Dynamic asymmetries of cardiac output transients in response to muscular exercise in man

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1. We determined the kinetics of cardiac output ($\dot{Q}$) with respect to oxygen uptake ($\dot{V}_{O_2}$) at the on- and off-transients of constant-load exercise. Six subjects performed constant-load exercise which consisted of 5 min rest, 5 min one-legged pedalling at 50 W and a 5 min recovery period.

2. The transient responses were characterized by first-order kinetics. There was no significant difference between the time constants for $\dot{V}_{O_2}$ ($\tau_{\dot{V}_{O_2}}$) at the on- (33·9 ± 3·5 s, mean ± S.E.M.) and off-transient (37·2 ± 2·9 s). The time constant for $\dot{Q}$ ($\tau_{\dot{Q}}$, 29·4 ± 3·2 s) was consistently shorter than $\tau_{\dot{V}_{O_2}}$ at the on-transient. However, $\tau_{\dot{Q}}$ was appreciably longer at the off-transient (44·3 ± 3·6 s) than the on-transient.

3. The results support the contention that the time constant for the on-transient of $\dot{Q}$ is appreciably faster than that for $\dot{V}_{O_2}$ and hence there seems little justification for the notion that the time constants for the kinetics of $\dot{V}_{O_2}$ are determined by the limitations of blood flow in the transient. The asymmetry of $\dot{Q}$ kinetics, with the off-transient $\tau_{\dot{Q}}$ being appreciably slower than the on-transient $\tau_{\dot{Q}}$, serves to maintain a sufficiently high oxygen flow to the muscle during recovery from exercise at a time when the muscle oxygen uptake remains high.

The O_2 content of the venous effluent (C_{v,O_2}) of skeletal muscle, or for any other tissue, depends upon the content of its arterial inflow (C_{a,O_2}) and the ratio of its metabolic rate ($\dot{V}_{O_2}$) to blood flow ($\dot{Q}$).

The mean capillary partial pressure of O_2 (P_{O_2}) and the driving pressure for O_2 transfer to mitochondria are both related to venous O_2 pressure (P_{v,O_2}), and hence C_{v,O_2} (Wagner, Hoppeler & Saltin, 1991). Consequently, muscle tissue oxygenation is crucially dependent upon the ratio $\dot{V}_{O_2}/\dot{Q}$ (Van Lieuw, 1973; Meuer, Ahrens & Ranke, 1985). Although both cardiac output and skeletal muscle blood flow increase as linear functions of $\dot{V}_{O_2}$ during steady-state exercise (Guyton, Jones & Coleman, 1973; Cerretelli & Marconi, 1986), the relationship has an intercept on the $\dot{Q}$-axis with the result that both muscle and mixed venous O_2 content decrease hyperbolically with work rate (Whipp & Ward, 1982).

During the non-steady-state phase of exercise C_{v,O_2} was determined by the relative time constant for $\dot{V}_{O_2}$ ($\tau_{\dot{V}_{O_2}}$) and $\dot{Q}$ ($\tau_{\dot{Q}}$) in addition to the final steady-state values or 'gains', for example:

$$C_{v,O_2} = C_{a,O_2} - \left\{ \frac{\dot{V}_{O_2,rest} + \Delta\dot{V}_{O_2}(1 - \exp(-t/\tau_{\dot{V}_{O_2}}))}{\dot{Q}_{rest} + \Delta\dot{Q}(1 - \exp(-t/\tau_{\dot{Q}}))} \right\}. \quad (1)$$

At work rates where the $\dot{V}_{O_2}$ and $\dot{Q}$ transients show first-order kinetics, $\tau_{\dot{Q}}$ is smaller than or similar to $\tau_{\dot{V}_{O_2}}$ (Davies, di Prampero & Cerretelli, 1972; Miyamoto, Hiura, Tamura, Nakamura, Higuchi & Mikami, 1982; De Cort, Innes, Barstow & Guz, 1991). De Cort *et al.* (1991) reported $\tau_{\dot{Q}}$ to be 20–25 s compared with 30–40 s for $\tau_{\dot{V}_{O_2}}$.

It is important, with respect to tissue oxygenation, to know whether there is on–off symmetry for the $\dot{Q}$ kinetics, as has been demonstrated for $\dot{V}_{O_2}$ (Whipp, 1976; Griffiths, Henson & Whipp, 1986; Paterson & Whipp, 1991). If $\tau_{\dot{Q}}$ was appreciably shorter than $\tau_{\dot{V}_{O_2}}$ in the recovery phase, then tissue oxygenation could be stressed more 'after' exercise than during its performance.

The purpose of this investigation was to determine the kinetics of $\dot{Q}$ with respect to $\dot{V}_{O_2}$ for the on- and off-transients of constant-load exercise in normal subjects.

METHODS

Six healthy male volunteers agreed to serve as subjects. Each subject was accustomed to cycle-ergometer exercise but none of them took part in any form of supervised training or were competitive athletes. Each subject was fully informed of the purpose of this study and possible risks before signing an informed consent form. The approval of the University's

human ethics committee was obtained. The following values (mean ± S.E.M.) for the subjects were obtained: age, 25·8 ± 3·0 years; height, 174·8 ± 3·0 cm; weight, 73·7 ± 2·8 kg; and maximal oxygen uptake, 46·6 ± 1·7 ml kg^{-1} min^{-1}.

Initially, all subjects performed an incremental exercise test on an electrically braked computer-controlled cycle ergometer (Combi 232-C; Combi, Tokyo), to estimate the lactate threshold and maximal oxygen uptake to ensure that the work rate selected for the constant-load test was of moderate intensity. Constant-load exercise consisted of 5 min rest followed by 5 min one-legged pedalling at 50 W, using the subject's preferred leg. This was followed by a recovery period of 5 min. Prior to the start of exercise, the flywheel of the ergometer was driven at 60 r.p.m. by a motor, which was switched off at the onset of exercise so that the subjects were not compelled to overcome the flywheel inertia at the start of the test. The pedalling frequency was maintained at 60 ± 10 r.p.m. throughout the test. This protocol was repeated at least 8 times for each subject to establish an ensemble average with a high signal-to-noise ratio.

During exercise, ventilatory and gas exchange responses were measured with a computerized on-line breath-by-breath system (Minato RM-300; Minato Medical Sciences, Osaka, Japan). Inspired and expired gas volumes were measured using a hot-wire respiratory flow system. The flow signals were electrically integrated for each breath to calculate ventilation ($\dot{V}_E$). The concentrations of O_2 and CO_2 were analysed using a zirconium solid electrolyte oxygen analyser and an infrared carbon dioxide analyser, respectively (MG-360; Toray Engineering, Osaka, Japan). The time delays (transport and dynamic response delay) of gas concentration against gas flow were compensated for in order to determine breath-by-breath data (Beaver, Wasserman & Whipp, 1973).

Cardiac output ($\dot{Q}$) was determined continuously using an impedance technique (Kubicek, Karnegis, Patterson, Witsoe & Matton, 1966) with a computer-based automated system (Yoshida, Yamamoto, Naka & Udo, 1991; Yoshida, Udo, Ohmori, Matsumoto, Uramoto, & Yamamoto, 1992; Yoshida, Yamamoto & Udo, 1993). Two band electrodes were placed around the neck 3 cm apart (first and second electrodes), a third electrode at the level of the xiphisternum, and a fourth electrode 3 cm below the third. A constant current was applied to the outer two electrodes (first and fourth). The separate inner two electrodes (second and third) were used to measure voltage changes resulting from impedance variations within the segment. The changes in impedance (ΔZ), electrocardiogram (ECG), and the rate of change in impedance (dZ/dt) were determined. To avoid the effect of respiration on impedance signal, an ensemble-averaging technique was used in which the R wave of the ECG was used as a trigger to average impedance signals within a 4 s interval. Stroke volume (SV) was then computed according to the formula of Kubicek *et al.* (1966). This was multiplied by heart rate (HR) to give $\dot{Q}$. Thereafter, the time course of $\dot{Q}$ was calculated by interpolation of points to give second-by-second data which were then averaged for the repeated experimental numbers for each subject. The computer-aided thoracic impedance method for $\dot{Q}$ determination was validated and calibrated by comparison with the standard CO_2 rebreathing method (Hatcher & Srb, 1986; Yoshida *et al.* 1993). There was a high correlation between $\dot{Q}$ values determined by impedance and CO_2 rebreathing methods during exercise in individual subjects ($0{\cdot}88 < r < 0{\cdot}97$, $P < 0{\cdot}01$). The relative value of $\dot{Q}$, normalized to the resting value, was used in the present study because our major interest lay in the evaluation of the rate of change at the onset and offset of exercise.

To determine the time course of increase in $\dot{V}_{O_2}$ and $\dot{Q}$ at the onset and offset of exercise, a best fitting procedure was employed using least-square criteria with a time delay (Whipp, Ward, Lamarra, Davis & Wasserman, 1982) deleting the first 20 s of the response data. The $\dot{V}_{O_2}$ responses during this period are dependent on the pulmonary blood flow rather than reflecting the time course of tissue gas exchange (Whipp *et al.* 1982; Barstow, Lamarra & Whipp 1990).

Data are expressed as means ± S.E.M. as indicated. An analysis of variance (ANOVA) with repeated measurement was used to analyse changes within each of the experiments. A *post hoc* Scheffe's test for a significant F value was applied to specify where significant differences occurred. A probability level of $P < 0{\cdot}05$ was accepted as significant.

RESULTS

The transient responses of both $\dot{V}_{O_2}$ and $\dot{Q}$ were well characterized by our first-order model in all subjects (e.g. Fig. 1), and although there was a wide variation in value of the time constant among individual subjects, with τ ranging from 24 to 50 s for $\dot{V}_{O_2}$ and from 19 to 43 s for $\dot{Q}$, the subjects with the shortest $\tau_{\dot{V}_{O_2}}$ were typically also the ones with the shortest $\tau_{\dot{Q}}$ (Table 1). For example, for the first on-transient, the rank order for the subjects listed 1–6 were 4, 2, 3, 6, 5, 1 for $\dot{V}_{O_2}$ and 3, 2, 4, 6, 5, 1 for $\dot{Q}$. In

Table 1. Descriptive data of oxygen uptake ($\dot{V}_{O_2}$) and cardiac output ($\dot{Q}$) for on- and off-transients of exercise

	On-transient $\dot{V}_{O_2}$		On-transient $\dot{Q}$		Off-transient $\dot{V}_{O_2}$		Off-transient $\dot{Q}$	
Subject	Gain (ml min^{-1})	$\tau_{\dot{V}_{O_2}}$ (s)	Gain (%)	$\tau_{\dot{Q}}$ (s)	Gain (ml min^{-1})	$\tau_{\dot{V}_{O_2}}$ (s)	Gain (%)	$\tau_{\dot{Q}}$ (s)
1	570	50·42	101·7	43·07	578	43·59	56·6	58·31
2	506	26·23	38·1	22·36	513	33·81	35·5	31·87
3	420	31·33	67·2	19·65	493	41·89	56·4	35·00
4	448	24·23	36·2	27·64	562	24·78	43·3	46·79
5	374	37·25	55·9	34·55	396	45·38	73·1	45·32
6	515	33·83	75·9	29·33	574	33·86	46·3	48·37
Mean	472·2	33·88	62·5	29·43	519·3	37·22	51·9	44·28
± S.E.M.	26·6	3·51	9·23	3·17	25·9	2·91	4·91	3·58

addition, the subjects with the highest maximum $\dot{V}_{O_2}$, expressed in millilitres per kilogram per minute, typically had the fastest response kinetics for both variables.

There was no significant difference between $\tau_{\dot{V}_{O_2}}$ at the on-transient (33·9 ± 3·5 s, mean ± S.E.M.) and at the off-transient (37·2 ± 2·9 s). However, as shown in Fig. 2 and Table 1, $\tau_{\dot{Q}}$ was consistently and appreciably longer at the off-transient than at the on-transient. In all except two of the twelve individual cases, the off-transient $\tau_{\dot{Q}}$ was not only greater than the on-transient but also greater than that of the on- or off-transient $\tau_{\dot{V}_{O_2}}$. That is, the ratio of the time constants for $\dot{V}_{O_2}$ and $\dot{Q}$ ($\tau_{\dot{V}_{O_2}}/\tau_{\dot{Q}}$), the important determinant of the tissue oxygenation during the transient, was typically greater than 1·0 at the on-transient and consistently less than 1·0 at the off-transient (Fig. 2).

The sustained high cardiac output, which was demonstrated during the recovery phase, in our study appeared to be a result of both stroke volume and heart

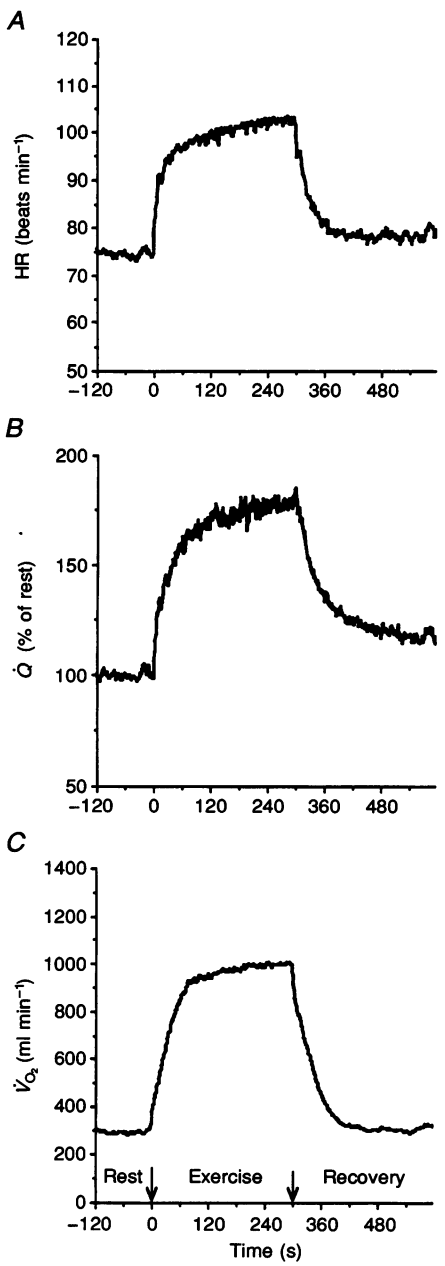

Figure 1
Group mean responses for heart rate (HR; *A*), cardiac output (*B*) and oxygen uptake (*C*) during a series of one-legged exercise and rest transients.

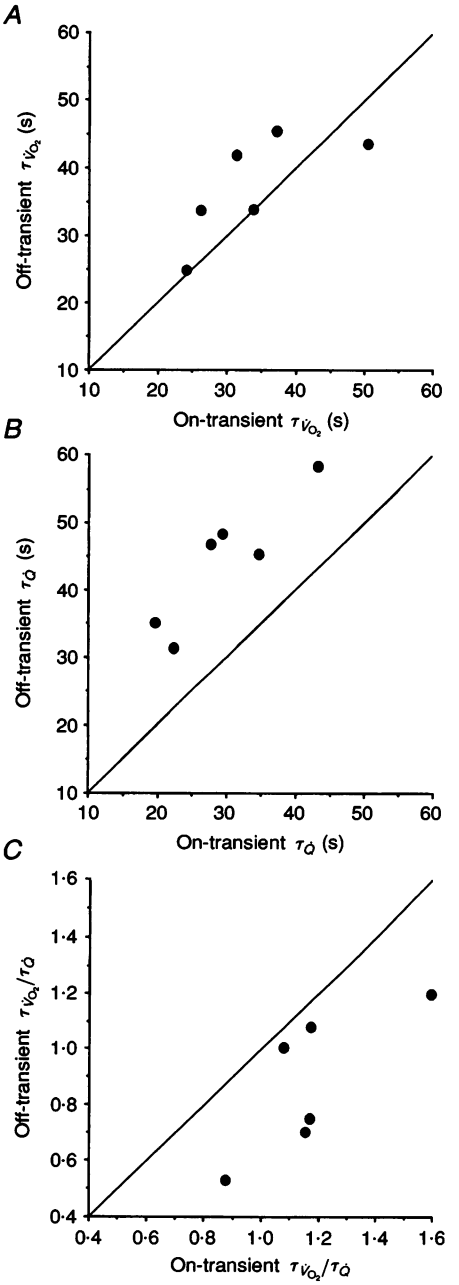

Figure 2
The relationships between on- and off-transient $\tau_{\dot{V}_{O_2}}$ (*A*), on- and off-transient $\tau_{\dot{Q}}$ (*B*), and on- and off-transient $\tau_{\dot{V}_{O_2}}/\tau_{\dot{Q}}$ (*C*), $\tau_{\dot{Q}}$ being faster than $\tau_{\dot{V}_{O_2}}$ at the on-transient but typically slower at the off-transient.

rate being maintained. As shown in Fig. 1 and also in Table 1, at the end of recovery periods $\dot{Q}$ remained some 15% above the control resting level, whereas heart rate remained only 5–6 beats min^{-1} above the control resting value. The sustained increase in heart rate (7%) therefore only accounted for approximately half of the residual increase in $\dot{Q}$.

DISCUSSION

It has been previously demonstrated (Griffiths *et al.* 1986; Paterson & Whipp, 1991) that there is no significant difference between $\tau_{\dot{V}_{O_2}}$ at the on- and off-transient. In contrast, we have demonstrated in the present study that $\tau_{\dot{Q}}$ is consistently and appreciably longer at the off-transient than at the on-transient.

Although most investigators concede that the oxygen uptake in skeletal muscle is preceded and controlled by the characteristics of the phosphate pool turnover (Whipp & Mahler, 1980; Krisananda, Moreland & Kushmeric, 1988; Brown, 1992), oxygen delivery to the tissue plays an important role in permitting the energy exchange to be aerobic (Wasserman, 1986; Hughson, 1990). Consequently, an increase in oxygen delivery to the skeletal muscle is required as the oxidative demands increase during the non-steady-state phase of exercise. This allows the mean capillary pressure to remain sufficiently high to provide the diffusional flux of oxygen (Wagner *et al.* 1991) to the site of its mitochondrial utilization, at rates which maintain the mitochondrial P_{O_2} at levels above that critical for maintaining oxygen utilization.

It is difficult to determine a value for mitochondrial P_{O_2} in exercising humans. This is not only because of the technical difficulties of sampling but also because the values are likely to vary considerably in different regions of the muscle. Mean capillary P_{O_2} is also technically complex to determine, requiring Bohr integration of the capillary profile. Several authors have therefore made inferences about the adequacy of oxygen utilization in human exercising muscle, by using the closest feasible estimate of the oxygen content and/or partial pressure of the venous effluent of the exercising muscle – i.e. by sampling femoral venous blood (Brooks, 1985; Poole *et al.* 1991; Wagner *et al.* 1991). However, the known heterogeneities of skeletal muscle blood flow and of oxygen utilization during exercise, coupled with the evidence of precapillary (arteriovenous) O_2 exchange (Duling & Berne, 1970; Van Lieuw, 1973; Meuer *et al.* 1985), makes it difficult, if not impossible, to infer regional muscular P_{O_2} levels from femoral venous blood sampling.

An alternative approach has been to estimate the temporal profile of the increase in blood flow following the onset of exercise, and to determine whether the time course of the change is sufficient for the increased nutrient needs of the contracting muscle throughout the transient state of exercise. In the steady state there appears to be no inadequacy of oxygen delivery at moderate workloads. It is therefore hard to see how oxygen flow to the muscle could be limiting oxygen uptake in the transient, if the time constant for cardiac output ($\tau_{\dot{Q}}$) is faster than that of oxygen uptake ($\tau_{\dot{V}_{O_2}}$), as has been repeatedly demonstrated and confirmed by this study. If C_{v,O_2} is sufficiently high that there is no evidence for limitations of oxygen delivery in the steady state, then $\tau_{\dot{Q}}$ being smaller than $\tau_{\dot{V}_{O_2}}$ (eqn (1)) is evidence that the nutrient flow of oxygen must be even greater for the metabolic rate throughout the transient.

However, virtually no consideration has been given to the off-transient in this regard. It is known that the on- and off-transient responses of $\dot{V}_{O_2}$ to moderate-intensity constant-load exercise are symmetrical, i.e. that the time constants for the on- and off-responses are not significantly different (Griffiths *et al.* 1986; Paterson & Whipp, 1991). Furthermore, the oxygen uptake responses to sinusoidally varying workloads are themselves sinusoidal (Casaburi, Whipp, Beaver, Wasserman & Koyal, 1977; Miyamoto, Nakazono, Hiura & Abe, 1983), i.e. they do not show the distortions which would be apparent if the on- and off-transient dynamics were different. Barstow *et al.* (1990) recently recognized that if $\dot{Q}$ dynamics were similarly symmetrical at the on- and off-transient, i.e. if the time constant for the off-transient was the same as that for the on-transient, the $\dot{V}_{O_2}/\dot{Q}$ ratio would necessarily rise during the non-steady state owing to the faster rate of change of $\dot{Q}$. This would result in C_{v,O_2} and P_{O_2} falling appreciably more and possibly to critical levels.

The time constant for the off-transient in $\dot{Q}$ was appreciably longer than that for its on-transient response, and although not considered in this regard, the phenomenon may also be seen in the results of Davies *et al.* (1972), Miyamoto *et al.* (1982) and Eriksen, Waaler, Walloe & Wech (1990). This slowing of the $\dot{Q}$ kinetics at the off-transient of exercise therefore allows sufficient nutrient flow of oxygen to the muscle during the phase when its metabolic rate remains high, assuming of course that the relatively high cardiac output in this phase is a result of relatively high flow to the exercising muscles (Clausen, 1976). It seems likely that this is the case, with metabolic factors maintaining the exercise-muscle component of the peripheral vascular conductance at higher levels. Although potassium has been reported to decrease very rapidly at the off-transient of exercise (Yoshida, Chida, Ichioka, Makiguchi, Eguchi & Udo, 1990), adenosine production is likely to continue at a high rate while the oxygen uptake remains high. Similarly, local osmolarity will also be maintained at a high level during this phase, in which glycolytic and fatty acid fluxes remain high. In addition, the vascular dilatory effects of the slow discharge of CO_2 from its capacitative storage within the muscle would maintain the demand for high muscle blood flow, and hence cardiac output, during this phase. Consequently, the interesting speculation by Barstow *et al.* (1990) that tissue oxygenation may be stressed more greatly at the off-

transient than the on-transient, appears not to be a problem in reality as a result of the marked increase in the off-transient $\tau_{\dot{Q}}$.

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