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THE HUMAN VENTILATORY RESPONSE TO STIMULATION BY TRANSIENT HYPOXIA

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SUMMARY

1. The detailed pattern of transient changes in breathing pattern has been studied following a brief hypoxic stimulus (three breaths of nitrogen) in nine healthy subjects. All showed an increase in ventilation of which the magnitude and relative contributions of volume and frequency varied between subjects.

2. Ventilation, tidal volume, inspiratory, expiratory and total breath time were recorded or derived breath-by-breath; for each of these variables, several test sequences were time-averaged at half-second intervals for each individual; similarly, time-averages were obtained for percentage changes from base line over all nine subjects.

3. There was an increase in inspiratory time accompanying the increasing tidal volume, in all but two subjects. This was statistically significant over all subjects, and in five individuals. Frequency changes were the resultant of alterations in the two phases; when total breath duration decreased it was always linked to a decrease in expiratory time.

4. Further analysis of the initial part of the response suggests that an increase of the duration of an inspiration may be the first change allowing an increase in tidal volume, before the 'drive' increases; this may be a dynamic feature of the control system whatever the nature and site of action of the stimulus.

INTRODUCTION

Most alterations in breathing which occur in normal life are transient or continually adjusted. Traditional physiological studies of stimulated breathing were made mostly in steady states. Although there have been many reports concerning responses during transients, for example at the start of increased muscular activity (Beaver & Wasserman, 1968), or during the first breaths of the response to rising CO_2 or falling O_2 in the inspired gas (Gardner, 1980), changes of pattern in this 'dynamic' phase are referred to as unexpected or paradoxical when they diverge from the established, static, steady-state conditions. The steady state of stimulation must surely be rare naturally, and is not even easy to achieve artifically, so it is not inappropriate to be primarily interested in the alterations in pattern during a changing stimulus: they are likely to be the essential stuff of continual adjustment.

In steady-state responses to raised CO_2 it is generally agreed that at moderate levels of stimulation there is an increase in tidal volume and a decrease in breath duration,

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and that this latter is achieved by shortening of the expiratory phase whilst inspiration lasts as long as in the unstimulated condition (Clark & von Euler, 1972; Cunningham & Gardner, 1972, 1977; Newsom Davis & Stagg, 1975). Our own observations, although made during the changing state of hyperoxic rebreathing and during a few minutes of hypoxia, were similar (Jennett, Russell & Warnock, 1974). Differing results have been reported for progressive isocapnic hypoxia (Rebuck, Rigg & Saunders, 1976) which suggest that inspiratory duration is decreased even at moderate levels of stimulation when it is unchanged in the same subject during progressive hypercapnia.

During transient states, Gardner (1980) has now suggested that the pattern of change is different according to the extent to which the stimulus is centrally or peripherally mediated, which in effect accounts for differences between CO_2 in high O_2, and hypoxia. Thus, when alveolar O_2 concentration was stepped down at constant CO_2, no significant alteration in the time for inspiration (T_I) was reported, whereas when alveolar CO_2 concentration was stepped up there was an initial increase in T_I. Such an increase has been described also in cats at the beginning of the response to a rise in CO_2 (Bradley, von Euler, Marttila & Roos, 1974); they ascribed the effect to a more rapid raising of the 'inspiratory off-switch threshold' than of the rate of firing of inspiratory neurones. A similar initial lengthening of T_I occurred in our own experience in anaesthetized cats, in response not only to CO_2 but also to transient hypoxic stimulation (Jennett, 1978), suggesting that peripheral chemoreceptor stimulation also could have effects on the two components separately; this was in agreement with the effect of the removal of stimulation of carotid chemoreceptors in cats reported by Hanson, Nye & Torrance (1978).

Because of the finding in cats, it seemed not unlikely that initial inspiratory lengthening might be a response common to both peripheral and central stimulation in man also; the results in Gardner's three subjects studied in isocapnic hypoxia did not exclude this: they showed small, individually non-significant, changes in the appropriate direction (Gardner, 1980).

In the present study we have used very brief hypoxia, in the form of three breaths of nitrogen ('N_2-test'), to study the alterations in the pattern of the breathing cycle when peripheral chemoreceptors are stimulated in man. We have averaged results over a group of subjects with the object of distinguishing common features of the response from individual variations. Results suggest that there is indeed an initial lengthening of the inspiratory period, that it is small but transiently precedes as well as accompanies the increase in mean inspiratory flow rate which accounts for a large part of the response. A preliminary report of some of these results has been made (Dutia, Jennett, MacKay & Moss, 1980).

METHODS

Subjects were students or technicians, healthy volunteers aged between 18 and 22. They were informed of the general nature of the study and their consent obtained. All tests reported for any one subject were carried out in one session; sessions were at no particular time of day, but subjects did not attend shortly after a meal or after strenuous activity. They were semi-recumbent and so placed that they were unable to watch the apparatus, or to see when inspired gas was changed. No special measures were taken to distract them, but procedures were not continued on those who

were unable to settle into a relaxed state with steady resting air-breathing. This naturally selected eight women and one man on these grounds alone from among fourteen volunteers. The nine were treated as one group, as values for air-breathing parameters for the one man were within the same range as for the women.

Continuous recordings, using the procedure and methods described below, were usually made for no longer than half an hour at a time. Intervals between such runs avoided restlessness and accumulation of moisture in the apparatus.

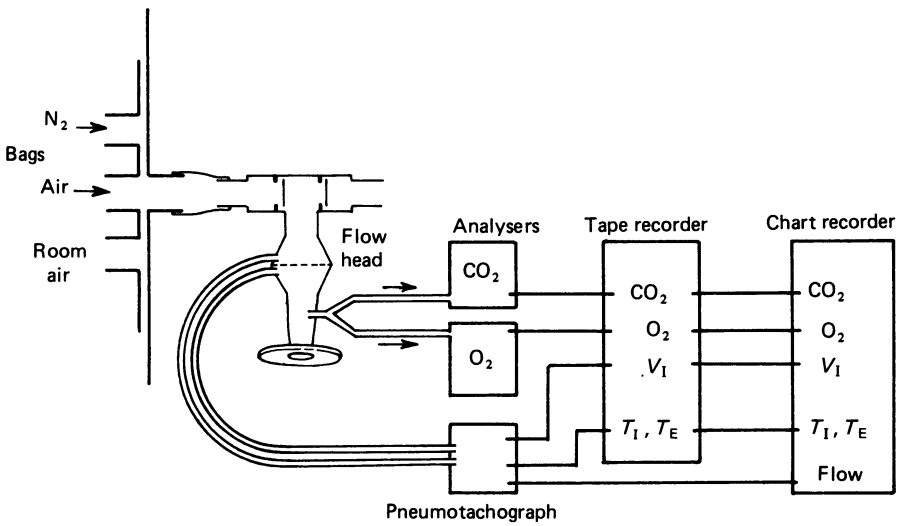

Fig. 1. Arrangements of apparatus. The subject breathes through a mouthpiece, flowhead and low resistance valve box. Inspired gas is changed by sliding to an alternative inlet during expiration. Chart recordings as shown in example in Fig. 2.

Procedure

Air-breathing records were made until the subject had settled to a reasonably steady eupnoeic steady state as evidenced by the end-tidal P_{CO_2}; about 1 min of definitive base-line recording preceded a switch to nitrogen for three breaths. After the switch back to air, a period of 2–3 min was allowed, (more than adequate for restoration of end-tidal P_{CO_2}) before the new base-line recording preceding the next test. In three of the subjects, air was substituted for the test gas, and a full set of control tests carried out in an exactly similar manner; as no consistent changes were found in these experiments, it was not felt necessary to carry out full controls on all subjects. Ten to twenty N_2-tests were carried out in one session, some of which were necessarily rejected because of spurious breaths, sighs or swallows at crucial moments, switching imperfections and so forth. Each subject was asked afterwards about any possible awareness of alterations in inspired gas. Any suggestion of detection, perhaps change in temperature or awareness of switching, caused the run to be rejected and repeated with appropriate modifications.

Apparatus

Breathing circuit (Fig. 1). A conventional rubber mouthpiece and a nose-clip were used; inspired and expired gas were separated by means of a Perspex valve box, either one with light rubber flaps similar to the Collins J-valve, or one similar to the Lloyd valve (both made in our own workshop). Inspired gases were in PVC Douglas bags filled at least ½ hr beforehand. Air or N_2 could be delivered alternatively to the inspired side of the valve via either a thee-way tap or a sliding selector. The gas was changed by hand during the subject's expiration. A pneumatochograph flow head was placed between the valve and the mouthpiece (flow head no. 1; Computing spirometer CS7, Mercury Electronics, Scotland Ltd). A sampling tube from the mouthpiece led to a Beckman OM11 O_2

analyser and a Beckman LB2 CO_2 analyser, calibrated before each experimental run with gases of certified composition (B.O.C).

Recording

To-and-fro air-flow was recorded only on a U.V. oscillograph (S.E.L.); four other variables were recorded both on magnetic tape (Racal Thermionic) and on the U.V. oscilloscope (Fig. 2): integrated inspired tidal volume (V_I), end-tidal CO_2, (using the peak-holding facility of the LB2), airway O_2 %, and a square-pulse signal which changed direction with the air-flow, being triggered simultaneously with the integrating circuit of the pneumotachograph at a small threshold value of inspiratory flow.

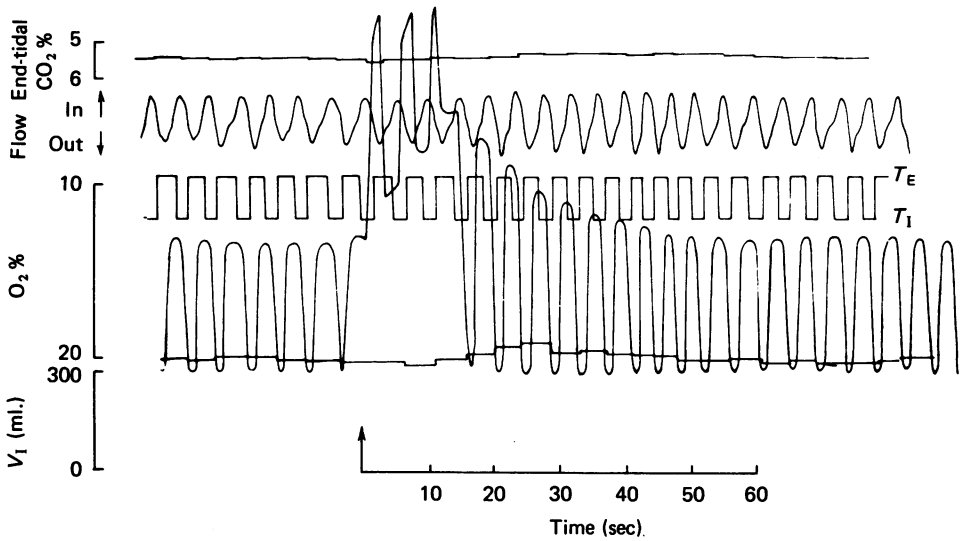

Fig. 2. Example of chart record of one N_2-test. From above downwards: peak (end-expiratory) airway CO_2; to-and-fro airflow; timer output (upper horizontal lines give duration of expiration, lower lines inspiration); airway O_2, zero at top, showing three breaths of N_2; peak integrated volume = inspired tidal volume. Time zero is taken from the start of inspiratory airflow of first breath of N_2.

Analysis

For each experiment the FM tape was processed by computer collection and analysis, using a PDP-8 computer and a programme written in FOCAL by one of us (VAM); for each breath, the start of inspiration was located from the timing signal, and CO_2, O_2 and inspired volume were each sampled after an appropriate delay to find values for that breath; inspiratory time (T_I) expiratory time (T_E) and total breath time (T_T) were taken from the timing signal, and each value of inspired volume (V_I) and T_T were used to derive the breath-by-breath ventilation ($\dot{V}_I$). All values for all breaths were printed out; each test run with its preceding reference period was identified and checked against the U.V. chart record. An editing routine next enabled correction or exclusion of extra 'breaths' from false triggering, or of sections including deep sighs or other interruptions; tests were also excluded if the U.V. chart record of flow showed any unintentional interruption during switching of gases, or any sign of a sticking valve. In this manner the number of tests validated for analysis amounted to six to ten for each subject.

The edited data were printed out and put onto punched paper tape for further processing.

Analysis for each subject

All valid tests were time-averaged (Dutia & Moss, 1980). The programme was used to obtain for each variable and for each test, values at 0·5 sec intervals from time zero (start of first N_2 inhalation) and the mean and standard error during the reference period. Each of the tests was successively

averaged in, to yield a plot of the average values against time, for example of tidal volume for that subject (Fig. 3). The standard error of the mean of the variable at each 5 sec interval was plotted and those values indicated which were significantly different (by t test) from the base-line mean. Each of the five variables of the breathing pattern were treated in this way for each subject ($\dot{V}_I$, V_I, T_I, T_E, T_T).

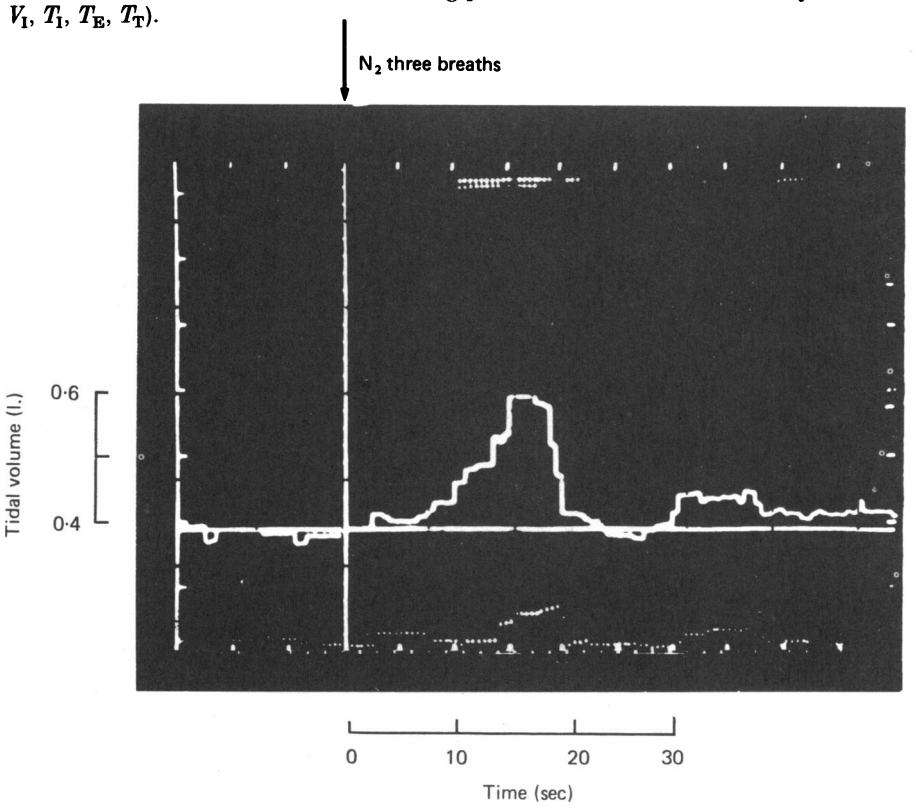

Fig. 3. Example of computer plot of tidal volume against time, representing eight averaged test results for one of the subjects. *Horizontal line*: reference air-breathing value taken from average over 40 sec preceding the test; values for only the final 15 sec are plotted. *Vertical line*: time zero, as defined by start of first inspiration of N_2. Values for tidal volume at each consecutive 0·5 sec interval from zero have been taken from each run, averaged, and the value plotted. The dots at the bottom show the value of the S.E. of mean for each 0·5 sec value; each mean has been compared by t test with the reference pre-test mean and the dots at the top show which values were statistically different (single row: $P < 0{\cdot}05$; double row: $P < 0{\cdot}01$). In the next three figures, plots similar to this have been re-traced.

Analysis over all subjects

A similar time-average for each variable was derived; the averaged data for each individual were used: values at each 0·5 sec interval were standardized by expressing each as a percentage of the reference value. Thus a composite picture was obtained for the patterns of the response in time, with an indication of the latency, extent and significance of change in each of the variables, and of the interrelation between them.

The use of a 0·5 sec interval for averaging meant that the value for any one variable, for any one breath, would be sampled several times, depending on its T_T value. The advantage of this system was that it allowed differences in breath duration from one test to another to be dealt with, and more importantly, differences in breath duration from one individual to another. This avoided the need to choose the breath closest to each of a series of selected times or to accept that times and breath numbers were reasonably synchronized (Gardner, 1980).

RESULTS

Averaged response of each individual

Results of all valid and complete tests for any one subject were averaged, and each variable was plotted against time. These plots all showed a brief increase in *ventilation* after an appropriate latency from the first breath of N_2; the increase attained

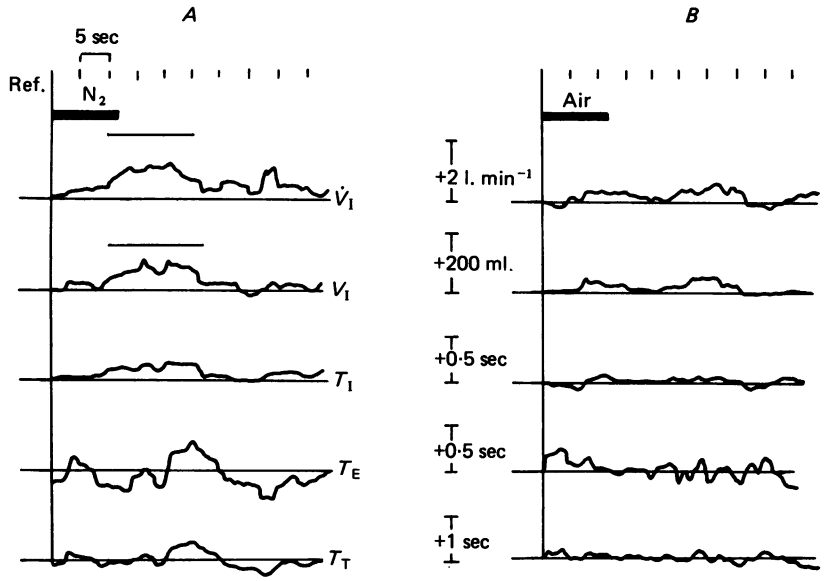

Fig. 4*A*, example of plots of all five variables against time, for one subject, averaged over six tests. From above downwards, ventilation, breath-by-breath; inspired tidal volume; time for inspiration; time for expiration; total breath time. Base line shows air-breathing pre-test mean in each case; scales show changes from reference value. Horizontal lines above the top two plots indicate period of significantly increased values; this subject showed an increase in T_I (third plot) but the between-test variation was large and it was not statistically significant. But note similar shape of upper three plots, whereas lower two are different and roughly parallel to each other. Note also the suggestion of a second peak in ventilation mediated in this subject by an increase in frequency (T_T and T_E decreased). *B*, the same variables, for the same subject, obtained by averaging over six control tests, in which three breaths of air were used instead of three breaths of N_2. Variations are non-significant, but there is a parallel between the top three plots, and between the lower two.

statistical significance ($P < 0{\cdot}01$ at its peak) in all but one of the subjects. The first significant change was attained between 8·5 and 20 sec, and the time of the peak ranged from 15·5 to 27 sec. The magnitude of the significant increases ranged from 24% to 79% above base-line ventilation.

Fig. 4*A* is an example of the averaged plots of each variable for one of the subjects; 4*B* shows similar averaging techniques applied to control (air-to-air) tests in the same subject.

Tidal volume increased significantly in seven subjects. In the other two there was similarly an apparent increase, but this was not statistically significant due to large test-to-test variation. The latency and the time of the peak of the tidal volume

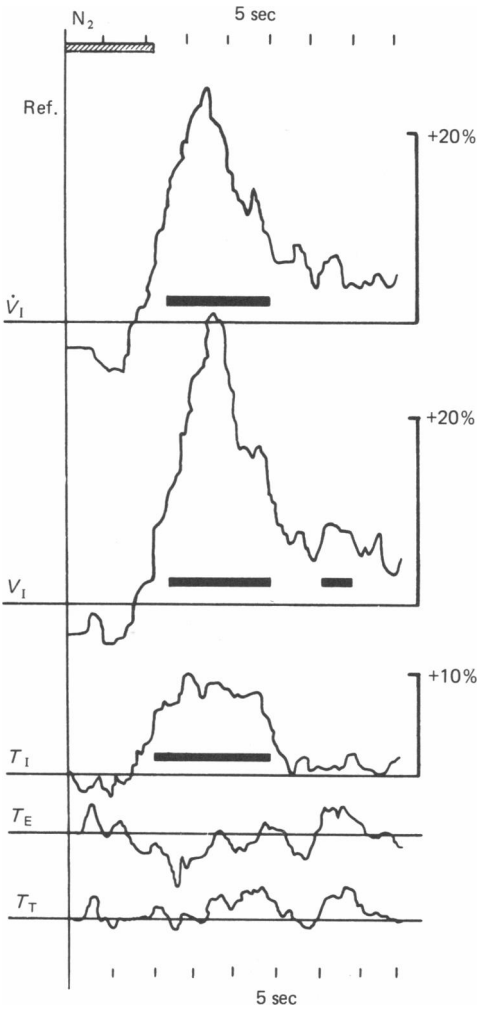

Fig. 5. Averaged plots, as in Fig. 4, over all nine subjects. The average values for each individual have been normalized so that all could be expressed as percentage change from base line and an over-all time-average of these changes computed. The thick bars show periods of statistical significance. Note that T_I increases as volume increases, but its pattern is different after the peak of ventilation: T_I is back to base line whilst volume and ventilation are still elevated. T_E and T_T follow a quite different pattern, but resemble each other, except in the first part of the response where T_E decreases, balancing the increase in T_I at that time.

increased were in each subject virtually the same as those of ventilation, so that the two responses appeared roughly in parallel.

Inspiratory time, T_I increased in seven subjects, and the increase attained significance in five. This lengthening appeared to accompany the start of the increase in tidal volume (but see Fig. 7) and reached a maximum either sooner or simultaneously. However, in many subjects the two variables were clearly independent during the return towards base line: tidal volume remained elevated, or showed a tendency to

a biphasic response, when T_I had already decreased to its reference value. The subject of Fig. 4 does not show this feature, but Fig. 5 reveals it as a significant pattern on averaging the results.

Total breath time, T_T, decreased significantly in a third of the subjects (three), implying that an increase in respiratory frequency contributed to the increase in ventilation; when this occurred it was always associated with a decrease in *expiratory*

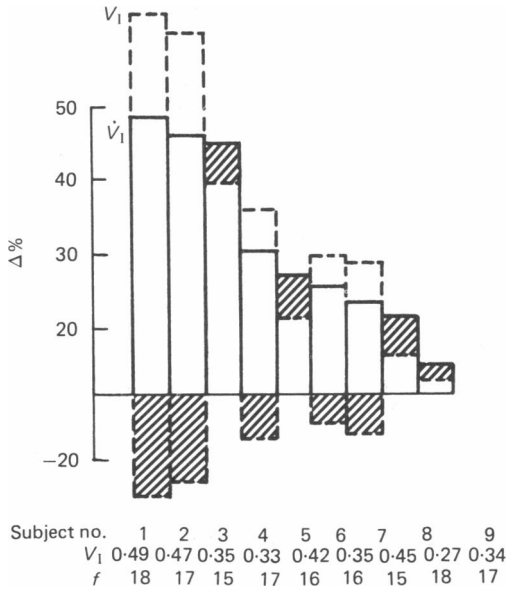

Fig. 6. Subjects numbers 1–9 represented in rank order (left to right) according to the magnitude of the increase in ventilation during N_2-tests. The % increase in ventilation for each subject is shown by the height of the continuously outlined block. The % contribution of tidal volume (V_I) is indicated by the dashed line. The % change in frequency (f) (increase *or* decrease) is shown by the hatched block. Thus, for example, for subject no. 1 an increase in V_I was partly counterbalanced by a decrease in f, whereas in subject no. 3, an increase in both V_I and f contributes. Values below each column indicate average air-breathing V_I (l) and f (breaths/min) for each subject.

time, T_E, and this decrease was significant in five; T_E and T_T *increased* significantly in one subject. The relationship between T_I and T_E showed no consistent pattern.

The two subjects who did not respond with an increase in inspiratory time were the two with the smallest ventilatory response and the smallest tidal volume response (Fig. 6); but showed a decrease in T_T, effected by a decrease in T_E.

Averaged response of group

The fractional changes from reference value for each variable were averaged over all nine subjects and plotted at 0·5 sec intervals from the start of the first breath of N_2 (Fig. 5). Averaging was separately applied to the group of seven subjects who clearly showed an increase in T_I with V_I and $\dot{V}_I$. The extent and significance of changes, their latency and the time to the peak change were found from the average plots.

All nine subjects

Ventilation rose above the mean reference value at 7 sec from the start of the first breath of N_2; the increase was statistically significant from 11 to 23 sec, but it had not returned to base line in 45 sec. The peak was at 17 sec and was 27 % above air breathing base line.

Tidal volume rose above reference value at 7 sec; the increase was statistically significant from 13 to 25 sec, with a peak of 29 % above reference value at 17 sec. There was also a small second significant peak at 30–35 sec, confirming the suggestion of two phases to the response which had been noted on five of the individual average plots.

Inspiratory time rose above reference value at 7 sec and attained a significant increase between 10 and 25 sec with a peak at 14 sec (i.e. slightly before the peak ventilation and tidal volume); it had returned to base line at 35 sec when $\dot{V}_I$ and V_T were still elevated.

Expiratory time showed no changes which attained statistical significance. The changes followed the general shape of the alterations in total breath time; the two were not parallel, because in the early part of the response the lengthening T_I tended to cancel out the shortening T_E so that T_T did not tend either to rise or fall; after the peak of the response, however, T_E and T_T did become more parallel as T_I returned to normal (see Fig. 5).

Total breath time showed no significant changes.

Averaged results for the seven subjects who showed lengthening of T_I

The only difference of note in the averaged results when the two atypical subjects were excluded, was the emergence of a statistically significant increase in T_T accompanying the peak of the ventilatory response; this was related to a tendency to lengthened T_E as well as to the greater average lengthening of T_I compared with the over-all average.

The parallel between tidal volume and inspiratory time appeared as close or closer than in the over-all average, during the rising phases and peak of the response, and again the return to base line of T_I was evident whilst volume was still elevated. However, when values of tidal volume ÷ inspiratory time ('drive' as quoted *inter alia* by Clark & von Euler (1972) and Cunningham & Gardner (1977)) were plotted against time for the averaged results of these seven subjects and compared in detail with the plots of tidal volume and T_I, it appeared that during the 7·5–10 sec period, volume was increasing by virtue *only* of an increase in T_I, before the 'drive' started to increase (Fig. 7).

End-tidal P_{CO_2} decreased during the test by 0·2–0·4 kPa; these changes were small but statistically significant; the lowest value was reached between 20 and 25 sec, lagging the peak in ventilation by about 5 sec. The timing was such that the decrease in CO_2 could be held to account for the biphasic nature of the ventilatory response.

Magnitude of the hypoxic stimulus

The three breaths of N_2 caused a decrease in end-tidal P_{O_2} which reached its lowest value at around 12 sec. The value ranged in different subjects and tests from 6 to

9 kPa. The return to normoxia took 50–55 sec from the start of the test. Clearly it was not appropriate to study the stimulus–response relationship quantitatively as this is not a suitable method of administering a standard stimulus; we were not attempting to quantify the magnitude of ventilatory response, but rather the timing and the sequence of its components.

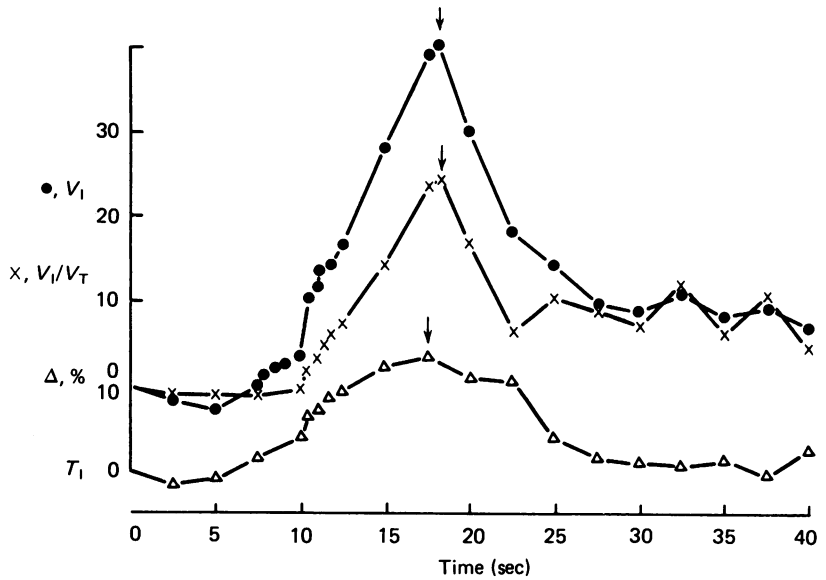

Fig. 7. Averages over seven subjects with T_I increase. N_2-test starts at time zero. Values at 2·5 sec intervals have been taken for tidal volume (●) and T_I (△), and the ratio V_I/T_I calculated (average inspiratory flow rate; ×); for the periods at the start of the change more frequent values have been taken also. The plot reveals a parallel rise in tidal volume and inspiratory time at the beginning of the response, before the mean flow increases. Arrows indicate time of peak increase in each variable.

DISCUSSION

Validity of methods

Tidal volume measurement

Electronic integration of inspiratory flow was used for tidal-volume measurement. The flow heads used were of semi-disposable type, and unheated. Calibration before and after experimental sessions of this brief duration have not shown any significant alterations. Inspired flow was always integrated, so the humidity and temperature of the gas were constant; the viscosity change during nitrogen inhalation is seen in the averaged results as a small decrease in tidal volume below the base line (Fig. 5). The tidal volume is very slightly underestimated (by about 1 %) throughout because the integration starts at a positive threshold value for flow.

Ventilation was derived from tidal volume and breath duration, and was therefore subject to the imprecisions of both.

Inspiratory and expiratory duration

The start of inspiration was marked by inspiratory flow crossing a small positive threshold value. There was therefore an underestimation of inspiratory, and overestimation of expiratory duration throughout. When inspiratory flow accelerated more rapidly as ventilation was stimulated, the threshold was passed sooner at the start of inspiration, and later at the end of inspiration, thus tending to show a relative increase in inspiratory and decrease in expiratory duration, even though the real periods might be unchanged. This effect was shown to be too small to account for our results as follows: during resting air-breathing and during continuous increases in tidal volume and ventilation, the air-flow pattern and the inspiratory-duration marker were both recorded at fast paper speed. Real inspiratory time was measured by hand from the flow trace, and values compared with 'measured' time for the triggering device, breath-by-breath. T_I tended to increase slightly *more* with increasing V_I when it was measured 'real' than when it was measured by the timing device. We are therefore convinced that the significant increase in T_I which we have shown is not an artifact but is part of the initial dynamic response of the respiratory control system. This is further sustained by the observation that T_I varied independently of V_I during the response, and particularly that T_I returned to base line whilst tidal volume and ventilation were still elevated (Fig. 5).

Comparison with other results employing isocapnic hypoxia

There are at first glance contradictions between our results and those of others, notably the report by Gardner (1980) that although an increase in T_I occurred during the on-transient to hypercapnia with high O_2, and also to hypercapnia with hypoxia, it did not occur with isocapnic hypoxia. This suggested that the T_I lengthening was dependent on central stimulation by CO_2. The initial part of the response to our N_2-test should reveal similar characteristics to the initial part of his response to alveolar isocapnic hypoxia, unless any differences can be related to the squarer step produced by Gardner's method.

Gardner reports results from three subjects for isocapnic hypoxic steps. The individual results are presented separately. In the one example shown as a plot against time, T_I appears to be slightly above reference value for the first 10–20 sec as ventilation is increasing; in the three V_T/T_I plots, the points representing the smaller breaths during the 'on' transient all have T_I values greater than the reference mean. The magnitude of these changes is approximately 0·1 sec or 10 % lengthening for a 25 % increase of V_T which is of the same order as the changes we have shown. This suggests that our averaging over many subjects has confirmed a change which Gardner's results did show in at least one individual.

The fact remains that Gardner showed in two subjects a much greater initial lengthening of T_I when the stimulus contained CO_2 than when it was hypoxic only. One might argue that if T_I lengthening is the first effect with any stimulus, then the stimulus which gives rise to the most slow increase in inspiratory activity (hyperoxic hypercapnia) will allow the most obvious increase in T_I, at relatively low tidal volumes, before the drive 'catches up' and effects matching between the two changes.

Comparison with other reports: differences between effects of different stimuli

It has been reported that the steady-state tidal volume/frequency pattern is peculiar to an individual rather than to a stimulus, when ventilation is stimulated (Hey, Lloyd, Cunningham, Jukes & Bolton, 1966); but some reports suggest that there is a greater effect on frequency in hypoxia than in hypercapnia, when the method used is rebreathing (Rebuck *et al.* 1976) and that the shortening of duration in progressive isocapnic hypoxia was associated with a shortening of T_I. We have not been able to confirm this, using a similar method (S. Jennett & K. MacKechnie, unpublished) and neither did Kosai (1978). Bechbache, Chow, Duffin & Orsini (1979) also compared hyperoxic with hypoxic rebreathing and found that in these conditions, as also in exercise and anxiety, different patterns could occur in the same subject; in most subjects they found that the pattern of the response in hypoxia extended or overlaid the pattern in hyperoxia.

If there were indeed a difference between the response pattern to hypoxia and that to hypercapnia (both studied by a rebreathing method), and if that difference were related to relative shortening of breaths in hypoxia, then Gardner's report (1980) of a hysteresis in hypercapnia, but not in hypoxia, could account for this as he suggests; in terms of the von Euler model, the T_I-lengthening effect would be continuously ahead of the drive-effect in hypercapnia. But if the T_I lengthening were the first component of *any* response, then rebreathing experiments might well give different answers to those in steady states; different stimuli would act differently only in accordance with their strength and rate of change, not by their different nature or site of action.

Random variations and 'on-transients': hypothesis for the universal first response

We suggest that any stimulus to increase breathing might elicit T_I-lengthening as the most rapid response. Random fluctuations in 'steady' breathing have been shown to demonstrate a positive correlation between volume and duration of inspiration (Stagg & Newsom Davies, 1974); we have confirmed this in our subjects by pooling, for each of them, all breaths in all reference air-breathing periods. Also Cunningham, Howson, Metias & Petersen (1980) have shown that during imposed exaggerations of oscillation of alveolar P_{CO_2}, a majority of tests show changes in V_T positively linked with changes in T_I, and without alterations in the V_T/T_I (compare Fig. 7).

We have found in cats (Jennett, 1978) and now also in man, that the first identifiable response to inhalational hypoxia occurs during inspiration; yet in animal experiments, employing more direct stimulation or inhibition of the chemoreceptors, the timing of the first effect has been shown to depend on the timing of the stimulus (or its removal) with respect to the phases of the breathing cycle (Eldridge, 1972; Black, McCloskey & Torrance, 1971). This suggests that lung to carotid circulation time may be linked to the length of the breathing cycle (Coulter, Fischer, Robbins & Weir, 1980).

We conclude that initial lengthening of inspiratory duration is likely to be a characteristic of the control system, being the first adjustment to hypoxia and possibly to any requirement of increased alveolar ventilation.

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