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ORIGINAL ARTICLE

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The role of pulmonary CO_2 flow in the control of the phase I ventilatory response to exercise in humans

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Abstract To gain an insight into the origin of the phase I ventilatory response to exercise (ph I) in humans, pulmonary ventilation ($\dot{V}_E$) and end-tidal partial pressures of oxygen and carbon dioxide ($P_{ET}O_2$ and $P_{ET}CO_2$, respectively) were measured breath-by-breath in six male subjects during constant-intensity exercise on the cycle ergometer at 50, 100 and 150 W, with eupnoeic normocapnia (N) or hyperpnoeic hypocapnia (H) established prior to the exercise test. Cardiac output ($\dot{Q}_c$) was also determined beat-by-beat by impedance cardiography on eight subjects during moderate exercise (50 W), and the CO_2 flow to the lungs ($\dot{Q}_c \cdot C_{\bar{v}}CO_2$ where $C_{\bar{v}}CO_2$ is concentration of CO_2 in mixed veneous blood) was estimated with a time resolution of one breathing cycle. In N, the initial abrupt increase of $\dot{V}_E$ during ph I ($\Delta\dot{V}_E$ approximately 18 $l \cdot min^{-1}$ above rest) was followed by a transient fall. When $P_{ET}CO_2$ started to increase (and $P_{ET}O_2$ decreased) $\dot{V}_E$ increased again (phase II ventilatory response, ph II). In H, during ph I $\Delta\dot{V}_E$ was similar to that of N. By contrast, during ph II $\Delta\dot{V}_E$ kept gradually decreasing and started to increase only when $P_{ET}CO_2$ had returned to approximately 40 mmHg (5.3 kPa). Thus, as a result of the prevailing initial conditions (N or H) a temporal shift of the time-course of $\dot{V}_E$ during ph II became apparent. No correlation was found between CO_2 flow to the lungs and $\dot{V}_E$ during ph I. These results are interpreted as suggesting that an increased CO_2 flow to the lungs does not constitute an important factor for the initial hyperventilatory response to exercise. They are rather compatible with a neural origin of ph I, and would support the "neurohumoral" theory of ventilatory control during exercise.

Key words Exercise · Ventilation · Respiratory control

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Introduction

Zuntz and Geppert (1886) have first described the sudden increase in pulmonary ventilation ($\dot{V}_E$) at the onset of constant-load exercise, later identified as the so-called fast component (Dejours 1963), or phase I (ph I) of the ventilatory response to exercise (Wasserman et al. 1986). Krogh and Lindhard (1913) have confirmed the existence of ph I, and referred it to a central command, an irradiation of impulses from the motor cortex to the respiratory centres. Alternatively, ph I has been attributed to an accumulation of metabolites in the active muscles, i.e. to a muscle chemoreflex, or to other reflex mechanisms from the exercising limbs. Indeed, the source of the afferent peripheral drive has long been a matter for debate, until McCloskey and Mitchell (1972) have shown in the cat that the instantaneous ventilatory response elicited by ventral root stimulation could be abolished by the anaesthetic blockade of groups III and IV afferents, but not of groups I and II, thereby ruling out the stimulation of articular receptors and muscle spindles as the reflex input. The origin of ph I has also been associated with the chemoreceptive function of hypothetical tissue receptors, a postulate, however, that lacks supporting experimental evidence (Wasserman et al. 1986).

Over the last two decades the neural peripheral origin of ph I has been questioned. Wasserman et al. (1974, 1986) have hypothesized that exercise hyperpnoea could result from an increased flow of CO_2 to the lungs,

defined as the product of cardiac output ($\dot{Q}_c$) times CO_2 concentration in mixed venous blood $\dot{Q}_c \cdot C_{\bar{v}}CO_2$), through the activation of hypothetical CO_2 receptors located either in the lungs and/or in the right heart. The ph I has also been associated with mechanical inputs from the heart to the respiratory centres (Jones et al. 1982). The latter hypothesis, however, has been challenged by recent experimental evidence on animals (Huszczuk et al. 1990) and humans (Marconi et al. 1991) carrying artificial hearts set at constant $\dot{Q}_c$. The CO_2 flow hypothesis has been tested by several authors. A close qualitative and quantitative relationship between $\dot{V}_E$ and $\dot{Q}_c$ during ph I has been found by Cummin et al. (1986), whereas according to other authors the increase in $\dot{V}_E$ has been more marked and abrupt than the increase in $\dot{Q}_c$ (Miyamoto et al. 1982; Adams et al. 1987; Morikawa et al. 1989). In none of these studies, however, have attempts been made to calculate and/or vary CO_2 flow to the lungs.

On the other hand, the central command theory of Krogh and Lindhard (1913) has undergone a recent resurgence. According to Eldridge et al. (1985) hypothalamic signals have been shown to be primarily responsible for the proportional drive of locomotion and respiration during exercise.

The aim of the present investigation was to test the theories underlying the CO_2-mediated compared to the neural origin of the ph I response to constant-intensity exercise in humans. This was attempted by measuring:

1. The time courses of $\dot{V}_E$ and of end tidal partial pressures of oxygen and carbon dioxide ($P_{ET}O_2$ and $P_{ET}CO_2$) during the rest-to-work transition of graded intensities, starting both in normocapnia and in hypocapnia.
2. The time courses of $\dot{Q}_c$ and CO_2 flow to the lungs at the onset of exercise, and their possible link to ph I. This approach was made possible by monitoring $\dot{V}_E$ and gas exchange as well as $\dot{Q}_c$ breath-by-breath (BbB) and beat-by-beat (bbb) respectively.

Methods

Subjects

A total of 11 healthy untrained male subjects

mean age 34.6 (SD 6.3) years, mean height 176 (SD 6) cm; mean body mass 75.7 (SD 11.8 kg)

volunteered for the study. They were informed about the protocols and the laboratory techniques and gave their consent to participate in the study, but were not informed as to the aim of the investigation, which was approved by the Ethics Committees of the institutions involved.

Measurements

A computerized metabolic cart (SensorMedics MMC 4400tc) was used for BbB assessment of $\dot{V}_E$, (in BTPS), $P_{ET}O_2$ and $P_{ET}CO_2$, respectively and gas exchange [O_2 uptake ($\dot{V}O_2$) in STPD, and CO_2 output ($\dot{V}CO_2$) in STPD]. The $\dot{V}_E$ was calculated by integration of the flow tracings recorded at the mouth of the subject by a low-resistance turbine flowmeter. Volume calibration was performed prior to each measurement, by means of a 3-l syringe, at three different flow rates usually observed at rest and during exercise. The $\dot{V}O_2$ and $\dot{V}CO_2$ were obtained from the time courses of partial pressure of O_2 and CO_2 (PO_2 and PCO_2) at the mouth throughout the respiratory cycle, and from established mass balance equations. Differences in response time of flow meter and gas analysers were corrected for in the computation of gas exchange parameters. The method used in the present study to determine BbB gas exchange does not allow for the correction of changes, during successive breaths, of pulmonary gas stores.

The $\dot{Q}_c$ was determined on a bbb basis by impedance cardiography. A prototype of an impedance cardiograph designed at the Department of Biomedical Engineering at the University of Stuttgart (Germany) was used. A constant current of 4 mA rms at a frequency of 100 kHz was applied to the chest by two disposable self-adhesive electrodes. Two separate electrodes were used to measure the changes of voltage resulting from variations of impedance within the chest volume under consideration. The four-spot electrode array was placed according to the scheme of Kubicek et al. (1966). Baseline thoracic impedance (Z_0), change of impedance (dZ/dt) and maximum of impedance derivative (dZ/dt_{max}) were automatically derived together with left ventricular ejection time ($LVET$), heart rate (HR) and the electrocardiogram. Stroke volume (SV) was calculated according to the equation of Kubicek et al. (1966):

$$SV = r\ (l/Z_0)^2\ (dZ/dt_{max})LVET \quad (1)$$

where l is the distance between the inner electrodes and r the resistivity of blood at 100 kHz.

Experimental procedure and calculations

The respiratory variables were obtained on 6 of the 11 subjects during constant intensity exercise at 50, 100, 150 W carried out on an electrically braked cycle ergometer (Bosch ERG 551). A particular effort was made to eliminate all sources of noise from the room and to make the subject feel as comfortable as possible. The subject sat on the cycle ergometer either breathing room air for 5 min (normocapnic mode, N) or hyperventilating ($\dot{V}_E$ about three times the resting level, mainly as a consequence of an increase in tidal volume V_T) for the first 4 min and resuming spontaneous $\dot{V}_E$ over the 5th min (hypocapnic mode, H). The level of hyperventilation was chosen to induce $P_{ET}CO_2$ values of about 20–25 mmHg (2.7–3.3 kPa). Each subject practiced the chosen hyperventilatory pattern during the training experiments. No subject experienced any symptoms during and after the hyperventilatory procedure. The subject was then asked by voice to carry out the required exercise without warning, to avoid a ventilatory anticipation of exercise onset. Exercise was started from a standardized position of the legs allowing the fastest start, i.e. with the left pedal arm in a frontal horizontal plane. The required intensity was attained within 3 s. A pedalling rate of 60 (SD 2) rpm was chosen. The $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2$, gas exchange ratio (R), $P_{ET}O_2$ and $P_{ET}CO_2$ were recorded BbB over the whole experimental period. Both in N and in H, four repetitions were performed at each exercise intensity. In three cases the exercise duration was 1 min, but in the last trial the exercise was carried out for 5 min.

The ph I is usually defined as the period between the start of exercise and the beginning of changes in mixed venous blood and alveolar gas O_2 and CO_2 partial pressures (P_AO_2 and P_ACO_2) (Whipp 1987; Whipp and Ward 1980). The duration of ph I was thus calculated as the time elapsing from exercise onset to the instant when an abrupt change in the slope of the $P_{ET}CO_2$ and $P_{ET}O_2$

versus time curves became evident. The amplitude of ph I was obtained as the difference between the peak $\dot{V}_E$ within ph I and the average $\dot{V}_E$ immediately preceding the start exercise (after hyperventilation in H). The time to reach the peak $\dot{V}_E$ response after exercise onset was also calculated.

On a separate occasion, $\dot{Q}_c$ was determined on 8 subjects (5 of whom were different from those participating in the gas exchange analysis series) during 50-W exercise periods in the N mode. The same experimental procedure as for the determination of the respiratory variables was applied. On 2 subjects, the $\dot{Q}_c$ measurements at 50-W were repeated in H. The $\dot{Q}_c$ was not measured at exercise intensities higher than 50 W, to avoid artefacts from moving electrodes at higher exercise intensities (see Discussion).

The CO_2 flow to the lungs was calculated throughout the first 60 s of exercise as follows:

$$CO_2 \text{ flow} = \dot{Q}_c \cdot C_{\bar{v}}CO_2 \quad (2)$$

where, by rearranging Fick's equation:

$$CO_2 \text{ flow} = C_aCO_2 + \dot{V}CO_2/\dot{Q}_c \quad (3)$$

where C_aCO_2 is the concentration of carbon dioxide arterial blood.

The $\dot{Q}_c$ measurements corresponding to the average value calculated over one breathing cycle ($1/f_r$) were used. The C_aCO_2 was calculated from the partial pressure of carbon dioxide in the arterial blood (P_aCO_2) by means of the nomogram of Dill et al. (1937). The P_aCO_2 was estimated from $P_{ET}CO_2$ as (Jones et al. 1979):

$$P_aCO_2 = 5.5 + 0.90 P_{ET}CO_2 - 0.0021 V_T \quad (4)$$

Statistics

The effects of exercise intensity and PCO_2 on the characteristics of ph I were analysed by two-way ANOVA. When needed, a z-test was used to identify significant differences. The relationship between CO_2 flow to the lungs and $\dot{V}_E$ was determined by linear regression. The level of significance was set at $P < 0.05$.

Results

Ventilatory response

Mean resting and steady-state exercise values for $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2$, R, $P_{ET}O_2$ and $P_{ET}CO_2$ are shown in Table 1. Individual examples of the time course of $\dot{V}_E$ following the onset of exercise, in which the ph I is highlighted, are shown in Fig. 1 (the first 2 min of the 5 min exercise test, BbB values) for the three tested exercise intensities in normocapnia (N, left panel) and hypocapnia (H, right panel). The $P_{ET}O_2$ and $P_{ET}CO_2$ are also given. Figure 2 is an individual summary of the time courses (up to 2 min) of $\dot{V}_E$ and $P_{ET}CO_2$ for the 5-min 50-W intensities. The corresponding time courses of $\dot{V}O_2$ and $\dot{V}CO_2$ are given in Fig. 3. In N $\dot{V}_E$ increased abruptly after the onset of work (ph I). In 48 out of 72 experiments, this increase was followed by a clear transient fall in $\dot{V}_E$, which in 15 cases was associated with a slight decrease in $P_{ET}CO_2$. When $P_{ET}CO_2$ started to increase and $P_{ET}O_2$ to decrease above and below resting levels, respectively (end of ph I), $\dot{V}_E$ began to increase again (ph II) towards a steady state. In H, an abrupt $\dot{V}_E$ increase, similar to that in N, was accompanied by a slight increase in $P_{ET}CO_2$ and by a decrease in $P_{ET}O_2$ (not shown in Fig. 2) towards the values preceding hyperventilation. However, contrary to N, the sudden changes in the slope of the $P_{ET}CO_2$ or $P_{ET}O_2$ versus the time curves, indicating end of ph I, were not followed by an immediate increase in $\dot{V}_E$ (ph II). Rather, $\dot{V}_E$ stayed low, sometimes even below the pre-exercise values. Accordingly, $P_{ET}O_2$

Table 1 Pulmonary ventilation ($\dot{V}_E$), O_2 consumption ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), gas exchange ratio (R), end tidal partial pressures of O_2 and CO_2 ($P_{ET}O_2$ and $P_{ET}CO_2$), in normocapnia (N) and in hypocapnia (H), at rest and at the steady state of different exercise intensities; $n = 72$ at rest and 18 during exercise

		$\dot{V}_E$ ($l \cdot min^{-1}$)	$\dot{V}O_2$ ($l \cdot min^{-1}$)	$\dot{V}CO_2$ ($l \cdot min^{-1}$)	R	$P_{ET}CO_2$ (mmHg)	$P_{ET}CO_2$ (mmHg)
Rest							
N	Mean	10.3	0.30	0.31	1.03	106	38
	SD	1.3	0.05	0.06	0.09	7	3
H	Mean	9.7	0.19	0.21	1.14	123	24
	SD	2.6	0.06	0.07	0.19	6	2
50 W ($\sim 25\%$ $\dot{V}O_{2\,max}$)							
N	Mean	25.7	0.94	1.01	1.08	103	45
	SD	2.7	0.08	0.13	0.08	5	3
H	Mean	25.0	0.96	0.92	0.96	101	41
	SD	2.6	0.07	0.12	0.15	6	5
100 W ($\sim 45\%$ $\dot{V}O_{2\,max}$)							
N	Mean	45.3	1.54	1.79	1.16	104	45
	SD	6.6	0.18	0.23	0.04	7	4
H	Mean	42.8	1.52	1.61	1.07	103	44
	SD	7.3	0.08	0.26	0.19	8	3
150 W ($\sim 70\%$ $\dot{V}O_{2\,max}$)							
N	Mean	66.8	1.98	2.49	1.26	109	43
	SD	12.7	0.11	0.15	0.06	11	7
H	Mean	69.5	1.98	2.38	1.21	111	41
	SD	21.2	0.13	0.25	0.18	11	8

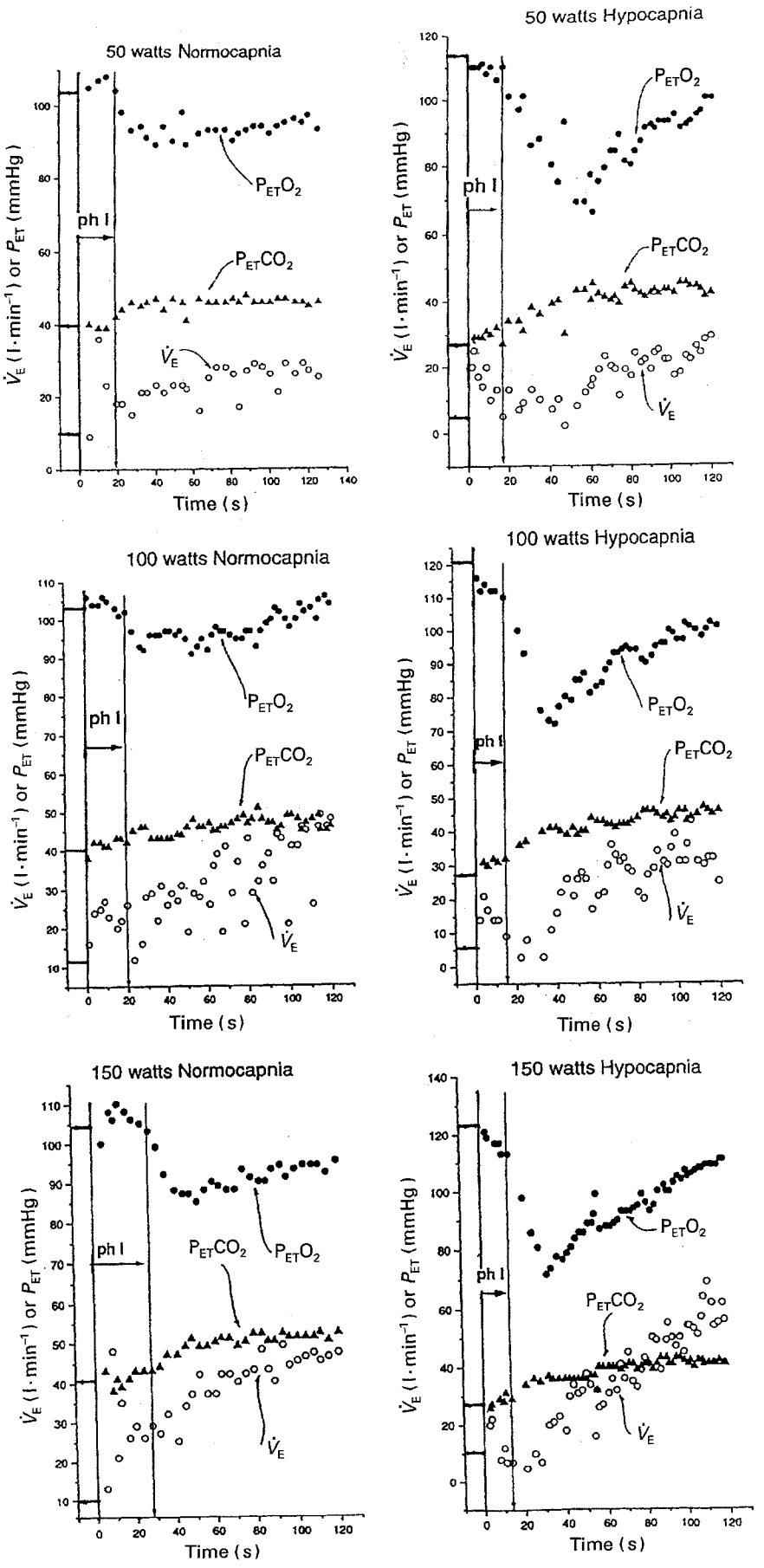

Fig. 1 Examples of pulmonary ventilation ($\dot{V}_E$) and end tidal partial pressures of O_2 and CO_2 ($P_{ET}O_2$ and $P_{ET}CO_2$ respectively), during the first 2 min of 50-W (*upper panel*), 100-W (*middle panel*) and 150-W (*lower panel*) constant-intensity exercise, in normocapnia and in hypocapnia. The *horizontal lines* before exercise onset (time = 0) represent the average values calculated over the last 30 s before exercise onset. The *vertical arrows* indicate the limits of the first phase ventilatory response to exercise (ph I). *Each panel* gives the results of one test for a typical subject

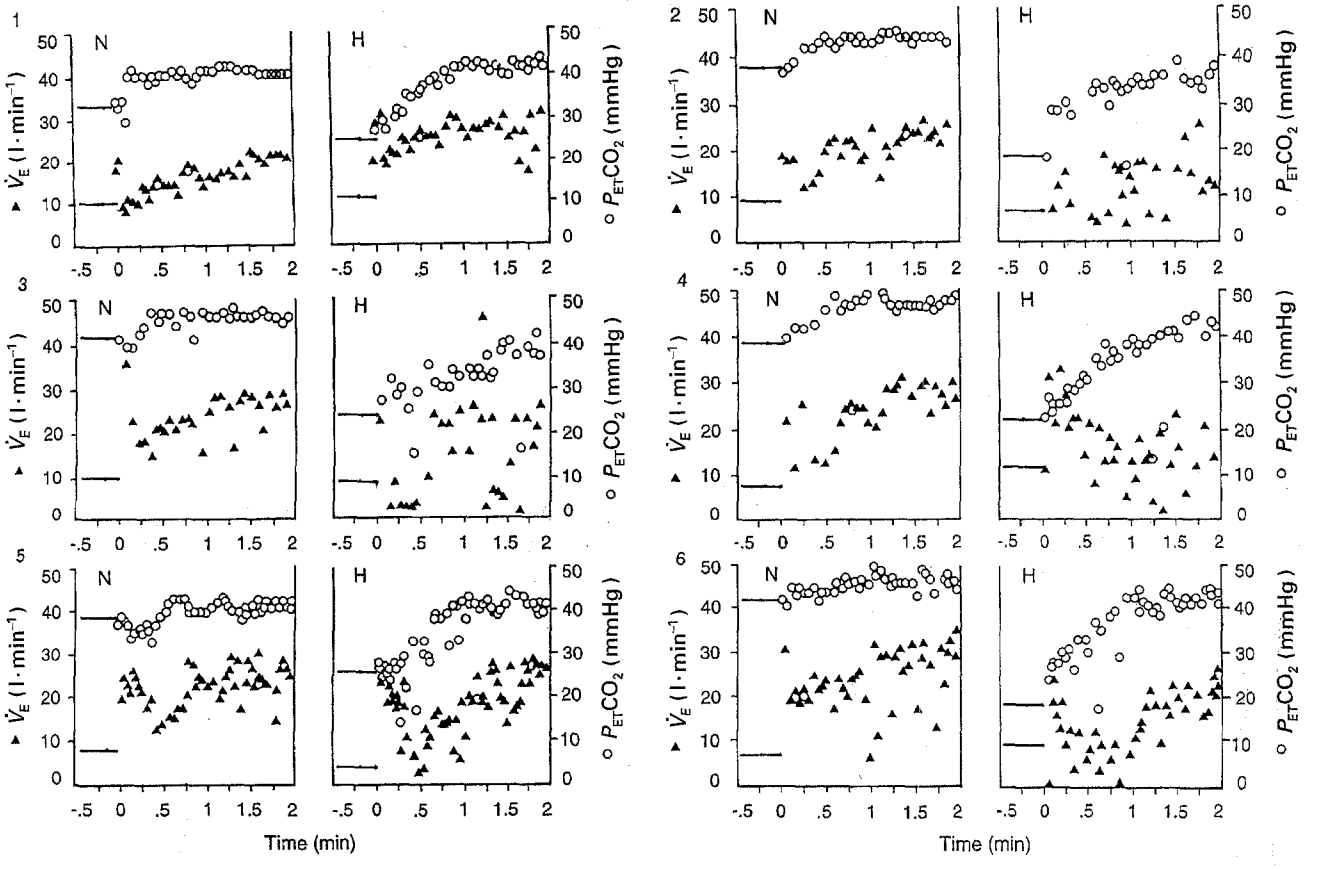

Fig. 2 Pulmonary ventilation ($\dot{V}_E$) and end tidal partial pressure of CO_2 ($P_{ET}CO_2$) during the first 2 min of 50-W constant-intensity exercise, in normocapnia (*N*) and in hypocapnia (*H*). The *horizontal lines* before exercise onset (time = 0) represent the average values calculated over the last 30 s before exercise onset. *Each panel* gives the results of one test for each of six subjects

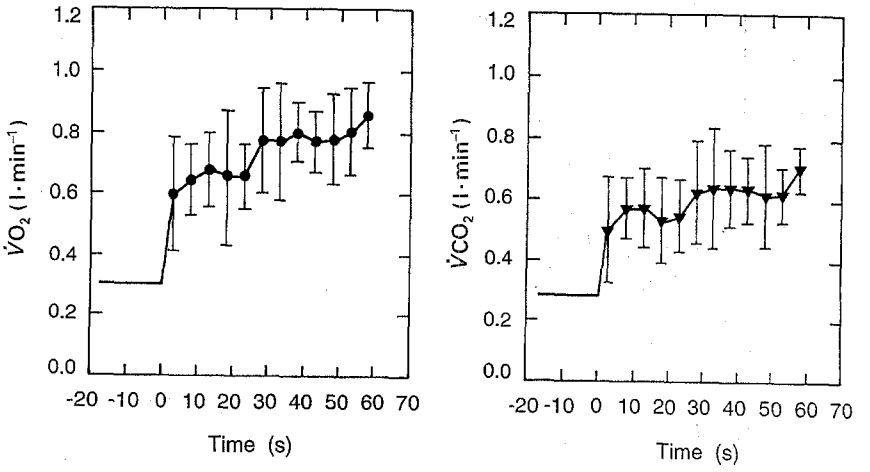

Fig. 3 Average time courses of O_2 uptake ($\dot{V}O_2$) and CO_2 output ($\dot{V}CO_2$) following the onset of 50-W exercise in normocapnia. The *horizontal lines* before exercise onset (time = 0) represent the average values calculated over the last 30 s before exercise onset. *Bars* indicate standard deviations

decreased even below 80 mmHg (10.7 kPa) and $P_{ET}CO_2$ continued to increase. It was only when $P_{ET}CO_2$ reached about 40 mmHg (5.3 kPa) (Fig. 2) that $\dot{V}_E$ increased again (start of ph II). The average amplitude and duration of ph I for all subjects and all conditions are shown in Table 2, together with the corresponding average $P_{ET}O_2$ and $P_{ET}CO_2$ throughout the response. The size of ph I was not significantly different between N and H, and was independent of the exercise intensity. By contrast, the duration of ph I was longer in H than in N. The time elapsing from the end of ph I and the start of ph II in H, calculated from the 5-min exercise tests, was 30.0 (SD 6.4) s, and did not vary with the exercise intensity. The $P_{ET}CO_2$ at the

Table 2 Characteristics of the first phase ventilatory response to exercise (ph 1). See text for details. $P_{ET}O_2$, $P_{ET}CO_2$ End partial pressure of oxygen and carbon dioxide, respectively

	Normocapnia			Hypocapnia		
Power (W)	50	100	150	50	100	150
Duration (s)						
Mean	25.5	22.6	21.3	27.3	22.9	21.6
SD	3.8	4.1	2.4	2.9	4.7	4.5
Amplitude ($l \cdot min^{-1}$)						
Mean	16.8	17.2	22.3	20.2	21.6	20.1
SD	3.1	3.1	3.7	4.1	8.8	9.4
Time to peak (s)						
Mean	8.1	11.6	11.6	8.1	7.0	7.8
SD	1.8	3.2	5.0	2.8	2.1	2.7
$P_{ET}O_2$ (mmHg)						
Mean	105	106	108	113	116	113
SD	5	5	4	7	5	7
$P_{ET}CO_2$ (mmHg)						
Mean	40	39	38	29	28	30
SD	3	3	2	4	2	4

start of ph II was 39.6 (SD 3.1) mmHg [5.3 (SD 0.41) kPa].

$\dot{Q}_c$ and CO_2 flow to the lungs

Individually calculated values for $\dot{Q}_c$ and for the CO_2 flow to the lungs during the 1st min of exercise, and the corresponding $\dot{V}_E$ response curves, are shown in Fig. 4 (50 W, N mode). The CO_2 flow to the lungs at rest varied between 130 and 200 $mmol \cdot min^{-1}$, attaining about 300–350 $mmol \cdot min^{-1}$ at steady state. In the few measurements carried out in the H mode, CO_2 flow to the lungs at rest was approximately halved, and was still lower than in N after 5 min of exercise. In contrast to $\dot{V}_E$, which increased abruptly at onset of exercise (ph I), CO_2 flow to the lungs over the first 10–15 s of exercise did not change substantially, both in N and in H, even though the trend was towards a slight increase. In any case, no correlation between CO_2 flow to the lungs and $\dot{V}_E$ could be observed during ph I ($r = 0.22$; $P = 0.28$; $n = 27$) in the subjects on whom a simultaneous determination of these two parameters was obtained.

Discussion

Reliability of $\dot{Q}_c$ measurements

There are only two techniques that can provide, noninvasively, $\dot{Q}_c$ or SV bbb, these are impedance cardiography and Doppler ultrasound techniques. Both techniques as a result of the underlying principles are indirect, and thus, in this respect there is no clear advantage of one over the other. Indeed, there are common problems for both techniques, which may not be relevant for measurements at rest but may become important during exercise, mainly because of body movements. For the impedance technique it is mainly the movement of the electrodes that can cause artefacts, whereas for the Doppler technique placement and stability of the Doppler probe becomes increasingly difficult during exercise. As a consequence, $\dot{Q}_c$ measurements in the present study were restricted to moderate exercise (50 W), in which the movements of the upper part of the body were limited, and therefore did not significantly interfere with the measurements. The reliability of Z as an indirect index of $\dot{Q}_c$, even during exercise, has been supported by numerous studies (e.g. Kobayashi et al.

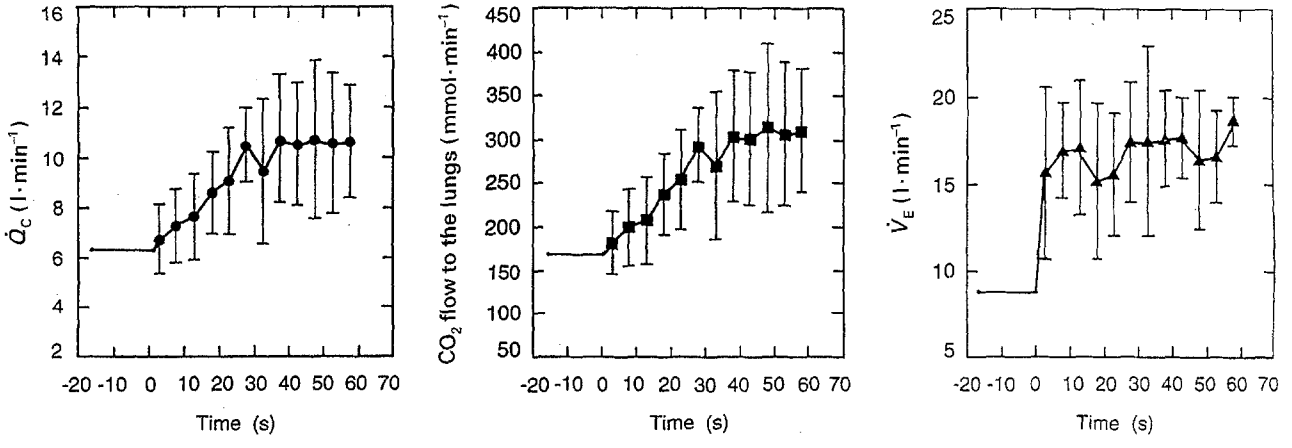

Fig. 4 From *left to right*, cardiac output ($\dot{Q}_c$), CO_2 flow to the lungs and pulmonary ventilation ($\dot{V}_E$) as a function of exercise time (50 W in normocapnia). The *horizontal lines* before exercise onset (time = 0) represent the average values calculated over the last 30 s before exercise onset. *Bars* represent standard diviations. Data are from the three subjects who underwent simultaneous determinations of $\dot{Q}_c$ and $\dot{V}_E$. The $\dot{Q}_c$ and CO_2 flow represent average values calculated over one breathing cycle

1978; Edmunds et al. 1982; Hatcher and Srb 1986; Niizeki et al. 1989). What matters for the present study is that the relative changes (compared to the resting baseline) of $\dot{Q}_c$ were properly followed, the absolute values being less important. Indeed, the results would be essentially the same if the changes of Z, rather than the calculated SV, were used as an indirect index of $\dot{Q}_c$. In any case, the marked disparity of CO_2 flow and $\dot{V}_E$ time courses at the onset of exercise (see below) would be preserved.

The kinetics of $\dot{Q}_c$ reported in the present study appear somewhat slower than those described by Cummin et al. (1986) and by Yoshida et al. (1993), but substantially confirm previous results that have been obtained by other authors by means of impedance cardiography (Miyamoto et al. 1982; Morikawa et al. 1989) or Doppler ultrasound techniques (Adams et al. 1987).

On the origin of the ph I ventilatory response to exercise

In N, initiated from rest in the upright posture, ph I appeared in more than 95% of the trials and lasted for a few breathing cycles. Its amplitude was invariant with exercise intensities from 50 W to 150 W. These observations do not fully confirm previous results which have been obtained by Asmussen and Nielsen (1948), by Dejours et al. (1961) and by Pearce and Millhorn (1977), who have observed a slight increase in the amplitude of ph I with increasing exercise intensity. The present results suggest that ph I may be an all or nothing type of response. As to the constancy of the size of ph I, preliminary results obtained in our laboratory indicate that the inertia encountered by the subject at the very beginning of pedalling is essentially independent of the imposed (50–150 W) exercise intensity. Consequently, a similar initial strain on the muscles could be expected. This might explain why the ph I magnitude does not change with the exercise intensity. The mean size of the ph I in N was not significantly different from that in H. This finding is in contrast with the results of Asmussen (1973), who has failed to detect ph I after voluntary hyperventilation in O_2 in 2 subjects. Also Ward et al. (1983) have found that ph I was drastically reduced after voluntary hyperventilation. On the other hand, they are in agreement with earlier results of Lefrançois and Dejours (1964), who have shown that after hyperventilation ph I is independent of the initial P_ACO_2 level. The apparent discrepancies regarding ph I following hyperventilation could be due in part to a difference in measurement accuracy (Asmussen 1973), or possibly to differences in the procedure adopted for data averageing. Also the shorter interval (15–20 s) imposed between the end of hyperventilation and exercise onset by Ward et al. (1983) may be of importance.

With regard to the origin of ph I, recent experimental evidence from animals or humans carrying an artificial heart set at given $\dot{Q}_c$ levels (Huszczuk et al. 1990; Marconi et al. 1991) has argued against the effectiveness of mechanical cardiodynamic receptors, such as those hypothesized by Jones et al. (1982). On the other hand, according to Wasserman et al. (1974, 1986), ph I could be elicited by an augmented CO_2 flow to the lungs, as a consequence of the sudden increase in $\dot{Q}_c$ at the onset of exercise. This hypothesis is contradicted by the present results. Indeed, in contrast to $\dot{V}_E$, at the onset of constant-intensity exercise CO_2 flow to the lungs did not increase significantly during ph I, and therefore cannot be held responsible for the $\dot{V}_E$ increase. This was particularly evident in H, a condition in which, despite a drastic reduction in CO_2 flow to the lungs, ph I was no different from that in N.

As mentioned above, the method used in the present study for the BbB assessment of gas exchange did not correct for changes of pulmonary gas stores in between breaths. This could potentially lead to some errors in the determination of BbB $\dot{V}CO_2$, which we used for the estimation of $C_{\bar{v}}CO_2$ (Eq. 3). However, the risk of introducing significant errors should be minor, if we consider that, as has been shown by di Prampero and Lafortuna (1989), changes in pulmonary CO_2 stores do not significantly affect BbB $\dot{V}CO_2$, at variance with what has been described for pulmonary O_2 stores and $\dot{V}O_2$.

The present evidence against a humoral origin of ph I strengthens the hypothesis that neural mechanisms are responsible for it. It has been shown that the firing of cortical and/or subcortical (hypothalamic) motor centres during constant-intensity exercise is maintained after the onset of exercise (Eldridge et al. 1985). This being the case, the present results would appear more compatible with the hypothesis of an *exercise reflex* control of ph I, rather than of a *central command* mechanism. In fact:

1. The initial rise of $\dot{V}_E$ was followed by a marked drop, particularly in H;
2. A considerable time lag between the end of ph I and the beginning of ph II was found in H.

The observed ph I may indeed be qualitatively related to the input from group III spinal afferent fibres in response to muscle contraction. In fact, this response is characterized by a strong initial firing activity, followed by rapid adaptation. The latter has been shown to be completed in the cat within 20 s of the contraction period (Kaufman et al. 1983), and seems therefore compatible with the time course of $\dot{V}_E$ during ph I, as described in the present study.

The results of the present study are substantially compatible with the neuro-humoral hypothesis proposed by Dejours (1963). According to this author the ventilatory response to exercise has a dual origin: a fast, short-lasting neural phase, followed by a chemically-driven response elicited by the work-dependent

increase in blood PCO_2. A novel finding from this study is the clear-cut temporal dichotomy between the fast and the slow components of the $\dot{V}_E$ response to exercise, never detected so clearly in previous studies. Indeed, the ventilatory increase during phase I was reversed after a few seconds following onset of exercise. In N this tendency was masked in part by the incoming slow component of ventilation (ph II), but when exercise was preceded by voluntary hyperventilation (H) a complete temporal dissociation between the fast and the slow components of the $\dot{V}_E$ response to exercise became evident.

In conclusion, the results of the present study will appear to be against the hypothesis of a metabolic (CO_2 flow to the lungs) control of ph I. Concerning the neural origin of ph I, they would appear compatible with a reflex drive of the type *exercise reflex*, rather than with a central command control mechanism.

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