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THE PATTERN OF BREATHING FOLLOWING STEP CHANGES OF ALVEOLAR PARTIAL PRESSURES OF CARBON DIOXIDE AND OXYGEN IN MAN

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SUMMARY

1. The pattern of breathing during the approach to the steady state following step changes of end-tidal P_{CO_2} and P_{O_2} has been determined in normal conscious human subjects. Three types of step were studied: (*a*) steps of $P_{A,\,CO_2}$ against a constant background of hyperoxia ($P_{A,\,O_2} \sim 200$), an almost pure intracranial chemoreceptor stimulus, (*b*) steps of $P_{A,\,O_2}$ between $\sim$ 50 and 80 torr against a background of constant mild hypercapnia, an arterial chemoreceptor stimulus, and (*c*) steps of $P_{A,\,CO_2}$ against a background of constant hypoxia ($P_{A,\,O_2} \sim 50$), a mixed stimulus. Steps were small and the responses barely detectable by the subjects.

2. Steps of CO_2 in hyperoxia produced the slowest approach to the steady state. A single exponential fitted the ventilation response up to about 4 min (mean half time 83 sec for the 'up' and 69 sec for the 'down' transients). During the transient the pattern of change of tidal volume (V_T) and expiratory time (T_E) was the same as in the steady state. Inspiratory time (T_I), however, in the early part of the transient, changed in the opposite direction to T_E, returning to its steady value only after $1\frac{1}{2}$–3 min. This effect occurred in both 'up' and 'down' transients and resulted in a smaller change of respiratory frequency than would have been predicted from the steady-state response.

3. Hypoxic steps produced the fastest approach to the steady state with mean half-times for ventilation of 10·9 sec for the 'up' transients and 6·6 sec for the 'down'. T_I followed the same pattern during the transient as in the steady state, whereas T_E, following the step out of hypoxia, lengthened to far beyond its final steady value within five breaths of the step, only returning to its steady-state value 3–4 min after the step. This resulted in an exaggerated change of frequency during the early part of the transient.

4. Steps of CO_2 in hypoxia, a mixed peripheral and central chemoreceptor stimulus, showed a ventilation response which was best fitted by two exponentials, the half-times of which were consistent with those obtained for the separate responses. The patterning was also consistent with a mixed response, more so for T_I than for T_E.

5. The steady-state pattern derived from the pre-switch means was consistent with the pattern previously described.

6. Possible mechanisms are discussed. It is suggested that these results could

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explain the different patterns seen in the past by those using re-breathing and steady-state techniques.

7. The validity of using one or two breath oxygen or nitrogen tests (or other similar tests) as a quantitative measure of the hypoxic response in man is questioned.

INTRODUCTION

In fit young human subjects, Hey, Lloyd, Cunningham, Jukes & Bolton (1966) using steady-state techniques found that when breathing was stimulated by a variety of different means the resulting pattern of change of tidal volume (V_T) and respiratory frequency (f) was the same in nearly all cases. The relationships between the components of frequency, inspiratory and expiratory times (T_I and T_E respectively) and tidal volume have more recently been described for man by Clark & von Euler (1972), Gardner (1977) and Cunningham & Gardner (1977). Using steady-state techniques Gardner (1977) found that T_I and T_E, like f, were related to V_T in the same way for both arterial and intracranial chemoreceptor stimulation. These findings might suggest that within the 'black box' of the brain stem, afferents from both chemoreceptors converge onto a common locus before pattern generation occurs.

On the other hand, in re-breathing experiments in which the stimuli of breathing progressively increase, no steady state being established, the combination of f and V_T at any level of ventilation has been found to depend upon whether the main stimulation is due to the accumulation of carbon dioxide or hypoxia (in man: Haldane, Meakins & Priestley, 1919; Rebuck, Rigg & Saunders, 1976; numerous student practical classes, D. J. C. Cunningham, private communication; and in apnoeic anaesthetized dogs: Cherniack, Kelsen & Lahiri, 1977).

The work in this paper was initiated to investigate further an observation on data originally gathered by Miller (Miller, Cunningham, Lloyd & Young, 1974; Pearson & Cunningham, 1973). During the eight breaths following a two-breath relief of steady hypoxic and hyperoxic hypercapnia, frequency changed less in relation to V_T than would have been expected from the steady-state pattern. How and when f finally 'caught up' with V_T was not known.

The results to be presented go some way towards answering these questions as well as reconciling the differences outlined above. The complete time courses of changes of V_T, T_I, T_E and other derived variables, as well as the relationships between them, have been delineated following step changes of alveolar P_{O_2} at a constant raised alveolar P_{CO_2} (a pure arterial chemoreceptor stimulus), of alveolar P_{CO_2} in high oxygen (an almost pure intracranial chemoreceptor stimulus, Miller *et al.* 1974) and of alveolar P_{CO_2} at a constant level of hypoxia (a mixed arterial and intracranial chemoreceptor stimulus).

In the past it has been more usual to study the effect of steps of inspired gas tension (e.g. Grodins, Gray, Schroeder, Norins & Jones, 1954). Because of the need to wash out residual volume such steps tend to produce slow and unreproducible changes in arterial gas tensions. By employing steps of alveolar tension in the present work it was hoped to enhance any physiological changes while minimizing any random variation inherent in even the best planned human experiments. A similar technique has been described by Swanson & Bellville (1975).

The results confirm the findings of Gardner (1977) for the steady-state pattern but show that when the arterial P_{O_2} and P_{CO_2} are changing rapidly, not only is the patterning of V_T against T_I and T_E different from that of the steady state, but the effects of changing P_{O_2} differ from those of changing P_{CO_2}, as in the rebreathing experiments.

Some of these results have already been published as communications (Gardner, 1974, 1978) and, together with other results, will appear in an abstract (Gardner, Cunningham & Petersen, 1979).

METHODS

Apparatus

Two different open-circuit systems were used. In both, subjects sat in a comfortable chair while breathing into the apparatus through a rubber mouthpiece with the nose occluded by a nose clip.

The first system is a modified version of that used previously (Gardner, 1977) It was used for the earlier experiments (apparatus code 1 in Table 1). A Lloyd valve separated inspiratory and expiratory pathways. Gas meter and wedge spirometer (re-set to zero at the end of each expiration) in the expiratory pathway measured expired tidal volume and flows. Inspired gas could be taken from one of two lines; a new type of silent 12 V solenoid-operated rotary stopcock situated near the subject was used to switch from one to the other. On each line a bank of rotameters, controlled by needle valves, and supplied by individual gas cylinders, allowed continuous manipulation of the composition of the gas, the flow of which was arbitrarily set at a constant 70 l./min past the stopcocks. The unused portion vented to the atmosphere. A separate suction line between the stopcock and the Lloyd valve ensured presentation of a new gas mixture at the inspiratory flap of the valve within the time of a fraction of a breath after switching from one line to the other. T_I and T_E were derived from the zero points of the mouth pressure swings sensed by a capacitance manometer (M.D.C. 301, Hilger-I.R.D. Ltd, London) and displayed on a split time-ramp (Gardner, 1977).

In the second system (Fig. 1) a single pneumotachograph (Fleisch Type 2, P. K. Morgan, Chatham, Kent) was used for all flow and volume measurements. It was connected by T-piece directly into a common inspiratory line from which the subject both inspired and expired. As in the first system, double inspiratory lines were connected to solenoid operated stopcocks; opening of one stopcock allowed inspiratory gas to be diverted into the common inspiratory line and so past the T-piece while the gas in the other line passed to a blow-off. The ends of the blow-offs for the two lines were connected via a simple arrangement of condoms to form valves; diversion of one gas mixture past the subject caused a small drop of pressure in that line, causing the blow-off to shut and that of the other line to open. The pneumotachograph flow signal was displayed on a Devices pen recorder as well as being processed by a Data General computer (Nova 8). The signal was digitized on-line at 20 ms intervals and stored on cassette tape in 7-min blocks. Further processing to derive T_I, T_E, T_T, inspired and expired tidal volumes, peak and mean flows and minute ventilations was performed off-line.

This system (apparatus code 2 in Table 1) allowed the study of a flow signal undistorted by artifacts due to valves or switching between the phases. The computer allowed the measurement and processing of a greater number of variables than would have been possible by hand.

In both systems gas was sampled at about 0·5 l./min from near the subject's mouth and continuously monitored for P_{O_2} and P_{CO_2} by mass spectrometer (VG-Micromass Ltd, Winsford, Cheshire, England). These signals were recorded on moving paper on a multi-channel pen recorder and were measured by hand; in the second system they were also processed by the computer to allow correction of the signal from the pneumotachograph for the effects of changing viscosities of the inspired and expired gases.

Volume was derived from pneumotachograph flow by electronic integration; calibration was with a 1 l. pump.

In experiments involving hypoxic steps oxygen saturation at the ear was recorded continuously using an uncalibrated ear oximeter (Waters Instruments, Rochester, Minn.; 90% response time in less than 0·5 sec).

Both systems were silent in operation. It was impossible to detect steps even with full knowledge of the apparatus and experimental protocol; very occasionally hyperpnoea was noticed by subjects towards the end of an 'up' transient.

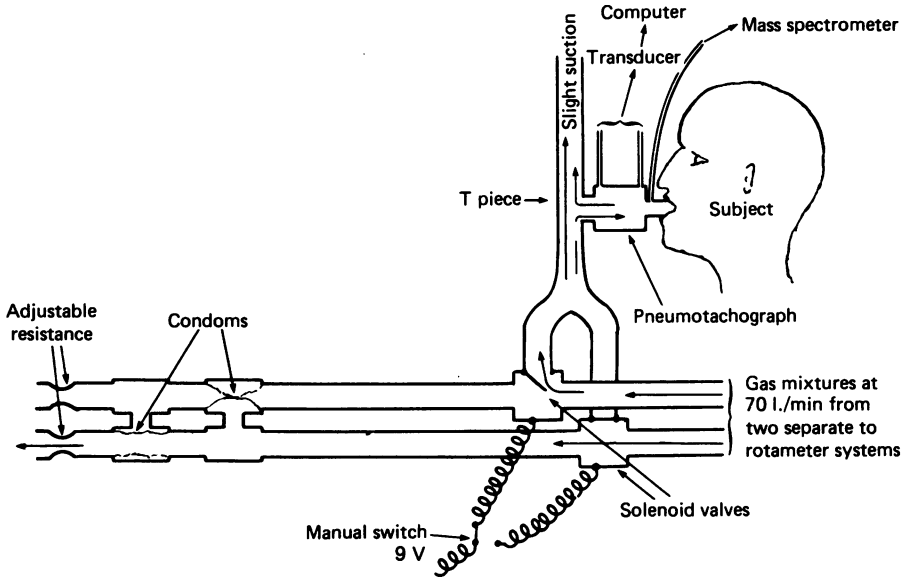

Fig. 1. A schematic representation of the second of the two sets of experimental apparatus described in the text. The subject both inspires and expires through a single heated pneumotachograph.

Experimental design

To obtain an approximately square step of alveolar gas tension it was necessary to make complicated and precisely timed changes in the subject's inspired gas tensions.

Initial 'overshoot' for one or two breaths to ensure rapid change of alveolar gas composition was followed by an immediate 'undershoot' which was gradually lessened over the subsequent minutes to keep alveolar levels constant as ventilation changed. At the same time the inspired composition of the gas not participating in the step had to be manipulated to keep its alveolar level constant. These changes in inspiratory gas composition had to be set up one or two respiratory cycles before the breaths whose compositions they were designed to stabilize. The magnitudes of the adjustments were guessed in the light of previous experience; even the best founded guesses were liable to be frustrated by subject idiosyncrasies in individual runs and, in steps involving the arterial chemoreceptors, the relatively undamped nature of the responses.

The apparatus was used in various ways to produce these steps. Usually gas mixtures were set up in the inspiratory line not in use at that moment. At a roughly fixed time after the previous step the solenoid valves near the subject were switched during expiration allowing inspiration of the new gas mixture on the next breath. Subsequent changes were made either by continuing to manipulate the mixture in that bank of rotameters, or by switching back to the other bank after the initial breaths.

Examples of the manipulations required to produce the steps are shown in the two sections of experimental trace reproduced in Fig. 2. An 'up' step is shown on the left, a 'down' step on the right. Here and subsequently in this paper the words 'up' and 'down' in relation to the steps refer to the direction of change of ventilation and not necessarily to the direction of change of the predominant gas tension. This example shows isocapnic steps of hypoxia. Note that two breaths of nitrogen (with the appropriate CO_2) were given initially in the step up. In the lower trace an ear oximeter record shows the speed of change of the arterial oxygen saturation.

Three types of step were studied: (1) steps of alveolar P_{O_2} between about 50 and 85 torr

against a background of constant mild hypercapnia; (2) steps of alveolar P_{CO_2} between two levels approximately 5 torr apart against a background of constant hypoxia (P_{A,O_2} approx. 50 torr); (3) steps of alveolar P_{CO_2} between two levels 5–10 torr apart against a background of hyperoxia (P_{A,O_2} approx. 200 torr). The exact levels are shown in Table 1.

In general the amplitude of the steps was determined by trial and error to produce an easily analysed but small change of V_T (which it was hoped would be largely undetected by the

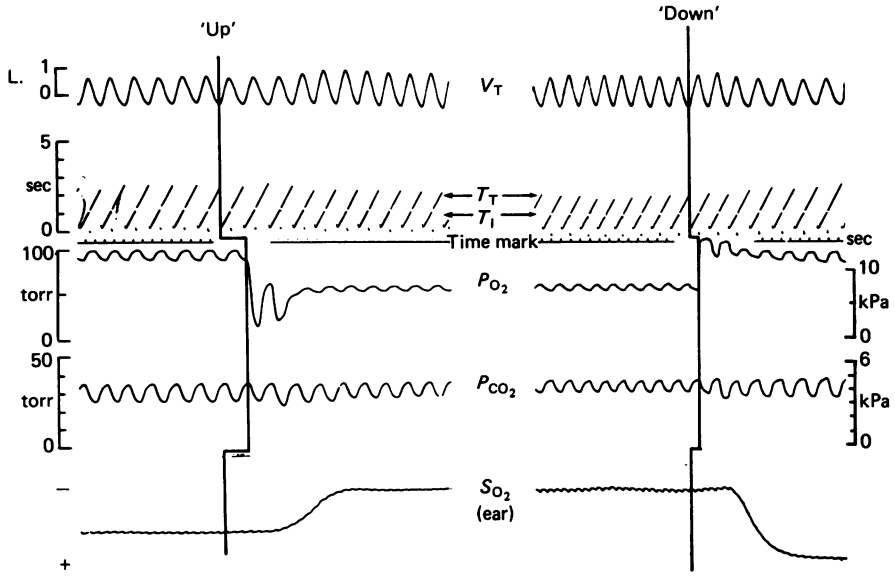

Fig. 2. Two representative sections of experimental trace showing, on the left, a step from mild to moderate hypoxia (an 'up' step) and on the right, a step in the opposite direction (a 'down' step). The vertical line shows the start of the breath receiving the new gas mixture. The traces are described from above downwards. (1) Tidal volume (V_T) derived from free integration of the flow signal from the pneumotachograph; inspiration is upwards. (2) Time ramp; the height to the break is proportional to inspiratory time (T_I); the height to the top is proportional to cycle duration (T_T). (3) Time marker in seconds. (4) P_{O_2}: a continuous record from 'between the teeth'; the upper border gives inspired levels, the lower border end-tidal levels; note temporary reversal of the gradient when two breaths of near N_2 are given on the 'up' step. (5) P_{CO_2}; as for P_{O_2}, but inspired end-tidal gradients are in the opposite direction; note the manipulations of the inspired levels to keep the alveolar levels constant. (6) Ear oximeter trace, uncalibrated, showing arterial saturation. The delay is due to lung–ear circulation time.

subject) combined with a reasonable change of T_E (see Gardner, 1977). Small steps allowed the completion of the majority of the step within one or at the most two breaths; the lower gas tension was set sufficiently high to allow enough undershoot to achieve this. It was hoped that the above steps would represent (in order) a nearly pure arterial chemoreceptor stimulus, a mixed arterial and intracranial chemoreceptor stimulus, and a nearly pure intracranial chemoreceptor stimulus (see Discussion); at a P_{A,O_2} of 50–55 there is a reasonable peripheral stimulus without obvious signs of central depression.

Steps were repeated in alternate directions every 7–8 min (12–14 for subject 379).

Six subjects were studied. Profiles were obtained for all three types of step in subjects 411 486 and 534. Only steps of CO_2 in high oxygen were studied in the other three (part of the set reported in Gardner, 1974 and 1978.

Subjects were all students in their early twenties; half were physiologists but none were aware of the exact nature or aim of the experiments. They were encouraged to read throughout

TABLE 1. Experimental details and values for the steady state at the end of each transient. Pattern values are not shown (cf. Fig. 3). Column 2 shows the number of individual transients contributing to each final mean profile. Column 3 shows the type of apparatus used (see text). Columns 4 and 5 show mean steady-state end-tidal gas values. Column 6 shows mean steady-state end-tidal ventilation. Column 7 shows the half-times for the exponential approach of ventilation to the steady-state. In all cases, 'up' and 'down' refer to the direction of change of ventilation during the transient while 'high' and 'low' refer to the ends of the two transients. The slashes in column 7, CO_2 steps in hypoxia, separate the two half-times derived by exponential peeling.

(1) Subject no. and sex	(2) No. of individual transients 'up', 'down'	(3) Apparatus code	(4) P_{A,CO_2} (torr) high, low	(5) P_{A,O_2} (torr) high, low	(6) $\dot{V}$ (l. min^{-1}) high, low	(7) $t_{\frac{1}{2}}$ (sec) 'up', 'down'
CO_2 steps in hyperoxia						
411, ♂	12, 13	1	42·8, 38·8	~200	25·7, 11·8	53, 37
486, ♀	9, 9	2	43·5, 37·8	~200	31·1, 12·8	107, 50
534, ♀	8, 8	2	39·8, 33·2	~200	35·6, 15·3	88, 121
379, ♀	14, 15	1	42·4, 32·0	~200	25·3, 7·5	—
430, ♂	16, 15	1	43·8, 38·9	~200	29·3, 12·3	—
422, ♀	9, 11	1	—	~200	34.5, 20·6	—
Hypoxic steps in isocapnia						
411	12, 11	2	41·0, 41·4	126·0, 50·5	33·8, 14·0	—, 6·6
486	7, 9	2	35·9, 35·9	86·0, 52·0	38·4, 18·3	15·1, 8·0
534	7, 9	2	33·8, 33·4	87·0, 53·9	16·9, 11·0	6·6, 5·4
CO_2 steps in hypoxia						
411	8, 7	2	42·3, 37·4	53·3, 51·6	30·2, 10·9	22/130, 10/64
486	11, 13	2	37·1, 33·1	52·3, 52·3	32·1, 10·6	18/134, 10/46
534	9, 9	2	36·8, 31·8	54·3, 52·6	33·6, 13·0	14/54, 11/70

the experiments which lasted 2–3 hr with one or two 10 min rest periods. Written consent was obtained from all subjects.

Data analysis

Breathing in the conscious human is inherently noisy; it appears to be controlled by a variable combination of automatic brain-stem mechanisms and more random higher centre influences. Amplification of the former in relation to the latter can be achieved by averaging the responses to a constant repetition of the same stimulus; the random responses tend to cancel. In the present experiments, for each type of step between seven and sixteen nearly identical steps in each direction for each subject were time-averaged to produce a single composite step.

The end of each step served as the pre-switch control value for the next step in the opposite direction. To minimize the effect of small differences between like steady states every variable measured for each breath after the step was first subtracted from its pre-switch control value (usually the mean of the twenty breaths but sometimes ten or fifteen before the step).

The method of time averaging differed in detail for different subjects. In all cases every breath was analysed for the first half minute after the step, time zero being taken as the beginning of inspiration of the breath receiving the new gas mixture (labelled as breath 0). Times and breath numbers were reasonably synchronized in this early part of the transient.

Thereafter, in the early experiments (apparatus code 1 in Table 1) only the breath closest to each of a series of selected times after the step was chosen for subsequent averaging across like runs. Up to 3½ min after the step these times were 0·2 min apart, resulting in the analysis of roughly one breath in four. After 3½ min and up to the end of the run, breaths were selected at ½ min intervals. The variables for the breaths occurring at the same time in all like runs were then averaged to produce the final profile. This analysis was done by hand with some computer assistance.

In later experiments (apparatus code 2 in Table 1), when fuller computer facilities were

available, the variables (again expressed as differences) for every breath in the transient were first averaged within each run over successive ¼ min intervals from ½ min after the step until the end of the transient, again after treating each breath individually for the first 30 sec. These averages were then averaged across like runs to produce the final profile as above.

For each variable, significance of the difference of each averaged breath after the step from its pre-switch mean was determined by paired t test (occasionally Wilcoxon Rank Test). To determine the start of a trend away from the pre-switch mean, arbitrary criteria were set that if at least two consecutive breaths were significant at the 5% level the first of these two would signify the start of the trend.

To determine the significance of the hysteresis loops in the V_T–time plots the individual standard errors were averaged for the points in each separate transient where any marked separation occurred between the two transients. When refitted to the middle of each leg of the loop as ± 2 S.E. bars, an impression of significance of the hysteresis can be gained by the overlap or otherwise of the bars.

For the three main subjects, the ventilation *vs.* time relationships were converted into semi-log form. Asymptotes were chosen to produce the straightest fit as judged by eye and least square regressions gave the half-times, in some cases after exponential peeling (Riggs, 1963).

Subject selection

Subjects were selected on the basis of pilot experiments (steady-state CO_2 inhalation) by the following criteria: (1) that they were able to and chose to read without prompting throughout most of the experiment, (2) that they were happy about completing the whole series of experiments (indicating lack of anxiety about the procedure) and (3) that they were not unduly curious or introspective about the apparatus or aim of the experiments. Only one subject was rejected after the start of a step series; his breathing showed an unacceptable degree of breath-by-breath scatter due to swallowing artifacts.

Editing of individual breaths and runs

During the analysis, single breaths were eliminated if any one variable of that breath lay more than about a third outside the average for that section of the trace as judged by eye. If there was any doubt the breath was left. Most breaths so removed were obvious augmented breaths or artifacts due to swallowing; they comprised no more than about 10% of the breaths in each run and often considerably less.

Because of the difficulties referred to above, the final gas profiles in individual steps were not always ideal and it was necessary to eliminate the most glaring examples from the analysis. Failure to hold the unstepped gas constant during a switch (with limits of about 1·5 torr for P_{A,CO_2} and 3–5 torr for P_{A,O_2}), failure to complete the step within three breaths (due to misjudgement of the inspiratory overshoot) and wildly oscillating steady levels (due to over-correction) were the most usual reasons for rejection. Rejection was always based entirely on gas profiles and never on the ventilatory responses.

RESULTS

Information about both steady-state and transient responses of the arterial and intracranial chemoreceptors was obtained.

Fig. 3 shows the steady-state values for V_T plotted against those for T_I and T_E. The pattern is as described by Gardner (1977), with near constancy of T_I and shortening of T_E as V_T increases; there is no consistent difference between the pattern in hypoxia and hyperoxia.

The patterning during the approach to the steady state is shown in Figs. 4–6.

Fig. 4 shows the time course of change of the major variables following each type of step. Hypoxic steps produced the fastest changes, steps of CO_2 in hyperoxia the slowest, as confirmed by exponential analysis of ventilation against time (Fig. 6;

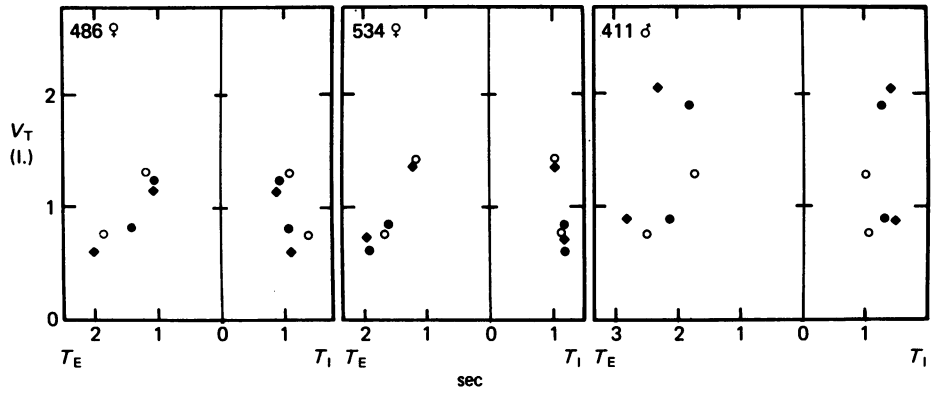

Fig. 3. Plots of tidal volume against inspiratory and expiratory times. The symbols show the pre-switch mean final steady-state values for each of the three main subjects for the three types of step (●, steps of hypoxia, constant CO_2; ○, step of CO_2, constant high O_2; ◆, steps of CO_2, constant low O_2). Note the relative constancy of T_I in relation to T_E and the intermingling of points for the three types of step.

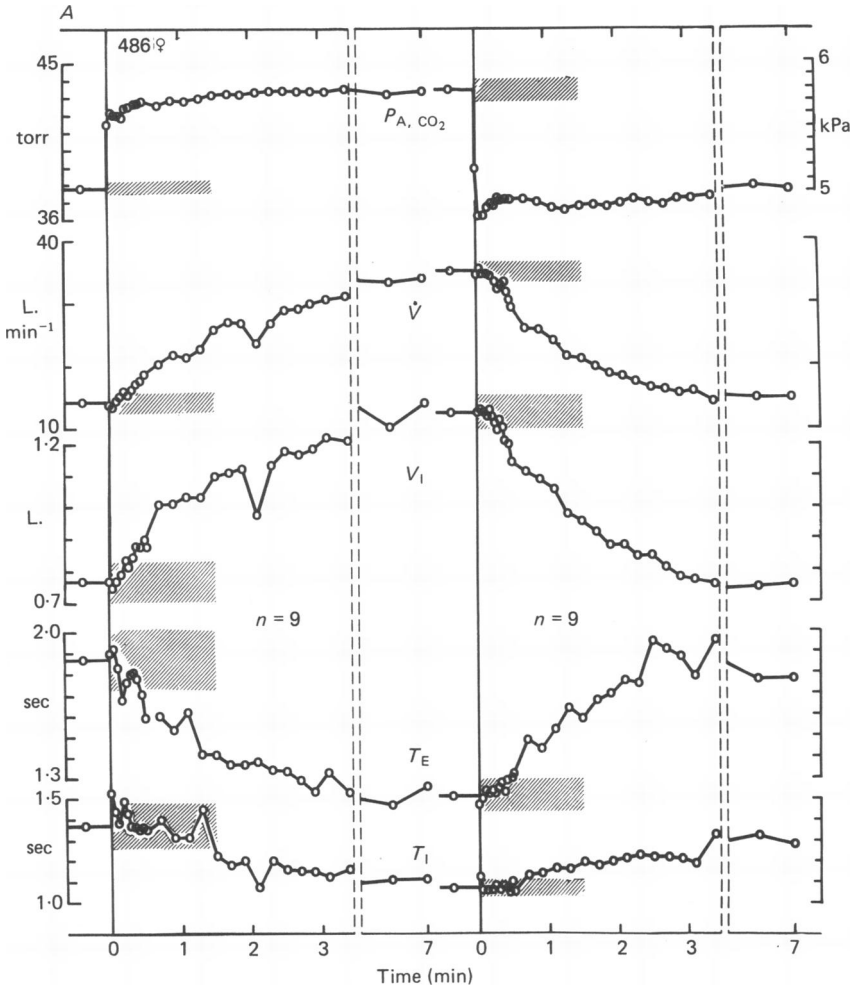

Fig. 4*A*. For legend see p. 64.

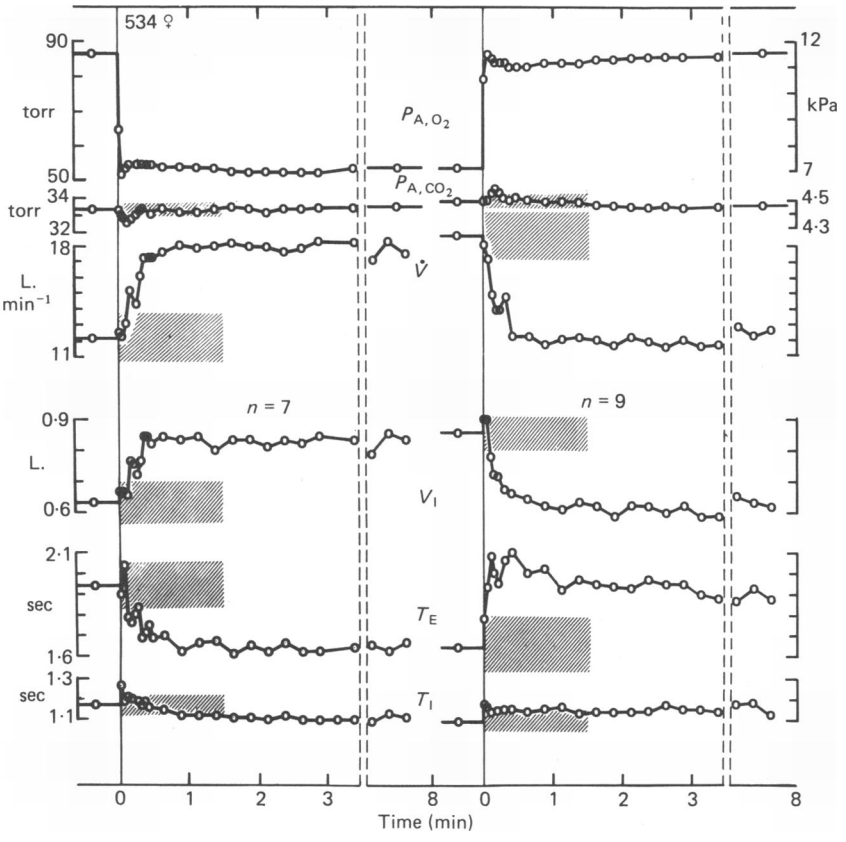

Fig. 4*B*. For legend see p. 64.

Table 1 for half-times). In Fig. 4 it can be seen that V_T and T_E in general change in mirror image fashion and that changes of T_I are much smaller than those of T_E.,

Single exponentials adequately fitted the ventilation responses to hypoxic steps (Fig. 6*C*), and to steps of CO_2 in hyperoxia up to about the fourth minute (Fig. 6*A*), beyond which a second exponential appeared to be required in some subjects. Two exponentials were needed to describe the ventilation responses following CO_2 steps in hypoxia (Fig. 6*B*).

Asymmetrical (and unexpected) responses in 'on' and 'off' transients are (with the exception of T_E changes in steps from low to high oxygen), not obvious in the time plots shown in Fig. 4. The T_E response (Fig. 4*B*, right) shows an initial abrupt overshoot followed by a slower return towards the steady-state level over the following 3–4 min. T_E was still changing after V_T had reached a plateau. This pattern was consistent in all subjects.

Asymmetrical responses, as disclosed by hysteresis, are more clearly seen in Fig. 5 where V_T has been plotted against T_I and T_E for all measured points during both 'up' and 'down' transients. The described T_E response in hypoxic steps is reflected by marked and significant hysteresis in Fig. 5*B*; there was in this type of step no T_I hysteresis.

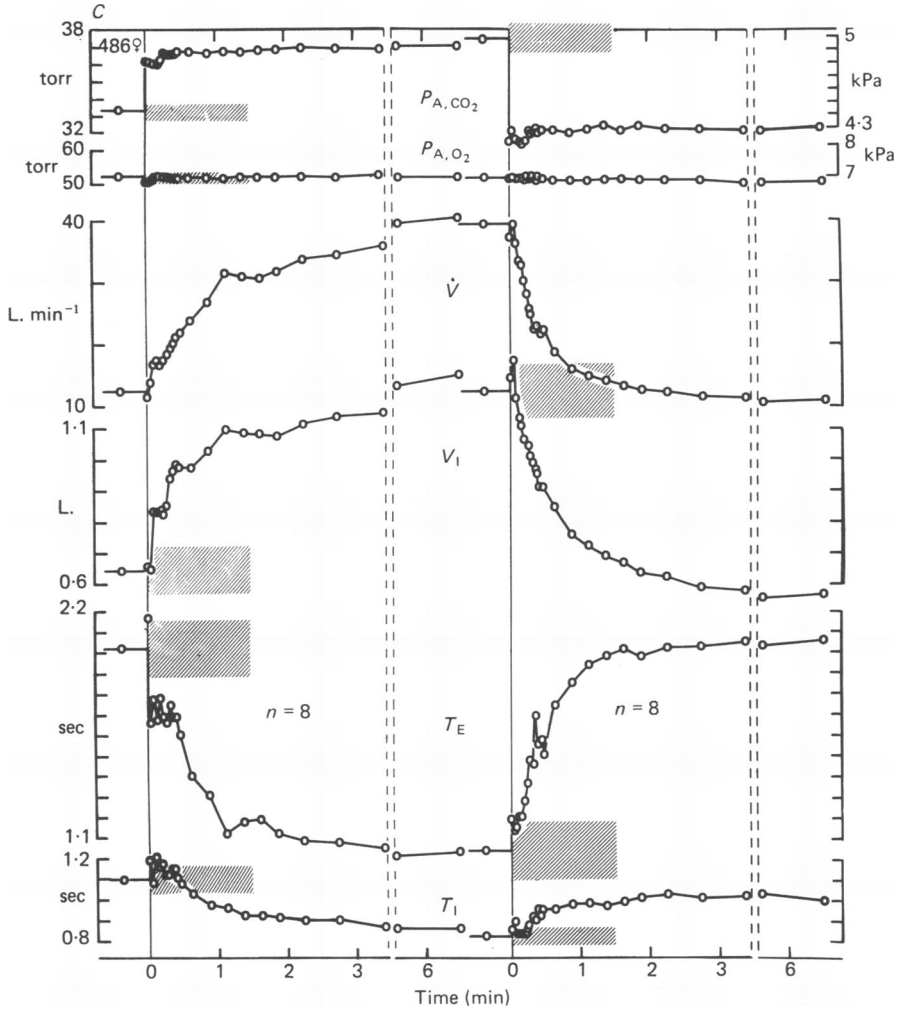

Fig. 4. These plots show a representative example for each of the three types of step of the final time profiles for the end-tidal gas tensions (upper two traces), for minute ventilation (third trace) and for tidal volume, inspiratory and expiratory times (in the lower three traces). The number of individual transients (n) contributing to each profile is shown. Time in minutes is on the abscissa. The vertical lines at time '0' show the time of the step, 'up' on the left, 'down' on the right. The pre-switch means are shown to the left of these lines. The shaded areas show the average scatter (as 4 S.E.) across all points during the first 1½ min of the transient. Note that in A and C there is probably encroachment into range 2.

On the other hand, for CO_2 steps in hyperoxia there was a significant and usually symmetrical hysteresis in T_I for 50 % of subjects studied (Fig. 5A; see also Fig. 1, Gardner, 1974) but no consistent separation for T_E in any subjects. There was a tendency for T_I and T_E to change in opposite directions during the first 1½–3 min of each transient, resulting in a reduced or absent change of T_T. Note that in subject 486 there appeared to be a breakpoint (Gardner, 1977) above which the hysteresis was markedly reduced.

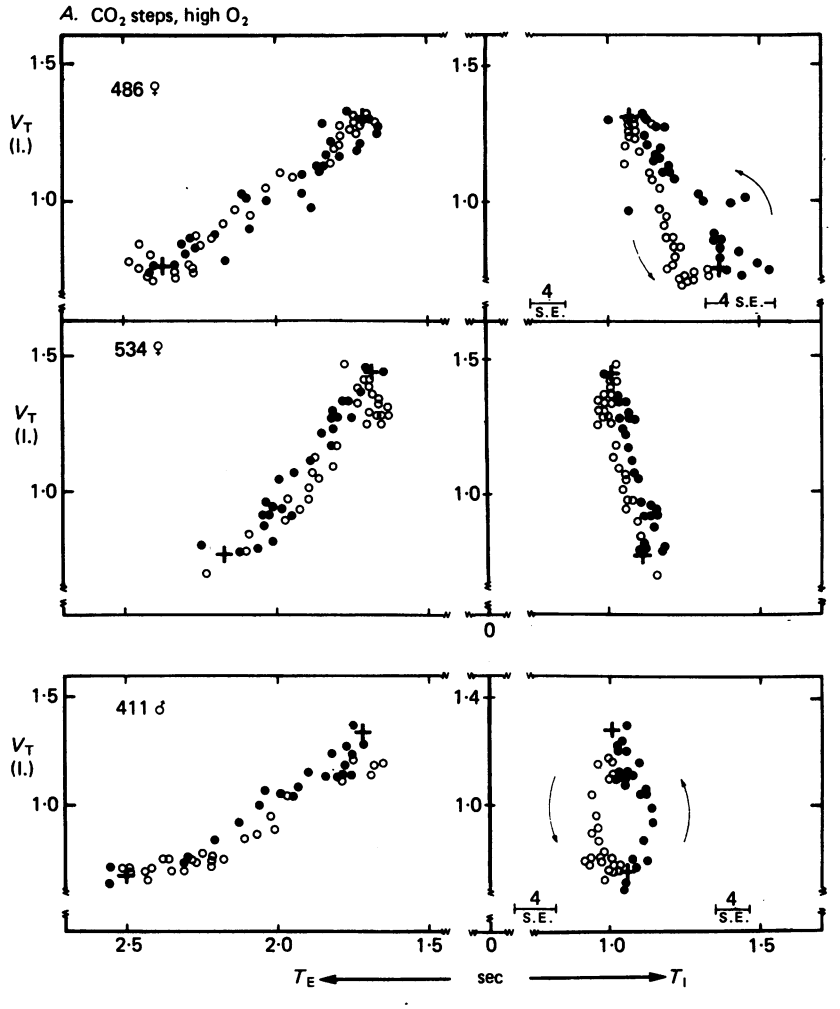

Fig. 5*A*. For legend see p. 67.

The same subjects showed virtually the same hysteresis in T_I for CO_2 steps in hypoxia as for CO_2 steps in hyperoxia (Fig. 5*C*). There was also a small and barely significant hysteresis in T_E over the first 3–4 breaths following the 'down' step but this was not comparable to the response following the step out of hypoxia.

Plots of T_I and T_E against V_T/T_I (slope of inspiratory activity; Clark & von Euler, 1972; Gardner, 1977) showed the same hysteresis loops as described above, as did plots of T_E against peak inspiratory flow.

Latency of first significant change

Table 2 shows the latencies to the first significant change following each step. Responses involving the arterial chemoreceptors occurred within two or three breaths whereas the purely central responses were delayed a further one or two breaths or more. There was an occasional tendency for changes to occur on the first

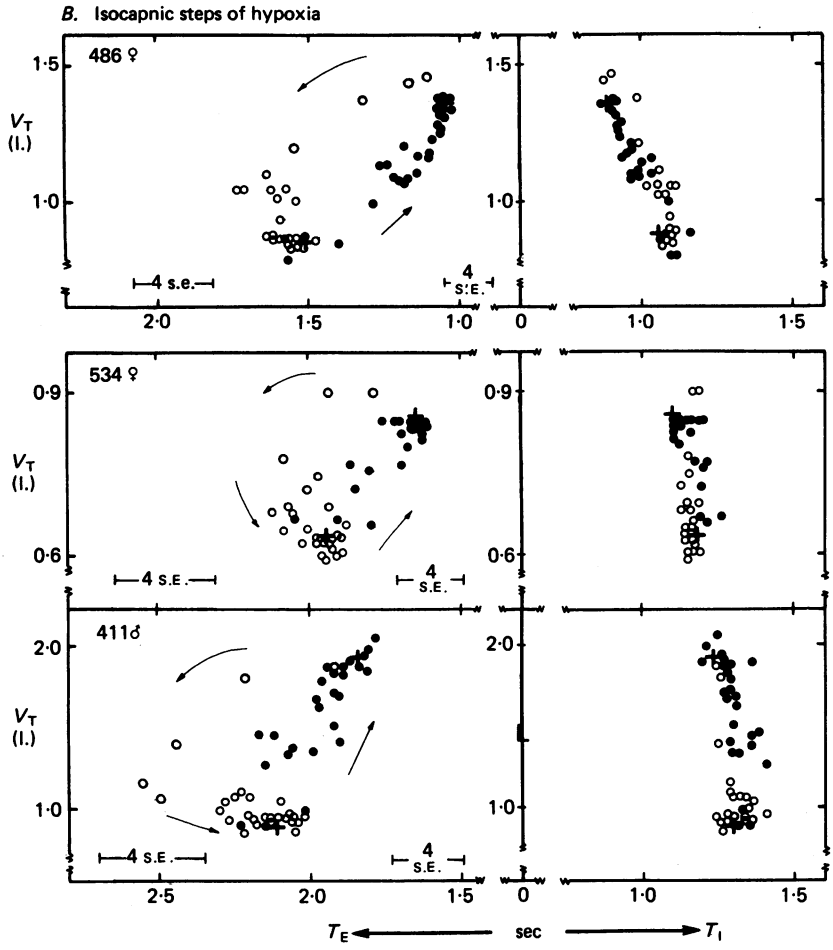

Fig. 5*B*. For legend see p. 67.

breath receiving the new gas mixture. The most striking example of this occurred in T_E following the step out of hypoxia; this change was significant for one out of three experiments when analysed by the *t* test (Table 2) but was significant in all when re-analysed by the Wilcoxon Bank Test.

DISCUSSION

It is suggested that, at a $P_{A,\,O_2}$ of about 200 torr, CO_2 steps primarily stimulate only the intracranial chemoreceptors whereas isocapnic hypoxic steps stimulate only the arterial receptors. Some of the evidence for this should be examined.

In the cat, firing in the carotid sinus nerve changes progressively less as $P_{A,\,O_2}$ increases (see Torrance, 1974; Lahiri & DeLaney, 1975), matching the hyperbolic hypoxic response of man (see Cunningham, 1974). A value of 160 torr for $P_{A,\,O_2}$ has been proposed as the 'cut off' point for arterial chemoreceptor activity in man (Dejours, Labrousse, Raynaud, Giraud & Teillac, 1958); at a value of ~ 200 torr it

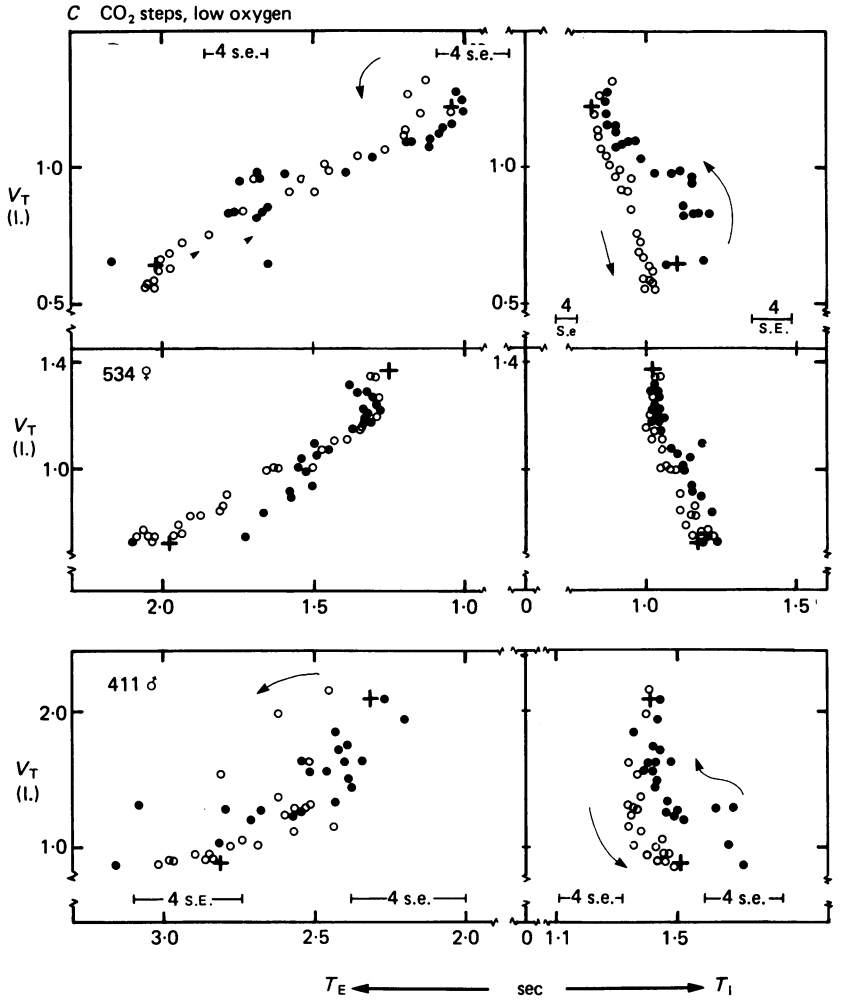

Fig. 5. Plots of tidal volume against T_I and T_E (shown reversed). *A*, CO_2, high O_2; *B*, isocapnic steps of hypoxia; *C*, CO_2 steps, low O_2. The mean values during the 'up' transient (filled symbols) are shown compared with the mean values during the 'down' transient. The pre-switch means are shown by crosses. The arrows enclose significant hystereses. The bars beneath each half of the loops represent 4 standard errors; each is the mean of the individual values for the majority of the points involved in that half of the separation. The same three subjects are shown for each of the three types of step.

can be assumed that such activity, if not absent, is small in comparison with intracranial chemoreceptor activity.

Carotid body resection abolishes or reverses the hypoxic response in man (e.g. Bellville, Whipp, Kaufman, Swanson, Aqleh & Wiberg, 1979) and in dogs (Mitchell, 1965). Respiratory depression appears to be the only central effect of hypoxia (e.g. see Cunningham, 1974), probably not important in the present experiments as subjects could read and concentrate normally throughout.

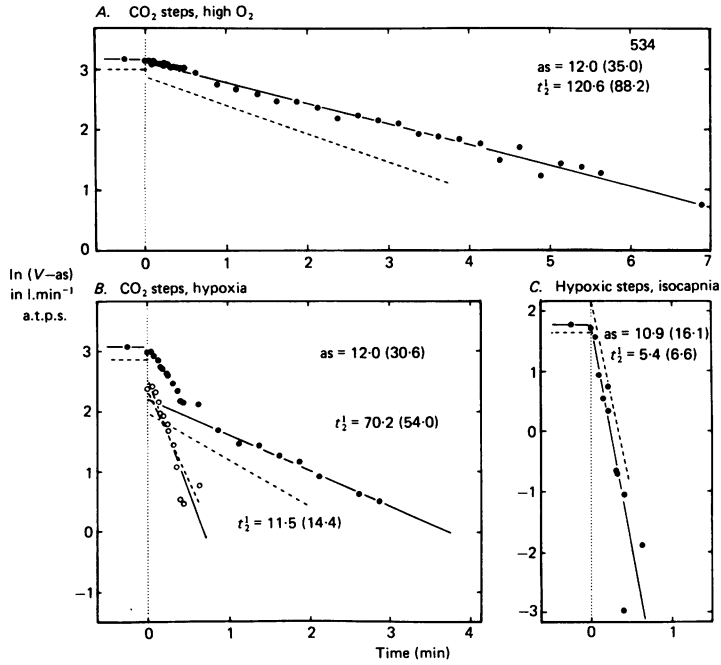

Fig. 6. Semi-log plots of ventilation against time in one subject for the three types of step (*A*, CO_2 steps, high O_2; *B*, CO_2 steps hypoxia; *C*, hypoxic steps, isocapnia). The filled symbols and continuous fitted regression lines refer to the 'down' transient in each case; the 'up' transient is illustrated only by the (dashed) regression lines. The open symbols in *B* show the residual after 'peeling' the first component. The abscissa is the same as in Fig. 4. The asymptotes (in l. min^{-1}) employed in the curve fitting (as) are shown on each plot as well as the half-times in seconds (cf. also Table 1). The numbers for the 'up' transients are shown in parentheses after those for the 'down' transients.

Time course of ventilation responses

The present results confirm and quantify the known difference in response times between the arterial and intracranial chemoreceptors (e.g. Miller *et al.* 1974). End-tidal steps have previously been used by Swanson & Bellville (1975) but they did not study patterning. The half-times reported here for ventilation (Table 1) are largely consistent with their findings as well as those reported for steps of inspired gas tension (e.g. for CO_2, Dripps & Comroe, 1947; Bernards, Dejours & Lacaisse, 1966; Reynolds, Milhorn & Holloman, 1972; Gelfand & Lambertsen, 1973; and for O_2, Reynolds & Milhorn, 1973).

The two-stage response of ventilation to steps of CO_2 in hypoxia is a new finding but is not unexpected for a mixed central and peripheral stimulus; the two half-times extracted by exponential peeling were consistent with those for the pure central and peripheral responses.

The most surprising aspect of this part of the results was the relative slowness of the peripheral chemoreceptor response (time to plateau, $\frac{1}{2}$–1 min). As a consequence, responses obtained with one or two breath tests with O_2, N_2 or CO_2 (e.g. Dejours, 1962; see Cunningham, 1974) or other equivalent tests (e.g. Flenley, Brash, Clancy,

TABLE 2. The latency to the first significant change after the step, expressed either in terms of breath no. after the step or in minutes after the step (figures in parentheses). The criteria for a significant change are described in the text, as are the respiratory symbols. I and E refer to inspiratory and expiratory variables respectively. The first breath receiving the new inspirate is called breath 0. 'Nil' means that no two consecutive breaths during the run deviated significantly from the pre-switch mean; a blank space means that no values were available. In each case the latencies for 'up' and 'down' transients are shown, separated by a comma.

Subject no.	$V_{T,I}$	$V_{T,E}$	T_I	T_E	T_T	$\dot{V}_I$	$\dot{V}_E$
CO_2 steps in hyperoxia							
411		(0·4), 0	(0·6), nil	(0·4, 0·4)	(0·4, 0·4)	4, 9	3, 4
486	7, 10	4, 10	(1·5, 0·7)	(0·5), 10		4, 9	4, 7
534	4, 6	5, 6	0, 7	6, (0·7)	7, (1·2)		4, 1
379		5, 5	2, 2	1, 3	3, (1·1)		4, 4
430		5, 6	nil, nil	5, 7	5, 7		5, 6
422		6, 5	7, (1·5)	4, 7	7, (0·5)		7, 5
Hypoxic steps in isocapnia							
411	2, 1	2, 1	2, 4	(0·5), 1		2, 0	2, 0
486	3, 0	3, 3	7, 3	2, 2	3, 1	3, 2	3, 1
534	3, 2	2, 2	(1·5, 0·5)	6, 0	(0·5), 0	3, 1	3, 1
CO_2 steps in hypoxia							
411	1, 1	1, 1	nil, nil	(0·5), 0	(0·5, 1·5)	2, 1	0, 1
486	2, 3		2, 7	1, 3			
534	2, 2	2, 2	(0·5), 11	1, 7	1, 7	2, 0	2, 0

Cooke, Leitch, Middleton & Wraith, 1979) are hardly justifiable as quantitative estimates of the peripheral chemoreceptor contribution to the total respiratory drive; they remain useful qualitatively (e.g. Miller *et al.* 1974).

Dynamic responsiveness of the human respiratory system

The patterns during the transients show that there is a dynamic component of the response of the intact human respiratory system to CO_2 and O_2. Moreover this response is different for CO_2 and O_2. This is particularly unexpected in view of the findings of Hey *et al.* (1966) which implied the presence of a self-contained 'pattern generator' responding in the same way to all inputs.

T_I, and to a greater extent T_E, are complex variables capable of being influenced by many mechanical and reflex factors apart from brain stem pace-maker mechanisms and chemoreceptors. Possible mechanisms for the dynamic responses should be considered.

The CO_2 effect. Over the first 1 or 2 min after a step of CO_2 in either direction, T_I, in comparison to T_E, changed less than would have been expected from the steady-state response, or sometimes in the opposite direction, resulting in a reduced or absent change of frequency as described by Pearson & Cunningham (1973). The latency of onset would seem to rule out 'airway chemoreceptors' as contributing to the effect (Cunningham, Drysdale, Gardner, Jensen, Petersen & Whipp, 1977); moreover it occurred largely in 'range 1' in which the control of T_I is probably independent of the vagus (Clark & von Euler, 1972).

No T_I hysteresis occurred in the hypoxic steps; the arterial chemoreceptors are

not implicated. Bradley, von Euler, Marttila & Roos (1974) found a hysteresis like the one described here following steps in conscious and anaesthetized cats; they showed that it was due to neuronal mechanisms, possibly a dissociation between the rates of response of their 'A' and 'C' pool neurones to CO_2. In the present experiments better matching between these two response rates in some subjects than others could explain the absence of hysteresis in 50% of subjects studied. Such a mechanism could also explain why the V_T–T_I loops were almost identical for CO_2 steps in hypoxia and hyperoxia (compare Figs. 5*A* and *C*) when the speed of looping was three times faster in one case than the other (compare Figs. 4 and 5); i.e. the looping seemed to be more closely related to the change of V_T than to the more fundamental change of P_{A,CO_2} which presumably changed with roughly the same time course in both cases (see discussion by Miller *et al.* 1974).

The O_2 effect. The dynamic response to hypoxic steps comprised a lengthening of T_E out of proportion to the shortening of V_T following a step out of hypoxia, resulting in an exaggerated change of frequency. The V_T–T_E relationship following the step into hypoxia (Fig. 5*B*) was similar to the steady-state pattern described by Gardner (1977) suggesting that the dynamic effect was confined to the 'down' transient. It is likely that the peripheral chemoreceptors were mediating this response.

The first four breaths after the step contributed to a significant percentage of the overshoot, ruling out any central chemoreceptor involvement (Miller *et al.* 1974).

Hanson (1979), studying anaesthetized cats examined the response of the carotid body to isocapnic steps of hypoxia similar to those used in the present study. He found a marked and reproducible undershoot of activity following the step out of hypoxia (c.f. Black, McClosky & Torrance, 1971) but no comparable overshoot during the 'up' transient. Reflex effects were not measured, but an overshoot in T_E has been described by Widdicombe & Winning (1974) in the anaesthetized cat following the sudden relief of hypoxia. Both at the onset (Marek, Prabhakar & Loeschcke, 1978) and at the offset (Eldridge, 1974) of steady electrical stimulation of the central end of the carotid sinus nerve the resulting change of V_T occurred not abruptly but gradually over a time course of 200–300 sec, presumably due to central neuronal mechanisms. Such a mechanism could explain the slow return of T_E to the steady state after the overshoot in the present results.

The carotid body responses to CO_2 and O_2 appear to be closely linked (e.g. Lahiri & DeLaney, 1975; see also Torrance, 1974). It is a little surprising therefore that there was not a more impressive dynamic response in T_E following CO_2 steps in hypoxia in the present experiments. In cats the aortic chemoreceptors are more responsive to a dynamic than to a static CO_2 stimulus (Hanson, Rao & Torrance, 1979), as is the carotid body (Black *et al.* 1971); such effects, if present in man, would appear to have little reflex relevance.

Other possible mechanisms for the O_2 effect such as change of airway resistance or some aspect of lung mechanics cannot be ruled out but would seem unlikely. **Functional residual capacity was not measured.**

The steady state pattern

The present technique involves the repeated application of a small stimulus producing ventilatory changes in general below the threshold for awareness; any

possible contribution of conscious awareness of hyperpnoea is thus minimized with maximization of the signal to noise ratio. Using this inherently better technique it is reassuring that the same steady-state pattern has emerged (Fig. 3) as previously described using cruder techniques (Gardner, 1977). Once again, the steady-state peripheral and central chemoreceptor patterns are interchangeable; this point would now seem to be beyond dispute.

Patterning in re-breathing vs. the steady state

These results could explain and reconcile the different findings of those using steady-state and re-breathing techniques (see Introduction). However, the rate of change of arterial gas tension was much faster in these experiments than in the average re-breathing run (see ear oximeter trace in Fig. 4*B*). Whether the dynamic effects are still present with slower changes has yet to be determined.

Long-term changes

It is possible that the pattern continues to change beyond the 6–10 min usually allowed for the 'steady state' to develop. Loeschcke, Katsaros, Albers & Michel (1963) showed that after a change of CO_2 it took 25 min for ventilation to attain a plateau but only 15 min for frequency, implying that the V_T–f relationship was changing over the whole of this time. Therefore, although Hey *et al.* (1966) found a unique pattern for most respiratory stimuli between the sixth and tenth minute there is no guarantee that this continues to apply over longer time courses.

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