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THE EFFECTS OF VARIOUS TIME PATTERNS OF ALVEOLAR CO_2 AND O_2 ON BREATHING IN MAN

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Abstract. We have studied the responses of human arterial chemoreceptors to various patterns of quick change of stimulation. (i) Transient abolition of hypercapnia lowers $\dot{V}_E$ after 2 breaths (chemoreceptor latency) only if PAO_2 is low, therefore hypoxia is necessary for an arterial chemoreceptor response to CO_2. (ii) Alternate breaths of euoxia and hypoxia, and of eucapnia and hypercapnia, separately and combined, have no special effect on mean $\dot{V}$. However, oscillating CO_2 commonly causes breath-by-breath alternation of $\dot{V}$, but only if hypoxia is present; oscillating only the low O_2 seldom causes oscillation of $\dot{V}$. Concluded (a) that chemoreceptor responses to ΔCO_2 are quicker than to ΔO_2; (b) that, above CO_2 threshold, response to rising CO_2 is equal and opposite to response to falling CO_2. (iii) Three time patterns of $PACO_2$ within single respiratory cycles have been compared in hypoxia. At a single *mean* arterial PCO_2, a small sharp fall of $PACO_2$ early in inspiration depresses mean $\dot{V}$, while a smaller sharp fall of $PACO_2$ late in inspiration increases mean $\dot{V}$. Concluded that human respiratory system distinguishes between these rather similar patterns presumably through arterial chemoreceptor pathway since the phenomenon depends on the presence of hypoxia. The importance of exact timing is emphasised.

At the same time as Haldane and Priestley (1905) initiated the modern era of respiratory physiology by introducing the concept of alveolar air, they reported measurements which indicate that the alveolar partial pressures of CO_2 and O_2 oscillate with a respiratory rhythm. Krogh and Lindhard (1913) showed that the swings of partial pressure increase with exercise. Nevertheless the possible significance of these oscillations for respiratory regulation was not appreciated until 1960 when Yamamoto and Edwards provided evidence that the respiratory control system might make use of the extra information they provide.

Now, as a result of the work of Purves (1966) and of Band, Cameron and Semple (1969), we know that oscillations of PCO_2 and PO_2, generated in the alveolar gas by the intermittency of the lung ventilation, penetrate through to the arterial blood, and are detected, transduced into neural signals and relayed to the central nervous system by the arterial chemoreceptors (Hornbein et al. 1961, Biscoe and Purves 1967). We also know that arterial chemoreceptors are capable of responding quickly to step changes of CO_2, but not so quickly to step changes of O_2 (McCloskey 1968), and that brief reflex responses in respiration are elicited by short pulses of CO_2 applied to the carotid chemoreceptors of the cat provided the timing is right (Black and Torrance 1967, Band et al. 1970).

Our purpose today is to describe experiments on healthy young men and women in which we have generated three separate unusual patterns of oscillations in alveolar gas partial pressures, and have looked for reflex respiratory responses.

The first of these patterns we mention only for completeness. Fenn and Craig (1963) showed that slow swings of alveolar PCO_2 of about 2 per minute, which were rather like some that occur in real life, were without measurable effect on mean ventilation other than that due to the mean level of $PACO_2$. These experiments were performed in high oxygen. We repeated them in hypoxia (Cunningham et al. 1964); adding an arterial chemoreceptor component to the signals received by the central nervous system did not alter the original negative finding. We need not consider further long-period oscillations of this type.

The other two types of alveolar oscillation are both abnormal in that they probably never occur in natural life. In one the inspired gas is altered in alternate breaths so that large swings of alveolar PCO_2 and PO_2, together or separately, occur from one breath to another, the ups and downs presumably occurring at exactly the same phase of successive respiratory cycles. The effects of such procedures on *mean* ventilation are zero and were published some years ago (Cunningham, Elliott, Lloyd, Miller and Young 1965); today we are reporting recent, and still incomplete, studies of the effects of such oscillations on breath-by-breath ventilation.

The third kind of oscillation studied is the one that occurs in "tube breathing", i.e. an alteration of the time-profile of alveolar PCO_2 and PO_2 *within* each cycle. The effects of actually breathing through a long tube (1200 cc) were reported for atmospheric-air breathing by Fenner, Jansson and Avery (1968), and at high and low PO_2 by Goode, Brown, Howson and Cunningham (1969); today we are reporting a further analysis of the problem based on a simulation of the tube-breathing time profiles without the tube.

Our basic thinking in this field is largely governed by a little-known series of experiments which we must summarize before dealing with the oscillations themselves. These experiments were performed in our laboratory by Miller (Cunningham, Lloyd, Miller and Young 1965), and were based on earlier work on the responses to step changes of alveolar gas pressures (Asmussen and Nielsen 1946, Bannister and Cunningham 1954, Dejours 1962, Bouverot et al. 1965). Figure 1 shows such an experiment. Above is a trace of PCO_2 at the mouth, $PICO_2$ being about 35 torr and

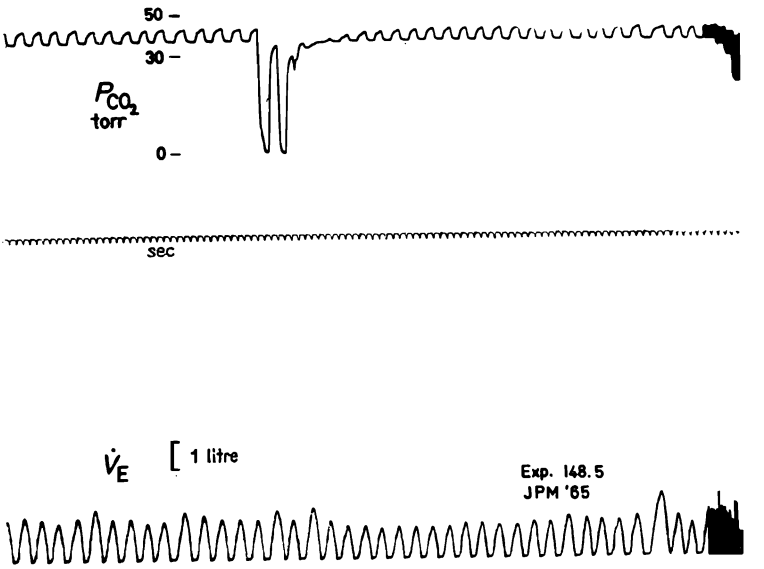

Fig. 1. Experimental record of the effects of the transient removal of CO_2 from inspired air on end-tidal PCO_2 (above) and on expiratory tidal volume (below). Determination at PAO_2 ca. 650 torr. (From Miller 1966.)

$PACO_2$ about 42 torr. Below is a record of the movements of a spirometer in the expiratory pathway. For two breaths the inspired PCO_2 is reduced to zero, inspired O_2 being maintained. $PACO_2$ falls abruptly to, and then below, the probable CO_2 threshold (Nielsen and Smith 1952); 4 or 5 breaths later there is an obvious reduction in ventilation. The mean latency of this response was determined in high oxygen and in hypoxia: for this purpose there were more than 200 determinations on three subjects.

Figure 2 shows the results on one subject. Breath-by-breath ventilation, averaged for all determinations, is plotted against time. The shaded area represents the two breaths over which the inspired gas was changed. The starting ventilation is chemically driven to a level about five times the resting. When CO_2 is abruptly removed against a background of mild

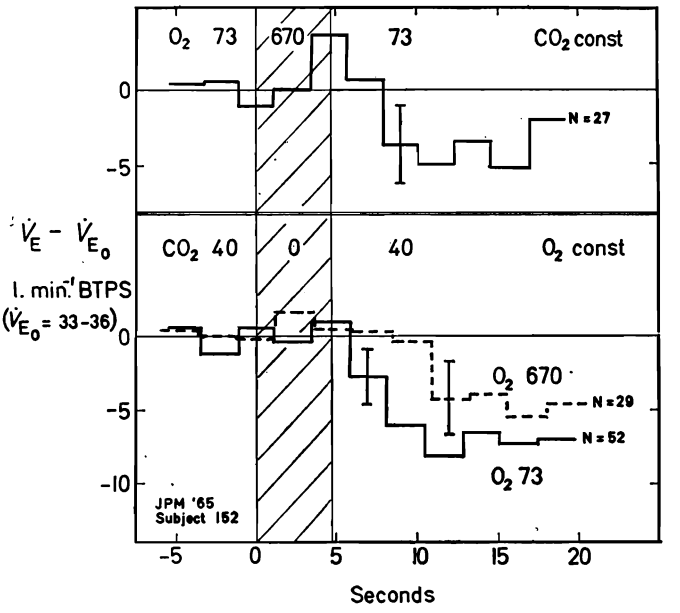

Fig. 2. Breath-by-breath changes of ventilation for one subject averaged separately for each of three types of determination plotted as a function of time. Dashed line, CO_2 inhalation in high oxygen (PAO_2 ca. 650 torr); both full lines, CO_2 inhalation in hypoxia (PAO_2 ca. 65 torr). In the lower part of the Figure, CO_2 removed from inspired air for 2 breaths, shown shaded. In upper part, 2 breaths of O_2 (still containing CO_2) given over this period. Vertical bars are $\pm 2 \times$ SE of mean difference from control ventilation, shown as horizontal line. (From Miller 1966.)

hypoxia, the first significant fall of ventilation occurs at the third breath. The top figure shows that the latency of the reflex response to removal of hypoxia under the same starting conditions is about the same or a bit longer, and thus both responses may be regarded as being mediated by the arterial chemoreceptors. Those who distrust on principle any experiment on intact man, however clear, should look at the paper of Leitner, Pagès, Puccinelli and Dejours (1965) where they will find confirmation on animals. The dashed line in the lower panel shows that when CO_2 is removed against a background of hyperoxia, there is not so much as a flicker in the ventilation at the time appropriate to arterial chemoreceptor responses: the first significant fall occurs two breaths later, and is presumably mediated by other receptors, probably within the skull.

We conclude that in man, unlike the cat, responses of arterial chemoreceptors to small changes in PCO_2 are detectable only when there is some accompanying hypoxic stimulation, that the response of the intracranial receptors *in situ* is probably too slow to pick up quick changes

and, incidentally, that the well-known multiplication between hypercapnic and hypoxic stimulation in man occurs partly or wholly at the arterial chemoreceptors.

These experiments of Miller's (1966) together with the known dynamic properties of cat chemoreceptors (McCloskey 1968), indicate that in a search for reflex effects of strange time-profiles in alveolar gas, positive results are most likely to be obtained when quick changes are made in PCO_2 rather than in PO_2 and when the effects on the arterial chemoreceptors are amplified by hypoxia.

The oscillations have been studied using apparatus that has evolved continuously during the period over which the experimental work has been performed. The current version of it is shown in Fig. 3. Two sepa-

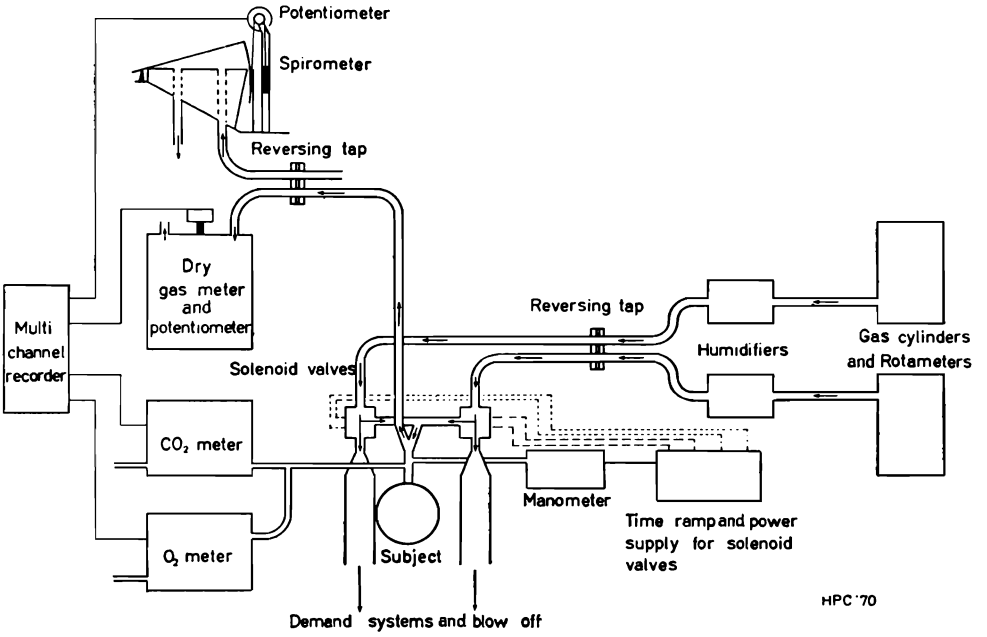

Fig. 3. General plan of apparatus: *see* text.

rate sets of rotameters allow the steady supply of an excess of each of two gas mixtures to the vicinity of the subject. The mixtures may be varied at a moment's notice to suit the exact requirements of the situation. Each gas mixture flows past a T-piece: the subject takes what he wants from the tail of the T and the excess escapes to the atmosphere through a reservoir tube. The tails of the T-pieces may be opened or closed by solenoid-operated plungers; only one is open at any one time so that inspired gas is available to the subject from one side or the other,

but never from both at once. The two inspiratory pathways are kept separate right up to the inspiratory valve by a longitudinal septum in the common part of the connecting tube. The solenoids are activated according to adjustable programmes, triggered from the beginning or the end of inspiration. These are signalled by the sudden change of mouth pressure that occurs when the phase is reversed. The subject breathes through supremely low-resistance, low-dead-space valves (the prototypes of the Lloyd valve, W. E. Collins Inc.). Gas from between the teeth is passed through rapid O_2 and CO_2 analysers (fuel cell, 211 M. C., Westinghouse Inc., and Uras M infra-red, Hartmann and Braun) for display of inspired and end-tidal partial pressures. Mean ventilation is measured with a low-resistance dry gas meter (Parkinson and Cowan, type CD4) or breath-by-breath tidal volume by open-circuit spirometry (Cunningham, et al. 1965).

The subject faces away from most of the apparatus, and is encouraged to read a book. In the experiments to be reported the test observations involve switching of the source of inspired gas from one side to the other, with small adjustments of timing and of gas composition in order to achieve the desired pattern on the PCO_2 and PO_2 trace. Control observations are made usually both before and after the test periods: the timing of the operation of the solenoids is the same, but the time-pattern of the alveolar gas partial pressures is the normal one because identical gas mixtures are supplied through both sides. The end-tidal CO_2 and O_2 of the control periods are matched graphically or experimentally with those of the test periods. The movement of the solenoids is audible, and was really rather loud in a small number of early experiments. Since, however, they operate in the test and control determinations alike, the subject has no means of distinguishing between the test and the control periods. The effect of solenoid noise on susceptible subjects has been to increase the variance of the observations rather than to introduce bias.

Alternate-breath oscillations. Figure 4 shows the sort of experiment we are carrying out. From above downwards we have the CO_2 trace, next the O_2 trace, both showing inspired and alveolar values, next the expiratory tidal volume, next breath duration and at the bottom an uncalibrated oximeter trace. In this example the PO_2 was swinging while the PCO_2 was nearly the same (about 42 torr) in both inspired gas mixtures; end-tidal PCO_2 was steady at about 45 torr. The inspired PO_2 was some 113 torr on one side and zero on the other. I should remind anybody who wishes to repeat the experiment that the second mixture, if supplied continuously, would be lethal. The inspiratory pathway was switched during each expiration so that the change was certainly complete before the start of inspiration and the subject received whole breaths of each mixture. The PO_2 trace has been offset so that the lower inspiratory

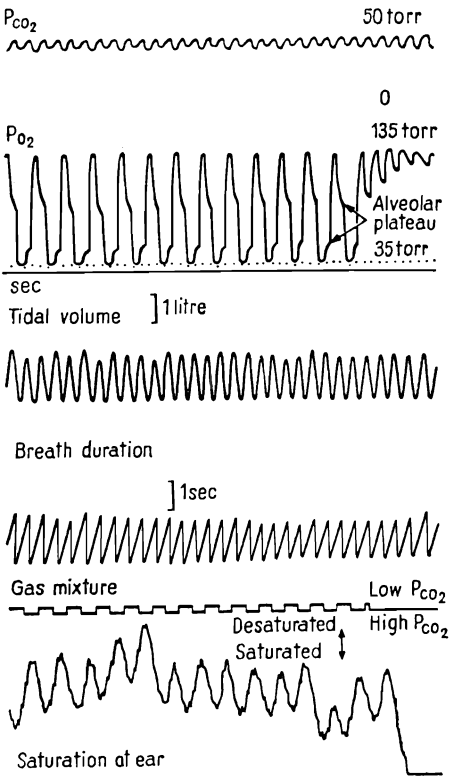

Fig. 4. Alternate breath oscillations: specimen trace. From above downwards: (i) PCO_2 at the mouth, inspired CO_2 from the two sources are almost equal and the alveolar oscillation is negligible; (ii) PO_2 at the mouth, inspiration of alternately 113 and 0 torr PO_2; end-tidal PO_2 swings between about 45 and 75 torr; (iii) time in seconds; (iv) expiratory tidal volume, note slight tendency to alternate breath oscillation of response; (v) breath duration which shows no regular oscillation in this section of the record; (vi) signal showing switching of solenoid valves; (vii) uncalibrated ear oximeter tracing.

value is off scale. The alveolar plateaux are apparent and the swing between alternate end-tidal values is about 30 torr; it may be argued that the peak to trough swings in alveolar PO_2 under these circumstances are probably of the order of 40 torr or more, around a mean in the region of 55–60 torr in most experiments. In experiments in which PCO_2 was made to oscillate the corresponding PCO_2 values were: end-tidal to end-tidal, 10–13 torr, around a mean 5–8 torr above resting, and estimated peak-to-trough alveolar, some 15–19 torr. The maximum rates of rise and fall of PCO_2 were probably the same in each direction, and occurred at exactly the same phase of successive cycles, i.e. early in inspiration. $PACO_2$ probably never fell to threshold. The figure illustrates a slight tendency for the tidal volume, but not the breath duration, to oscillate.

This is seen best by starting some three breaths from the left, and predicting, for successive breaths, "up, down, up, down...". After a short run, the pattern seems to be lost, but then reappears in the same phase a little further on. This non-parametric prediction method has been the basis for our analysis because even in records that are more convincing than this one, numerically the oscillations tend to get lost in the considerable random variation from breath to breath. I have shown this rather unconvincing record because the oximeter trace indicates that the oxygen signal to the arterial blood gets through. The run of small tidal volume oscillations in this example is too short to be significant on any test, and it is too early to say whether such O_2 oscillations do in general increase the tendency of tidal volume or ventilation to show short runs of oscillation. CO_2 oscillations in hypoxia in an earlier series [1] gave a clear result.

TABLE I

The effect of alternate breath *PA* CO_2 oscillations on the breath-by-breath ventilation. The figures give the probability that any observed alternate breath oscillation in $\dot{V}_E$ is due to chance. When $p > 0.05$ this is represented by n. s.

Experiment	Hypoxic control	Hyperoxic oscillation	Hypoxic oscillation
357,1	n. s.	n. s.	$p < 0.02$ $p < 0.001$
303,1	n. s. n. s.	n. s.	$p < 0.001$
219,8	n. s. n .s. $p < 0.01$	n. s.	$p < 0.05$ n .s.
225,21	n. s.	n. s.	$p < 0.001$ n. s. $p < 0.001$
292,1	n. s.	n. s.	$p < 0.01$
301,1	n .s. n. s.	n. s.	$p < 0.001$
Number significant	1/10	0/6	8/10

Table I shows a significant tendency for ventilation to wax and wane between alternate breaths in 8 out of 10 test determinations, with only one out of 10 significant in the control runs and none in the CO_2 runs in high O_2.

[1] To which two senior undergraduates, Messrs K. Lien and A. McPherson, contributed substantially.

These results, on a breath-to-breath basis, extend in a striking way our earlier published results, in which no sort of alternate-breath oscillation or combination of oscillations had any effect on *mean* ventilation. Putting the two sets of results together leads to the important conclusion that, while the individual pulses of chemoreceptor activity may produce separate reflex effects, the "ups" and the "downs", coming as they do at the corresponding parts of successive cycles, exactly cancel each other out. There is thus no special merit in "rate of rise" of stimulus as compared with "rate of fall", provided the troughs of the stimulus never fall below the stimulus threshold (*see* Nielsen and Smith 1952).

It remains to be seen whether the response of the system to an O_2 signal of this kind is fast enough to be picked up.

Within-breath oscillations. Breathing through a long tube of about 1200 cc capacity is a simple way of distorting the naturally-occurring oscillations in PCO_2 and PO_2 in alveolar air and arterial blood. The effects on the ventilation of so doing may be compared with the effects of producing the same changes in alveolar PCO_2 and PO_2 by what we may call the conventional methods of CO_2 inhalation. In this sort of comparison the subject breathes through respiratory valves placed either at the mouth or at the far end of the tube, and the end-tidal PO_2 and PCO_2 are matched in the two cases by appropriate adjustments to the inspired gas mixture. The effect of tube breathing on ventilation is certainly no great-

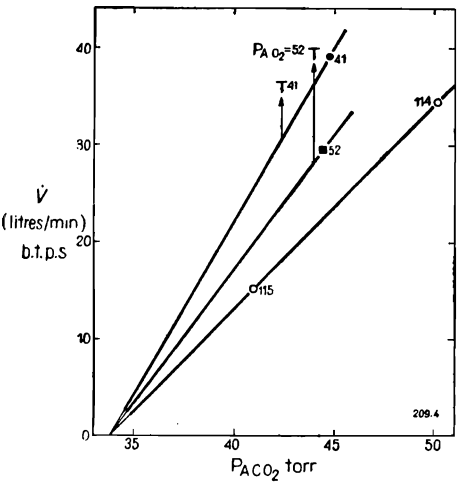

Fig. 5. Results of one experiment showing the relation between ventilation ($\dot{V}$), and alveolar PCO_2 during conventional CO_2 inhalation (points and oblique lines) and in tube breathing (the cross on the T). Numerals beside points are PAO_2. Note that in hypoxia, with alveolar gas pressures matched, tube breathing is associated with substantial hyperpnoea (denoted by vertical arrows).

er, and probably less than, the effect of conventional CO_2 inhalation as long as alveolar PO_2 is normal or high; however, as Fig. 5 shows, tube-breathing in moderate hypoxia produces much more ventilation than does the matched conventional CO_2 inhalation (Goode et al. 1969). The dependence of the response on hypoxia points to the crucial part played by the arterial chemoreceptors. The signal must be blood-borne and, if the end-tidal gases have been properly matched, we are left with two possibilities, first, that despite the alveolar matching, the arterial PCO_2, PO_2 or both are different in the two cases and, secondly, that the slightly altered time profile of the alveolar PCO_2 or PO_2 is detected by the chemoreceptors and acted upon by the medullary neural apparatus. We have now done sufficient arterial blood gas comparisons to exclude the first possibility, and so we are left with the second. What is this pattern? Figure 6 centre and left shows diagramatically how alveolar CO_2 changes

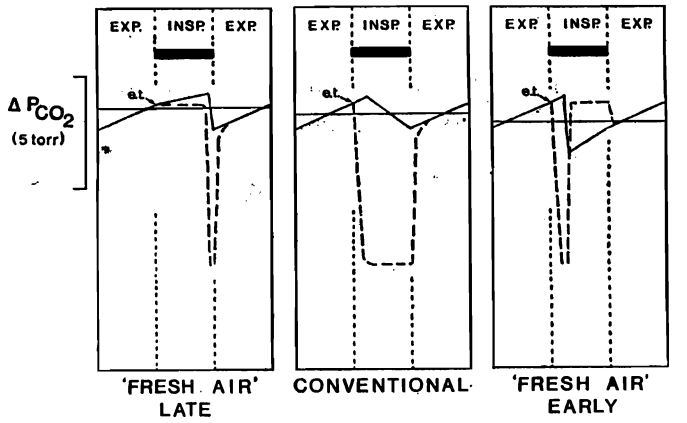

Fig. 6. Calculated time profiles (continuous lines) for alveolar CO_2 throughout the respiratory cycle, for the experiments using the apparatus shown in Fig. 3. Long dashed trace line indicates PCO_2 at the mouth during inspiration. Centre: conventional CO_2 breathing; left, simulated tube-breathing, i.e. "fresh air late"; right, "fresh air early". e.t. denotes end-tidal values; horizontal line across figure shows calculated mean alveolar PCO_2 for the three patterns.

over a respiratory cycle during conventional CO_2 inhalation and in tube-breathing respectively (*see* DuBois et al. 1952, Goode et al. 1969). During expiration the alveolar space is "private" and cannot be influenced from the outside: both patterns therefore show the same almost linear rise of PCO_2. During inspiration, however, while there is a steady, almost linear fall of PCO_2 in conventional breathing, in tube breathing over the first half to threequarters of the inspiration tube air of alveolar composition is inhaled, alveolar PCO_2 stays high or even

rises further, and it is only when the inhaled volume exceeds tube volume, towards the end of inspiration, that "fresh air" enters the alveoli. At this point there is a sharp but small fall of PCO_2. We have to imagine alveolar PO_2 as following an inverted but otherwise similar time course. By a process of elimination we were driven to the conclusion that it was this small difference in the inspiratory profile that was largely responsible for the effect of hypoxic tube breathing.

The next step was to simulate these profiles without the tube, using our gas-switching equipment to change the composition of the inspired gas in the middle of each inspiration. Simulated tube breathing is mimicked by supplying, first, hypoxic gas whose PCO_2 is adjusted to be identical with end-tidal, thus preventing $PACO_2$ from falling over the

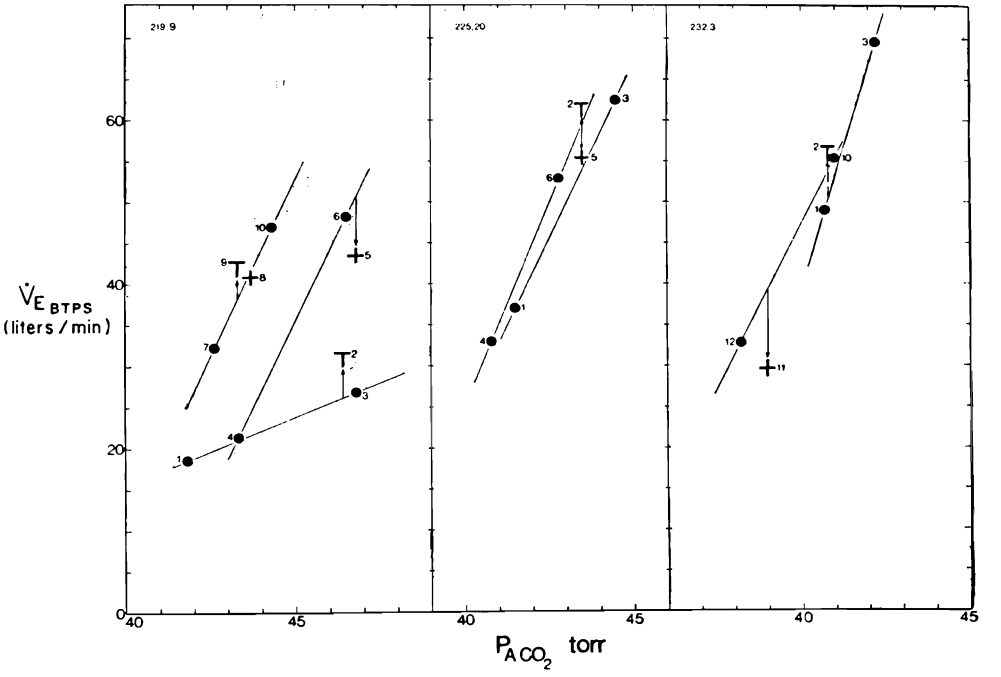

Fig. 7. Simulated tube breathing in steady hypoxia. Three typical experiments using apparatus shown in Fig. 3. $\dot{V}$ plotted against $PACO_2$. Numbers denote order of experiment. Each T ("fresh air late") and + ("fresh air early") point is between a pair of conventional points (closed circles joined by oblique line) in time, and its $PACO_2$ is either straddled by or is very close to the conventionally obtained $PACO_2$. PAO_2 55–60 torr throughout, but for any one test-control comparison, errors due to mismatching of PO_2 never amount to more than 0.5 torr in favour of hypothesis, and are usually contrary to it. The numerical differences that go to make up the mean differences shown in Table II are indicated by the vertical arrows.

first part of inspiration; this is followed by "hypoxic fresh air" late, which allows the small sharp fall of $PACO_2$ later on. The effect of this is compared with the effect of supplying identical mixtures down both inspiratory lines, the compositions being adjusted to match the "tube-breathing" end-tidal gases. The reconstruction on the left of Fig. 6 is actually based on a simulated rather than a genuine tube experiment.

Using this method, it has been possible to reproduce the tube profile for PCO_2 and PO_2 separately and together, and also to reverse the order from "fresh air late" to "fresh air early", which produces the pattern shown on the right of Fig. 6. Note the early fall of PCO_2, the slightly larger amplitude and the continued rise of PCO_2 over most of the cycle. The results of this work have been reported in abstract (Cunningham et al. 1971).

The experiments varying the PCO_2 profile only have shown the most clear-cut results. Three typical comparisons are shown in Fig. 7, which is a plot of ventilation against end-tidal PCO_2. The black spots are "conventional" points and the lines joining them are hypoxic CO_2 response lines. The numbers denote the order of the experiment. Capital T denotes the "simulated tube" pattern for CO_2, i.e. fresh air late; + denotes "fresh air early". The effects are small and somewhat variable, but the majority of the T-points lie above the lines, and the majority of the + lie below. The most constant finding has been the difference between T and +. All the CO_2 results are summarized in Table II. For "fresh air late" versus conventional, the mean difference in ventilation, i.e. the mean height of the vertical arrows of Fig. 7, was plus 2.5 litres/min in a total of 36 litres/min, a small but highly significant difference. The mean difference between "fresh air early" and "conventional" was negative,

TABLE II

Mean changes of ventilation (litres/min) associated with "within breath" oscillations of $PA\,CO_2$ in hypoxia. The two probability values are based on (1) the variances of the respiratory measurements alone and (2) on the sum of the respiratory variances and twice the blood gas variances

Comparison	n	$\Delta\dot{V}_E \pm$ SE	p_1	p_2
'Fresh air' late minus control	42	$+2.5\pm0.5$	< 0.001	< 0.02
'Fresh air' early minus control	24	-4.3 ± 1.4	< 0.01	< 0.05
$\Delta\dot{V}_E$ late minus $\Delta\dot{V}_E$ early	19	$+6.9\pm1.3$	< 0.001	< 0.01

Average control conditions ±SD: $PACO_2$ 44.4±2.3
PAO_2 57.0±3.3
$\dot{V}_E$ (litres/min BTPS) 36±14

and significant. The mean difference between "fresh air late" and "fresh air early", where direct comparisons were justified, was larger, had a smaller coefficient of variance, and was even more significant. The last column shows the probability values when a generous allowance is made for the variance of the blood gas estimations. The probability values are still within satisfactory limits, especially that for the difference "early versus late".

There were not so many observations on the effects of the corresponding PO_2 profiles, the CO_2 profile being held to the conventional pattern. None of the mean differences approached significance, and we are confident that, if there was any effect at all, it was of an altogether different order of magnitude from that produced by the CO_2 patterns. Likewise, superimposition of "early" and "late" O_2 patterns on simultaneous "early" and "late" CO_2 patterns produced effects which were essentially the same as those of the CO_2 patterns by themselves.

Finally, the mean effect of the simulated pattern was smaller than the effect of real tube breathing, admittedly measured on a different set of subjects; we are thus able to account for only about one quarter of the tube effect.

It may well be asked why we have come all the way from Oxford to talk about these small and variable effects. The answer is that the difference between the effects of the two patterns is nearly 20%, which is not so small, and is subject to much less variation than the other differences: it is the relation of this fairly constant difference to the conventional that is not very predictable.

It has been possible to control other variables to such an extent that we have been forced by our results to accept that pattern and timing of stimulation have primary effects of their own on human breathing, just as they have in the cat.

The results as a whole indicate that in man sudden changes of PCO_2 can induce changes of chemoreceptor activity whose effects can be detected on the efferent side of the respiratory reflex control system on a breath-to-breath basis. The effectiveness of the CO_2-induced chemoreceptor signal is dependent upon amplification by hypoxia, but sudden changes in hypoxia itself are less capable of generating an effective signal. Our more detailed conclusions are as follows:

The new work on alternate-breath oscillations allows us to say that rates of rise and rates of fall of PCO_2, if they occur at corresponding points in the respiratory cycle, have equivalent positive and negative effects, a conclusion which is superficially at variance with that of Dutton, Fitzgerald and Gross (1968) (but *see also* Bhattacharyya et al. 1970).

With regard to the within-breath patterns, the following points stand out. First, the rate of rise of PCO_2 was the same in all three patterns, and so was not responsible for the effects. Secondly, the amplitude of the swings between troughs and peaks of PCO_2 were greater in the "fresh air early" experiments, in which ventilation was lowest. Thirdly, ventilation was highest when $PACO_2$ was maintained high early in inspiration rather than being allowed to fall slowly, as in conventional CO_2 inhalation or sharply as in the "fresh air early" experiments. It could be that the critical, sensitive part of the cycle, in the sense of Black and Torrance (1967) and of Band, Cameron and Semple (1970) corresponds at the alveolar level in our subjects to a short period early in inspiration. It could also be that what really matters is the exact timing at some central synaptic level of the cut-off of afferent bombardment associated with the sharp fall of PCO_2.

The patterns actually studied are artificial, and it is difficult to think of circumstances under which they might occur in real life. Nevertheless the results obtained using them show that the respiratory system of man is sharply enough tuned to make use of the oscillations that occur naturally provided some hypoxic background is present (*see* Bhattacharyya et al. 1970). Whether the oscillations are actually made use of is not yet decided.

S. B. Pearson and R. H. K. Marsh were Medical Research Council Scholars.

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