Eur J Appl Physiol (2004) 93: 9–18
DOI 10.1007/s00421-004-1149-7

ORIGINAL ARTICLE

**Ruddy Richard · Evelyne Lonsdorfer-Wolf
Stéphane Dufour · Stéphane Doutreleau
Monique Oswald-Mammosser · Véronique L. Billat
Jean Lonsdorfer**

Cardiac output and oxygen release during very high-intensity exercise performed until exhaustion

Accepted: 5 April 2004 / Published online: 27 July 2004

Abstract Our objectives were firstly, to study the patterns of the cardiac output ($\dot{Q}$) and the arteriovenous oxygen difference [$(a-\bar{v})O_2$] responses to oxygen uptake ($\dot{V}O_2$) during constant workload exercise (CWE) performed above the respiratory compensation point (RCP), and secondly, to establish the relationships between their kinetics and the time to exhaustion. Nine subjects performed two tests: a maximal incremental exercise test (IET) to determine the maximal $\dot{V}O_2$ ($\dot{V}O_2$peak), and a CWE test to exhaustion, performed at $p\,\Delta 50$ (intermediate power between RCP and $\dot{V}O_2$peak). During CWE, $\dot{V}O_2$ was measured breath-by-breath, $\dot{Q}$ was measured beat-by-beat with an impedance device, and blood lactate (LA) was sampled each minute. To calculate $(a-\bar{v})O_2$, the values of $\dot{V}O_2$ and $\dot{Q}$ were synchronised over 10 s intervals. A fitting method was used to describe the $\dot{V}O_2$, $\dot{Q}$ and $(a-\bar{v})O_2$ kinetics. The $(a-\bar{v})O_2$ difference followed a rapid monoexponential function, whereas both $\dot{V}O_2$ and $\dot{Q}$ were best fitted by a single exponential plus linear increase: the time constant (τ) $\dot{V}O_2$ [57 (20 s)] was similar to τ $(a-\bar{v})O_2$, whereas τ for $\dot{Q}$ was significantly higher [89 (34) s, $P<0.05$] (values expressed as the mean and standard error). LA started to increase after 2 min CWE then increased rapidly, reaching a similar maximal value as that seen during the IET. During CWE, the rapid component of $\dot{V}O_2$ uptake was determined by a rapid and maximal $(a-\bar{v})O_2$ extraction coupled with a two-fold longer $\dot{Q}$ increase. It is likely that lactic acidosis markedly increased oxygen availability, which when associated with the slow linear increase of $\dot{Q}$, may account for the $\dot{V}O_2$ slow component. Time to exhaustion was larger in individuals with shorter time delay for $(a-\bar{v})O_2$ and a greater τ for $\dot{Q}$.

Keywords Oxygen slow component · Cardiac output · Arteriovenous oxygen difference · Time to exhaustion

R. Richard (✉) · E. Lonsdorfer-Wolf · S. Dufour · S. Doutreleau
M. Oswald-Mammosser · J. Lonsdorfer
Unité de Physiologie et des Explorations Fonctionnelles de l'Exercice, Service de Physiologie Clinique,
Hôpitaux Universitaires de Strasbourg, Hôpital Civil, BP 426,
67091 Strasbourg Cedex, France
E-mail: Ruddy.Richard@physio-ulp.u-strasbg.fr
Tel.: +33-3-88116122
Fax: +33-3-88116467

V. L. Billat
Département STAPS, UFR de Sciences, Université d'Evry
Val-d'Essonne, 91025 Evry Cedex, France

Introduction

Physiological factors contributing to cycling endurance performance [oxygen consumption ($\dot{V}O_2$), ventilatory and/or lactate thresholds] have been widely investigated (Foster et al. 1978; Hawley and Noakes 1992; Noakes et al. 1990). Nevertheless, the exact mechanisms forcing an athlete to stop at exhaustion while exercising at a given sub-maximal power output are not fully understood. However, it has been established that the accumulated oxygen deficit is an important correlate of the capacity to sustain sub-maximal exercise for long periods (Demarle et al. 2001; Hagberg et al. 1980). Therefore, the time to exhaustion (Tlim) could be related to some features of the $\dot{V}O_2$ kinetics, suggesting a link between Tlim and the rapidity of the aerobic metabolism to adapt. However, the role of the cardiac output ($\dot{Q}$) and of the arteriovenous oxygen difference [$(a-\bar{v})O_2$] in determining the $\dot{V}O_2$ response, and especially in setting the time to exhaustion during very heavy exercise, is to the best of our knowledge lacking at present.

The reasons for the lack of such measurements could be that routine $\dot{Q}$ measurements with either direct Fick, isotopic, or thermodilution methods (Warburton et al. 1999a) are unusual in healthy subjects, and that during high intensity exercise, indirect methods such as CO_2 or acetylene rebreathing tests are not appropriate for repeated $\dot{Q}$ measurements (Warburton et al. 1999b).

In previous studies (Charloux et al. 2000; Richard et al. 2001) we validated the impedance cardiograph

method against the invasive direct Fick method during both constant load and exhaustive incremental exercises. Beat-by-beat changes in the cardiac bioimpedance permit continuous measurements of stroke volume (SV), heart rate (HR) and $\dot{Q}$. Thus, if associated with breath-by-breath gas exchange measurements for $\dot{V}O_2$ determination, continuous $(a-\bar{v})O_2$ difference can be calculated with the Fick (Fick 1870) equation for oxygen since $\dot{V}O_2$ and $\dot{Q}$ are measured by different methods.

During constant load exercise below the anaerobic threshold (AT) (Wasserman et al. 1973), the $\dot{V}O_2$ response reaches a steady state in 2–3 min. The kinetics of $\dot{V}O_2$ uptake, as well as of $\dot{Q}$ and its components SV and HR, are well described by a monoexponential curve (De Cort et al. 1991). Above the AT, the $\dot{V}O_2$ steady state is delayed because a slow component of $\dot{V}O_2$ kinetics—of delayed onset—is superimposed on the fundamental exponential response. According to Poole (1994) and Whipp (1994), a $\dot{V}O_2$ steady state can be obtained, but it is increasingly delayed as the exercise intensity above AT increases. Subsequently, at a given high workload an additional $\dot{V}O_2$ component continues to develop until the subject reaches exhaustion.

Above a second threshold, termed the respiratory compensation point (RCP), i.e. the onset of exercise-induced hyperventilation related to the failure of the buffering mechanisms to maintain blood pH (Beaver et al. 1986), this additional $\dot{V}O_2$ component causes $\dot{V}O_2$ to attain the $\dot{V}O_2$peak value reached during an incremental work test. The higher the intensity of a constant load above the second threshold, the shorter will be the time to fatigue (reviewed by Billat et al. 1999). The muscular recruitment and local metabolic aspects of the mechanisms of this $\dot{V}O_2$ profile have been investigated (Poole 1994; Scheuermann et al. 2001). The relationship between $\dot{V}O_2$ and time to fatigue has been mentioned for the on-transient phase ($\dot{V}O_2$ adjustment during the rest to exercise transition) of oxygen kinetics (Ozyener et al. 2001; Paterson and Whipp 1991), but the time courses of $\dot{Q}$ (SV and HR) and ($a-\bar{v})O_2$ have not been investigated.

During very heavy leg exercise, where slow $\dot{V}O_2$ kinetics reflect a failure to deliver adequate O_2 to the muscles, we can pose the following questions: at what moment of a subject's constant load exercise is the maximal blood O_2 extraction obtained; and do the kinetics of the $\dot{Q}$ adjustment result in an inadequate O_2 delivery? To address these questions we performed a set of experiments where the exercise intensity was above the second threshold (RCP), i.e. at a median power ($p\Delta 50$) between the power associated with the RCP and peak effort. Thus the patterns of the simultaneous $\dot{Q}$ (SV, HR), ($a-\bar{v})O_2$ and LA responses during very high CWE may contribute to better understanding of the mechanisms leading to exhaustion.

Methods

Subjects

Nine healthy non-smoking volunteers (three females, six males) participated in this study. All subjects knew the protocol and the potential risks, and had given their informed consent. The protocol was approved by our Institutional Review Board. The physical characteristics of the subjects are reported in Table 1. All were free of cardiac and pulmonary disease.

Exercise procedures

Two tests [an incremental exercise test (IET), and a constant work rate exercise test (CWE)] were performed at 3-day intervals in an air-conditioned room at 21°C, 3 h after a light breakfast. The exercises were performed with the subjects in an upright position on an electronically braked cycle ergometer (Medifit 1000 S, Belgium). The seat and handlebar heights were set for each subject and held constant for all their tests. The pedalling frequency was constant at 70 rpm.

Incremental exercise test

Peak oxygen uptake

The exercise started at 80 W (60 W for the women) and the workload was increased in increments of 40 W (30 W for the women) every 3 min up to exhaustion. We took the peak oxygen uptake ($\dot{V}O_2$peak) as the maximal $\dot{V}O_2$ corresponding to the highest 30 s oxygen uptake measured during the last stage of the IET.

Table 1 Individual subject values: physical characteristics, peak oxygen consumption ($\dot{V}O_2$) and time until exhaustion during the incremental exercise

Subject	Age (yr)	Body mass (kg)	Height (cm)	Body fat (%)	$\dot{V}O_2$ peak (ml/kg per min)	Time to exhaustion (min)
1	40	78	178	21	56.5	11.17
2	22	77	182	11	55.8	12.00
3	30	63	177	14	42.4	9.25
4	26	69	179	12	57.2	8.50
5	33	65	181	16	54.6	7.00
6	38	81	180	21	57.0	13.17
7	32	59	174	18	44.0	8.50
8	29	68	172	22	43.9	20.00
9	29	64	173	26	49.2	15.75
Mean ± SD	31 (6)	69 (8)	177 (4)	18 (6)	51.2 (6.3)	11.70 (4.13)

Threshold determinations

The AT and RCP thresholds were determined both by gas exchange and lactate methods. Gas exchange thresholds were assessed using the methods reported by Wasserman (Wasserman et al. 1999). The AT was identified by the V-slope method of Beaver (Beaver et al. 1986) as the breakpoint in the plot of $\dot{V}CO_2$ as a function of $\dot{V}O_2$. At that point the ventilatory equivalent for oxygen ventilation $\dot{V}E/\dot{V}O_2$ increases without an increase in $\dot{V}E/\dot{V}CO_2$. This corresponds to the beginning of a sustained increase in the blood lactate concentration. The RCP is the threshold between AT and $\dot{V}O_2$peak, above which the ventilatory equivalent for CO_2, $\dot{V}E/\dot{V}CO_2$, starts to increase while $\dot{V}E/\dot{V}O_2$ continues to increase, reflecting the ventilatory compensation for the metabolic lactic acidosis induced by exercise (Wasserman et al. 1986).

Blood lactate thresholds were determined according to the method of Aunola and Rusko (1984, 1988). The AT was the intensity for which a sustained LA increase was measured. The RCP corresponds to the intensity above which an increase of 1 mmol/l or more of LA occurs, above a threshold of 3.5 mmol/l.

Constant work rate exercise

The subjects performed an exhaustive cycling exercise at $p\,\Delta 50$ interpolated from the IET. After a 15 min warm-up period below each subject's AT followed by a 5 min rest period, a square-wave transition from rest to $p\,\Delta\,50$ was applied, the subject being free to choose the start within a 20 s window. Each subject was then encouraged to sustain this load until exhaustion. This intensity was chosen to induce a $\dot{V}O_2$ slow component leading to the maximal $\dot{V}O_2$ in less than 20 min. At this intensity and duration, $\dot{V}O_2$ and HR increases are probably not influenced by thermoregulatory factors or by a shifted lipolysis (Cheatham et al. 2000; Gaesser and Poole 1996).

Measurements

Gas exchange variables

During all the exercises, $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$ were measured breath-by-breath with an open-circuit metabolic cart with rapid O_2 and CO_2 analysers (breath-by-breath metabolic measurement, Sensor Medics MSE). Before each individual exercise test, the pneumotachograph was calibrated with several strokes given by a 3 l calibration syringe. The gas analysers were calibrated using reference gases with known O_2 and CO_2 concentrations (12% O_2, 5% CO_2). Since breath-by-breath $\dot{V}O_2$ artificially increases the variability and yields spuriously long time constants (Capelli et al. 2001; Cautero et al. 2002, 2003), breath-by-breath data was later reduced to 30 s averages for the IET and to 10 s averages for the kinetics of the CWE (Lamarra et al. 1987).

Blood lactate

During both the IET and CWE tests, a 20-gauge catheter was inserted into an antecubital vein. Samples of 2 ml of venous blood were collected into iced tubes and immediately analysed. Blood lactate (LA) was measured in whole blood by the biochemical lactate oxidase reaction with reference to a calibration curve of a Chiron Diagnostics 800 Design (Ciba Corning Bayer France). For the IET, samples were taken at the end (minute 3) of each exercise step. In the CWE, blood was sampled during the last minute of rest, following the warm-up, and at each minute of the exercise.

$(a-\bar{v})O_2$ and $\dot{Q}$ determinations

$\dot{Q}$ was measured with the PhysioFlow (Manatec PF 0561, France) thoracic impedance device, which records SV and electrocardiographic (ECG) signals continuously. HR was obtained from the R-R intervals on the ECG first derivative d(ECG)/d t, which provides a more stable signal than the ECG trace itself. $\dot{Q}$ measurement by the device is based on arguments developed in Charloux et al. (Charloux et al. 2000). $\dot{Q}$ is given by the following formula: $\dot{Q} = \text{HR}\times\text{SVi}\times\text{BSA}$ where $\dot{Q}$ is expressed in l/min, SVi is the SV index (ml/m^2) and BSA is the body surface area. With the impedance device, a first evaluation of SVi, called SVi_{cal}, is computed during a calibration procedure based on 24 consecutive heartbeats recorded in the resting condition. This evaluation retains the largest impedance (Z) variation during the systole ($Z_{\max} - Z_{\min}$) and the largest rate of variation of the impedance signal [$(\text{d}Z/\text{d}t)_{\max}$, called the contractility index]. The SVi calculation also depends on the thoracic fluid inversion time (TFIT, in m/s) measured on the first derivative of the impedance signal (Fig. 1). The TFIT is the time interval between the first zero value following the beginning of the cardiac cycle (beginning of the ECGs QRS) and the first nadir after the peak of the ejection velocity ($\text{d}Z/\text{d}t)_{\max}$). Subsequently, the TFIT is weighted using a specific algorithm (Charloux et al. 2000). During the data acquisition phase, the parameter variations were analysed and compared to those obtained during the calibration procedure. For this experiment, SV and HR were measured continuously beat-to-beat throughout each test and later reduced to 10 s averages for the CWE and 30 s averages for the IET.

$(a-\bar{v})O_2$ determination

To obtain $(a-\bar{v})O_2$ we used the Fick equation applied to oxygen where $[(a-\bar{v})O_2\ \text{ml}/100\ \text{ml}] = (\dot{V}O_2\ \text{ml/min})/(\dot{Q}\ \text{l/min})$. Values from instantaneous measurements of $\dot{V}O_2$ and $\dot{Q}$ were averaged over 10 s periods. The averages

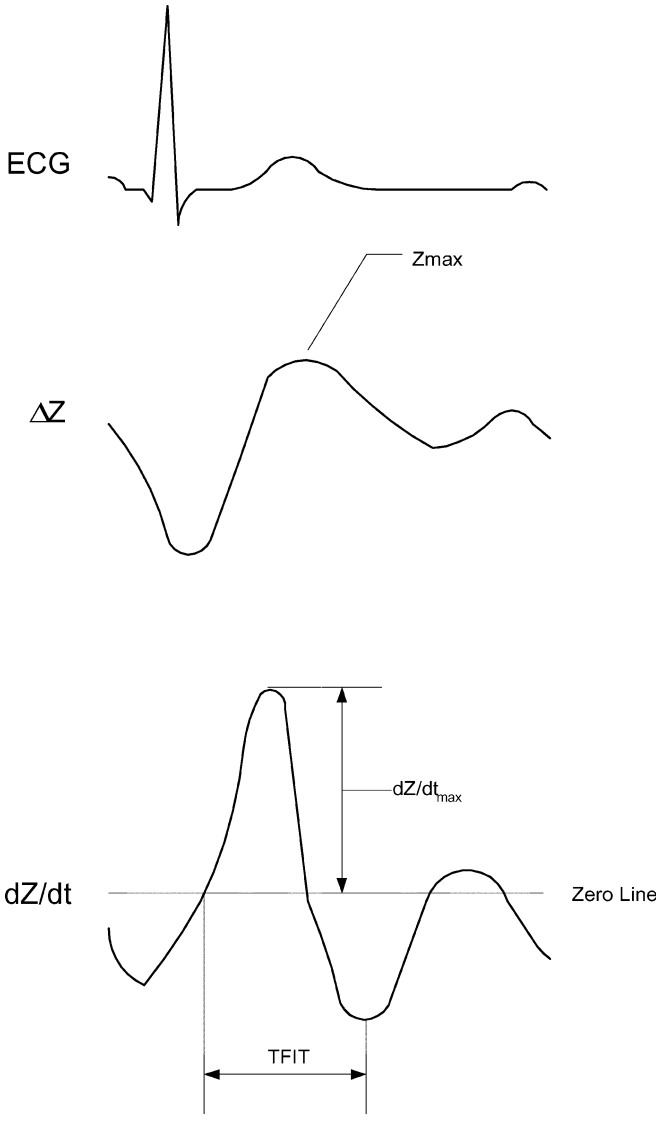

Fig. 1 Waveforms obtained with the impedance device. The *upper trace* is the electrocardiogram (ECG), the *middle* and *lower* traces are impedance variations during the systole (ΔZ) and its first derivative, d Z/d t, respectively. Thoracic fluid inversion time (*TFIT*) and d Z/d t_{max} are indicated on the latter waveform

were synchronised and associated for the same time period.

Data analysis

$\dot{V}O_2$, $(a-\bar{v})O_2$ and cardiodynamic variables

Figure 2 shows typical responses for one subject. An iterative non-linear regression using the Sigma Plot software (SPSS, Chicago, Ill., USA) was employed to determine the $\dot{V}O_2$, HR, SV, $\dot{Q}$ and $(a-\bar{v})O_2$ kinetics. Both phase I (cardiodynamic) and phase II (metabolic) were grouped together to form the first exponential term (Bearden and Moffatt 2000). The slow component kinetics (phase III) began afterwards to form the second term (Scheuermann et al. 2001). Three distinct formulations (Barstow and Mole 1991) were tested. For instance, for $\dot{V}O_2$, using a single exponential model (Model 1)

$$\dot{V}O_2(t) = \dot{V}O_{2\,b} + A_1 \times \left[1 - e^{\left(-(t-TD)/\tau\right)}\right] \times u_1$$

where TD is the time delay from the onset of exercise (s), t the time, $u_1 = 0$ when $t < TD$, $u_1 = 1$ when $t \geq TD$, $\dot{V}O_{2b}$ is the baseline value of $\dot{V}O_2$, A_1 is the asymptotic amplitude and τ is the time constant.

Using a two exponential model (Model 2)

$$\dot{V}O_2(t) = \dot{V}O_{2\,b} + A_1 \times \left[1 - e^{\left(-(t-TD1)/\tau 1\right)}\right] \times u_1 + A_2 \times \left[1 - e^{\left(-(t-TD2)/\tau 2\right)}\right] \times u_2$$

where TD_1 and TD_2 are the time delays from the onset of exercise and from the second exponential increase respectively, $u_1 = 0$ when $t < TD_1$, $u_1 = 1$ when $t \geq TD_1$, $u_2 = 0$ when $t < TD_2$, $u_2 = 1$ when $t \geq TD_2$; $\dot{V}O_{2b}$ is the baseline value; A_1 and A_2 are asymptotic amplitudes, and τ_1 and τ_2 are the time constants.

The third formulation uses a monoexponential term plus a linear component (Model 3)

$$\dot{V}O_2(t) = \dot{V}O_{2\,b} + A\left[1 - e^{\left(-(t-TD1)/\tau\right)}\right] + S(t - TD_2)$$

where $\dot{V}O_{2b}$ the baseline value of $\dot{V}O_2$, A the amplitude of the exponential term, TD_1 the time delay for the exponential, τ the time constant of the exponential, S the slope of the linear component and TD_2 the time delay for the beginning of the linear component. The Fisher test (using Sigma Plot software) was used to choose the model associated with the highest F value.

Statistical methods

Differences between the physiological variables (all of which were expressed as the mean value plus the standard error) were evaluated by analysis of variance for the repeated measurements (kinetic parameters during the CWE), or by use of the Wilcoxon test for the dependent paired values obtained during the IET and CWE. Correlations were computed using Spearman's test. Differences were considered significant at a P value of < 0.05.

Results

General description of the exercise tests

Peak values and values at AT and RCP, for $\dot{V}O_2$, $\dot{Q}$, $(a-\bar{v})O_2$ and LA during the IET and the CWE are presented in Table 2. During the IET, subjects reached 278 (55) W. This effort was maximal since the respiratory exchange ratio was 1.14 (0.03) and the LA was 11.0 (2.1) mmol/l. The $\dot{V}O_2$ (AT) and $\dot{V}O_2$ (RCP) represented respectively 62% and 86% of the $\dot{V}O_2$peak. The mean

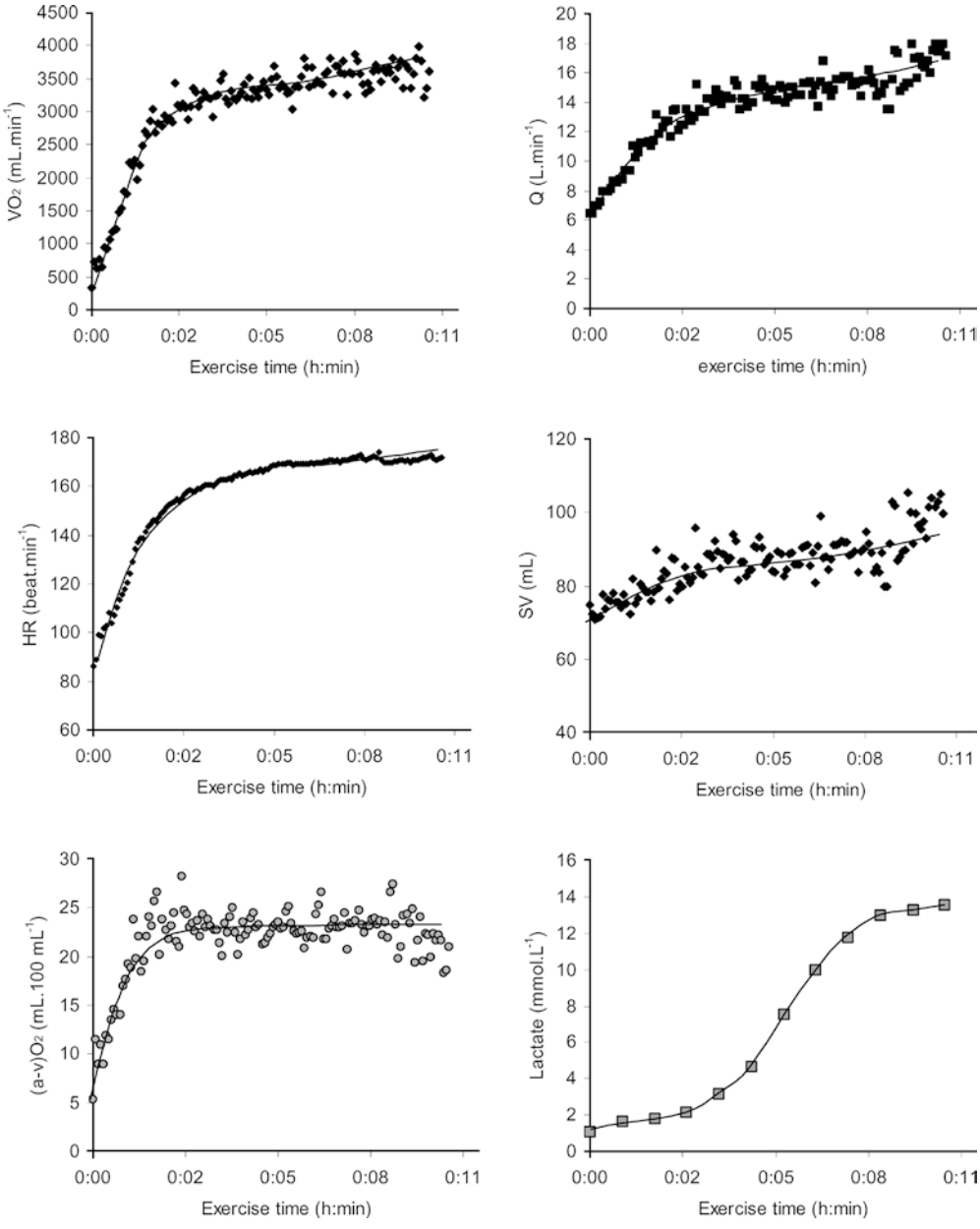

Fig. 2 Typical oxygen uptake ($\dot{V}O_2$), cardiac output ($\dot{Q}$), heart rate (HR), stroke volume (SV), arteriovenous oxygen difference [$(a - \bar{v})O_2$] and lactate responses in one subject during constant load exercise to exhaustion. Breath-by-breath values of $\dot{V}O_2$ as well as $\dot{Q}$, HR and SV, measured continuously, were smoothed to 10 s averages. Exercise to exhaustion was performed at $p\Delta 50$

Table 2 Power, oxygen consumption ($\dot{V}O_2$), cardiac output ($\dot{Q}$), arteriovenous oxygen difference [$(a-\bar{v})O_2$] and lactic acid (LA) values [mean (SD)] reached during the incremental exercise test (IET) at the anaerobic threshold, the respiratory compensation point, $p\Delta 50$, and at peak power. Corresponding values are presented for the constant work exercise (CWE) at minute 2 (with the onset of lactic acidosis), minute 4 (at onset of the $\dot{V}O_2$ linear increase after the second time delay) and at exhaustion

	Incremental exercise				Constant work exercise [251 (48) W]		
	Anaerobic threshold	Respiratory compensation point	$p\Delta 50$	Peak power	minute 2 (LA onset)	minute 4 (TD_2 $\dot{V}O_2$)	Exhaustion
Power (W)	173 (46)	220 (43)	251 (48)	278 (55)	–	–	–
$\dot{V}O_2$ (ml/min)	2,223 (262)	3,064 (638)	3,222 (690) [a]	3,577 (765)	2,509 (674)	2,892 (812)	3,680 (821) [a]
$\dot{Q}$ (l/min)	16.4 (4.5)	20.4 (3.9)	21.3 (2.9)	21.7 (3.3)	16.0 (8.1)	18.5 (3.0)	22.0 (4.9)
$(a-\bar{v})O_2$ (ml/100 ml)	13.5 (3.8)	14.2 (2.7)	15.8 (4.1)	16.8 (4.0)	16.1 (5.0)	16.2 (5.2)	17.2 (4.7)
LA (mmol/l)	2.3 (0.4)	5.1 (1.5)	7.4 (1.9) [a]	11.0 (2.1)	1.8 (0.3)	3.9 (1.0)	12.8 (2.1) [a]

[a]significant difference of $P < 0.05$ between the IET at 90% $\dot{V}O_2$ peak and the CWE test at its peak value

power and $\dot{V}O_2$ values for the group, with each subject exercising at 90% of his $\dot{V}O_2$peak, were 251 (48) W and 3,222 (690) ml/min respectively.

During the CWE at 251 (48) W the subjects reached exhaustion after 11.7 (4.1) min (7.0–20.0), reaching their ''time limit''. It is noteworthy that the $\dot{V}O_2$ at exhaustion [3,680 (821) ml/min] was significantly higher than at the p Δ50 of IET ($P < 0.05$). The maximal $\dot{V}O_2$ during CWE was not significantly higher than the IET $\dot{V}O_2$ peak [3,577 (765) ml/min] at 278 (55) W. The $\dot{V}O_2$ at the onset of LA accumulation, at minute 2 of CWE, was similar to the $\dot{V}O_2$ (AT) during the IET (Table 2). At minute 4 of the CWE (when a slow regular $\dot{V}O_2$ increase began then continued for the remainder of the exercise), $\dot{V}$ O_2 was similar to the RCP $\dot{V}O_2$ value during the IET.

Parameter kinetics

Baseline values for the rest period following the 15 min warm-up exercise were not different from the subjects' basal pre-exercise values. The profiles of $\dot{V}O_2$ demand and cardiovascular responses (HR, SV and $\dot{Q}$) were best fitted by the single exponential plus linear increase model. The $(a-\bar{v})O_2$ difference increased monoexponentially without a linear component ($S = 0$ in the third model) to a steady state (Figures 2 and 3, Table 3).

Kinetics for the arteriovenous oxygen difference

The TD_1 value was similar to the TD_1 for $\dot{V}O_2$ (P = 0.84), SV (P = 0.07), HR (P = 0.72) and $\dot{Q}$ (P = 0.95). The τ value was similar to τ for $\dot{V}O_2$ (P = 0.14) but was significantly shorter than τ for SV, HR and $\dot{Q}$. With an A value of 11.2 (3.6) ml/100 ml, $(a-\bar{v})O_2$ reached 16.6 (6.0) ml/100 ml after 1.5 min of exercise. Subsequently, $(a-\bar{v})O_2$ did not vary significantly up to the end of exercise.

Patterns of $\dot{V}O_2$ kinetics; comparison with HR, SV, $\dot{Q}$ and $(a-\bar{v})O_2$

$\dot{V}O_2$ uptake first followed a simple exponential rise with $TD_1 = 25$ (7) s, $\tau = 53$ (20) s and A = 2,257 (767) ml/min. This rapid response gave way to an additional slow

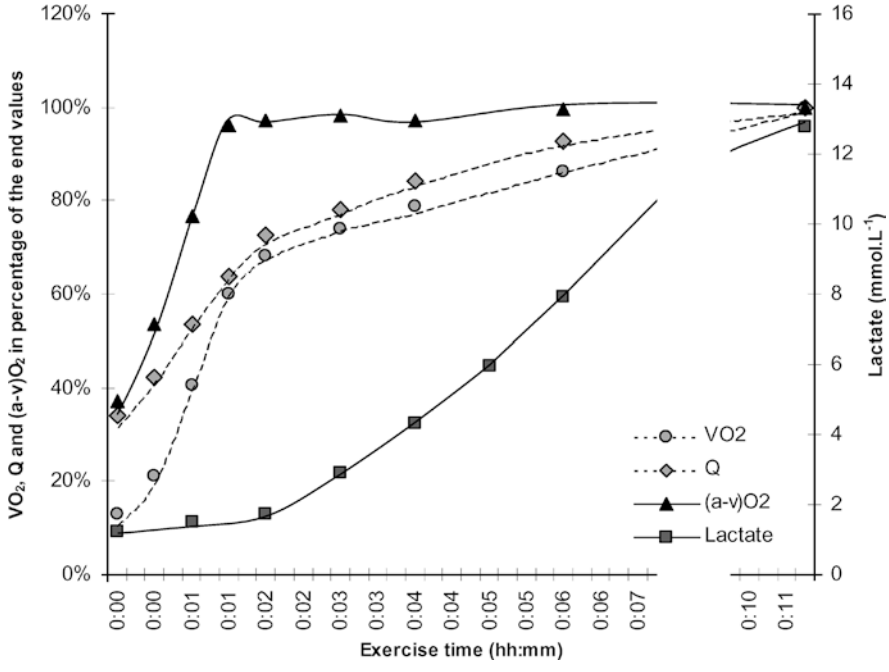

Fig. 3 Time courses of oxygen uptake ($\dot{V}O_2$), cardiac output ($\dot{Q}$) and arteriovenous oxygen difference [$(a-\bar{v})O_2$] and plasma lactate concentration during constant work rate exercise to exhaustion; mean values are expressed as the percentage of the maximal mean values

Table 3 Parameter values [mean (SD)] resulting from the fitting of oxygen consumption ($\dot{V}O_2$), cardiac output ($\dot{Q}$), stroke volume (SV), heart rate (HR) and arteriovenous oxygen difference [$(a-\bar{v})O_2$] during exercise to exhaustion. The values for the amplitude and the slope are expressed as ml/min for $\dot{V}O_2$, l/min for $\dot{Q}$, ml for SV, beats/min for HR and ml/100 ml for $(a-\bar{v})O_2$

	$\dot{V}O_2$	$\dot{Q}$	SV	HR	$(a-\bar{v})O_2$
Time constant [τ(s)]	53 (20)[a]	89 (34)[a,b]	72 (24)[a]	91 (53)[a]	39 (18)[a]
Amplitude	2,257 (767)	12.0 (3.8)	26 (8)	86 (11)	11.2 (3.6)
Time delay 1 [TD_1 (s)]	25 (7)	23 (7)	36 (11)	21 (9)	23 (17)
Time delay 2 [TD_2 (s)]	224 (67)[c]	384 (61)[c]	389 (92)[c]	375 (110)[c]	–
Slope (per second)	1.663 (0.980)	0.0099 (0.0079)	0.0368 (0.0283)	0.0277 (0.0094)	–

[a]significant difference of $P < 0.05$ between τ for $(a-\bar{v})O_2$ and τ for $\dot{Q}$, SV and HR
[b]significant difference of $P < 0.05$ between τ $\dot{V}O_2$ and τ $\dot{Q}$
[c]significant difference of $P < 0.05$ between TD_2 for $\dot{V}O_2$ and TD_2 for $\dot{Q}$, SV and HR

linear component that began after a TD_2 of 224 (67) s. SV, HR, $\dot{Q}$ and $(a-\bar{v})O_2$ had similar TD_1 values before increasing (Table 3). τ for $\dot{V}O_2$ was not significantly different from τ for SV, HR and $(a-\bar{v})O_2$ but was shorter than τ for $\dot{Q}$ [53 (20) s versus 89 (34) s ($P<0.05$)]. The τ value for $\dot{V}O_2$ correlated with the τ value for $(a-\bar{v})O_2$, ($r=0.73, P<0.05$); the faster the time for blood deoxygenation, the faster the oxygen uptake increase. The A of $\dot{V}O_2$ correlated with the A of $\dot{Q}$ ($r=0.74, P<0.05$). TD_2 for the $\dot{V}O_2$ slow component was significantly shorter than TD_2 for $\dot{Q}$, SV and HR [224 (67) versus 384 (61) s, 389 (92) s and375 (110) s respectively, $P<0.05$; Table 3].

$\dot{Q}$ versus HR and SV kinetics

These three variables had similar TD_1, τ, and TD_2 values. The A of $\dot{Q}$ correlated with A of SV ($r=0.67$, $P<0.05$).

Lactate increase during CWE

No significant LA increase above resting values was observed until the end of minute 2 of the exercise [1.8 (0.3) versus 1.2 (0.2) mmol/l at rest; Fig. 3]. LA increased slowly but significantly from minute 2 to minute 4, reaching 3.0 (0.4) mmol/l (at minute 3) and 3.9 (1.0) mmol/l (at minute 4). It then increased rapidly until the end of the exercise and reached similar maximal values as during the IET (Table 2, Fig. 3). It is noteworthy that during the third minute of the exercise (about 2 min 30 s of CWE), LA reached the same value as LA at AT during IET, and that the time for $(a-\bar{v})O_2$ to reach 95% of its maximal value after 3 τ (117 s) was similar to that for LA to increase. Furthermore, the fourth minute of exercise, when LA increased rapidly, corresponded to the onset of the slow linear increase for $\dot{V}O_2$ [$TD_2=224$ (67) s].

Time to exhaustion

The time to exhaustion was inversely correlated with the TD_1 of $(a-\bar{v})O_2$ ($r=-0.817, P<0.01$) and of SV ($r=-0.658, P<0.05$), and τ for $\dot{Q}$ ($r=-0.678, P<0.05$), as well as the slope of the $\dot{V}O_2$ increase during the slow phase after TD_2 ($r=-0.715, P<0.05$). The time to exhaustion was positively correlated with the magnitude of the LA increase from TD_2 to the end of exercise ($r=0.808$, $P<0.01$).

Discussion

During the high intensity $p\Delta 50$ CWE, with the exception of the $(a-\bar{v})O_2$, no variables reached a steady state. Their end values at exhaustion were similar to their maximal IET values. Subjects reached exhaustion at 11.7 (4.1) min. The $\dot{V}O_2$ kinetics were characterised by two responses: an initial rapid response during the four initial minutes of exercise followed by a slower second component where the maximal $\dot{V}O_2$ reached at exhaustion exceeded that predicted by the $\dot{V}O_2$/work rate relationship (Roston et al. 1987). With continuous determination of the components of the Fick formula for $\dot{V}O_2$, we obtained the typical kinetic patterns which describe the above-mentioned $\dot{V}O_2$ responses.

$(a-\bar{v})O_2$ and O_2 release to exercising leg muscles

After the onset of exercise, the $(a-\bar{v})O_2$ difference rapidly increased with $\tau=39$ (18) s and almost reached its maximal value after 1.5 min. After this time $(a-\bar{v})O_2$ was constant for the remainder of the exercise. Our results agree with the recent study of Chuang et al. (2002), who found that tissue deoxygenation kinetics were significantly faster than $\dot{V}O_2$ and HR kinetics during high-level CWE. They showed that tissue deoxygenation followed first-order kinetics with a 16–17 s time constant.

Stringer et al. (1994) demonstrated how LA accumulation facilitates O_2 release and thus muscle O_2 consumption during a 6 min high CWE load. The subjects in our group had about the same average physiological characteristics as those in Stringer's study. Thus our non-invasive results are in agreement with the conclusions of Stringer et al. (1994), which were based on blood gas measurements. They observed that femoral vein P O_2 decreased abruptly to 20 mmHg within 30 s and remained constant until the end of exercise. The oxygenated haemoglobin venous saturation fell from 50% to 20% during the first minute of exercise but continued to decrease for the entire 6 min, if the exercise was performed above the AT. These data are of major interest since Poole (1994) has demonstrated that changes of $\dot{V}O_2$ uptake under a similar CWE load closely reflect those occurring within the exercising legs.

In our study, the subjects were asked to exercise until exhaustion; reaching the AT $\dot{V}O_2$ at minute 2 and the RCP $\dot{V}O_2$ at minute 4, whereas the maximal $(a-\bar{v})O_2$ extraction was obtained after 1.5 min and remained constant thereafter. The increase in LA (minute 2) and the onset of lactate acidosis (minute 4) were essential for continuing exercise because the H^+ that accompanies the LA increase facilitates the dissociation of oxyhaemoglobin. The resulting Bohr effect accounts for the supplementary blood O_2 release (Grassi et al. 1999; Stringer et al. 1992). The onset of the slow $\dot{V}O_2$ increase at the time of the RCP, where LA increases rapidly, accounts for the important respiratory role that lactate acidosis plays during heavy exercise (Wasserman 1994).

We may assume that arterial O_2 content in our subjects with normal pulmonary function did not change and that the rapid $(a-\bar{v})O_2$ increase resulted mainly from the rapid decrease of the femoral venous blood O_2 content. That the pulmonary mixed venous blood

deoxygenation ($C\bar{v}O_2$) remained stable at minute 2 for the remainder of the exercise period does not mean that femoral venous blood O_2 content did not continue to decrease in relation to an increasing Bohr effect.

$\dot{Q}$ kinetics and time course of $\dot{V}O_2$

We found that the cardiorespiratory parameters were best fitted with a monoexponential plus linear dependence. The linear $\dot{V}O_2$ increase, as for HR, $\dot{Q}$ and SV, attests to a slow persistent increase in the oxygen deficit. The $\dot{Q}$ increase observed during the first 2 min of exercise can equally be explained by a parallel increase of its components HR and SV, reaching respectively 73, 83 and 87% of their end values. The amplitude of the monoexponential increase of $\dot{Q}$ was correlated with that of the SV, suggesting that SV is a determining factor of $\dot{Q}$.

From minute 2 to minute 4, $\dot{V}O_2$ continued to increase, but more slowly and in parallel with the $\dot{Q}$ increase, whereas $(a-\bar{v})O_2$ remained unchanged. The product of $\dot{Q}$ and the unchanging maximal value for $(a-\bar{v})O_2$ caused $\dot{V}O_2$ to increase from 68% (minute 2) to 79% (minute 4) of the end-exercise $\dot{V}O_2$ uptake. At the end of that period $\dot{Q}$ reached 84% of the end value, $(a-\bar{v})O_2$ was maximal and $\dot{V}O_2$ uptake was similar to $\dot{V}O_2$ RCP during IET.

From the second time delay (TD_2), we observed the onset of the slow component phase of the cardiorespiratory parameters. The TD_2 values for $\dot{Q}$, SV and HR were 50% longer than those of $\dot{V}O_2$. This difference in the TD_2 values may be due to the first monoexponential phase where the $\dot{V}O_2$ time constant is almost half the $\dot{Q}$ TD_2 value. From TD_2 $\dot{V}O_2$ to the time limit, the monoexponential $\dot{V}O_2$ gave way to a slow component, which increased linearly to the maximal end values, $\dot{V}O_2$ increasing with approximately the same slope as $\dot{Q}$.

In our study, the high intensity—as well as the fact that phases 1 and 2 are taken together—contribute to the long τ $\dot{Q}$ observed in comparison with other studies (De Cort et al. 1991; Yoshida and Whipp 1994; Yoshida et al. 1993). The contribution of the cardio-dynamic phase when a low power exercise was applied was quite important, and Yoshida et al. have showed that the τ values for $\dot{Q}$ are of 6–7 s for the cardiodynamic phase (Yoshida et al. 1993). Also, when the cardiodynamic phase was artificially reduced (the flywheel of the ergometer turned by a motor) the values of τ in phase 2 were 23–24 s for an exercise intensity which remained two-fold lower than that of our study (Yoshida and Whipp 1994). In our study the two phases are grouped, and coupled with the influence of the power applied, contributed to the long τ $\dot{Q}$ observed. When the exercise intensity was significantly higher (from 40% to 80% of the subjects' maximum power), Davies et al. (1972) showed that the half time for $\dot{Q}$ was increased to the same value as that of $\dot{V}O_2$.

The precise mechanisms controlling the $\dot{V}O_2$ slow component remain largely conjectural (Xu and Rhodes 1999). We observed that the $\dot{V}O_2$ obtained at the beginning of the slow linear component corresponded closely to the $\dot{V}O_2$ recorded at RCP during the IET. Given that RCP has been found to correspond to an increase in neuromuscular activity during incremental cycle exercise (Bearden and Moffatt 2001) and that the $\dot{V}O_2$ slow component was reported to be correlated with greater muscle use (Saunders et al. 2000), these two factors suggest a greater solicitation of fast-twitch motor units (Shinohara and Moritani 1992). Together with these previous findings, our results are in agreement with the neuromuscular hypothesis for the $\dot{V}O_2$ slow component. The recently reported negative correlation between the amplitude of the $\dot{V}O_2$ slow component and percentage of type I muscle fibres (Barstow et al. 1996), as well as the fact that pedalling frequency influences the amplitude of the $\dot{V}O_2$ slow component, also agree with this hypothesis. Therefore, we can consider that the $\dot{Q}$ slow component developed progressively to maintain a sufficient O_2 supply to the less efficient fast-twitch muscle fibres (Crow and Kushmerick 1982). Because of their lower oxidative capacity and higher LDH activity, fast-twitch fibers can produce LA more easily than slow-twitch fibres. Their progressively greater use during the $\dot{V}O_2$ slow component may explain the associated important increase in blood LA often described at exercise intensities beyond the AT (Roston et al. 1987).

Relationship between cardiovascular variables and time to exhaustion at $p\ \Delta 50$

The significant correlation we observed between the $\dot{Q}$ time constant and the time to exhaustion agree with previous findings. Indeed, we can speculate that a faster $\dot{Q}$ increase at the onset of exercise allows faster oxygen delivery to the working muscles, contributing to reduce the oxygen deficit and to increase the time to exhaustion. Such a mechanism is also suggested by the faster HR adjustment that appears after training (Hagberg et al. 1980; Yoshida et al. 1992). Faster circulatory adjustments and therefore better oxygen delivery could have accounted for a reduced oxygen deficit after training, thus contributing to increase the time to fatigue. In our study, we did not found any relationship between HR and time to exhaustion, but the TD_1 of SV was inversely correlated with the time to exhaustion, reflecting the earlier SV contribution to the oxygen delivery.

The time to exhaustion was inversely correlated with the slope of the $\dot{V}O_2$ increase during the slow phase after TD_2 and was 50% lower than found for well-trained subjects (Billat et al. 1998a, 1998b). This has already been suggested by Whipp who stated that the more rapidly $\dot{V}O_2$ reaches its maximal value, the shorter the tolerable duration of the exercise will be (Whipp 1994).

Methodological considerations

The calculation of $(a-\bar{v})O_2$ using the Fick equation for O_2 (Fick 1870) needs an independent measure of $\dot{V}O_2$ and $\dot{Q}$. De Cort at al. (1991) applied this principle using the pulsed Doppler ultrasound method to measure $\dot{Q}$. With the impedance method, we obtained direct beat-by-beat $\dot{Q}$ measurements averaged to 30 s intervals during IET and 10 s intervals during CWE. In previous studies we obtained a good correlation between the direct Fick and the impedance method, confirming that the impedance device provides accurate $\dot{Q}$ measurements during both constant and incremental exercises (Charloux et al. 2000; Richard et al. 2001). This group of nine subjects showed typical features for the adjustments observed in moderately-trained subjects exercising at a high constant load. Nevertheless, it is necessary to confirm these results for a large population and at different training levels.

Conclusion

In very intensive exercise performed above the load for RCP, all the factors that contribute to improving the oxygen release and anaerobic glycolysis for regenerating ATP are involved up to the time to exhaustion. The first part of the time to exhaustion (the cardiodynamic and metabolic phases) was characterised by an important blood oxygen extraction, almost maximal at AT $\dot{V}O_2$ (minute 2), coupled with an exponential increase for $\dot{Q}$. Thus the rapid $\dot{V}O_2$ uptake increase parallels the $(a-\bar{v})O_2$ curve, and LA begins to accumulate when the leg critical capillary$P$ O_2 is reached. The slow $\dot{V}O_2$ component which develops at minute 4 is LA accumulation dependent: anaerobic glycolysis becomes an important source of ATP and lactic acidosis facilitates a supplementary oxyhaemoglobin dissociation. This O_2 release, coupled with the slow linear $\dot{Q}$ increase, accounts for the slow $\dot{V}O_2$ component and for the correlation of the time to exhaustion with the magnitude of the LA increase.

Acknowledgements We thank the subjects for their helpful participation in the study and the GRAPPE Association for its assistance. The experiments comply with the current laws of the country in which they were performed.

References

Aunola S, Rusko H (1984) Reproducibility of aerobic and anaerobic thresholds in 20–50 year old men. Eur J Appl Physiol Occup Physiol 53:260–266

Aunola S, Rusko H (1988) Comparison of two methods for aerobic threshold determination. Eur J Appl Physiol Occup Physiol 57:420–424

Barstow TJ, Mole PA (1991) Linear and nonlinear characteristics of oxygen uptake kinetics during heavy exercise. J Appl Physiol 71:2099–2106

Barstow TJ, Jones AM, Nguyen PH, Casaburi R (1996) Influence of muscle fiber type and pedal frequency on oxygen uptake kinetics of heavy exercise. J Appl Physiol 81:1642–1650

Bearden SE, Moffatt RJ (2000) VO(2) kinetics and the O(2) deficit in heavy exercise. J Appl Physiol 88:1407–1412

Bearden SE, Moffatt RJ (2001) Leg electromyography and the VO_2-power relationship during bicycle ergometry. Med Sci Sports Exerc 33:1241–1245

Beaver WL, Wasserman K, Whipp BJ (1986) A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 60:2020–2027

Billat V, Binsse V, Petit B, Koralsztein JP (1998a) High level runners are able to maintain a VO_2 steady-state below VO_2max in an all-out run over their critical velocity. Arch Physiol Biochem 106:38–45

Billat VL, Richard R, Binsse VM, Koralsztein JP, Haouzi P (1998b) The V(O_2) slow component for severe exercise depends on type of exercise and is not correlated with time to fatigue. J Appl Physiol 85:2118–2124

Billat LV, Koralsztein JP, Morton RH (1999) Time in human endurance models. From empirical models to physiological models. Sports Med 27:359–379

Capelli C, Cautero M, di Prampero PE (2001) New perspectives in breath-by-breath determination of alveolar gas exchange in humans. Pflugers Arch 441:566–577

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

Charloux A, Lonsdorfer-Wolf E, Richard R, Lampert E, Oswald-Mammosser M, Mettauer B, Geny B, Lonsdorfer J (2000) Non-invasive cardiac output evaluation at rest and during exercise by a new impedance cardiograph device: comparison with the "direct" Fick method. Eur J Appl Physiol 82:313–320

Cheatham CC, Mahon AD, Brown JD, Bolster DR (2000) Cardiovascular responses during prolonged exercise at ventilatory threshold in boys and men. Med Sci Sports Exerc 32:1080–1087

Chuang ML, Ting H, Otsuka T, Sun XG, Chiu FY, Hansen JE, Wasserman K (2002) Muscle deoxygenation as related to work rate. Med Sci Sports Exerc 34:1614–1623

Crow MT, Kushmerick MJ (1982) Chemical energetics of slow- and fast-twitch muscles of the mouse. J Gen Physiol 79:147–166

Davies CT, Di Prampero PE, Cerretelli P (1972) Kinetics of cardiac output and respiratory gas exchange during exercise and recovery. J Appl Physiol 32:618–625

De Cort SC, Innes JA, Barstow TJ, Guz A (1991) Cardiac output, oxygen consumption and arteriovenous oxygen difference following a sudden rise in exercise level in humans. J Physiol (Lond) 441:501–512

Demarle AP, Slawinski JJ, Laffite LP, Bocquet VG, Koralsztein JP, Billat VL (2001) Decrease of O(2) deficit is a potential factor in increased time to exhaustion after specific endurance training. J Appl Physiol 90:947–953

Fick A (1870) Uber die messung des blutquantums in den hertzventrikeln. Verhandlungen der Physikalisch Medizinschen Gesellschaft zu Wurzberg 2

Foster C, Costill DL, Daniels JT, Fink WJ (1978) Skeletal muscle enzyme activity, fiber composition and VO_2 max in relation to distance running performance. Eur J Appl Physiol Occup Physiol 39:73–80

Gaesser GA, Poole DC (1996) The slow component of oxygen uptake kinetics in humans. Exerc Sport Sci Rev 24:35–71

Grassi B, Quaresima V, Marconi C, Ferrari M, Cerretelli P (1999) Blood lactate accumulation and muscle deoxygenation during incremental exercise. J Appl Physiol 87:348–355

Hagberg JM, Hickson RC, Ehsani AA, Holloszy JO (1980) Faster adjustment to and recovery from submaximal exercise in the trained state. J Appl Physiol 48:218–224

Hawley JA, Noakes TD (1992) Peak power output predicts maximal oxygen uptake and performance time in trained cyclists. Eur J Appl Physiol Occup Physiol 65:79–83

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

Noakes TD, Myburgh KH, Schall R (1990) Peak treadmill running velocity during the VO_2max test predicts running performance. J Sports Sci 8:35–45

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

Paterson DH, Whipp BJ (1991) Asymmetries of oxygen uptake transients at the on- and offset of heavy exercise in humans. J Physiol (Lond) 443:575–586

Poole DC (1994) Role of exercising muscle in slow component of VO_2. Med Sci Sports Exerc 26:1335–1340

Poole DC, Barstow TJ, Gaesser GA, Willis WT, Whipp BJ (1994) VO_2 slow component: physiological and functional significance. Med Sci Sports Exerc 26:1354–1358

Richard R, Lonsdorfer-Wolf E, Charloux A, Doutreleau S, Buchheit M, Oswald-Mammosser M, Lampert E, Mettauer B, Geny B, Lonsdorfer J (2001) Non-invasive cardiac output evaluation during a maximal progressive exercise test, using a new impedance cardiograph device. Eur J Appl Physiol 85:202–207

Roston WL, Whipp BJ, Davis JA, Cunningham DA, Effros RM, Wasserman K (1987) Oxygen uptake kinetics and lactate concentration during exercise in humans. Am Rev Respir Dis 135:1080–1084

Saunders MJ, Evans EM, Arngrimsson SA, Allison JD, Warren GL, Cureton KJ (2000) Muscle activation and the slow component rise in oxygen uptake during cycling. Med Sci Sports Exerc 32:2040–2045

Scheuermann BW, Hoelting BD, Noble ML, Barstow TJ (2001) The slow component of O(2) uptake is not accompanied by changes in muscle EMG during repeated bouts of heavy exercise in humans. J Physiol 531:245–256

Shinohara M, Moritani T (1992) Increase in neuromuscular activity and oxygen uptake during heavy exercise. Ann Physiol Anthropol 11:257–262

Stringer W, Casaburi R, Wasserman K (1992) Acid-base regulation during exercise and recovery in humans. J Appl Physiol 72:954–961

Stringer W, Wasserman K, Casaburi R, Porszasz J, Maehara K, French W (1994) Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. J Appl Physiol 76:1462–1467

Warburton DE, Haykowsky MJ, Quinney HA, Humen DP, Teo KK (1999a) Reliability and validity of measures of cardiac output during incremental to maximal aerobic exercise. Part I: conventional techniques. Sports Med 27:23–41

Warburton DE, Haykowsky MJ, Quinney HA, Humen DP, Teo KK (1999b) Reliability and validity of measures of cardiac output during incremental to maximal aerobic exercise. Part II: novel techniques and new advances. Sports Med 27:241–260

Wasserman K (1994) Coupling of external to cellular respiration during exercise: the wisdom of the body revisited. Am J Physiol 266:E519–E539

Wasserman K, Whipp BJ, Koyl SN, Beaver WL (1973) Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol 35:236–243

Wasserman K, Whipp BJ, Casaburi R (1986) Respiratory control during exercise. In: Cherniack NS, Widdicombe G (eds) Handbook of physiology, vol 2. American Physiological Society, pp 595–619

Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ (1999) Principles of exercise testing and interpretation, 3rd edn. Lea and Febiger, Philadelphia

Whipp BJ (1994) The slow component of O_2 uptake kinetics during heavy exercise. Med Sci Sports Exerc 26:1319–1326

Xu F, Rhodes EC (1999) Oxygen uptake kinetics during exercise. Sports Med 27:313–327

Yoshida T, Whipp BJ (1994) Dynamic asymmetries of cardiac output transients in response to muscular exercise in man. J Physiol (Lond) 480:355–359

Yoshida T, Udo M, Ohmori T, Matsumoto Y, Uramoto T, Yamamoto K (1992) Day-to-day changes in oxygen uptake kinetics at the onset of exercise during strenuous endurance training. Eur J Appl Physiol 64:78–83

Yoshida T, Yamamoto K, Udo M (1993) Relationship between cardiac output and oxygen uptake at the onset of exercise. Eur J Appl Physiol 66:155–160