Journal of Physiology (1992), **457**, *pp.* 539–557
With 7 figures
Printed in Great Britain

DYNAMICS OF THE VENTILATORY RESPONSE IN MAN TO STEP CHANGES OF END-TIDAL CARBON DIOXIDE AND OF HYPOXIA DURING EXERCISE

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(*Received 21 November 1991*)

SUMMARY

1. Four human subjects exercised in hypoxia (end-tidal partial pressure of O_2 (P_{ET,O_2}) *ca* 55 Torr; heart rate *ca* 100–130 beats min^{-1}), and the contribution to the respiratory drive of the peripheral and central chemoreflex pathways have been separated on the basis of the latencies and the time courses of the responses to sudden changes of stimulus.

2. The subjects were exposed to repeated end-tidal step changes in P_{CO_2} of *ca* 3–3·5 Torr (at nearly constant P_{ET,O_2}) and P_{O_2} (between *ca* 55 and 230 Torr) at three regions along the expiratory ventilation $\dot{V}_E$–P_{ET,CO_2} response line (hypocapnia, eucapnia, hypercapnia). The dynamics of the ventilatory responses were calculated using a two-compartment non-linear least-squares optimization method.

3. The component of the response attributable to the peripheral chemoreflex loop may in some subjects contribute up to 75% of the ventilatory drive during mild hypocapnic hypoxic exercise and *ca* 72% of the total gain following steps of P_{ET,CO_2} during hypoxic exercise. These data support the notion that the effectiveness of the peripheral chemoreceptor pathway is enhanced in moderate exercise.

4. During hypoxic exercise, the time delays and time constants attributed to the peripheral chemoreflex pathways (*ca* 3·5 and 9 s respectively) and to the central chemoreflex pathways (*ca* 9·5 and 47 s respectively) are some of the shortest reported.

5. The dynamics of the peripheral and central chemoreflex pathways appeared to be largely independent of each other.

6. There was a notable absence of systematic change of inspiratory and expiratory durations during the step-induced transients.

INTRODUCTION

The relations between expiratory ventilation ($\dot{V}_E$) and the end-tidal partial pressure of CO_2 (P_{ET,CO_2}), which are the CO_2 response lines, have been determined during exercise at various steady oxygen tensions by several groups (Asmussen & Nielsen, 1957; Bhattacharyya, Cunningham, Goode, Howson & Lloyd, 1970; Masson

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& Lahiri, 1974). During exercise, the mean slope of the CO_2 response line in euoxia and hyperoxia is about the same as during rest. The effect of hypoxia on $\dot{V}_E$ is augmented in exercise (for references see Cunningham, 1987), but the mean $\dot{V}_E$–P_{ET,CO_2} slope is usually less than at corresponding degrees of hypoxia at rest; furthermore, these hypoxic CO_2 response lines show no sign of the CO_2 threshold that is so prominent in the hypoxic CO_2 response lines at rest (Nielsen & Smith, 1952). The absence of a CO_2 threshold is not attributable to leftward shifting of the CO_2 response line by metabolic acidosis as the subjects were alkalotic rather than acidotic (Bhattacharyya *et al.* 1970; Masson & Lahiri, 1974).

On the other hand, Cummin, Alison, Jacobi, Iyawe & Saunders (1986), using CO_2 administration, have reported an increased slope of the $\dot{V}_E$–alveolar P_{CO_2} (P_{A,CO_2}) relation close to the eucapnic point even in light exercise in euoxia. However, their timing of the crucial determinations was such as to straddle the peak of the early change of blood lactic acid (Cunningham & Douglas, 1987); such small transient changes of lactic acid during the early determinations would be capable of producing small lateral displacements of P_{A,CO_2}. When the exercise intensity is well below the anaerobic threshold, as in the experiments to be reported here, the effects of any early rise of blood lactic acid have passed within about the initial 10 min.

Several groups have investigated the latencies (e.g. Lefrançois, Gautier, Pasquis, Cevaer, Hellot & Leroy, 1972; Miller, Cunningham, Lloyd & Young, 1974) and the dynamic responses of the peripheral and central chemoreflex pathways to end-tidal steps of CO_2 during euoxic or hypoxic rest (e.g. Bellville, Whipp, Kaufman, Swanson, Aqleh & Wiberg, 1979; Gardner, 1980), but as yet no information is available on these dynamic responses in physical exercise.

The aim of this investigation was to examine the dynamics of the peripheral and central chemoreflex pathways during mild exercise in moderate hypoxia, first by performing repeated isoxic steps of P_{ET,CO_2} between several points along the $\dot{V}_E$–P_{ET,CO_2} response line, and second by performing repeated steps in the end-tidal partial pressure of O_2 (P_{ET,O_2}) at three regions along the CO_2 response lines. Assuming that the peripheral and central chemoreflex pathways each act as a first-order linear system, the resultant output (ventilation) would then be in a form suitable for estimating the dynamics (time delays, time constants, and gains) of each pathway using a two-compartment non-linear least-squares optimization program. Data from the P_{ET,CO_2} on- and off-transients would also provide information for testing the predicted interaction between the peripheral and central chemoreceptor pathways reported by Robbins (1988).

Some of the preliminary findings have already appeared in abstract (Macfarlane & Cunningham, 1985; Macfarlane, 1986).

METHODS

Apparatus

The general arrangement of the apparatus was similar to that of Ward & Cunningham (1977). In outline, inspiratory gases were humidified at 37 °C and delivered in excess from two assemblies of rotameters. These fed into solenoid-operated rotatory valves that permitted rapid and silent switching between separate inspiratory mixtures; the surplus escaped to the atmosphere. The subjects breathed through a mouthpiece and a small dead-space, low-resistance Lloyd valve that separated the inspiratory and expiratory pathways; the nose was occluded. Expiratory gases

passed through a 4·25 l mixing chamber, a low-resistance gas meter and a wedge spirometer (SP 70, Cryotech, Wallingford, Berks, UK) that was emptied to a set volume during each inspiration. Its movement was detected by an inductance coil, the output of which was proportional to flow; integration yielded a volume signal that was independent of the physical properties of the gas. Volume calibration was performed with a 1·0 l reciprocating pump and by comparison with the gas meter trace. The mouth pressure, measured with a capacitance manometer (M.D.C. 300, Hilger-I.R.D. Ltd, London), was displayed as a respiratory duration time ramp that was briefly interrupted at the start of each expiration; inspiratory and expiratory times, T_I and T_E, were derived from the ramp (Gardner, 1980). Respiratory gas tensions were measured using a quadrupole mass spectrometer (Centronics MGA 200, Croydon, UK), which sampled gas at about 50 ml min^{-1} from between the flaps of the Lloyd valve; calibrations were performed before and after each run with a chemically analysed standard gas.

The subjects exercised on an electromagnetically braked cycle ergometer (Ergotest Universal, Jaeger, Würzburg, Germany) with their heart rates continuously monitored using a Tunturi Cardiotester (Cardionics ab, Skarhdmen, Sweden). Arterial oxygen saturation (S_{a,O_2}) at the ear was recorded continuously using an uncalibrated ear oximeter (Waters Instruments, Rochester, MI, USA; 95% response in less than 0·1 s). The uncalibrated oximeter was used to provide information on the time course of changes in S_{a,O_2} in the region of the carotid body, absolute values being unimportant.

Respiratory volumes, times and gas compositions were recorded digitally in real time on a minicomputer (Eclipse S/140, Data General, Slough, UK) and displayed along with S_{a,O_2} on a multichannel pen recorder (Devices M19) (Macfarlane, Painter & Pilsbury, 1985).

Experimental procedures

The subjects were four healthy male volunteers to whom the general, but not the specific, nature of the experiments had been explained. Written consent was obtained from all subjects. The procedures to which the subjects were subjected were well within the limits agreed with the Hospital Committee on Ethics of Clinical Investigation.

No measurements made during rest are recorded here. The subjects were asked to keep their pedalling frequency within 5 rev min^{-1} of whatever rate they chose, usually 55–65 rev min^{-1}. They were encouraged to read, whilst keeping an eye on the cycle's tachometer throughout each experimental run; these typically lasted less than 30 min with not more than three runs in a typical 3-h session. The load was adjusted to maintain the heart rate between 100–130 beats min^{-1}.

The various step changes between quasi-steady states are shown diagrammatically in Fig. 1*A* and *B*. The reference point for these was F (eucapnic–euoxic exercise). In the first series of experiments (CO_2 steps in steady hypoxia, P_{ET,O_2} *ca* 55 Torr), A represented the hypocapnic–hypoxic exercise point (no CO_2 added to inspirate and the inspiratory O_2 adjusted to maintain P_{ET,O_2}), B represented the eucapnic–hypoxic point (sufficient CO_2 added to the inspirate to render P_{ET,CO_2} isocapnic with F and inspiratory O_2 adjusted accordingly), and C was the hypercapnic–hypoxic point, with P_{ET,CO_2} *ca* 3·5 Torr above eucapnic. These isoxic CO_2 steps were executed in alternate directions.

The second series of experiments was a study of the responses to repeated step changes of P_{ET,O_2} between mild hypoxia and mild hyperoxia (P_{ET,O_2} *ca* 55 and 230 Torr respectively), at three levels of P_{ET,CO_2} as depicted in Fig. 1*B*. As in series 1, the reference point for these steady states was F (eucapnic–euoxic exercise). In Fig. 1*B*, D was the eucapnic–hyperoxic point (P_{ET,O_2} *ca* 230 Torr); at E the same degree of hyperoxia was present but P_{ET,CO_2} was raised by *ca* 3·5 Torr. The corresponding hypoxia states were B and C; they and the hypocapnic–hypoxic state A have already been characterized in the description of the first series above. The steps involving no change in P_{ET,CO_2} (B ↔ D and C ↔ E) were repeated in alternate directions at intervals not less than 60 s, while the steps involving changes of P_{ET,CO_2} (the remainder) were repeated in alternate directions at intervals not less than 180 s.

In order to obtain approximately square step changes it was necessary not only to change the primary gas (CO_2 for steps of P_{ET,CO_2}), including some degree of overshoot of the inspiratory CO_2 (see Fig. 2, CO_2 trace), but also to adjust the gas whose end-tidal value was to be maintained in the face of rapidly changing ventilation (Fig. 2, O_2 trace). The amount of adjustment was judged by anticipation and visual feedback from the mass spectrometer tracings, but was often vitiated by subject idiosyncracies (coughs, sighs, fidgeting, etc.); the criteria for data rejection are described

below. The first step changes to be used in the data analysis were performed after the exercise had been in progress for *ca* 10 min.

Data analysis

The breath which contained the first inspirate of the step change was designated breath '0', with the six breaths before it providing a 'preswitch mean'; the seven individual breaths after it (rapid phase of the ventilatory response) and the means of six breaths centring at every 30 s postswitch

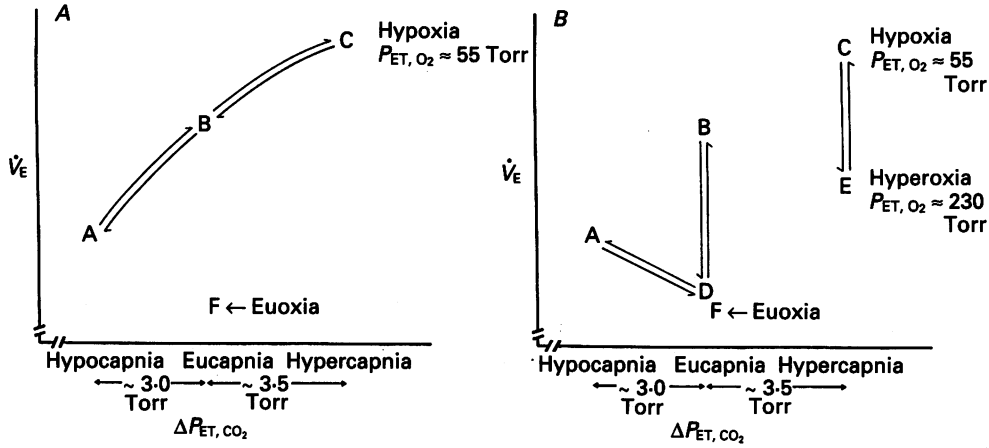

Fig. 1. Schematic representation of the ventilation codes A to E, relative to the reference point F (air breathing exercise with the heart rate in the range 100 to 130 beats min^{-1}). In Fig. 1*A*, repeated step changes in P_{ET,CO_2} were performed during constant hypoxia (P_{ET,O_2} maintained *ca* 55 Torr) between hypocapnia (A) and eucapnia (B; mean ± S.D. P_{ET,CO_2} for the four subjects was 44 ± 1 Torr), and between eucapnia (B) and hypercapnia (C). In Fig. 1*B*, repeated step changes in P_{ET,O_2} were performed between hypoxia (P_{ET,O_2} *ca* 55 Torr) and hyperoxia (P_{ET,O_2} *ca* 230 Torr); (i) during constant eucapnia between B and D, (ii) during constant hypercapnia between C and E, and (iii) non-isocapnically between A and D.

interval (slow phase of the ventilatory response) were analysed. The respiratory variables recorded for each breath were expiratory volume (V_T), times (T_I and T_E), P_{O_2} and P_{CO_2} at the mouth, and single-breath expiratory ventilation $\dot{V}_E = V_T/(T_I + T_E)$ was derived. For each individual step change the differences in these variables were calculated with respect to their own preswitch mean; the six breaths at the end of each step served as a preswitch mean for the next step in the opposite direction.

Since respiratory data are typically noisy, criteria were necessary for the elimination of outlier breaths from the analysis. No data smoothing was employed. In the first series, background isoxia was regarded as acceptable if no single P_{ET,O_2} deviated by more than 5 Torr from that of the breaths surrounding it. In the isocapnic steps of the second series, isocapnia was acceptable when no single P_{ET,CO_2} deviated by more than 3 Torr from the six-breath preswitch mean and no two consecutive P_{ET,CO_2} by more than 2 Torr. These criteria are like those of Gardner (1980); in the majority of the transitions analysed the background P_{ET,CO_2} or P_{ET,O_2} remained well within these limits.

The analysis of the first eight breaths was crucial (e.g. Fig. 2), and steps of each kind were repeated until approximately ten non-isocapnic and twenty isocapnic steps without a substantial blemish in the first eight breaths had been recorded. The six-breath means at 30 s intervals were of less individual importance in determining the shapes of the exponentials and a few of them included breaths sufficiently aberrant to warrant the exclusion of the whole mean of six. On rare occasions an outlying point was excluded if it drastically vitiated the exponential curve fitting routine; this occurred in less than 3% of the data points analysed.

While the isocapnic steps of P_{ET,O_2} should present an almost pure change in arterial chemoreceptor stimulation, the P_{ET,CO_2} steps of series 1 and the steps in and out of hypocapnia in series 2 (D↔A) should present changes in both arterial and central chemoreceptor stimulation. An estimate of lung-to-peripheral chemoreceptor transport time, D_p, was first gained from the averaged data for each kind of step for every subject (Ward & Bellville, 1983). An iterative non-linear least-squares optimization program was then used for fitting a single exponential to the remaining data of the isocapnic steps of series 2 and a double exponential to the non-isocapnic data for both series.

Single exponentials used were given by

$$y = G_p e^{-(t/T_p)} + \dot{V}_o, \quad (1)$$

or

$$y = G_p[1 - e^{-(t/T_p)}] + \dot{V}_o, \quad (2)$$

and double exponentials by

$$y = \{G_p e^{-(t/T_p)}\} + \{G_c e^{-((t-t_d)/T_c)}\} + \dot{V}_o, \quad (3)$$

or

$$y = \{G_p[1 - e^{-(t/T_p)}]\} + \{G_c[1 - e^{-((t-t_d)/T_c)}]\} + \dot{V}_o, \quad (4)$$

where y = response at time (t); t = time; G_p = peripheral gain; T_p = peripheral time constant; G_c = central gain; T_c = central time constant; t_d = peripheral-to-central time delay; $\dot{V}_o$ = background ventilation. The units of y, G_p, G_c, and $\dot{V}_o$ are l min^{-1} and time is in seconds. The lung-to-central time delay (D_c) was calculated from the sum of ($D_p + t_d$). The program calculated the standard deviation of the 'best fitted' exponentials using

$$\text{S.D.} = \sqrt{\{\text{residual}/(n-p)\}}, \quad (5)$$

where n = number of step changes analysed and p = number of parameters estimated.

As in the study by Bellville *et al.* (1979) the time constants reported are for the entire reflex pathway and include the time constants of the sensors, the neural processing and the effectors.

In eqns (1)–(4) the gains are expressed in l min^{-1} and are the means of the part of the changes in ventilation that is attributable to the pathway in question. In order to facilitate comparisons between subjects, as well as between different states and values reported in the literature, these gains have been expressed per unit change of stimulus in Tables 1 and 2. When, however, the changes in stimulus are in both CO_2 and hypoxia for G_p but in CO_2 only for G_c, comparison between gains expressed per unit change of stimulus has little meaning and the actual magnitude of the changes are therefore given, in the G-columns of Table 3, as l min^{-1}.

RESULTS

Peripheral delays D_p

The means of the peripheral delays measured from the oximeter traces in two subjects were 3·6 ± 0·3 s for steps out of hypoxia and 11·5 ± 1·7 s for steps into hypoxia. The 'on' effect is slower to develop for technical reasons (see below and Fig. 4). The corresponding means obtained by the exponential least-squares method were 3·6 ± 0·2 s and 11·4 ± 1·4 s. Direct measurement from this kind of oximeter trace gives values very close to the lung–carotid body delay (Jain, Subramanian, Julka & Guz, 1972).

Series 1: steps of P_{ET,CO_2} in hypoxia

Figure 2 shows an example of an experimental trace during a pair of isoxic CO_2 on- and off-transients (B to C, and C to B) during constant mild hypoxia. Moment-to-moment manipulation of the inspiratory gas composition resulted in a step change of P_{ET,CO_2} of approximately 3–3·5 Torr on breath 0. This was achieved by generating an overshoot in inspiratory P_{CO_2} (P_{I,CO_2}). An overshoot is, however, impossible when

a targeted P_{I,CO_2} of zero is approached from a higher value, and so the steps into hypocapnia (B to A) could not be completed on breath 0; the desired P_{ET,CO_2} was nevertheless approximated to within *ca* 0·5 Torr on breath 1. Furthermore, by lowering P_{I,O_2} appropriately during the upward P_{ET,CO_2} steps and raising it during the

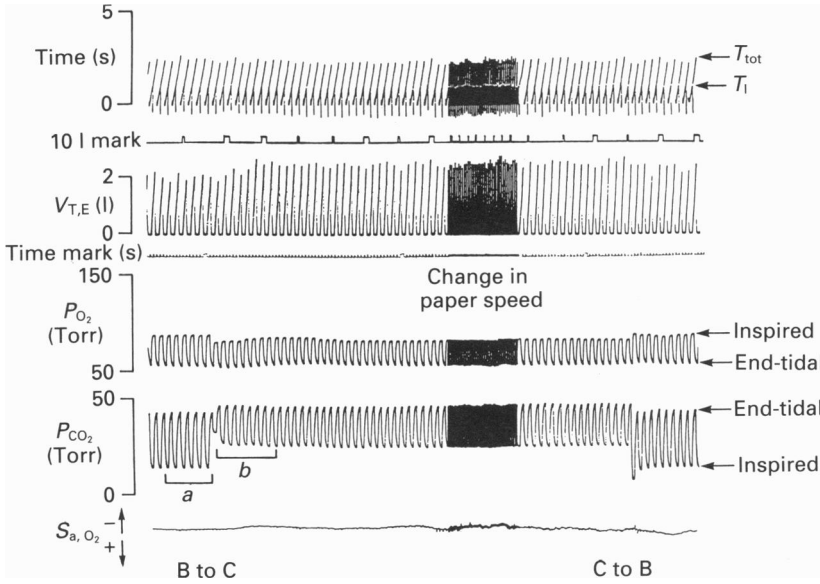

Fig. 2. A continuous experimental trace during an isoxic CO_2 on-transient (B to C in Fig. 1) and off-transient (C to B) for subject 646. From the top down: time ramp (s) – the height to the interrupt is inspiratory time (T_I), the height to the top is total cycle time (T_{tot}); mark at every 10 l expired; expiratory tidal volume ($V_{T,E}$); time mark (s); P_{O_2} and P_{CO_2} at the mouth (Torr); high-gain uncalibrated ear oximeter trace (S_{a,O_2}) – the small pulsations visible are usually $\pm 0{\cdot}5\,\%$ S_{a,O_2}. P_{ET,O_2} and hence S_{a,O_2} are held constant during the step into and out of hypercapnia (P_{ET,CO_2} change of ± 3 Torr). Note that the changes are predominantly in tidal volume rather than in respiratory times. The six breaths providing the preswitch mean are shown as '*a*'; the first eight postswitch breaths used in the analysis are shown as '*b*'.

downward steps, P_{ET,O_2} was held reasonably constant throughout the step changes in P_{ET,CO_2} and there were no significant fluctuations in the oximeter trace.

Figure 3 shows the average time course of the changes in P_{ET,CO_2}, P_{ET,O_2} and $\dot{V}_E$ following approximately twelve isoxic steps into and out of hypocapnia (B to A, and A to B) for one subject. An initial rapid change in ventilation is clearly evident, followed by a slower change as a new quasi-steady state was approached. After initiating the P_{ET,CO_2} step some small transient fluctuations in P_{ET,O_2} often occurred; these were generally in a direction that would have, if anything, attenuated the reflex ventilatory response. Following each step change in P_{ET,CO_2} there was no tendency for $\dot{V}_E$ to overshoot, and the CO_2 steps were too small to give rise to any clear changes in S_{a,O_2} by way of the Bohr effect.

The parameter estimates from fitting double exponentials to the $\dot{V}_E$ data from each series of isoxic CO_2 transitions are shown in Table 1. The means of the peripherally

mediated time delays, D_p, and time constants, T_p, resulting from the P_{ET,CO_2} steps were in accord with those in the hypoxia off-transients following the P_{ET,O_2} steps (Tables 2 and 3). The peripheral time constants centred around 9·3 s (range 4·9–15·3 s), with the only statistically significant difference ($P < 0·05$, t test) being

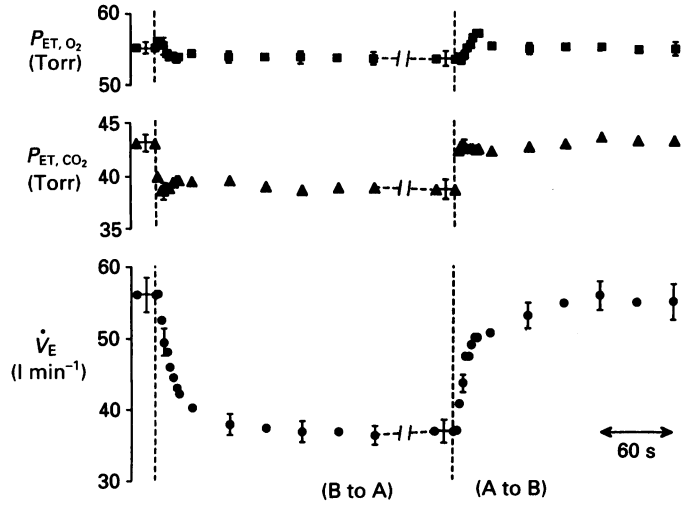

Fig. 3. The mean changes of P_{ET,CO_2} and P_{ET,O_2} (Torr) and $\dot{V}_E$ (l min^{-1}) following *ca* twelve steps into and out of hypocapnia (B to A, and A to B) for subject 646 exercising during hypoxia. The error bars are ±2 S.E.M. and were similar throughout. The dashed vertical lines mark the beginnings of each 3-min step and are preceded by two connected points that represent the six-breath preswitch means ±2 S.E.M. Data are plotted for the first eight postswitch breaths and then for a series of six-breath averages at each subsequent 30 s interval. The fall and rise in ventilation can be clearly seen.

between the steps out of hypocapnia (A to B) and out of hypercapnia (C to B). The central time delays, D_c, were relatively homogeneous, centring around 9·4 s (range 4·6–14·7 s) and in spite of the lack of statistical significance it was noted that the switches out of hypocapnia had the longest mean central time delay (*ca* 10·0 s) and those out of hypercapnia the shortest (*ca* 8·2 s). The time constants of the centrally mediated responses varied considerably between subjects (range 26·9–91·6 s, mean = 46·6 ± 20·2 s). There were no statistically significant differences between the mean values of any of the parameters obtained for corresponding pairs of on- and off-transients, whether time delays, time constants or gains of the peripherally mediated or centrally mediated responses (t tests for related samples).

Series 2: steps of hypoxia in isocapnia

An experimental trace of a pair of steps between hypoxia and hyperoxia recorded during steady hypercapnia is shown in Fig. 4. During steps out of hypoxia, P_{ET,O_2} was raised to *ca* 200 Torr on breath 0 by a single breath of nearly pure O_2; P_{ET,O_2} often overshot on breath 1 before being stabilized at *ca* 220–240 Torr. In the reverse direction, however, even using three to five breaths of pure N_2 did not result in a true

TABLE 1. The time delays (D), time constants (T) and gains (G) for the peripheral (p) and central (c) components of the ventilatory response to approximately ten P_{ET,CO_2} transitions during hypoxic exercise for all subjects

Subject	Transition	T_p (s)	$G_p/\Delta P_{ET,CO_2}$ (l min^{-1} Torr^{-1})	D_p (s)	T_c (s)	$G_c/\Delta P_{ET,CO_2}$ (l min^{-1} Torr^{-1})	D_c (s)	$\dot{V}_o$ (l min^{-1})	S.D. (l min^{-1})
619	A to B	5·7	1·9	4·3	80·1	0·5	10·3	45·8	2·3
	B to A	7·5	−2·1	4·9	27·2	−0·6	14·7	42·2	1·5
	B to C	7·1	1·6	5·5	48·5	0·4	9·7	57·8	2·4
	C to B	11·2	−1·9	3·3	26·9	−0·3	7·6	54·6	2·4
633	A to B	9·5	1·4	4·4	31·6	0·6	8·7	26·6	0·6
	B to A	10·7	−2·1	5·0	46·8	−0·6	10·8	25·6	0·8
	B to C	15·3	1·1	3·8	35·3	0·6	9·2	32·3	1·6
	C to B	10·4	−2·1	3·6	38·1	−0·5	5·4	30·1	0·5
637	A to B	7·5	2·1	3·1	33·9	0·4	11·4	33·9	0·9
	B to A	4·9	−1·5	1·4	56·6	−1·9	4·6	32·5	0·8
	B to C	7·9	2·2	6·0	27·9	1·1	12·4	45·7	1·6
	C to B	10·8	−2·1	4·1	30·4	−1·4	12·1	45·8	2·0
646	A to B	5·6	3·1	2·6	60·4	1·4	9·6	36·8	0·8
	B to A	14·6	−3·5	2·3	38·2	−0·5	7·7	37·0	1·0
	B to C	11·6	3·4	3·5	72·0	0·6	8·4	57·3	0·8
	C to B	8·4	−3·2	2·5	91·6	−2·1	7·5	53·0	1·0
Mean ± S.D.	A to B	7·1	2·1	3·6	51·5	0·7	10·0	35·8	
		1·8	0·7	0·9	23·1	0·5	1·1	7·9	
	B to A	9·4	−2·3	3·4	42·2	−0·9	9·5	34·3	
		4·2	0·8	1·8	12·5	0·7	4·3	7·0	
	B to C	10·5	2·1	4·7	45·9	0·7	9·9	46·0	
		3·8	1·0	1·2	19·5	0·3	1·7	12·0	
	C to B	10·2	−2·3	3·4	46·8	−1·1	8·2	46·0	
		1·2	0·6	0·7	30·2	0·8	2·8	11·3	

Included is the overall mean ± S.D. value for each transition. A negative gain indicates a resultant reduction in ventilation. Included is the background ventilation ($\dot{V}_o$) and the standard deviation of the fitted exponentials (S.D.) (see Methods, eqns (1)–(5)).

step change because an inspirate containing zero O_2 does not dilute the residual O_2 enough to lower P_{ET,O_2} to the target value; after initiating each down-step of P_{ET,O_2} there was a short delay before the oximeter detected a change.

Figure 5 shows the time course of the mean changes in P_{ET,CO_2}, P_{ET,O_2} and $\dot{V}_E$ following approximately twenty isocapnic steps out of and into hypoxia for one

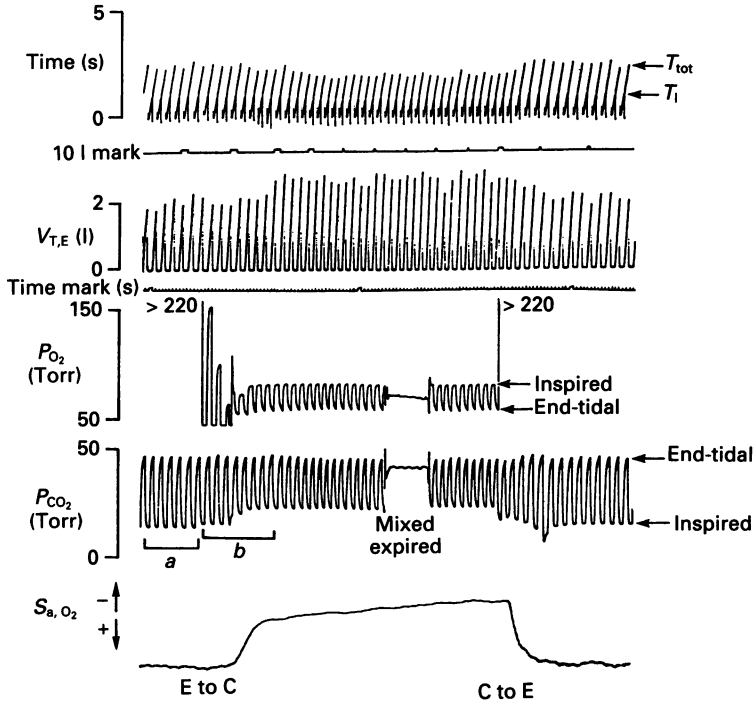

Fig. 4. A continuous experimental trace during an isocapnic O_2 step into (E to C) and out of hypoxia (C to E) for subject 646. Traces as in Fig. 2. When P_{ET,O_2} was *ca* 230 Torr (off scale) an approximate step in P_{ET,O_2} was achieved using four breaths of nearly pure N_2; the step into hyperoxia was achieved using a single breath of nearly pure O_2. Throughout P_{ET,CO_2} was held relatively constant. The six breaths providing the preswitch mean are shown as '*a*'; the first eight postswitch breaths used in the analysis are shown as '*b*'. Mixed expired gas composition (in the mixing chamber) was recorded between transitions.

subject. The ventilatory changes that follow a step out of hypoxia show a rapid single exponential decay, whilst with the steps into hypoxia $\dot{V}_E$ rose along a slightly sigmoidal pathway owing to the slow lung wash-out described above. Throughout the O_2 steps the P_{ET,CO_2} was held satisfactorily constant. There was no tendency for $\dot{V}_E$ to overshoot in any of the subjects.

The means of the parameters of eqns (1) and (2) for the isocapnic hypoxia steps are shown in Table 2. The time constants were relatively homogeneous with a mean of $8{\cdot}1 \pm 3{\cdot}0$ s, very close to the means for the CO_2 steps (Table 1). Seven out of eight of the time constants from the off-transients (B to D, C to E) were shorter than the on-transient ($P < 0{\cdot}05$, Sign test), but there was no significant difference between their

means (t test for related samples). There was considerable variation in the gains between subjects but the intra-subject gains for the on- and off-transients were very similar. There was a clear difference in the delays between the hypoxia off-transients (D to B, C to E) and the hypoxia on-transient (B to D, E to C), reflecting the

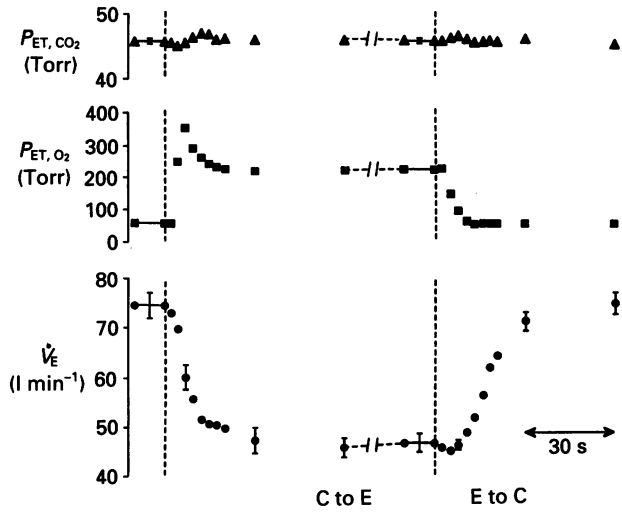

Fig. 5. The mean changes in P_{ET,CO_2} and P_{ET,O_2} (Torr) and $\dot{V}_E$ (l min^{-1}) following *ca* twenty steps out of and into hypoxia for one exercising subject (C to E, and E to C transitions, subject 646). The error bars are ± 2 S.E.M. and were similar throughout. The dashed vertical lines mark the beginnings of each 60 s step and are preceded by two connected points that represent the six-breath preswitch means ± 2 S.E.M. Data are plotted for the first eight postswitch breaths and then for a series of six-breath averages at 30 and 60 s. The fall and rise in ventilation can be clearly seen.

additional time required for the three to five breaths of pure N_2 to lower the initially high P_{ET,O_2} to values low enough to give detectable chemoreceptor effects.

Steps into and out of hypocapnic hypoxia

An example of an experimental trace taken during steps into and out of hypocapnic hypoxia is shown in Fig. 6. The time course of the mean changes in P_{ET,CO_2}, P_{ET,O_2} and $\dot{V}_E$ following approximately ten such steps in each direction for one subject is shown in Fig. 7; similar trends were seen in all subjects. On the second breath of the off-transient $\dot{V}_E$ dropped about half-way to a nadir value which was about 60% of the preswitch mean and was reached at about 20 s; it was followed by a rise to a steady value some 25% below the preswitch mean. During the overshoot it was not infrequent to see the $\dot{V}_E$ of individual breaths fall by up to 75% of the preswitch mean; this was largely associated with substantial expiratory pauses, even though exercise continued uninterrupted (right hand of Fig. 6). On restoring the hypoxia $\dot{V}_E$ rose rapidly to a peak at about 20 s and about 40% above the preswitch mean, after which it declined slowly to a steady value some 20–25% lower than the peak. The initial rise of $\dot{V}_E$ after the step into hypoxia was not as immediate as the

corresponding fall after the step out of hypoxia partly for reasons mentioned earlier in this section and partly because the P_{ET,O_2}–response relation is non-linear. The remarkable behaviour of respiratory times during the steps out of hypoxia seen in Fig. 6 also occurred in another subject, with similar tendencies seen in all subjects; these findings are commented on later. There was no corresponding shortening in the respiratory times during the steps in the reverse direction, into hypoxia.

TABLE 2. The time delays (D_p), time constants (T_p) and gains (G_p)/Δhypoxia) for the peripherally mediated ventilatory response to approximately twenty isocapnic P_{ET,O_2} transitions during hypoxic exercise for all subjects

Subject	Transition	T_p (s)	G_p/Δhypoxic unit (l min^{-1} (hypoxic unit)$^{-1}$)	D_p (s)	$\dot{V}_o$ (l min^{-1})	S.D. (l min^{-1})
619	B to D	4·2	−485	5·0	35·9	0·8
	D to B	5·3	476	8·6	35·7	1·0
	C to E	5·5	−365	3·8	42·0	0·5
	E to C	7·6	312	10·0	42·5	1·4
633	B to D	7·1	−301	2·9	23·1	0·7
	D to B	12·8	217	11·0	24·3	0·4
	C to E	4·7	−172	3·6	32·4	0·6
	E to C	12·2	143	12·5	33·0	0·8
637	B to D	10·9	−163	2·7	34·4	0·6
	D to B	4·7	177	11·6	34·6	0·7
	C to E	10·5	−153	0	40·0	0·4
	E to C	12·0	155	6·0	39·0	0·5
646	B to D	8·5	−877	3·6	27·8	0·5
	D to B	8·6	749	12·7	31·4	0·9
	C to E	5·0	−821	3·4	47·7	1·1
	E to C	9·2	871	11·6	47·1	0·6
Mean ± S.D.	B to D	7·7	−457	3·6	30·3	
		2·8	310	1·0	6·0	
	D to B	7·9	405	11·0	31·5	
		3·7	265	1·7	5·1	
	C to E	6·4	−378	2·7	40·5	
		2·7	311	1·8	6·3	
	E to C	10·3	370	10·0	40·4	
		2·2	342	2·9	5·9	

Included is the overall mean ± S.D. value for each transition. A negative gain indicates a resultant reduction in ventilation. Included is the background ventilation ($\dot{V}_o$) and the standard deviation of the fitted exponential (S.D.) (see Methods, eqns (1)–(5)). A hypoxic unit = $1/(P_{ET,O_2} - 32)$ (Lloyd, Jukes & Cunningham, 1958).

Table 3 contains the estimated parameters for the best double exponentials fitted to the non-isocapnic O_2 steps. The mean central time delays for the hypocapnic hypoxia off-transient of 18·9 ± 10·9 s and on-transient of 20·6 ± 1·0 s were the longest of the entire two series of experiments, as were the central time constants of 62·7 ± 28·0 s and 69·8 ± 25·7 s for the off- and on-transients respectively. On the other hand, the peripheral time constants and delay times were very similar to those for the isocapnic O_2 steps (Table 2).

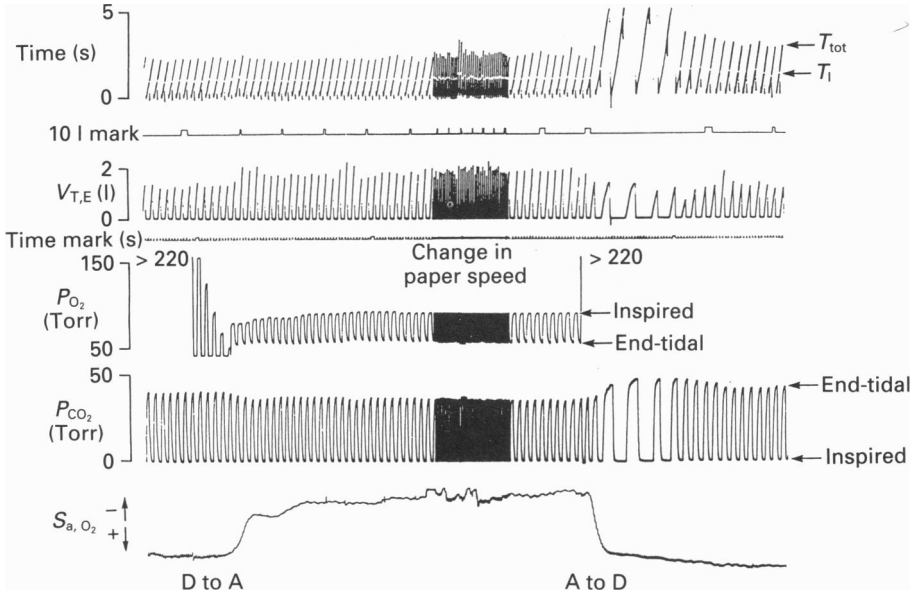

Fig. 6. A continuous experimental trace during a non-isoxic, non-isocapnic transition into (D to A) and out of hypocapnic hypoxia (A to D) for subject 646. Traces as in Fig. 2. There is a clear overshoot of V_T following the step into hypoxia, and an extreme hypoventilation following the step out of hypoxia with overshooting of respiratory volumes, times and P_{ET,CO_2}. Note that T_I transiently exceeds the 5 s full scale deflection. The speed of the chart recorder was reduced between transitions, over which period the experimenter adjusted the oximeter trace.

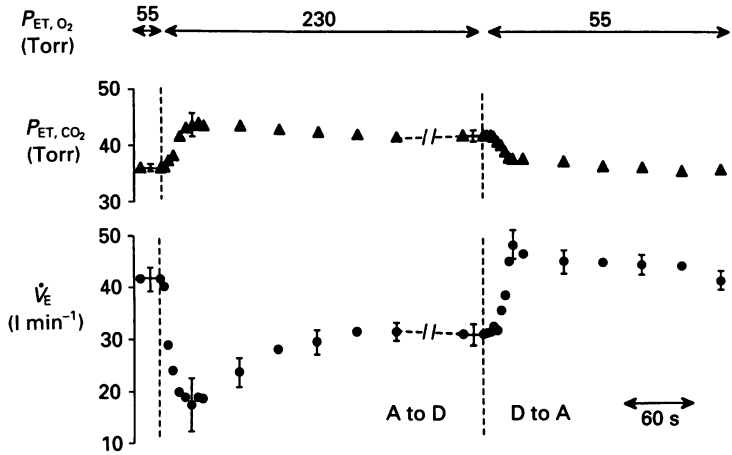

Fig. 7. The mean changes in P_{ET,CO_2} (Torr) and $\dot{V}_E$ (l min^{-1}) following *ca* ten non-isoxic, non-isocapnic steps out of and into hypocapnic hypoxia for one exercising subject (A to D, and D to A transitions, subject 646). The error bars are ± 2 S.E.M. and were similar throughout. The dashed vertical lines mark the beginnings of each 3-min step and are preceded by two connected points that represent the six-breath preswitch means ± 2 S.E.M. Data are plotted for the first eight postswitch breaths and then for a series of six-breath averages at each subsequent 30 s interval. The overshooting of the fall and rise in ventilation can be clearly seen.

The isocapnic relief from hypoxia during hypercapnia and eucapnia resulted in mean percentage reductions in $\dot{V}_E$ of $22{\cdot}5 \pm 10{\cdot}5\%$ and $33{\cdot}0 \pm 15{\cdot}8\%$ from the preswitch mean respectively, while following the non-isocapnic relief of hypoxia during hypocapnia $\dot{V}_E$ fell by $41{\cdot}2 \pm 16{\cdot}0\%$. The mean maximum percentage reductions in $\dot{V}_E$ following the steps out of hypoxia were therefore inversely related

TABLE 3. The time delays (D), time constants (T) and gains (G) for the peripheral (p) and central (c) components of the ventilatory response to approximately ten non-isocapnic P_{ET,O_2} transitions into and out of hypocapnic hypoxia during exercise for all subjects

Subject	Transition	T_p (s)	G_p (l min^{-1})	D_p (s)	T_c (s)	G_c (l min^{-1})	D_c (s)	$\dot{V}_o$ (l min^{-1})	S.D. (l min^{-1})
619	A to D	2·8	−20·6	2·9	54·4	14·7	12·5	21·0	1·4
	D to A	8·7	10·7	11·9	44·0	−7·5	21·2	31·3	3·1
633	A to D	7·3	−11·0	1·8	44·5	5·8	18·6	17·0	0·4
	D to A	10·5	8·0	12·1	63·4	−2·1	19·8	20·9	1·2
637	A to D	10·4	−7·2	3·9	104·2	2·3	10·0	29·5	1·0
	D to A	12·0	10·2	12·2	105·3	−3·9	19·7	26·8	1·1
646	A to D	4·4	−22·6	2·5	47·5	13·6	34·3	18·7	0·7
	D to A	7·4	19·3	11·0	66·3	−8·9	21·5	22·6	2·2
Mean ± S.D.	A to D	7·2	−15·4	2·8	62·7	9·1	18·9	21·6	
		3·0	7·4	0·9	28·0	6·0	10·9	5·5	
	D to A	9·7	12·1	11·3	69·8	−5·6	20·6	25·4	
		2·0	5·0	0·9	25·7	3·1	1·0	4·6	

Included is the overall mean ± S.D. value for each transition. A negative gain indicates a resultant reduction in ventilation. Included is the background ventilation ($\dot{V}_o$) and the standard deviation of the fitted exponentials (S.D.). Note that unlike Tables 1 and 2 the gains (G_p and G_c) are in l min^{-1} owing to the non-isocapnic nature of the transitions (see text).

to the steady-state P_{ET,CO_2} preceding each test. The mean peripheral time constant of the non-isocapnic transitions was not dissimilar to those during the isocapnic relief of hypoxia during eucapnia and hypercapnia (Tables 2 and 3).

Pattern of breathing

For all subjects the data from each transition were plotted on the V_T–T_E–T_I 'modified von Euler plot' (Kay, Petersen & Vejby-Christensen, 1975). There were no consistent patterns even within subjects; the changes in $\dot{V}_E$ took the form primarily of changes in V_T rather than of frequency, with T_E varying, if anything, more than T_I, and independently of it. The steps out of hypocapnic hypoxia (A to D) do, however, call for special mention. Here, each subject had a unique breathing pattern, with large changes in respiratory frequency as well as V_T, and with T_I showing similar changes to T_E (e.g. Fig. 6).

There was no obvious trend for T_I to lengthen early during steps into hypoxia (cf. Jennett, McKay & Moss, 1981).

DISCUSSION

Experimental techniques

A P_{ET,O_2} of approximately 55 Torr provides a moderate hypoxic stimulus to the peripheral chemoreceptors and probably does not induce a substantial degree of hypoxic depression (e.g. Edelman, Epstein, Lahiri & Cherniack, 1973), and while hypoxic depression may be accentuated by hypercapnia in resting subjects (Cherniack, Edelman & Lahiri, 1971) we know of no comparable effect in exercise. Since each transition was compared with its own preswitch mean, both reference and test values should have been equally affected by any hypoxic depression that occurred and its effects have therefore been ignored.

With practice, the normal manipulation of gas mixtures, guided visually and by anticipation, provided an acceptable success rate. An even higher success rate would probably be achieved with the computer-controlled method of Robbins, Swanson & Howson (1982) which is capable of inducing many special patterns of changes in alveolar gas.

Exercise at heart rates in the range 100 to 130 beats min^{-1} is well below the anaerobic threshold and does not induce metabolic acidosis in the steady state (Weltman, Snead, Seip, Schurrer, Weltman, Rutt & Rogol, 1990); indeed Bhattacharyya *et al.* (1970) and Masson & Lahiri (1974) observed slight metabolic alkalosis under comparable conditions, even in hypoxia.

The subjects' awareness of changes in gas tensions and ventilations was periodically checked and in spite of the frequent large changes in ventilation none of the subjects reported any influences of the experimental procedure other than the occasional strange taste which was probably associated with inspirates of raised P_{I,CO_2}. These results are consistent with those of Katz-Salamon (1984) and indicate that the results reflect essentially reflex responses only.

The CO_2 threshold

For all subjects the ventilatory response following CO_2 steps out of hypocapnia began with the dynamics associated with the peripheral chemoreceptors. These results appear to confirm that, despite the probable presence of some metabolic alkalosis (Masson & Lahiri, 1974), the supposed CO_2 threshold, though clearly demonstrable in rest (Nielsen & Smith, 1952), was displaced to lower values of P_{CO_2}, i.e., outside the range of hypocapnia that occurs in hypoxic exercise.

Exponential fitting

In this study a two-compartment model incorporating time delays, time constants and gains was used to estimate the relative contributions of the peripheral and central chemoreflex pathways to the ventilatory responses following repeated steps of P_{ET,CO_2} during mild exercise. Although some authors have attempted to justify a three-compartment model incorporating two central components (e.g. Gelfand & Lambertsen, 1983), for lack of convincing evidence to the contrary many researchers prefer the simpler model with a single central component (e.g. Swanson & Bellville, 1975; Bellville *et al.* 1979; Gardner, 1980; Robbins, 1988). The method of non-linear

least-squares iteration used to derive the best-fitted parameters is now regarded as superior to the traditional method of exponential peeling (e.g. Milhorn & Reynolds, 1976; Whipp, Ward & Wasserman, 1983). The superiority of the iterative method used here was in part confirmed with the aid of the noisy double exponential test data of Riggs (1970). Several authors have reported difficulty in fitting exponentials to unaveraged breath-by-breath data (Milhorn & Reynolds, 1976; Bellville *et al.* 1979), and the time averaging used here appears to alleviate much of this problem whilst maintaining physiological fidelity. In the anaesthetized cat the fast and slow dynamic responses to step changes of end-tidal gas can be derived by non-linear least-squares parameter estimation; the results represent faithfully the contributions of the respective peripheral and central reflex pathways (De Goede, Berkenbosch, Ward, Bellville & Olievier, 1985). There is little reason to doubt that this would also hold for humans.

Parameter estimates

Peripheral delays, D_p

Unlike Miller *et al.* (1974), we found little if any difference between the peripheral reflex latencies for CO_2 withdrawal (3·6 s) and O_2 withdrawal (3·2 s). These values are close to our own lung–ear circulation times and to the 3·7 s of Ward, Drysdale, Cunningham & Petersen (1979) in gentle exercise. We thus confirm that the lung-to-ear times and the peripheral chemoreflex latencies are about the same (Jain *et al.* 1972).

Peripheral-to-central delays, $(D_c - D_p)$

The mean peripheral-to-central delay for our exercising subjects was *ca* 6 s, which is longer than the 4 s assumed for resting subjects by Bellville *et al.* (1979); our values for D_p and D_c are consistently the lowest in the literature (see Table 1 of Cunningham, Robbins & Wolff, 1986). We attribute the shortness of the delays not only to the increased haemodynamics of exercise and the hyperkinetic influence of hypoxia and hypercapnia (Heistad & Kontos, 1983), but also to the possibility that in exercise the improved quick changes in the respiratory gas composition were transmitted to the arterial blood with greater fidelity than during rest (Ward & Bellville, 1983).

Peripheral time constants, T_p

Mean T_p for the various kinds of steps used were fairly uniform, though two of the differences were marginally significant (CO_2 steps, Table 1, A to B shorter than C to B; and Table 2, the steps out of hypoxia B to D and C to E and Table 3, A to D were together shorter than the steps into hypoxia, Table 2, D to B and E to C and Table 3, D to A). The results for the steps in and out of hypoxia agree with Gardner's (1980) results on resting subjects and can be attributed to the technical impossibility of producing large square waves of low P_{ET,O_2}; the off-transient values are probably the more reliable. With regard to the CO_2 steps, it is difficult to attribute any physiological significance to the small difference between the A–B and the C–B steps; the means of the steps in the opposite directions (B–A and B–C) were nearly equal. It is, therefore, likely that the dynamics of the peripheral chemoreflex loop were

largely, if not entirely, independent of the background level of P_{ET,CO_2} upon which each step change was imposed, and thus presumably of the degree of central chemoreflex stimulation.

Central time constants, T_c

The values of T_c for the non-isocapnic hypoxic steps (A–D, D–A, Table 3) should be treated with caution as the data from which they were derived were obtained during changes of P_{CO_2} in end-tidal gas that would have been ramp-like rather than steps in the chemosensitive areas. The more satisfactory values of T_c from the P_{CO_2} steps (Table 1) centred around 47 s and are smaller than the reported values of 65 s (Bellville *et al.* 1979) and 120 s (Gardner, 1980) for background hypoxia at rest, and than the 98 s (Swanson & Bellville, 1975) and 180 s (Bellville *et al.* 1979) for euoxia at rest. If the time constant of the central chemoreceptors is dependent upon cerebral perfusion, as assumed by Bellville *et al.* (1979), then the hyperkinetic effect of hypoxic exercise may have been responsible for our short values of T_c. T_c may also be dependent upon other factors controlling the rate of change of CO_2 in the tissues of the receptors, such as the local blood flow and the local metabolic production of CO_2, which may be accelerated by the increased neural activity (Raichle, 1987) in the respiratory centres associated with the hyperpnoea of hypoxic exercise. Although the results in this paper show that T_c was not significantly related to the background level of P_{ET,CO_2}, the relatively small steps of P_{ET,CO_2} (3–3·5 Torr) may have been insufficient to alter factors such as cerebral blood flow significantly; they may also reflect a lack of precision in the estimates of T_c.

Patterning

No clear V_T–T_I–T_E patterns were seen following the various kinds of step during hypoxic exercise, in contrast to the fairly definite patterns often seen in rest (Gardner, 1980). When V_T is high the slopes of the V_T, T_I and T_E relations are at a maximum (Kay *et al.* 1975) and the breath-by-breath variation gives rise to a lot of scatter that could mask any small trend that might underlie the mean values. However, other factors may be involved in some types of step: thus the gross changes seen at the off-transient in Fig. 6 are reminiscent of, though far from identical to, those described by Bartoli, Cross, Guz, Jain, Noble & Trenchard (1974), who studied sudden changes of airway P_{CO_2} in the dog; both would be consistent with an interruption of the neural phase-switching mechanism. More work is needed on this; in particular, it is noticeable that these large disturbances were confined to the A to D steps.

Contributions from peripheral and central reflex pathways

Although the mean nadir in $\dot{V}_E$ following a step rise in P_{ET,O_2} during hypocapnia was 41% of the preswitch mean, several subjects responded with a number of individual breaths falling by up to 75% (e.g. Fig. 6). Even if we neglect the Haldane effect on arterial pH and the possible after-discharge of the 'central neural processes' (Eldridge, 1974), which would follow a P_{ET,O_2} step and lead to an underestimation of the depression in ventilation, the peripheral chemoreceptors may contribute up to 41–75% of the ventilatory drive during this mild hypocapnic–hypoxic exercise. Such

potency of the peripheral chemoreceptor drive particularly during hypocapnic–hypoxic exercise has also been noted by Masson & Lahiri (1974).

Table 4 shows the mean gains and relative contributions of the peripheral and central chemoreceptors to the ventilatory responses following P_{ET,CO_2} switches into and out of hypocapnia, eucapnia and hypercapnia during mild exercise. There

TABLE 4. The mean (±S.D.) of peripheral and central gain (G_p and G_c, l min^{-1} (Torr CO_2)$^{-1}$) for all subjects and the percentage contribution of each (% p, % c) during the transitions following CO_2 steps

A. Background CO_2	Hypocapnia	Eucapnia	Hypercapnia
Transitions	A to B	B to A; B to C	C to B
$G_p/\Delta P_{ET,CO_2}$	2·1±0·7	2·2±0·9	2·3±0·6
$G_c/\Delta P_{ET,CO_2}$	0·7±0·5	0·8±0·5	1·1±0·8
% p:% c	75:25	73:27	68:32

B. Study	Bellville *et al.* (1979)		Mean of present series
Condition	Euoxic rest	Hypoxic rest	Hypoxic exercise
$G_p/\Delta P_{ET,CO_2}$	0·7±0·4	1·3±0·8	2·2±0·7
$G_c/\Delta P_{ET,CO_2}$	1·4±0·6	1·7±1·0	0·8±0·6
% p:% c	33:67	43:57	73:27

A: results grouped according to the background level of P_{ET,CO_2} upon which each CO_2 transition was imposed.

B: comparison of our mean results during hypoxic exercise with those of Bellville *et al.* (1979) from euoxic and hypoxic rest studies.

appears to be a slight tendency for the relative contribution of the peripheral gain to be inversely related to the background level of P_{CO_2} (Table 4*A*). Table 4*B* contains data from Bellville *et al.* (1979), who delivered similar P_{ET,CO_2} steps to euoxic and hypoxic subjects at rest, together with the comparable mean gains from our work. There is an obvious tendency for the relative contribution of the peripheral gain to be high during hypoxic rest (43%) and higher still during hypoxic exercise. Our results confirm that the dynamic responses of the peripheral chemoreflex pathway are enhanced during exercise in hypoxia. Several possible mechanisms have been suggested (see Cunningham, 1987); they include an increase of arterial potassium concentration in exercise (Band, Lim, Linton & Wolff, 1982) and also changes in the oscillatory component of the CO_2 stimulus (Yamamoto, 1960), which would decrease with increasing inspiratory CO_2; indeed, the figures in Table 4 suggest that in hypercapnia the peripheral chemoreflex pathway was slightly less dominant.

If a high level of central chemoreflex activity, with a long time constant and delay, were to enhance the effectiveness of the peripheral pathway (cf. Robbins, 1988), then G_p should appear to be greater during the down-steps of P_{ET,CO_2} (C to B and B to A, Fig. 1) than during the upsteps (B to C and A to B), and also in the hypercapnic O_2 steps between C to E than in the eucapnic steps between B to D in Fig. 1. Neither of these predictions is fulfilled in our results, and we may conclude that under our conditions the two pathways are largely independent of each other.

We are grateful to the late Dr E. S. Petersen for helpful advice and to Dr R. Painter, Dr D. J. Pilsbury, M. G. Howson and D. O'Connor for their assistance in these studies. D.J.M. was a

Commonwealth Scholar supported by the British Council/Association of Commonwealth Universities.

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