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A COMPARISON OF THE EFFECTS OF OSCILLATING AND STEADY ALVEOLAR PARTIAL PRESSURES OF OXYGEN AND CARBON DIOXIDE ON THE PULMONARY VENTILATION

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In 1960 Yamamoto put forward the interesting hypothesis that ventilation might respond less to a given steady P_{CO_2} than to an oscillating P_{CO_2} with the same mean value. He showed on theoretical grounds that the oscillations in the alveolar CO_2 pressure (P_{A,CO_2}) between inspiration and expiration would be much increased in exercise, but not when mean P_{A,CO_2} ($\bar{P}_{A,CO_2}$) was raised by CO_2 inhalation at rest. The hypothesis implied that oscillations in P_{CO_2}, known to occur in the alveolar gas (DuBois, Britt & Fenn, 1952), would, during exercise, penetrate far enough along the vascular tree to reach some receptors sensitive to CO_2. They would be more likely to reach as far as arterial chemoreceptors than the intracranial receptors. During rest the oscillations at the site of the receptors would be smaller or possibly absent.

The proposed responses to oscillations could probably be accounted for more or less completely by postulating a suitable rate of adaptation at the receptors or at some central synapses, and the Yamamoto hypothesis does not necessarily require the participation of a complex neural organization. In this respect it differs fundamentally from the superficially similar hypothesis of Fenn & Craig (1963), who, using the 'injected' CO_2 technique, were able to simulate in resting subjects the inverse relation between $\bar{P}_{A,CO_2}$ and ventilation that occurs in steady-state exercise. They thought that the central nervous system might be able to distinguish between the different forms of this relation found in CO_2 inhalation and in CO_2 'injection' or exercise, a property that would require a neural arrangement of considerable complexity. Fenn & Craig could not obtain evidence to support their hypothesis, nor could Cunningham, Lloyd & Patrick (1964).

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Experimental results bearing on the respiratory-cycle oscillations hypothesis of Yamamoto are equivocal. Thus rats whose venous blood was loaded with extra CO_2 (Yamamoto & Edwards, 1960) exhibited hyperpnoea without rise of mean arterial P_{CO_2} ($\bar{P}_{a,CO_2}$) whereas none of Kao's dogs (Kao, 1963; Kao, Michel, Mei & Li, 1963), which were in a similar experimental situation, showed hyperpnoea unless $\bar{P}_{a,CO_2}$ rose substantially. Likewise, of four human subjects given *ca.* 18% CO_2 every third or fourth breath, two (Riley, Dutton, Fuleihan, Nath, Hurt, Yoshimoto, Sipple, Permutt & Bromberger-Barnea, 1963) showed an increase in the slope of their CO_2 response curves as compared with the curves determined during conventional CO_2 inhalation, while the other two (reported by Fenn & Craig, 1963, as a supplementary finding in their paper on 'injected' CO_2) showed no change. Surprisingly Dutton, Chernick, Moses, Bromberger-Barnea, Permutt & Riley (1964) make no mention of this negative result in their latest paper. Finally, Grodins & James (1963) have shown that a computer may be programmed to give an analogue response in accordance with Yamamoto's hypothesis, while Cunningham (1963), using published data on men and women from many sources, has pointed out that the well-established factors, properly combined, can account for the hyperpnoea of exercise, leaving little or no room for newcomers in the field.

In this paper we are concerned with a comparison of the effects on total expired ventilation ($\dot{V}$ or $\dot{V}_E$, BTPS) of a combination of steady low P_{A,O_2} and high P_{A,CO_2} with the effects of the same (mean) $\bar{P}_{A,CO_2}$ and $\bar{P}_{A,O_2}$, but with the partial pressures of one or both gases oscillating about the mean in alternate breaths. We have worked in moderate hypoxia throughout because the respiratory effects of CO_2 are much greater in hypoxia (Nielsen & Smith, 1952; Cunningham, Patrick & Lloyd, 1964); indeed many individual units in the carotid glomi do not respond appreciably to CO_2 in pure O_2 (Neil & Joels, 1963); we have tried the effects of oscillations of P_{A,O_2} because in natural exercise they must be as great or greater than the CO_2 oscillations. We have also tried the effects of asphyxial oscillations (oscillations of P_{A,CO_2} and P_{A,O_2} simultaneously and in opposite directions, i.e. the higher CO_2 and the lower O_2 alternating with the lower CO_2 and the higher O_2), and of staggered asphyxial oscillations (P_{A,CO_2} and P_{A,O_2} oscillating simultaneously and in the same direction, i.e. the higher CO_2 and the higher O_2 alternating with the lower CO_2 and the lower O_2).

METHODS

The arrangement of the apparatus has been developed from that described by Cunningham, Cormack, O'Riordan, Jukes & Lloyd (1957).

Gas supplies. Any combination of O_2, N_2 and CO_2 could be supplied by either of two sets

of rotameters. The output of each was led through a separate humidifier to one of the two inlets of a zero-resistance reversing tap developed from the tap shown in Fig. 5 of Cunningham *et al.* (1957), and mounted firmly on a heavy stand behind the subject. It directed one gas mixture to the subject whilst allowing the other to escape to the atmosphere. Rotation of the proximal plate through 90° substituted the second mixture for the first. Its outlet led to the subject through 91 cm of 2·86 cm internal-diameter, nearly smooth-bore armoured tubing (capacity about 0·7 l.). This tap was later replaced by one with three plates of which the outer two, bearing the four inlets and four outlets, are fixed and are separated by a rotatable polytetrafluoroethylene centre plate. The centre plate is pierced so that only one pair of opposed channels is open at a time; rotation of the centre plate through 90° closes this pair of channels and opens the other pair.

The full flow from the reversing tap was carried to a T-piece within 15 cm of the inspiratory valve, and the surplus gas supply blew off down a long 2·86 cm diameter tube. With the usual total flow of 71 l./min a fresh mixture reached the T-piece almost exactly 1 sec after the tap was turned. Breath-by-breath oscillations in the inspired gas mixture were produced by an observer turning the reversing tap near the beginning of expiration, which could be judged by watching for the opening of the expiratory valve flap from behind the subject.

Respiratory valves. The subject breathed through a mouthpiece attached to Perspex valves which included the best features of the very low-resistance type 1 valve of Bannister & Cormack (1954) and the low-dead-space valve of Cunningham, Johnson & Lloyd (1956).

Ventilation. Pulmonary ventilation was measured by passing the expired gas straight through two 10 l. capacity low-resistance dry gas meters (Parkinson & Cowan Industrial Products, London, E.C. 1, type CD) connected in parallel: their resistance is much less than half the resistance of a single meter. They were kept in an incubator at 37° C to prevent condensation and to give measurements at BTPS. The spindles of the meters were rigidly coupled. $\dot{V}$ was usually measured over several 20 l. cycles. The coupling shaft drove a 360° potentiometer connected with a 1·5V source to a pen recorder, so that a single rotation of the potentiometer wiper showed as a double traverse of the pen, and individual expirations appeared as steps (Fig. 1).

Alveolar partial pressures of O_2 and CO_2. During steady states end-tidal gas was collected by the method of Brismar, Hesser & Matell (1962) with minor modifications (Cunningham, Lloyd & Patrick, 1963) and analysed rapidly for CO_2 by a Uras-M infra-red analyser (Hartmann & Braun, Frankfurt-am-Main) and in one experiment for O_2 with a paramagnetic oxygen analyser (Servomex Controls Ltd., Crowborough, Sussex); O_2 was obtained by volumetric analysis alone in the other experiments. The outputs of the analysers were displayed on a multi-channel hot-stylus recorder (Hellige & Co., Freiburg-im-Breisgau), the zero of the CO_2 record being offset to allow greater amplification. The analysers were calibrated with standard mixtures approximately every 10 min.

During each experimental period involving real or control oscillations of CO_2 breath-by-breath recording was performed in order to check that the timing of the tap turning was correct. Since this series was completed the response time of the paramagnetic oxygen analyser has been greatly shortened (*ca.* 0·4 sec for 90 % response, D. J. C. Cunningham & J. M. Young, unpublished) and the efficacy of the inspiratory O_2 oscillations in changing P_{A,O_2} has been demonstrated on another subject (Fig. 1). After a short period of breath-by-breath recording, end-tidal sampling was resumed and a slowly collected sample ($\sim$1 min) was stored for chemical analysis with the Lloyd–Haldane apparatus.

Subjects. The subjects were three healthy male undergraduate volunteers. Their physical characteristics are shown in Table 1. They were told nothing of the purpose of the experiments and when questioned afterwards they showed themselves quite unaware of the procedures and were aware only of moderate hyperpnoea; even heavily loaded questions at the end of the series of experiments failed to suggest to them that anything approaching oscilla-

tions of inspired gases had taken place, with one exception, to be mentioned later. The tracing shown in Fig. 1 was recorded on a young adult female subject on a separate occasion.

Procedure. The experiments were performed in the morning and the subject had been allowed only a cup of tea without sugar since the previous evening.

TABLE 1. Ages and body measurement of subjects

Subject	Age (yr)	Height (cm)	Weight (kg)
149	26	174	70
150	22	160	57
152	23	182	78·5

The subject sat comfortably in a dentist's chair and nearly all the apparatus was placed behind him, outside his field of vision. He was encouraged to read a book.

The steady-state $\dot{V}$, P_{A,CO_2}, P_{A,O_2} relation was outlined (cf. Fig. 7 of Cunningham, Patrick & Lloyd, 1964) either at the beginning or the end of each experiment. The subject was initially given a CO_2-in-air mixture (sufficient to give $\dot{V} \sim 40$–50 l./min) for about 20 min before any measurements were made, and all further mixtures or pairs of mixtures for the high-$\dot{V}$ points had about the same mean inspired CO_2 ($\bar{P}_{I,CO_2}$). In the experiment illustrated (Fig. 2) this procedure was less successful than usual in preventing drift in the response. Oscillation periods were then started, beginning with control oscillations between identical mixtures from the two sets of rotameters. Such control oscillations were interposed in such a way that no test period was separated from a control by more than one other test period. A typical sequence is shown in the legend to Fig. 2. A control or test oscillation period lasted 8–10 min, during the first 3–4 min of which breath-by-breath mouth P_{CO_2} was recorded and a suitable rhythm of tap turning found; for the last 4–7 min end-tidal gas was collected and its composition ($\bar{P}_{A,CO_2}$, $\bar{P}_{A,O_2}$) recorded. When there was doubt about the rhythm of tap turning, breath-by-breath recording settled the matter; however, the tap operator soon became very skilled.

At the end of two experiments something like the procedure of Riley *et al.* (1963) was tried: an oscillatory cycle consisted of three breaths of a CO_2-in-air mixture low in CO_2 (1·4 % CO_2) followed by a single breath of about 18 % CO_2 in air, the exact amount being adjusted to give the same P_{A,CO_2} as previously.

RESULTS

Alveolar gases during oscillations. Figure 1 shows a recording from near the mouth for both gases, recorded at slow, then fast paper speeds. The values for P_{CO_2} above 60 torr and below 20 torr are off the scale because the central part of the infra-red analyser trace has been expanded at the expense of the ends. The change in P_{A,CO_2} between the end of one alveolar plateau and the beginning of the next is 10–12 torr in this case. The corresponding difference for P_{A,O_2}, ~ 20 torr, is greater by a factor larger than the reciprocal of the respiratory quotient, probably because lung tissue has some CO_2-buffering capacity (Fenn, DuBois & Britt, 1951). For two complete cycles of oscillation of P_{CO_2} (four breaths) in the figure the probable fluctuations in P_{A,CO_2} over the respiratory cycle are indicated with interrupted lines, with the principles of DuBois *et al.* (1952) in mind. The fluctuations are perhaps 50 % greater than those obtained merely by

joining the ends of successive alveolar plateaux and the rate of change of P_{A,CO_2} during inspiration is probably ~ 14 torr/sec. The oscillations in P_{A,O_2} could be treated in the same way.

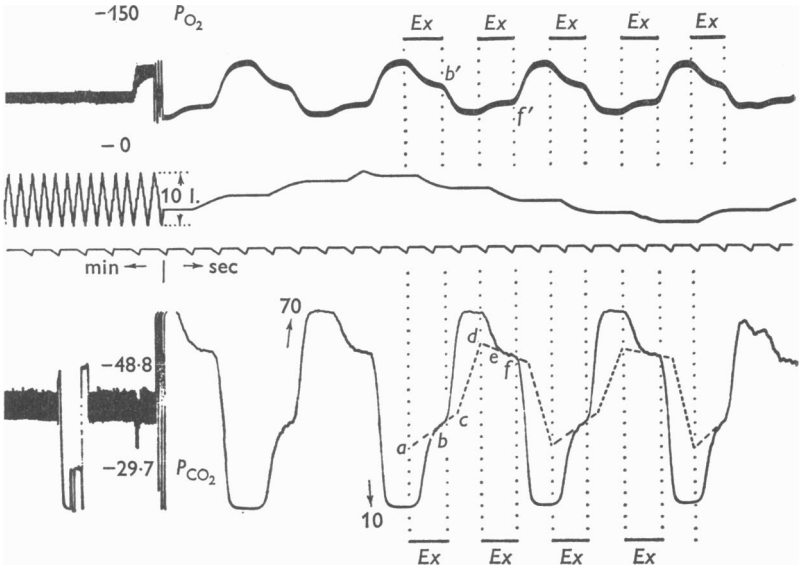

Fig. 1. Experimental record of asphyxial oscillation. From above records are P_{O_2} (torr), V_E (l., BTPS), time (min at extreme left, sec for remainder), and P_{CO_2} (torr). Bars labelled *Ex* denote expiration. Arrows indicate P_{I,CO_2} (torr)—off CO_2 scale. Oscillations start seven breaths before end of slow paper speed. Between successive end-tidal values ΔP_{CO_2} $(f-b) \doteqdot 12$ torr and ΔP_{O_2} $(f'-b') \doteqdot -20$ torr. Probable maximum ΔP_{CO_2} $(d-a) \doteqdot 19$ torr. Slope between adjacent alveolar plateaux (b to e) $\doteqdot 6$ torr CO_2/sec. Probable maximum rate of rise of CO_2 (c to d) $\doteqdot 14$ torr CO_2/sec.

There is no evidence that during the oscillations of inspired gas mixtures the subjects took more of one gas mixture than the other (see e.g. table in legend to Fig. 2) and so it seems that ventilation did not vary regularly between alternate breaths.

Effect of oscillating alveolar gas pressures on ventilation. For all four experiments $\dot{V}$ was plotted against $\bar{P}_{A,CO_2}$ and the most complete result is shown in Fig. 2. In this experiment some drift occurred, as shown by the movement upwards and to the left of successive control points (open circles). The plus and multiply signs outline the steady-state $\dot{V}$, P_{A,CO_2}, P_{A,O_2} relation, which is as commonly found. $\bar{P}_{A,O_2}$ lay between 59·1 and 63 torr for all oscillation and control points. B (the common intercept of the $\dot{V}$, P_{A,CO_2} isoxic lines on the P_{CO_2} axis; Lloyd & Cunningham, 1963) is joined to the uppermost control point to give the slopes of the lines

through all the control points, it being assumed that the drift was confined to a change of B; lines of this slope are interpolated between the control points on the assumption that the drift occurred at a uniform rate. These lines make possible the small corrections required for accurate comparisons

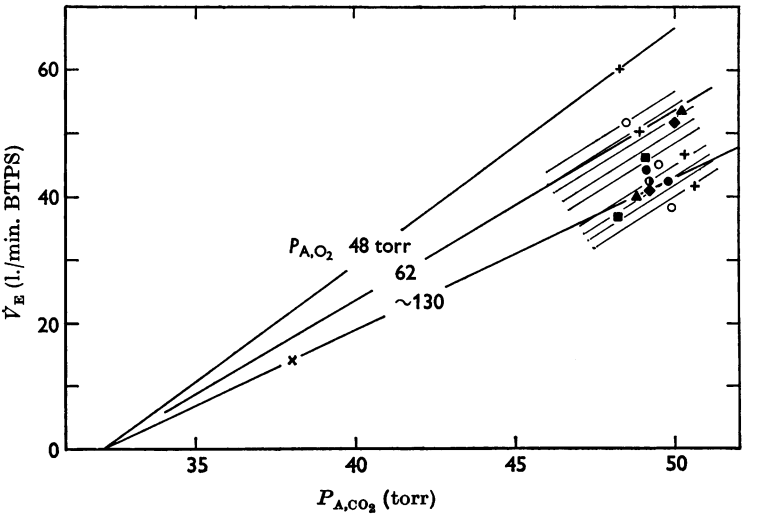

Fig. 2. Comparison between $\dot{V}_E$, P_{A,CO_2}, P_{A,O_2} relation with inspired and alveolar gas pressures steady (heavy lines +, ×) and with oscillating inspired and alveolar gas pressures. The faint parallel lines are interpolated between the three control oscillation points (○). Alveolar gas pressures plotted and appearing in the following explanatory table are mean values obtained by slow end-tidal sampling. ◑, Riley technique cycle consisted of one breath 18% CO_2 in air followed by three breaths of 1·4% CO_2 in air.

		Sequence of points	P_{I,CO_2} (torr)	P_{I,O_2} (torr)	$\bar{P}_{A,O_2}$ (torr)	$\bar{P}_{A,CO_2}$ (torr)	$\dot{V}_E$ (l./min)
○	Control oscillations	1	44 ⇌ 44	69 ⇌ 69	59·7	49·9	38·2
		6			61·9	49·5	45·0
		11			60·4	48·5	51·7
■	Asphyxial oscillations	2	14 ⇌ 69	100 ⇌ 39	61·7	48·2	36·7
		7	14 ⇌ 74		63·0	49·1	46·0
◆	Staggered asphyxial oscillations	3	14 ⇌ 69	39 ⇌ 100	59·7	49·2	41·0
		8	14 ⇌ 74		59·5	50·0	51·5
●	Hypoxia oscillations	4	44 ⇌ 44	39 ⇌ 100	60·0	49·8	42·2
		9			59·1	49·1	44·2
▲	CO_2 oscillations	5	14 ⇌ 69	69 ⇌ 69	62·5	48·8	40·0
		10	14 ⇌ 74		62·1	50·2	53·4
+	Steady states	12	44	71	61·9	48·9	50·2
×		13	44	57	48·4	48·3	60·2
		14	44	141	131·0	50·3	46·5
		15	15	162	136·4	38·0	14·0
		16	44	141	130·4	50·6	41·7
◑	Riley	17	10 ⇌ 127 ~	140	131·5	49·2	42·5

in respect of $\dot{V}$ between the oscillation and the steady points, though cursory inspection shows clearly that no great effect was produced by any of the varieties of oscillation.

Figure 3 makes a comparison for all experiments between ventilation during oscillations and the ventilation to be expected with the alveolar gases held steady at the mean partial pressures found. The oblique line expresses equality and the points are clustered around it.

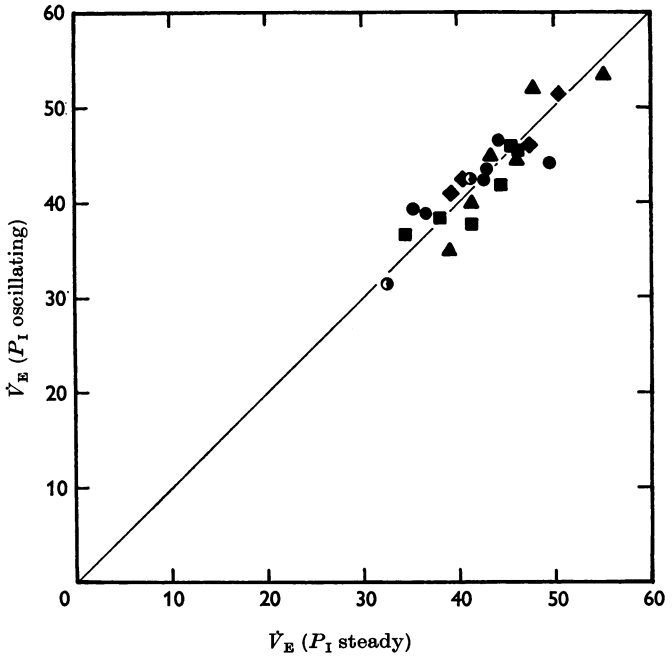

Fig. 3. Results of all experiments. $\dot{V}_E$ during alveolar P_{CO_2} and P_{O_2} oscillations plotted against control $\dot{V}_E$ (adjusted to the same $\bar{P}_{A,CO_2}$ as described in text). Line of equality shown. Symbols as in Fig. 2.

'Riley' oscillations. The result of one such determination appears in Fig. 2; it and one other appear in Fig. 3. In this case too oscillations are apparently without effect. Both subjects, however, complained, and one expressed violent dislike of some individual breaths which 'caught the back of the throat like ether' at regular intervals. None of the main subjects nor the female accessory subject spontaneously compared the taste with that of aerated (i.e. CO_2-containing) drinks. It seems impossible that a subject would be unaware of this procedure. Under our conditions subjects report an unpleasant sensation when isolated inspirations contain 12% CO_2 or more.

DISCUSSION

It is quite clear that our procedures have failed to reproduce the $\dot{V}$, P_{A,CO_2}, P_{A,O_2} relation found in normal exercise; indeed, we have no evidence that the oscillations we produced in alveolar gas pressures had any respiratory effect at all.

It remains for us to consider whether we succeeded in producing an oscillating signal in the vicinity of the receptors and if so how it differed from the proposed naturally occurring one.

The amplitude of the experimental oscillations in the pressures of both gases in the alveolar air was probably at least as great as that found in moderate exercise. The frequency was only half the respiratory frequency, but, because of the peculiar shape of the P_{A,CO_2} and P_{A,O_2} time curves indicated in Fig. 1, the maximum rates of change were probably of the same order as in moderate exercise.

Until recently there has been no certainty that oscillations in alveolar gas pressures penetrate even as far as the arterial blood under any circumstances, but Purves (1965), using a fast-responding oxygen electrode, has reported oscillations in carotid P_{a,O_2} with a respiratory rhythm in the anaesthetized resting cat and the new-born lamb. That the oscillations penetrate from carotid blood to the carotid chemoreceptors themselves is suggested by a plot of impulse frequency in Hering's nerve against time during moderate hypoxia in the anaesthetized cat which appears in a paper by Hornbein, Griffo & Roos (1961). If the small oscillations of P_{O_2} seen in alveolar air in resting human subjects penetrate to the receptors, as they probably do in the cat, the larger oscillations in both P_{O_2} and P_{CO_2} should penetrate also, whether they be our artificial ones or those occurring naturally in exercise.

There are important differences between the circulatory states of our subjects and those of exercising subjects; thus the increased circulation rate and probable reduction in the volume of residual blood in the left heart at the end of systole during exercise should reduce smudging of the signals in transit to the carotid chemoreceptors. Furthermore, if there is a substantial arterio-receptor P_{O_2} and P_{CO_2} difference (cf. Neil & Joels, 1963), the increased heart rate and pulse pressure of exercise might generate or increase P_{O_2} and P_{CO_2} oscillations with a cardiac frequency at the receptors, even with a steady arterial P_{O_2} and P_{CO_2}.

Enough has been said to indicate the uncertainties of applying our results too confidently to the problem of exercise hyperpnoea. Nevertheless, we should be surprised if we failed to induce substantial increases in the rates of change of P_{O_2} and P_{CO_2} in the receptors. While our procedures could not mimic exercise completely, the consistency with which we

obtained negative results argues against the Yamamoto hypothesis of the stimulating action of P_{CO_2} oscillations, and against any extension of the hypothesis to include P_{O_2} or asphyxial oscillations.

In a very recent paper Riley and his co-workers (Dutton *et al.* 1964) have reported that single breaths of 20% CO_2 + 21% O_2 + 59% N_2 interspersed between 6–11 breaths of air alter markedly the $\dot{V}$, $\bar{P}_{a,CO_2}$, relation in lightly anaesthetized dogs. That repeated 'slugs' of CO_2 in air at these intervals produce a nearly steady ventilation is not surprising (cf. the two-component response of Dejours's dogs, 1963), but the difference between the overall results of Dutton *et al.* and our own requires discussion. In the first place, although the conditions of experiment were very different in many respects, the rates of rise of P_{CO_2} were of the same order of magnitude. Secondly, our imposed oscillations occurred at a higher general level of ventilation and were much more frequent. Thirdly, we provided a substantial hypoxic background for multiplication by the changing P_{CO_2} in the peripheral chemoreceptors. Despite these similarities and differences, which in our opinion should favour a positive result in our experiments rather than in those of Dutton *et al.*, it is these workers who report that oscillations of P_{CO_2} are an effective stimulus to ventilation. We are surprised that they regard the results of Hornbein, Roos & Griffo (1961) as indicating the extra efficacy of a rising stimulus in promoting increases in ventilation. The differences between these transient responses and the unmeasurably small (i.e. within the probable S.E.) steady responses at the same P_{A,O_2} are quantitatively accountable for in terms of differences in P_{A,CO_2}, which, of course, falls in hyperventilation induced by agents other than CO_2 unless it is maintained by appropriate experimental procedures (cf. Haldane & Poulton, 1908; Cormack, Cunningham & Gee, 1957). The features of the experiments of Fitzgerald, Zajtchuk, Penman & Perkins (1964) quoted by Dutton *et al.* in support of their concept are certainly partially and possibly completely accounted for in the same way, namely by secondary changes in central CO_2.

Our results have a bearing on two other points of general interest. (1) If in our experiments P_{O_2} and P_{CO_2} oscillated as we think, a recording from the afferent nerves would be expected to show bursts of increased activity with alternate breaths. There was, however, no substantial difference between the volumes of alternate breaths and so it appears either that this particular pattern of phasic activity was not relayed through to the motor side or else that its peaks and troughs were always out of phase with the respiratory cycle. (2) Cormack *et al.* (1957), who held P_{A,CO_2} constant during and after the sudden application of a steady hypoxic stimulus, found that ventilation rose steadily to a plateau with no sign of overshoot; i.e. they saw no decline from the plateau such as occurs when

P_{A,CO_2} is allowed to fall as a consequence of the hyperpnoea. The experiments now reported confirm the earlier finding in that the hypoxia receptors do not respond more to a rising stimulus than to a steady one.

SUMMARY

1. We have examined the effect on pulmonary ventilation in three resting normal human subjects of induced breath-by-breath oscillations in P_{A,CO_2}, in P_{A,O_2} or in both simultaneously.

2. The experiments were done against a background of substantial hyperpnoea induced by hypercapnia and moderate hypoxia. Since ventilation was high, breath-by-breath alternation of inspired mixtures produced large and rapid changes of alveolar partial pressures. During the oscillations mean P_{A,CO_2} and P_{A,O_2} were determined by slow end-tidal sampling.

3. The ventilations observed during the oscillations of P_{A,CO_2} and P_{A,O_2} were compared with the $\dot{V}$ predicted for the observed mean P_{A,CO_2} and P_{A,O_2} from the measured steady-state $\dot{V}$, P_{A,CO_2}, P_{A,O_2} relation. No systematic differences were found.

4. The results are discussed in relation to current reports in the literature of the efficacy of oscillating signals in stimulating ventilation.

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