CARDIAC OUTPUT, OXYGEN CONSUMPTION AND ARTERIOVENOUS OXYGEN DIFFERENCE FOLLOWING A SUDDEN RISE IN EXERCISE LEVEL IN HUMANS

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SUMMARY

1. To investigate the relative contributions of increases in cardiac output and arteriovenous oxygen difference to the increase in oxygen consumption during exercise, the ventilatory and cardiovascular responses to a sudden transition from unloaded cycling to 70 or 80 W were measured in six normal healthy subjects.

2. Oxygen consumption ($\dot{V}_{O2}$) was measured breath-by-breath and corrected for changes in lung gas stores. Cardiac output ($\dot{Q}$) was measured beat-by-beat using pulsed Doppler ultrasound, and blood pressure was measured beat-by-beat using a non-invasive finger cuff (Finapres). All data were calculated off-line, second-by-second.

3. Arteriovenous oxygen difference (A–V $O_2$) was calculated from $\dot{Q}$ and $\dot{V}_{O2}$ using the Fick Principle. Left ventricular afterload was calculated by dividing $\dot{Q}$ by mean blood pressure.

4. The data for $\dot{Q}$ and $\dot{V}_{O2}$ were closely fitted by single exponential curves (mean $r^2$ 0.84 and 0.90 respectively; $r$ is the correlation coefficient). These curves yielded mean time constants for the increases in $\dot{Q}$ and $\dot{V}_{O2}$ of 28 and 55 s respectively following the increase in exercise level. In each individual subject, the time course of adjustment of $\dot{Q}$ was faster than that of $\dot{V}_{O2}$. There was a mean lag of 15 s from the start of the new exercise level before the derived A–V $O_2$ began to increase; the mean time constant for A–V $O_2$ was 57 s.

5. If A–V $O_2$ had remained constant, the observed rise in $\dot{Q}$ alone would have resulted in an average of 87% of the increase in $\dot{V}_{O2}$ which was observed after 5 s. If $\dot{Q}$ had remained constant, the observed increase in A–V $O_2$ would have led to only 8% of the actual increase in $\dot{V}_{O2}$ after 5 s.

6. Mean and systolic blood pressure rose and afterload fell immediately after the onset of the increased workload. The time constants of the systolic blood pressure and afterload responses to exercise varied widely and ranged from 37 to 81 and 10 to 26 s respectively ($n = 4$).

7. We conclude that $\dot{Q}$ is responsible for most of the early increase in $\dot{V}_{O2}$ following a sudden increase in exercise workload. Blood pressure responses to exercise are slower than $\dot{Q}$ and $\dot{V}_{O2}$ responses, probably due to the rapid decrease in afterload.

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8. The dominant contribution of $\dot{Q}$ to adaptation to changing workload may be physiologically important particularly in heart disease, where decreased ability to increase cardiac output may limit the capacity to cope with changing metabolic needs during everyday activities.

**INTRODUCTION**

Oxygen consumption ($\dot{V}_{O_2}$) measured at the mouth increases very rapidly (i.e. with a half-time of around 30 s) after a sudden increase in exercise workload (Margaria, Mangili, Cuttica & Cerretelli, 1965; Cerretelli, Sikand & Fahri, 1966; Davies, Di Prampero & Cerretelli, 1972; Whipp & Wasserman, 1972; Hagberg, Nagle & Carlson, 1978; Casaburi & Wasserman, 1986). This may occur either as a result of increased blood flow to the lungs (i.e. increased cardiac output, $\dot{Q}$) or of a decrease in the oxygen content of the blood delivered to the lungs, or a combination of both factors. One of the fundamental beliefs in exercise physiology is that there is a lag between the onset of an increase in exercise workload and the arrival of the hypoxic blood from the exercising muscle at the lungs. It has therefore long been assumed that the observed increase in $\dot{V}_{O_2}$ following an increase in exercise workload is entirely due to increased $\dot{Q}$ (Wasserman, Whipp & Davies, 1981; Weissman, Jones, Oren, Lamarra, Whipp & Wasserman, 1982; Whipp, Ward, Lamarra, Davies & Wasserman, 1982). This traditional belief has, however, recently been questioned by Casaburi, Daly, Hansen & Effros (1989), who found that pulmonary artery desaturation occurred in humans within 4 s after a transition between rest and 150 W cycle exercise, i.e. earlier than the predicted circulation time of around 12–17 s (Barstow & Mole, 1987).

To investigate the relative contributions of $\dot{Q}$ and pulmonary artery desaturation to the early increase in $\dot{V}_{O_2}$ (i.e. the first minute after a change in exercise level), we have made simultaneous measurements of cardiac output (beat-to-beat using pulsed Doppler ultrasound) and $\dot{V}_{O_2}$ (breath-by-breath) following an abrupt increase in exercise. This study also provides the first detailed data on the time course of the cardiovascular responses to exercise in humans. Some of the results have been presented previously in preliminary form (De Cort, Innes & Guz, 1990).

**METHODS**

*Subjects*

One female and five male subjects (age range 26–38 years), selected for ease of obtaining high quality Doppler signals from the ascending aorta (Innes, Mills, Noble, Murphy, Pugh, Shore & Guz, 1987) were studied. All were healthy, and had no history of cardiovascular or respiratory disease. All had normal chest X-rays and lung spirometry; none were taking medication at the time of the study. One subject smoked occasionally, the others were non-smokers. All subjects gave informed consent for the study.

*Procedure*

The subjects sat upright on a cycle ergometer, breathing through a mouthpiece. After 4 min of unloaded pedalling, the workload was suddenly increased, without warning, to a level previously determined to be below that subject’s anaerobic threshold (Wasserman, Hansen, Sue & Whipp 1987). This was 70 W in one subject and 80 W in the other five subjects. The subjects continued to cycle for a further 4 min. This procedure was repeated five times, with a rest period of at least 10 min (until the resting heart rate had returned to the previously noted starting level) between each experiment.
Measurements

Ventilatory measurements. Oxygen, carbon dioxide and nitrogen tensions were measured continuously at the mouth with a mass spectrometer (Centronic 200 MGA, Croydon) and recorded on magnetic tape (Racial store 7), as were airflow (Fleisch no. 3 pneumotachograph, P. K. Morgan, Raynam, dead space 185 ml), and the electrocardiogram. The inspiratory–expiratory difference in $P_{ea}$ at the mouth was multiplied by the instantaneous airflow and integrated over time to yield breath-by-breath $\dot{V}_{O_2}$; this was done on-line by a commercial analog system (Buxco Electronics Inc., Sharon, USA). Breath-by-breath values were stored on floppy disc. Corrections for changes in lung gas stores were made off-line on a microcomputer (Arkel PC) using the method of Beaver, Lamarra & Wasserman (1981) to yield estimates of alveolar gas exchange.

Cardiac output. Cardiac output was measured non-invasively, beat-by-beat using spectral analysis (Doptek, Chichester) of pulsed Doppler ultrasound measurements of blood velocity in the ascending aorta, made using a suprasternal probe (Pedof. Vingmed A/S, Oslo, Norway). This method has previously been described and validated by Innes et al. (1987). Doppler signals were stored together with the respiratory signals on magnetic tape (Racial Store 7). The integral of aortic blood velocity was computed off-line from the digital spectral data using a laboratory microcomputer (Research Machines 380Z, Oxford). This integral was multiplied by a separate measurement of the aortic cross-sectional area (2-D echocardiogram, Irex, Ramsey, NJ, USA) to yield measurements of cardiac output beat-by-beat (Innes, 1987). Cardiac output was measured continuously from 30 s before the exercise workload transition to the end of the 4 min run.

Blood pressure. Blood pressure in the digital arteries was measured beat-by-beat throughout the study using a non-invasive finger cuff (Finapres, Ohmeda, Englewood, USA), and recorded on magnetic tape. Gripping the handlebars of the cycle ergometer produced artifactual blood pressure readings due to compression of the blood vessels supplying the finger with the cuff round it. The subjects were therefore instructed to keep the hand relaxed and any data showing movement artifacts were discarded. Blood pressure was only measured in subjects 2–6.

Data analysis

To correct for timing errors due to breath duration (changes in $\dot{V}_{O_2}$ could not be detected until the end of the breath in which they occurred), it was assumed that for a large sample of breaths, the mean timing error would be half a breath, and half the $T_{tot}$ (the total duration of the breath) for each breath was subtracted from the time of the end of that breath. This was because we wished to time-align the $\dot{V}_{O_2}$ with the $Q$ data, and in the latter signal no such error occurs. Cardiac output, $\dot{V}_{O_2}$ and blood pressure were calculated off-line second-by-second from the beat-by-beat or breath-by-breath data. This was done by taking the current value at 1 s time intervals after the onset of the increased exercise level, identified using a marker signal recorded on the tape at the time of the study. Arteriovenous oxygen difference ($A-V_{O_2}$) was then derived second-by-second using the Fick Principle (Fick, 1870).

$$Q = \frac{\dot{V}_{O_2}}{A-V_{O_2}}.$$ 

Therefore

$$A-V_{O_2} = \frac{\dot{V}_{O_2}}{Q}.$$ 

Since the subjects had normal lung function, it was assumed that arterial $O_2$ content did not change following the increase in exercise level; this was confirmed by ear oximetry in four of the subjects in preliminary studies.

The availability of beat-by-beat $Q$ and blood pressure readings makes it possible to calculate an index of the peripheral resistance faced by the left ventricle. This is not true total peripheral resistance since we did not have measurements of right atrial pressure, therefore we have calculated the effective afterload as mean arterial blood pressure (diastolic + pulse pressure/3) divided by cardiac output, also on a second-by-second basis. Inspection of the raw data suggested that the changes under study were occurring in a monoeponential fashion. The best-fit single exponential curves, and hence the time constants and onset delays, were therefore calculated for $\dot{V}_{O_2}$, $Q$, $A-V_{O_2}$ and afterload using a commercial software package (SPSSX Inc., Chicago, IL, USA), the equation of the curve being of the form

$$Y = A + B[1 - e^{-t/T_0}]$$.
where $A$ is the baseline level, $B$ is the gain of the response, $t$ is the time in seconds, $T_d$ is the time delay from the onset of the increased workload to the onset of the response and $\tau$ is the time constant of the response. To fit the curves, the computer program alters these parameters iteratively in order to minimize the residual sums of squares. In this calculation, the time delay ($T_d$) was constrained to be zero or above. As $Q$ and $A-V_0^2$ influence $\dot{V}_0$, interactively, the relative contributions of each of these variables to the early increase in $\dot{V}_0$, following the increase in exercise workload were calculated separately from the fitted curves by calculating the effect on the observed $\dot{V}_0$ responses if either $Q$ or $A-V_0^2$ remained constant while the other changed.

Fig. 1. Cardiorespiratory responses to an abrupt transition from unloaded pedalling to 80 W exercise (at time 0 s) in subject 2. Data are averages of five runs.

RESULTS

Time course of cardiovascular and ventilatory responses

The calculated exponential curves fitted the data well, $r^2$ indicating that between 72 and 92% (mean 84%) of the overall variance of $\dot{Q}$, and between 77 and 98%
CARDIOPULMONARY ADAPTATION TO EXERCISE

Cardiac output rose rapidly when the exercise workload was increased, and levelled out by around 90 s (Fig. 1). In three subjects there was no perceptible lag between the time of the increase in exercise workload and an increase in $\dot{Q}$ (Fig. 2, Table 1), while in the remaining three subjects $\dot{Q}$ began to increase within 3 s (four beats). Although most of the increase in $\dot{Q}$ was a result of increased heart rate (Fig. 3), stroke volume also contributed in most subjects, rising by $13 \pm 9$ ml (mean $\pm$ s.d.) in the steady state (Fig. 3). Curves were not fitted to the stroke volume data, since the response did not approximate to a monoexponential function. From the fitted curves for $\dot{Q}$, the time constant for the initial increase in $\dot{Q}$ (mean $\pm$ s.d., $n = 6$) was $27.7 \pm 6$ s (Table 1). In all six subjects, the fitted curves indicated a brief lag after the onset of the increased exercise level before $\dot{V}_{O_2}$ began to rise (Table 1), which varied between 3 and 12 s (0.7 to 3.9 breaths). The time course of the increase in $\dot{V}_{O_2}$ was slower than that of the $\dot{Q}$ response, only reaching a steady state by around 120–150 s in most of the subjects. The mean time constant for the initial rise in $\dot{V}_{O_2}$ was $55 \pm 21$ s (mean $\pm$ s.d., $n = 6$).
Fig. 3. Stroke volume (continuous line) and heart rate (–––) responses to exercise in six subjects. Data are averages of five runs.

Table 1. Time delays ($T_d$) and time constants ($\tau$) for $Q$, $\dot{V}_{O_2}$, and $A-V O_2$ responses to exercise

<table>
<thead>
<tr>
<th>Subject</th>
<th>$T_d$ (s)</th>
<th>$\tau$ (s)</th>
<th>$T_d$ (s)</th>
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<td>18*</td>
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<tr>
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<td>51.4</td>
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* Curves fitted to only the first 135 s of data.

In all the subjects there was a time lag (mean ± s.d. $15±8$ s, or $4.5±2.6$ breaths) between the increase in exercise level and the increase in $A-V O_2$. The time constant for $A-V O_2$ was $57±19$ (mean ± s.d.) s (Table 1).

Contribution of $\dot{Q}$ and $A-V O_2$ to $\dot{V}_{O_2}$

As there was a lag between the increase in exercise level and the increase in $\dot{V}_{O_2}$, the contributions of $\dot{Q}$ and $A-V O_2$ to the increase in $\dot{V}_{O_2}$ were calculated at times from the first increase in $\dot{V}_{O_2}$. If $A-V O_2$ had stayed constant when the workload...
Fig. 4. Percentage contribution of cardiac output (●) to the increase in $\dot{V}_{O_2}$ if $\dot{Q}$ were to remain constant, and $A-V\ O_2$ (○) to the increase in $\dot{V}_{O_2}$ if $A-V\ O_2$ was to remain constant. Time 0 s represents the start of the increased exercise level. Error bars show s.d.

Table 2. Time delays ($T_d$) and time constants ($\tau$) for mean BP, systolic BP and afterload responses to exercise

<table>
<thead>
<tr>
<th>Subject</th>
<th>$T_d$</th>
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<td>†</td>
<td>†</td>
<td>†</td>
<td>0</td>
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</tr>
</tbody>
</table>

* Blood pressure data not recorded in this subject.
† Calculated curves did not fit the data adequately ($r^2 < 0.5$).

increased, the observed increase in $\dot{Q}$ alone would have resulted in 87±21% (mean ± s.d.) of the observed increase in $\dot{V}_{O_2}$ 5 s after $\dot{V}_{O_2}$ began to increase (Fig. 4). This percentage contribution decreased very rapidly to 52±15% after 30 s and by 150 s had levelled out to 33±8%. The increase in $\dot{V}_{O_2}$ attributable to $A-V\ O_2$ alone if $\dot{Q}$ had not changed showed the opposite trend, starting off at a low level of 8±20% of the observed increase in $\dot{V}_{O_2}$ 5 s after $\dot{V}_{O_2}$ began to increase, and rising with time. After 150 s, increased $A-V\ O_2$ alone would have resulted in 43±7% of the observed increase in $\dot{V}_{O_2}$ (Fig. 4).

Blood pressure and effective afterload

Monoexponential curves fitted the blood pressure (BP) data adequately for four out of five subjects in whom it was measured ($r^2 = 0.54$–0.87 for mean BP, 0.85–0.93 for systolic) and afterload data for four of the five subjects ($r^2 = 0.77$–0.84). Systolic and mean blood pressure rose almost immediately following the increase in
workload (Table 2, Fig. 5); in two subjects no lag was discernible. In four subjects afterload decreased with no measurable lag. The time constant for the decrease in afterload was shorter than that for the rise in blood pressure in every case (Table 2).

![Graph showing cardiac output, mean and systolic blood pressure and afterload in subject 3 following a sudden increase in exercise level.](image)

**DISCUSSION**

This is the first second-to-second description of the time course of the changes in cardiac output, blood pressure and arteriovenous \( O_2 \) difference following an increase in exercise workload. The increase in cardiac output was found to have a faster time course than that of arteriovenous oxygen difference, thus cardiac output was demonstrated to be the dominant cause of the early rise in \( V_{O_2} \) following an increase in exercise level.

The development of the Doppler ultrasound method of measuring beat-by-beat \( \dot{Q} \) (Satumora 1957; Light, Cross & Hansen, 1974) and its beat-to-beat validation
CARDIOPULMONARY ADAPTATION TO EXERCISE

(Innes et al. 1987) has made it possible to describe the time course of the exercise response in greater detail than has previously been possible. The transient cardiovascular response to a transition from rest to upright or supine exercise in humans has previously been investigated by Loepky, Greene, Hoekenga, Caprihan & Luft (1981) by this method. However in that study only the first 20 s of exercise was recorded and no attempt was made to characterize the time constant and the time delay of the response. The current study extends these measurements to include the entire period of physiological adjustment to the new workload. In the studies of Loepky et al. (1981), the subjects 'counted down' towards the start of exercise. Anticipation of exercise could have affected heart rate or stroke volume before exercise began, or the cardiovascular response to exercise, whereas in the current studies the subjects were not aware of when the exercise workload was to be increased.

We found that Q increased with an approximately exponential time course, with time constants varying between 18 and 34 s, and in some subjects a brief lag was observed between the onset of the increased workload and an increase in Q. This does not agree with the findings of Miyamoto, Higuchi, Hiura, Nakazono & Mikami (1983), who reported that there was no discernible lag in Q (estimated by impedance cardiography) following the transition from rest to 50 or 100 W upright bicycle exercise. In that study, however, impedance values were averaged over ten to twenty cardiac cycles, which would impair the time resolution of the measurements, making it impossible to measure the size of lag observed here (3 s). Furthermore, the increase in venous return which occurs during exercise may change the impedance of the thorax (Du Quesnay, Stoute & Hughson, 1987) so quantification of transient changes in Q may not be as accurate by this method as with the Doppler method. Although measurement of Q using pulsed Doppler ultrasound is not an accurate method in all subjects, the subjects in the current study were carefully chosen, all having a good Doppler signal (i.e. minimal spectral broadening), and only data which was of consistently good quality was used (Innes, 1987).

The time course of the increase in \( \dot{V}_{O_2} \) has been well documented (Davies et al. 1972; Hagberg et al. 1978; Casaburi & Wasserman, 1986). The mean time constant for \( \dot{V}_{O_2} \) in the present studies was 55 s as opposed to 45 s in the studies of Wasserman, Whipp & Davies (1981). In the present study, small inaccuracies in the detail of the time course of both \( \dot{V}_{O_2} \) and consequently, A – V \( O_2 \) may have been introduced by the fact that \( \dot{V}_{O_2} \) was measured breath-by-breath, so the first increase in \( \dot{V}_{O_2} \) could not be detected until the end of the first breath after the increase in exercise workload. This means that the true lag before the increase in \( \dot{V}_{O_2} \) may be up to one breath shorter than the calculated lag. In this case, the lag before an increase in A – V \( O_2 \) would be underestimated to the same extent. An attempt was made to correct this error during data analysis by subtracting half the measured \( T_{tot} \) from the time of each breath, on the basis that changes in oxygen consumption were likely to occur at any time within a breath, so the mean timing error would be half a breath.

The lag between the increase in exercise level and increased pulmonary A – V \( O_2 \) difference might be expected to correspond to the circulation time from the exercising muscles to the lungs. Casaburi and co-workers (1989) found this lag to be shorter than expected (within 4 s) and suggested that mobilization of pooled hypoxic
blood in the inferior vena cava following the transition from rest to exercise may be responsible for the early pulmonary artery desaturation. The mean ± s.d. of the time lag before the increase in A–V O$_2$ difference in the present study was 14 ± 7 s, with individual values varying between 6 and 28 s. The difference between our findings and those of Casaburi et al. (1989) may be explained by the fact that our subjects performed transitions between unloaded and loaded pedalling, rather than a rest to exercise transition, thus inferior vena caval blood pooled at rest may already have been mobilized. The lag observed in the present studies between the increase in exercise level and the increase in A–V O$_2$ is thus more likely to represent the time lag before the arrival of blood from the exercising muscle at the lungs.

The time course of changes in blood pressure have not previously been reported in such detail, although the increase in systolic and mean blood pressure during exercise are well known (Astrand, Ekblom, Messin, Saltin & Stenberg, 1965). Blood pressure increased with either a very brief or no time lag after the onset of the increase in exercise level, however, the time course of the changes in blood pressure was slow compared to $\dot{Q}$ and $\dot{V}_{\text{O}_2}$. Calculated afterload falls early, as would be expected due to vasodilatation in the exercising muscle. The Finapres blood pressure monitor made it possible to obtain non-invasive beat-by-beat measurements of finger blood pressure; however this may differ somewhat from systemic arterial blood pressure, even at rest (Molhoek, Wesseling, Settels, Van Vollenhoven, Weeda, De Wit & Arntzenius, 1984; Wesseling, Settels & De Wit, 1986; Kurki, Smith, Head, Dec-Silver & Quinn, 1987; Imholz, Van Montfrans, Settels, Van Der Hoeven, Karemaker & Weiling, 1988). Recently, Idema, van den Meiracker, Imholz, Man-in-’t-Veld, Settels, Ritsema-van-Eek & Schalekamp (1989) have found that systolic pressure measured with the Finapres was greater than brachial systolic pressure by 26 ± 20 mmHg (mean ± s.d.) during exercise. We have found, however, that during similar workload transitions (unloaded pedalling to 80 W) in one subject, there was very good agreement between Finapres and contralateral radial artery pressure (Gould Statham Model P50 pressure transducer). For mean blood pressure, the mean difference (radial minus Finapres measurements) for single beats was 0.40 mmHg (n = 2100 beats), with a 95% confidence interval of ±9.9 mmHg. For this type of exercise the Finapres therefore appears to give accurate blood pressure measurements.

The rapid onset of the fall in afterload following the increase in exercise workload implies a close and probably neurogenic link between increased exercise level and dilatation of blood vessels in the exercising muscles. The subsequent slower time course of afterload changes may be due to metabolically induced changes in peripheral resistance which develop as the products of metabolism build-up as exercise continues.

Simultaneous dynamic measurements of gas exchange, stroke volume and blood pressure form a powerful tool for assessing the competence of the heart and the peripheral circulation to supply increased metabolic needs during exercise. Left ventricular dysfunction might be expected to limit the capacity to suddenly increase cardiac output, leading to increased reliance on widening arteriovenous oxygen difference. This remains to be tested in patients. The ability of the heart to cope with such transient changes in metabolic load is relevant to the continuously varying
exercise demands of everyday life. In addition, the protocols developed in this study may allow the assessment of the effect of drug therapy and rehabilitation regimes on the failing heart.

In conclusion, the current study has shown that cardiac output increases more rapidly following an increase in exercise workload than does \(A-V\) \(O_2\), thus most of the early increase in \(V_{O_2}\) is due to increased \(Q\). As exercise continues, however, increased \(A-V\) \(O_2\) contributes gradually more to increased \(V_{O_2}\). Blood pressure and afterload change immediately following an increase in exercise workload, however the time constant of the blood pressure response was very long compared to the \(Q\) and \(V_{O_2}\) responses due to the rapid decrease in afterload. This may reflect an initial neurogenic component in the decrease in peripheral resistance followed by a more slowly developing metabolic component. The techniques developed in this study may prove to be powerful in diagnosis and management of left ventricular dysfunction as well as in study of the function of the healthy heart during exercise.

REFERENCES


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