

## ORIGINAL ARTICLE

Paolo Cerretelli · Bruno Grassi · Lei Xi  
 Federico Schena · Claudio Marconi  
 Michael Meyer · Guido Ferretti

## The role of pulmonary CO<sub>2</sub> flow in the control of the phase I ventilatory response to exercise in humans

Accepted: 10 February 1995

**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<sub>2</sub> flow to the lungs ( $\dot{Q}_c \cdot C_{\bar{v}}CO_2$  where  $C_{\bar{v}}CO_2$  is concentration of CO<sub>2</sub> in mixed venous 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  $18 \text{ l} \cdot \text{min}^{-1}$  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<sub>2</sub> flow to the lungs and  $\dot{V}_E$  during ph I. These results are interpreted as suggesting that an increased CO<sub>2</sub> 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

### 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<sub>2</sub> to the lungs,

P. Cerretelli (✉) · B. Grassi · L. Xi · F. Schena · G. Ferretti  
 Department of Physiology, CMU, Université de Genève,  
 9 Avenue de Champel, CH-1211 Geneva 4, Switzerland

P. Cerretelli · B. Grassi · C. Marconi  
 Section of Physiology, Istituto di Tecnologia Biomedica Avanzata,  
 Consiglio Nazionale delle Ricerche, Milan, Italy

M. Meyer  
 Abteilung Physiologie, Max-Planck-Institut für Experimentelle  
 Medizin, Göttingen, Federal Republic of Germany

defined as the product of cardiac output ( $\dot{Q}_c$ ) times  $\text{CO}_2$  concentration in mixed venous blood ( $\dot{Q}_c \cdot C_{\bar{v}}\text{CO}_2$ ), through the activation of hypothetical  $\text{CO}_2$  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  $\text{CO}_2$  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  $\text{CO}_2$  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  $\text{CO}_2$ -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 ( $P_{\text{ET}}\text{O}_2$  and  $P_{\text{ET}}\text{CO}_2$ ) 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  $\text{CO}_2$  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),  $P_{\text{ET}}\text{O}_2$  and  $P_{\text{ET}}\text{CO}_2$ ,

respectively and gas exchange [ $\text{O}_2$  uptake ( $\dot{V}\text{O}_2$ ) in STPD, and  $\text{CO}_2$  output ( $\dot{V}\text{CO}_2$ ) 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  $\dot{V}\text{O}_2$  and  $\dot{V}\text{CO}_2$  were obtained from the time courses of partial pressure of  $\text{O}_2$  and  $\text{CO}_2$  ( $P\text{O}_2$  and  $P\text{CO}_2$ ) 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 ( $dZ/dt_{\text{max}}$ ) 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):

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

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  $P_{\text{ET}}\text{CO}_2$  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  $\dot{V}_E$ ,  $\dot{V}\text{O}_2$ ,  $\dot{V}\text{CO}_2$ , gas exchange ratio ( $R$ ),  $P_{\text{ET}}\text{O}_2$  and  $P_{\text{ET}}\text{CO}_2$  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  $\text{O}_2$  and  $\text{CO}_2$  partial pressures ( $P_A\text{O}_2$  and  $P_A\text{CO}_2$ ) (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  $P_{\text{ET}}\text{CO}_2$  and  $P_{\text{ET}}\text{O}_2$

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  $\text{CO}_2$  flow to the lungs was calculated throughout the first 60 s of exercise as follows:

$$\text{CO}_2 \text{ flow} = \dot{Q}_c \cdot C_{\bar{v}}\text{CO}_2 \quad (2)$$

where, by rearranging Fick's equation:

$$\text{CO}_2 \text{ flow} = C_a\text{CO}_2 + \dot{V}\text{CO}_2/\dot{Q}_c \quad (3)$$

where  $C_a\text{CO}_2$  is the concentration of carbon dioxide arterial blood.

The  $\dot{Q}_c$  measurements corresponding to the average value calculated over one breathing cycle ( $1/f_i$ ) were used. The  $C_a\text{CO}_2$  was calculated from the partial pressure of carbon dioxide in the arterial blood ( $P_a\text{CO}_2$ ) by means of the nomogram of Dill et al. (1937). The  $P_a\text{CO}_2$  was estimated from  $P_{\text{ET}}\text{CO}_2$  as (Jones et al. 1979):

$$P_a\text{CO}_2 = 5.5 + 0.90 P_{\text{ET}}\text{CO}_2 - 0.0021 V_T \quad (4)$$

## Statistics

The effects of exercise intensity and  $P\text{CO}_2$  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  $\text{CO}_2$  flow to the lungs and  $\dot{V}_E$  was determined by linear regression. The level of significance was set at  $P < 0.05$ .

## Results

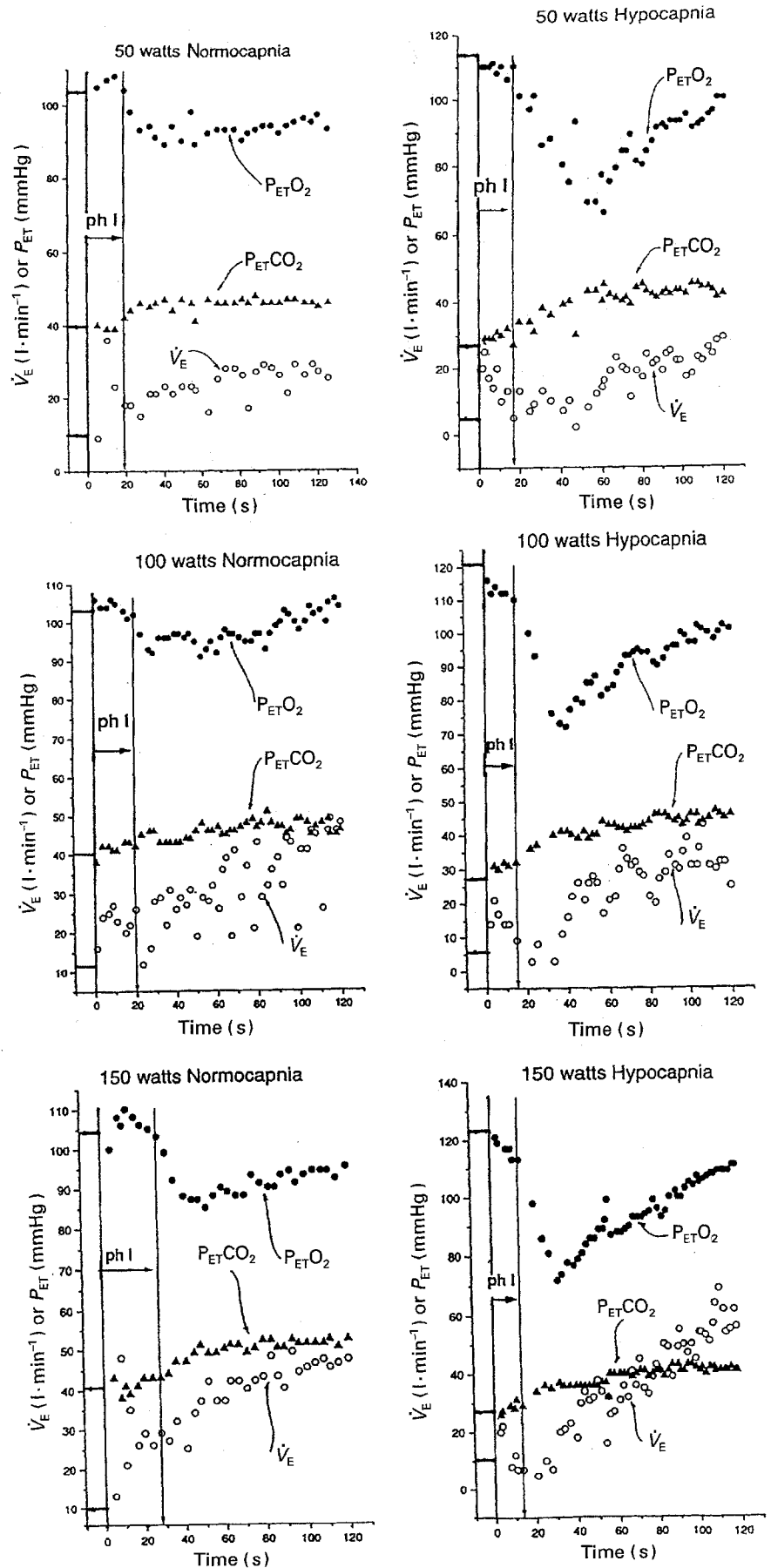
### Ventilatory response

Mean resting and steady-state exercise values for  $\dot{V}_E$ ,  $\dot{V}\text{O}_2$ ,  $\dot{V}\text{CO}_2$ ,  $R$ ,  $P_{\text{ET}}\text{O}_2$  and  $P_{\text{ET}}\text{CO}_2$  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  $P_{\text{ET}}\text{O}_2$  and  $P_{\text{ET}}\text{CO}_2$  are also given. Figure 2 is an individual summary of the time courses (up to 2 min) of  $\dot{V}_E$  and  $P_{\text{ET}}\text{CO}_2$  for the 5-min 50-W intensities. The corresponding time courses of  $\dot{V}\text{O}_2$  and  $\dot{V}\text{CO}_2$  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  $P_{\text{ET}}\text{CO}_2$ . When  $P_{\text{ET}}\text{CO}_2$  started to increase and  $P_{\text{ET}}\text{O}_2$  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  $P_{\text{ET}}\text{CO}_2$  and by a decrease in  $P_{\text{ET}}\text{O}_2$  (not shown in Fig. 2) towards the values preceding hyperventilation. However, contrary to N, the sudden changes in the slope of the  $P_{\text{ET}}\text{CO}_2$  or  $P_{\text{ET}}\text{O}_2$  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,  $P_{\text{ET}}\text{O}_2$

**Table 1** Pulmonary ventilation ( $\dot{V}_E$ ),  $\text{O}_2$  consumption ( $\dot{V}\text{O}_2$ ),  $\text{CO}_2$  output ( $\dot{V}\text{CO}_2$ ), gas exchange ratio ( $R$ ), end tidal partial pressures of  $\text{O}_2$  and  $\text{CO}_2$  ( $P_{\text{ET}}\text{O}_2$  and  $P_{\text{ET}}\text{CO}_2$ ), 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

		$\dot{V}_E$ ( $\text{l} \cdot \text{min}^{-1}$ )	$\dot{V}\text{O}_2$ ( $\text{l} \cdot \text{min}^{-1}$ )	$\dot{V}\text{CO}_2$ ( $\text{l} \cdot \text{min}^{-1}$ )	$R$	$P_{\text{ET}}\text{CO}_2$ (mmHg)	$P_{\text{ET}}\text{O}_2$ (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 (~ 25% $\dot{V}\text{O}_{2\text{max}}$ )							
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 (~ 45% $\dot{V}\text{O}_{2\text{max}}$ )							
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 (~ 70% $\dot{V}\text{O}_{2\text{max}}$ )							
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



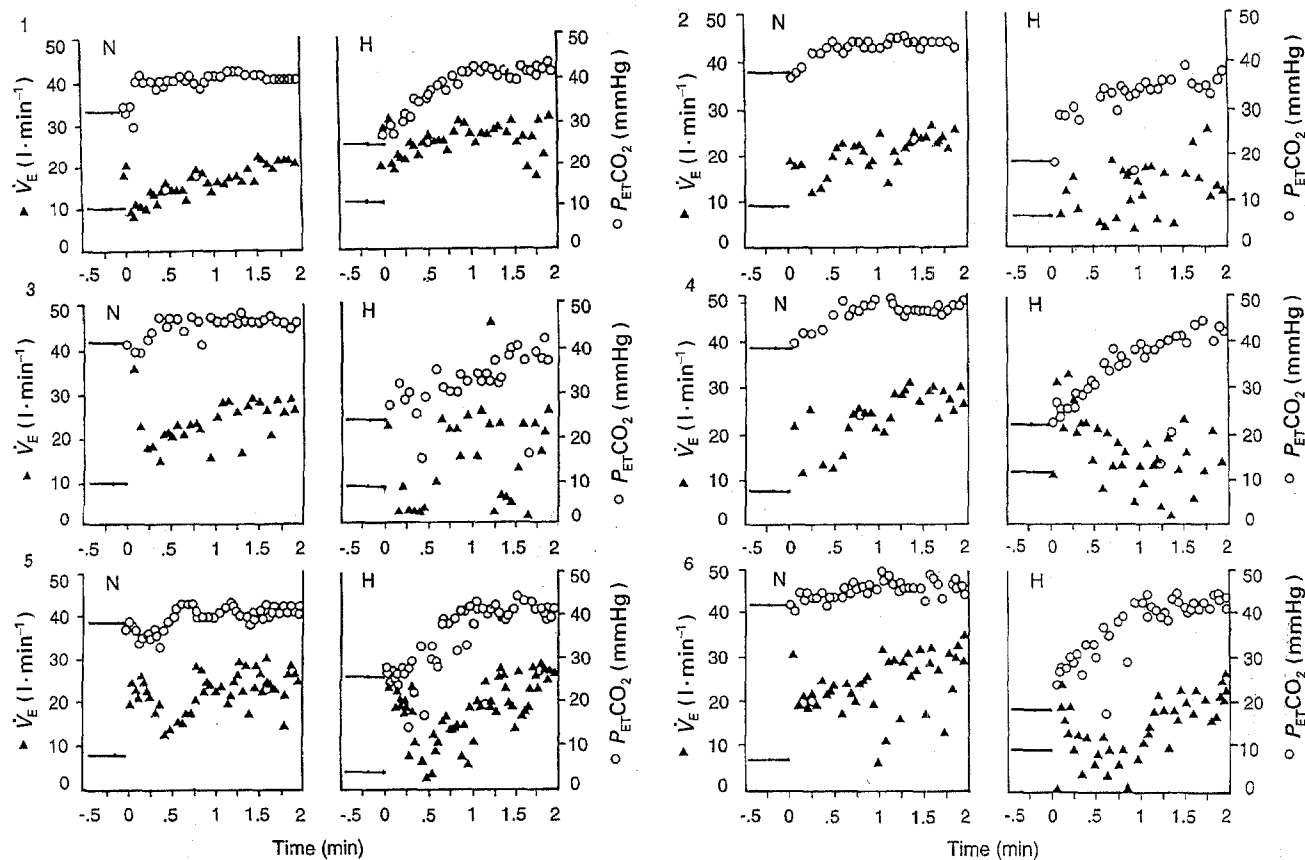
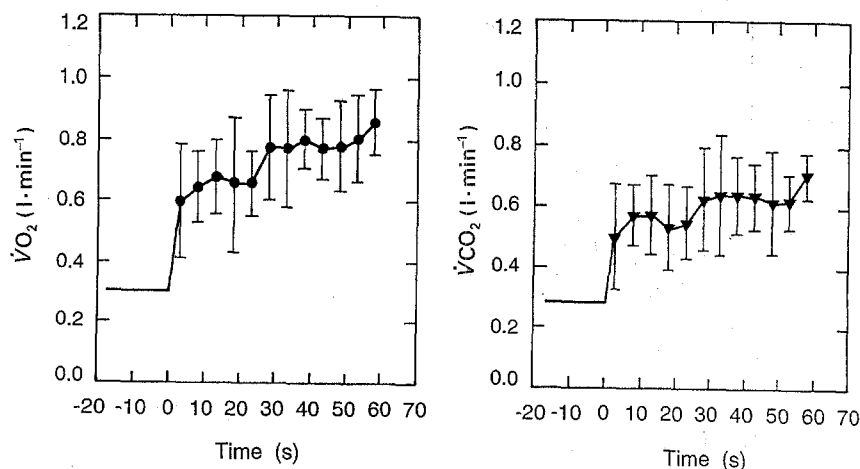


Fig. 2 Pulmonary ventilation ( $\dot{V}_E$ ) and end tidal partial pressure of  $\text{CO}_2$  ( $P_{ET}\text{CO}_2$ ) during the first 2 min of 50-W constant-intensity exercise, in normocapnia (N) and in hypocapnia (H). The horizontal lines before exercise onset (time = 0) represent the average values 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  $\text{O}_2$  uptake ( $\dot{V}\text{O}_2$ ) and  $\text{CO}_2$  output ( $\dot{V}\text{CO}_2$ ) 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  $P_{ET}\text{CO}_2$  continued to increase. It was only when  $P_{ET}\text{CO}_2$  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  $P_{ET}\text{O}_2$  and  $P_{ET}\text{CO}_2$  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  $P_{ET}\text{CO}_2$  at the

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

	Normocapnia			Hypocapnia		
	50	100	150	50	100	150
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 ( $l \cdot \text{min}^{-1}$ )						
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

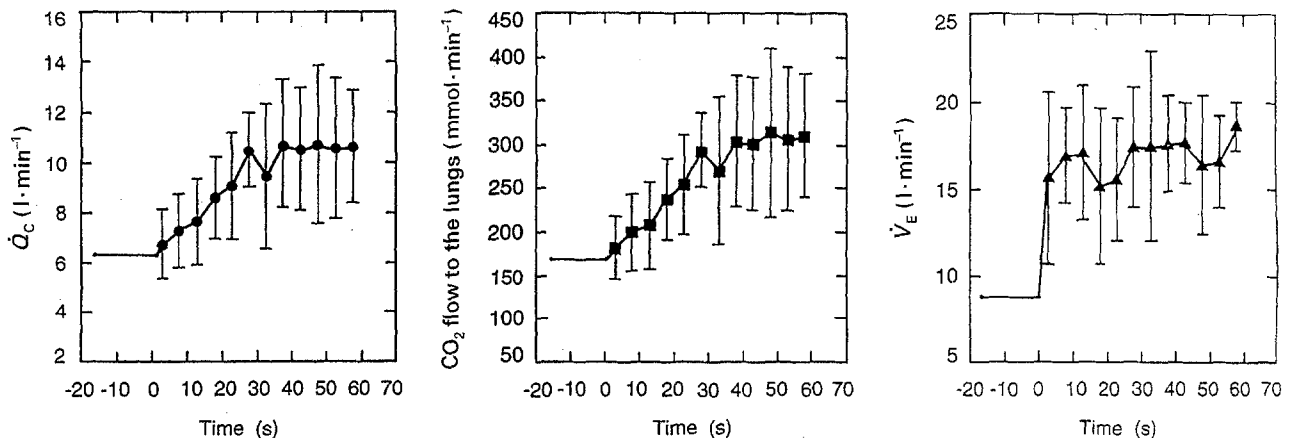
Individually calculated values for  $\dot{Q}_c$  and for the  $CO_2$  flow to the lungs during the 1st min of exercise, and the corresponding  $\dot{V}_E$  response curves, are shown in Fig. 4 (50 W, N mode). The  $CO_2$  flow to the lungs at rest varied between 130 and 200  $\text{mmol} \cdot \text{min}^{-1}$ , attaining about 300–350  $\text{mmol} \cdot \text{min}^{-1}$  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 deviations. 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  $\text{CO}_2$  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  $\text{O}_2$  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  $P_A\text{CO}_2$  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 averaging. 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  $\text{CO}_2$  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  $\text{CO}_2$  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  $\text{CO}_2$  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  $\dot{V}\text{CO}_2$ , which we used for the estimation of  $C_{\bar{v}}\text{CO}_2$  (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  $\text{CO}_2$  stores do not significantly affect BbB  $\dot{V}\text{CO}_2$ , at variance with what has been described for pulmonary  $\text{O}_2$  stores and  $\dot{V}\text{O}_2$ .

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.

**Acknowledgements.** The authors thank Dr. Pierre Dejours and Dr. Sukhamay Lahiri for constructive criticism, Mr. Angelo Colombini and Mr. Christian Moia for technical assistance. This work was partially supported by Grant no. 3228719.90 of the Fonds National Suisse for the Scientific Research, and by the Carlos and Elsie De Reuter Foundation, Geneva, Switzerland.

## References

- Adams L, Guz A, Innes JA, Murphy K (1987) The early circulatory and ventilatory response to voluntary and electrically induced exercise in man. *J Physiol (Lond)* 383:19–30
- Asmussen E (1973) Ventilation in the transition from rest to exercise. *Acta Physiol Scand* 89:68–78
- Asmussen E, Nielsen N (1948) Studies on the initial changes in respiration at the transition from rest to work and from work to rest. *Acta Physiol Scand* 16:270–285.
- Cummin ARC, Iyawe VI, Mehta N, Saunders KB (1986) Ventilation and cardiac output during the onset of exercise, and during voluntary hyperventilation in humans. *J Physiol (Lond)* 370:567–583
- Dejours P (1963) The regulation of breathing during muscular exercise in man. A neuro-humoral theory. In: Cunningham DJC, Lloyd BB (eds) *The regulation of human respiration*. Blackwell, Oxford, pp 535–547
- Dejours P, Flandrois R, Lefrançois R, Teillac A (1961) Étude de la régulation de la ventilation au cours de l'exercice musculaire chez l'homme. *J Physiol (Paris)* 53:321–322.
- Dill DB, Edwards HT, Consolazio WV (1937) Blood as a physico-chemical system. XI. Man at rest. *J Biol Chem* 118:635–648
- di Prampero PE, Lafortuna CL (1989) Breath-by-breath estimate of alveolar gas transfer variability in man at rest and during exercise. *J Physiol (Lond)* 415:459–475
- Edmunds AT, Godfrey S, Tooley M (1982) Cardiac output measured by transthoracic impedance cardiography at rest, during exercise and at various lung volumes. *Clin Sci* 63:107–113
- Eldridge FL, Millhorn DE, Kiley JP, Waldrop TG (1985) Stimulation by central command of locomotion, respiration and circulation during exercise. *Respir Physiol* 59:313–337
- Hatcher DD, Srb OD (1986) Comparison of two noninvasive techniques for estimating cardiac output during exercise. *J Appl Physiol* 61:155–159
- Huszcuk A, Whipp BJ, Adams TD, Fisher AG, Crapo RO, Elliott CG, Wasserman K, Olsen DB (1990) Ventilatory control during exercise in calves with artificial hearts. *J Appl Physiol* 68:2604–2611
- Jones NL, Robertson DG, Kane JW (1979) Difference between end-tidal and arterial  $PCO_2$  in exercise. *J Appl Physiol* 47:954–960
- Jones PW, Huszcuk A, Wasserman K (1982) Cardiac output as a controller of ventilation through changes in right ventricular load. *J Appl Physiol* 53:218–224
- Kaufman HP, Longhurst JC, Rybicki KJ, Wallach JH, Mitchell JH (1983) Effects of static muscular contraction on impulse activity of groups III and IV efferents in cats. *J Appl Physiol* 55:105–112
- Kobayashi Y, Andoh Y, Fujinami T, Nakayama K, Takada K, Takeuchi T, Okamoto M (1978) Impedance cardiography for estimating cardiac output during submaximal and maximal work. *J Appl Physiol* 45:459–462
- Krogh A, Lindhard J (1913) The regulation of respiration and circulation during the initial stages of muscular work. *J Physiol (Lond)* 47:112–136
- Kubicek WG, Karnegis JM, Patterson RP, Witsoe DA, Mattson RH (1966) Development and evaluation of an impedance cardiac output system. *Aerospace Med* 37:1208–1212
- Lefrançois R, Dejours P (1964) Étude des relations entre stimulus ventilatoire gaz carbonique et stimulus ventilatoire neurogéniques de l'exercice musculaire chez l'homme. *Rev Fr Etud Clin Biol* 9:498–505
- Marconi C, Grassi B, Meyer M, Cabrol A, Cabrol C, Cerretelli P (1991) Ventilatory and gas exchange kinetics in a human recipient of a Jarvik-7 total artificial heart (Letter to the Editor). *J Appl Physiol* 70:1406–1407
- McCloskey DI, Mitchell JH (1972) Reflex cardiovascular and respiratory responses originating in exercising muscles. *J Physiol (Lond)* 224:173–186
- Miyamoto Y, Hiura T, Tamura T, Nakamura T, Higuchi J, Mikami T (1982) Dynamics of cardiac, respiratory and metabolic function in men in response to step work load. *J Appl Physiol* 52:1198–1208
- Morikawa T, Ono Y, Sasaki K, Sakakibara Y, Tanaka Y, Maruyama R, Nishibayashi Y, Honda Y (1989) Afferent and cardiodynamic drives in the early phase of exercise hyperpnea in humans. *J Appl Physiol* 67:2006–2013
- Niizeki K, Miyamoto Y, Doi K (1989) A comparison between cardiac output determined by impedance cardiography and the rebreathing method during exercise in man. *Jpn J Physiol* 39:441–446
- Pearce DH, Millhorn HT Jr (1977) Dynamic and steady-state respiratory responses to bicycle exercise. *J Appl Physiol* 42:959–967
- Ward SA, Whipp BJ, Koyal S, Wasserman K (1983) Influence of body  $CO_2$  stores on ventilatory dynamics during exercise. *J Appl Physiol* 55:742–749
- Wasserman K, Whipp BJ, Castagna J (1974) Cardiodynamic hyperpnea: hyperpnea secondary to cardiac output increase. *J Appl Physiol* 36:457–464
- Wasserman K, Whipp BJ, Casaburi R (1986) Respiratory control in exercise. In: Cherniack NS, Widdicombe JG (eds) *Handbook of physiology, section 3. The respiratory system, vol. II*. American Physiological Society, Washington, DC, pp 595–619
- Whipp BJ (1987) The control of exercise hyperpnea. In: Whipp BJ (ed) *The control of breathing in man*. Manchester University Press, London, pp 87–118
- Whipp BJ, Ward SA (1980) Ventilatory central dynamics during muscular exercise in man. *Int J Sports Med* 1:146–159
- 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
- Zuntz N, Geppert J (1886) Über die Natur der normalen Atemreize und den Ort ihrer Wirkung. *Pflügers Arch* 38:337–338