulation and gas exchanges to incremental and decremental ramp exercise. J Appl Physiol 72:2244–2254

Molé PA, Coulson RL, Caton JR, Nichols BG, Barstow TJ (1985) In vivo 31P-NMR in human muscle: transient patterns with exercise. J Appl Physiol 59:101–104

Özyener F, Rossiter HB, Ward SA, Whipp BJ (2001) Influence of exercise intensity on the on-and off-transients kinetics of pulmonary oxygen uptake in humans. J Physiol (Lond) 533:891–902

Paterson DH, Whipp BJ (1994) Asymmetries of oxygen uptake transients at the on- and offset of heavy exercise in humans. J Physiol (Lond) 443:575–586

Piiper J, Spiller P (1970) Repayment of O_2 debt and resynthesis of high-energy phosphates in gastrocnemius muscle of the dog. Am J Physiol 28:657–662

Prampero di PE, Margaria R (1968) Relationship between O_2 consumption, high-energy phosphates and the kinetics of the O_2 debt in exercise. Pflügers Arch 304:11–19

Prampero di PE, Davies CTM, Cerretelli P, Margaria R (1970) An analysis of O_2 debt contracted in submaximal exercise. J Appl Physiol 29:547–551

Prampero di PE, Boutellier U, Pietsch P (1983) Oxygen deficit and stores at the onset of muscular exercise in humans. J Appl Physiol 55:146–153

Prampero di PE, Mahler PB, Giezendanner D, Cerretelli P (1989) Effects of priming exercise on $\dot{V}O_2$ kinetics and O_2 deficit at the onset of stepping and cycling. J Appl Physiol 66:2023–2031

Rossiter HB, Ward SA, Doyle VL, Howe FA, Griffiths JR, Whipp BJ (1999) Inferences from pulmonary O_2 uptake with respect to intramuscular [phosphocreatine] kinetics during moderate exercise in humans. J Physiol (Lond) 518:921–932

Rossiter HB, Ward SA, Kowalchuk JM, Howes FA, Griffiths JR, Whipp BJ (2002) Dynamic asymmetry of phosphocreatine concentration and O_2 uptake between the on- and off- transients of moderate and high-intensity exercise in humans. J Physiol (Lond) 541:991–1002

Rowell LB, O'Leary DS, Kellogg Dl Jr (1996) Integration of cardiovascular control systems in dynamic exercise. In: Rowell LB, Shepherd JT (eds) Handbook of physiology, Section 12, exercise: regulation and integration of multiple systems. Oxford University Press, New York, pp 770–838

Tschakovsky ME, Hughson RL (1999) Interaction of factors determining oxygen uptake at the onset of exercise. J Appl Physiol 86:1101–1113

Walsh B, Tonkonogi M, Söderlund, Hultman E, Saks V, Sahlin K (2001) The role of phosphorylcreatine and creatine in the regulation of mitochondrial respiration in human skeletal muscle. J Physiol (Lond) 537:971–978

Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ (1999) Principles of exercise testing and interpretation. Lippincott Williams and Wilkins, Philadelphia, pp 73–76

Whipp BJ, Mahler M (1980) Dynamics of pulmonary gas exchange during exercise. In: West J (ed) Pulmonary gas exchange. Academic Press, New York, pp 33–96

Whipp BJ, Ward SA (1990) Physiological determinants of pulmonary gas exchange kinetics during exercise. Med Sci Sports Exerc 22:62–71

Whipp BJ, Wasserman K (1972) Oxygen uptake kinetics for various intensities of constant-load work. J Appl Physiol 33:351–356

Wigertz O (1971) Dynamics of respiratory and circulatory adaptation to muscular exercise in man. Acta Physiol Scand (Suppl 363):1–32