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EVIDENCE FOR INTERACTION BETWEEN THE CONTRIBUTIONS TO VENTILATION FROM THE CENTRAL AND PERIPHERAL CHEMORECEPTORS IN MAN

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SUMMARY

1. The question of whether there is any interaction between the peripheral and central chemoreceptor contributions to ventilation in man has been addressed.

2. Subjects were exposed to an end-tidal P_{CO_2} of *ca.* 10 Torr above resting for 8 min at an end-tidal P_{O_2} of 100 Torr. The end-tidal P_{CO_2} was then reduced to near eucapnia. This provided a period of time when the P_{CO_2} at the peripheral chemoreceptors would be near eucapnia, but would still be raised at the central chemoreceptors.

3. Against the background above, the effect of an hypoxic end-tidal step from a P_{O_2} of 100 Torr to a P_{O_2} of 50 Torr was studied, and compared with the effect of the same step when both sets of chemoreceptors were near eucapnia.

4. Three subjects were studied, each contributing twelve sets of data to each of the three protocols required for the comparisons.

5. In two of the three subjects, the ventilatory response to hypoxia was augmented when central P_{CO_2} was high.

6. The results support the idea that there is an interaction between the central and peripheral chemoreceptors in man. The consequences of this and other possible interpretations of the results are discussed.

INTRODUCTION

In man it is well known that hypoxia and hypercapnia in combination (asphyxia) stimulate ventilation to a greater degree than would be expected from their individual effects (Nielsen & Smith, 1952; Lloyd, Jukes & Cunningham, 1958). The question this finding raises is where does the interaction occur? In the cat it is clear that carbon dioxide and hypoxia interact at the peripheral chemoreceptor (Hornbein, Griffo & Roos, 1961; Lahiri & Delaney, 1975). Although less direct, the evidence in humans for interaction between CO_2 and hypoxia at the peripheral chemoreceptors is strong. Miller, Cunningham, Lloyd & Young (1974) examined the effect of withdrawing inspired CO_2 for two breaths under conditions of hyperoxic hypercapnia and hypoxic hypercapnia. The short-latency fall in expiratory ventilation ($\dot{V}_E$) attributable to reduced peripheral chemoreceptor activity was only observed under conditions of hypoxic hypercapnia. Thus the effect of withdrawing CO_2 on the short-

latency (peripheral chemoreceptor) response is clearly modulated by the degree of hypoxia.

The next question that arises is whether the peripheral chemoreceptor is the only site of interaction between CO_2 and hypoxia, or whether some interaction occurs between the central and peripheral chemoreceptors. The literature here becomes rather more complex and conflicting (Cunningham, Robbins & Wolff, 1986). There is some fairly compelling evidence in the anaesthetized cat that there is no interaction between the peripheral and central chemoreceptors. Van Beek, Berkenbosch, de Goede & Olievier (1983) used an artificial brain stem perfusion technique to vary the central and peripheral chemoreceptor environment separately. They found the ventilatory responses to varying the peripheral and central chemoreceptor stimulation were independent and additive, without any interaction. For humans the experimental evidence is scanty and anecdotal. The purpose of this study is to try and answer the question in humans – is there any interaction between the peripheral and central chemoreceptors?

The idea behind the current study is to use the differing speeds of response of the central and peripheral chemoreceptors to enable a temporal separation of their chemical stimulation. Essentially the subject is exposed to euoxic hypercapnia until a reasonable steady state develops. A step decrease in the end-tidal partial pressure of CO_2, P_{ET,CO_2}, to near eucapnia is then performed. After 30 s the P_{CO_2} at the peripheral chemoreceptor should be near eucapnia, and the discharge from the peripheral chemoreceptor should be nearly normal. The central chemoreceptor environment changes more slowly, however, and the P_{CO_2} at the central chemoreceptor should still be quite high. At this point in time a step decrease of the end-tidal oxygen tension, P_{ET,O_2}, is performed. The ventilatory effects of the hypoxic step may be obtained by subtracting from the ensuing ventilatory transient the effects of a control step of the decrease in P_{ET,CO_2} without the subsequent hypoxic step. This yields the ventilatory effects of hypoxia against a background of eucapnia at the peripheral chemoreceptors, but initial hypercapnia at the central chemoreceptors. The ventilatory effect of hypoxia against a constant background of eucapnia at both sets of receptors is obtained from a hypoxic step without any preceding period of hypercapnia. The two effects may then be compared. If the responses are the same, then central hypercapnia does not affect the hypoxic response and there is no interaction between the peripheral and central chemoreceptors. If the responses are different then there is an interaction between central hypercapnia and hypoxic stimulation, and consequently an interaction between the peripheral and central chemoreceptors. A preliminary report of these studies has appeared in abstract form (Robbins, 1988).

METHODS

Model studies

The problem of whether there is a component of the ventilatory response that depends on an interaction between the outputs of the peripheral and central chemoreceptors may be specified more formally as two competing models. The steady-state response characteristics of the additive model (no interaction) may be written as

$$\dot{V}_E = g_c i_c + g_p i_p, \tag{1}$$

where i_c and i_p are the outputs of the peripheral and central chemoreceptors and g_c and g_p their gain terms. The steady-state response characteristics of the multiplicative model may be written as

$$\dot{V}_E = g_c i_c + g_p i_p + g_m i_c i_p, \tag{2}$$

where g_m is the gain of the interactive term. The multiplicative model reduces to the additive model when $g_m = 0$.

The first question is can both models reproduce the steady-state ventilatory responses observed in man when hypercapnic and/or hypoxic? This question was reformulated to: can both models reproduce the ventilatory responses to hypercapnia and hypoxia as described by the Lloyd equation (Lloyd & Cunningham, 1963)

$$\dot{V}_E = D(P_{ET,CO_2} - B)(1 + A/(P_{ET,O_2} - C)), \quad (3)$$

where A, B, C and D are constants? Multiplying the equation out gives

$$\dot{V}_E = D(P_{ET,CO_2} - B) + DA(P_{ET,CO_2} - B)/(P_{ET,O_2} - C). \quad (4)$$

For the additive model an easy correspondence exists between its eqn (1) and the Lloyd equation (4). The left-hand term of eqn (4) may be ascribed to the central chemoreceptor ($g_c i_c$) and the right-hand term to the peripheral chemoreceptor ($g_p i_p$) (Miller *et al.* 1974).

For the multiplicative model there is no such easy correspondence between its eqn (2) and the Lloyd equation. Indeed, if the outputs of the peripheral and central chemoreceptors are linear with P_{CO_2}, then eqn (2) is incompatible with the Lloyd equation (Cunningham *et al.* 1986). However, if curvilinear outputs from the chemoreceptors with respect to P_{CO_2} are allowed, then a series of multiplicative models may be constructed. One of these was selected on the basis of having chemoreceptor outputs which looked relatively reasonable (see Results). These two models, one purely additive and one with a peripheral–central interactive term, give identical steady-state responses as summarized by the Lloyd equation.

The next problem was to extend these models to incorporate dynamic response characteristics. This was done by taking time constants and pure delays from the literature for the peripheral and central chemoreceptors as detailed by Robbins (1984). Simulations of several different experiments with the models were performed. This enabled an experimental protocol to be selected which should enable the two models to be distinguished.

Experimental study

Design of experiment. The study required three different experimental procedures, which are summarized in Fig. 1. The first involved a period of 8 min of hypercapnia at 10 Torr above resting P_{ET,CO_2}, with a P_{ET,O_2} of 100 Torr. A step change of the P_{ET,CO_2} to the resting value was then performed. This was followed after 30 s by a step change in P_{ET,O_2} from 100 to 50 Torr. This procedure was designated step type A. The other two procedures were controls. Step type B was similar to step type A, but without the hypoxic step. Step type C was a step from a P_{ET,O_2} of 100 Torr to a P_{ET,O_2} of 50 Torr but at a normal P_{ET,CO_2} without a preceding period of hypercapnia. By subtracting the ventilatory response to step type B from the ventilatory response to step type A, the effect on ventilation of the hypoxic step can be obtained. This hypoxic response can be compared with the ventilatory response to hypoxia obtained with step type C. If the response to hypoxia is unaffected by the relative hypercapnia at the central chemoreceptors (additive model), then the two responses should be the same. If the hypoxic response is affected by relative hypercapnia at the central chemoreceptors (multiplicative model), then the response to hypoxia in step type A should initially be greater than the response to step type C, only becoming the same when central eucapnia is restored.

Three different subjects were studied. The subjects were all healthy with no history of cardiovascular or respiratory disease. None of the subjects smoked, and none of the subjects was especially athletic. Their physical characteristics are detailed in Table 1.

Each subject was studied on a minimum of six different occasions. On each occasion three periods of breathing on the apparatus were planned, each lasting no more than 30 min, with at least 30 min separating each period. During the first period, one step type A protocol and one step type B protocol would be performed in random order. During the second period, two step type C protocols would be performed. For the third period a second step type A and step type B were performed in reverse order to that used during the first period. The final data collected were twelve steps of each type on each subject. Ethical permission for these studies had been obtained from the Oxford Regional Ethics Committee.

Apparatus. The general scheme for the apparatus is shown in Fig. 2. The subject is seated, and breathes through a mouthpiece whilst wearing a nose-clip. A turbine measuring device is used to

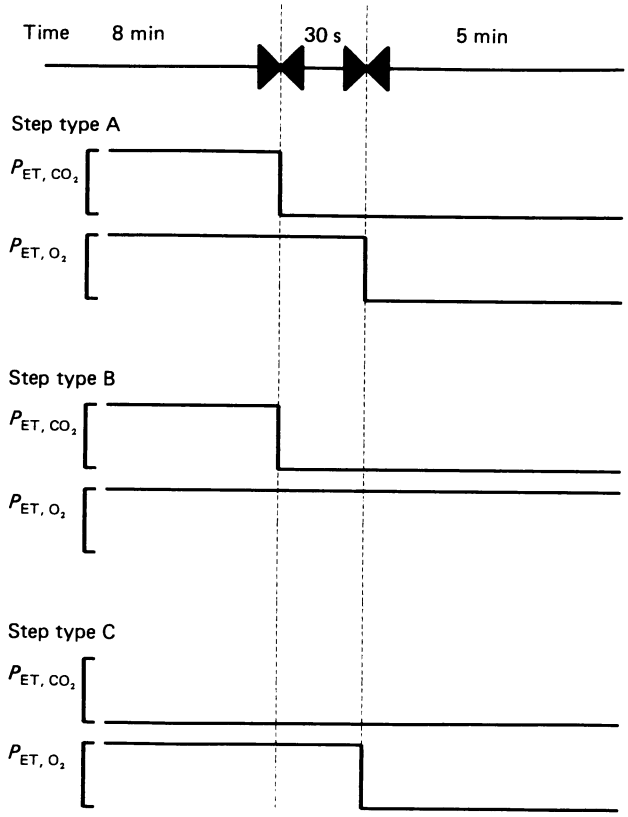

Fig. 1. Schematic diagram showing the changes in end-tidal P_{CO_2} and P_{O_2} imposed in each of the three experimental protocols employed.

TABLE 1. Physical characteristics of the subjects

Subject No.	Age (years)	Sex	Height (m)	Weight (kg)
711	35	M	1·73	83
713	20	M	1·84	67
714	19	F	1·60	64

sense respiratory volumes (Howson, Khamnei, O'Connor & Robbins, 1986) and a pneumotachograph senses respiratory flow and provides timing information. The gas composition at the mouth is measured continuously by mass spectrometry. Respiratory volumes, times and gas compositions are recorded digitally in real time by the data acquisition computer and displayed on a multichannel pen recorder. The inspired gas is mixed on a breath-to-breath basis using a fast gas-mixing system employing flow resistors which vary in resistance in a binary fashion and on/off solenoid valves. This has been described in more detail elsewhere (Howson, Khamnei, McIntyre, O'Connor & Robbins, 1987). Before the experiment starts, a respiratory model is run to predict the inspired gas compositions likely to generate the desired alveolar gas profile. The experiment is then started and these gas mixtures are generated by the fast gas-mixing system. During the experiment, each end-tidal value of P_{CO_2} and P_{O_2} is passed to the gas-mixing system computer from the data acquisition computer. The gas-mixing system computer can then modify the inspired gas mixture appropriately using an integral proportional controller to force the end-

tidal gases to follow the desired values. The scheme as it relates to an earlier version of the apparatus is described in more detail elsewhere (Robbins, Swanson & Howson, 1982).

Analysis of results. For each step type, a mean of the respiratory variables for the 2 min steady-state period prior to the first step was calculated along with means for each 30 s period following the step. The results so calculated could then be combined to yield an average response for each

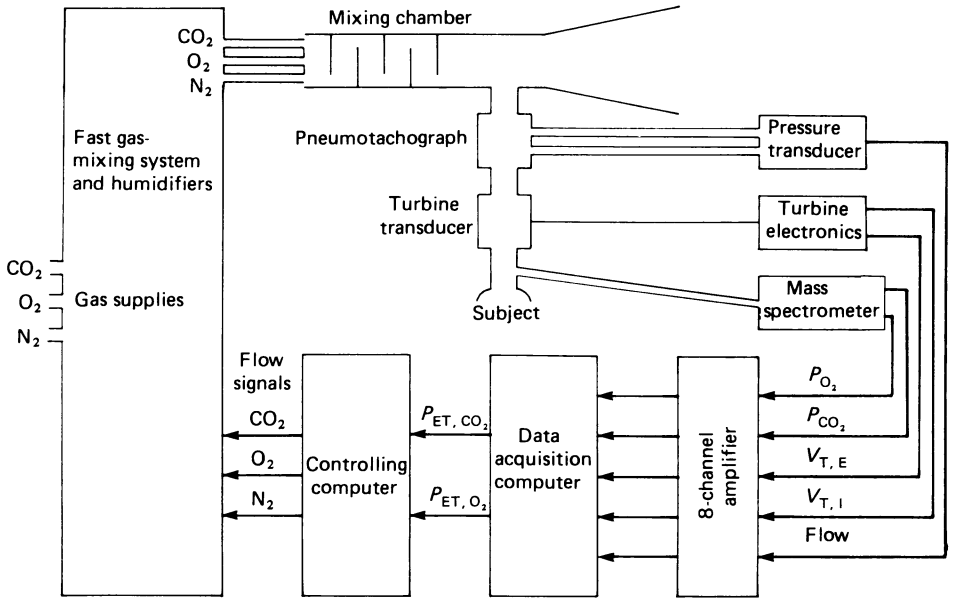

Fig. 2. General arrangement of apparatus. $V_{T,E}$, expiratory tidal volume; $V_{T,I}$, inspiratory tidal volume.

subject to each step type. Twelve individual responses contributed to each average response. The differences between the average responses for step type A and step type B were then calculated. The variances of the corresponding data points of step type A and step type B were assumed equal. This appeared generally true from the F ratio test. The variances of the differences between the corresponding data points therefore were calculated as the sum of the variances of the two data points with twenty-two degrees of freedom. The effect of hypoxia in step type C was assessed by subtracting each 30 s data point from the 2 min control point. The variance of the response was calculated as the sum of the variances of the two data points. However, in two of the three subjects (711 and 714), the variance of the 2 min control point appeared less than that of the subsequent 30 s data points (F ratio test). Consequently the degrees of freedom associated with the differences were calculated using a technique as described by Bailey (1981). The results of these calculations give the ventilatory response to hypoxia under the two sets of conditions. The two responses were compared with a single-tailed t test (variances not assumed equal). The null hypothesis was that the ventilatory response to hypoxia in step type A was the same as (or smaller) than the ventilatory response to hypoxia in step type C.

RESULTS

Model studies

The steady-state responses from the additive and multiplicative models are shown in Fig. 3. Both the additive and the multiplicative models shown produce exactly the same $\dot{V}_E$–P_{ET,CO_2}–P_{ET,O_2} responses as described by the Lloyd equation. At maximum stimulation, half the drive to breathe in the multiplicative model comes from the interactive term. One important point to note is that the CO_2 response curves from

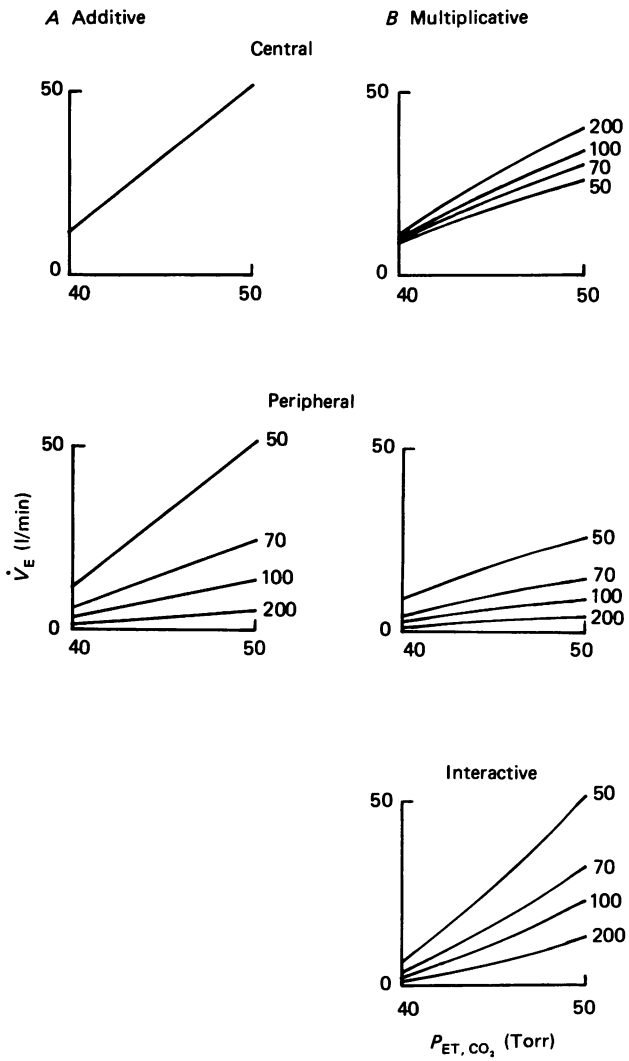

Fig. 3. Steady-state contributions to ventilation, $\dot{V}_E$, of the central and peripheral chemoreceptors for the additive model (*A*), and the central chemoreceptors, peripheral chemoreceptors and interactive term for the multiplicative model (*B*). P_{ET,O_2} values are shown as numbers to the right of the response curves. On adding the components, both models yield identical ventilatory responses to P_{ET,CO_2} and P_{ET,O_2}, as described by the Lloyd equation.

the receptors are linear for the additive model, but curvilinear with the convexity upwards for the multiplicative model. A second point is that the degree of interaction between CO_2 and O_2 is weaker at the peripheral chemoreceptor in the multiplicative model than in the additive model. The particular multiplicative model shown was generated by assuming the ratios of effectiveness of different levels of hypoxia at the peripheral chemoreceptor were constant at all P_{CO_2} values, and were in the same ratios as for total ventilation. This caused the central chemoreceptor to show some

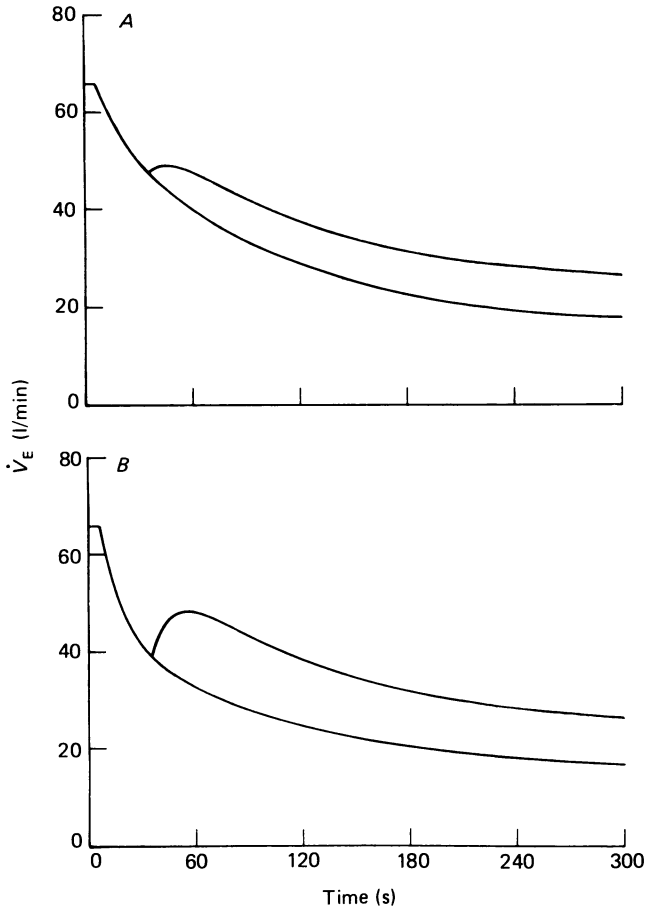

Fig. 4. Theoretical dynamic ventilatory responses, $\dot{V}_E$, of the additive model (*A*) and the multiplicative model (*B*) to a step decrease in P_{ET,CO_2} followed in 30 s by a step from a P_{ET,O_2} of 100 Torr to a P_{ET,O_2} of 50 Torr. The lower line in each case indicates the continuation of the ventilatory transient that would occur if the P_{ET,O_2} remained unchanged. Note the greater response to hypoxia during the transient from the multiplicative model.

hypoxic depression, and, rather less pleasingly, an interactive effect between the CO_2 and hypoxia centrally.

The two models were extended, by allocating time constants and pure delay terms to the peripheral and central chemoreceptors, in order to examine the dynamic behaviour of the two models. For these purposes the interaction between the peripheral and central chemoreceptor outputs was assumed to occur instantaneously, i.e. the dynamics of the interactive component depend only on the dynamics of the peripheral and central chemoreceptors. The response of the two models to the experimental stimuli used is shown in Fig. 4. It can be seen that, for the multiplicative model, the effect of hypoxia is greater during the CO_2 transient than in the ensuing steady state. This effect does not occur with the additive model.

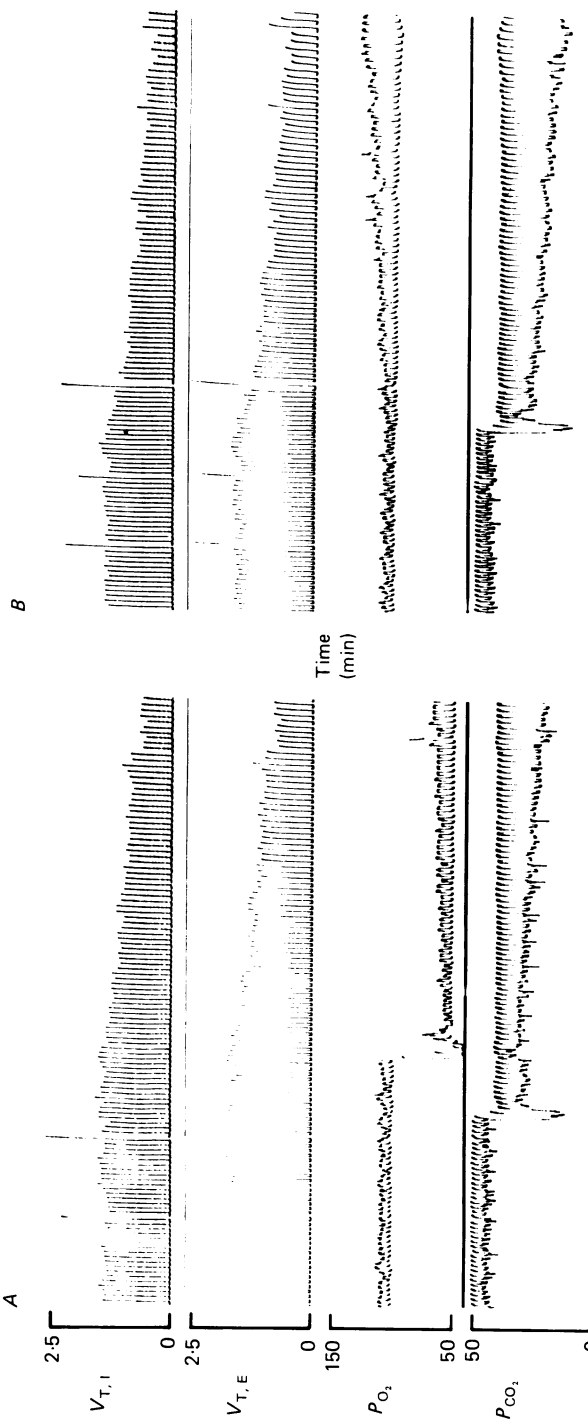

Fig. 5. Two sample experimental records. *A*, step type A protocol, and *B*, step type B protocol. From top to bottom the records are: inspiratory tidal volume, $V_{T,I}$ (l), expiratory tidal volume, $V_{T,E}$ (l), time marker (min), P_{O_2} at the mouth (Torr), and P_{CO_2} at the mouth (Torr).

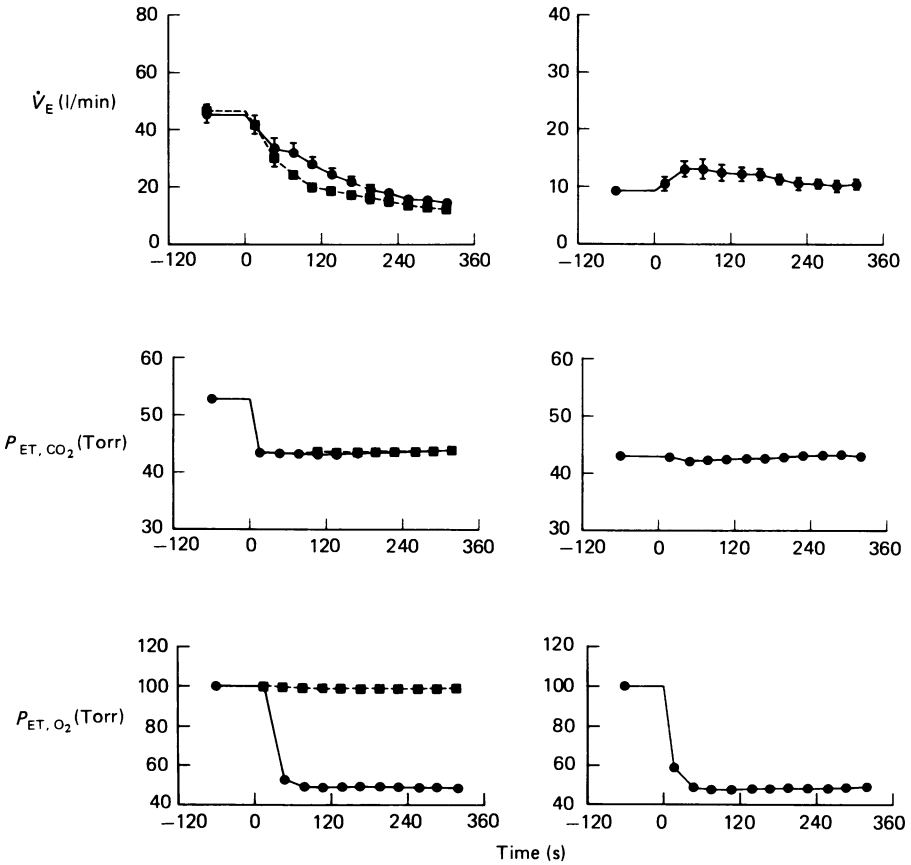

Fig. 6. Experimental results for subject 711. Top, ventilation (l/min); middle, end-tidal P_{CO_2} (Torr), and bottom, end-tidal P_{O_2} (Torr). Left, step type A protocol (●) and step type B protocols (■). Right, step type C protocol. Results are means for twelve steps of each step type. Error bars show 2 S.E.M. if errors exceed the size of the symbols.

Experimental study

Two experimental records are shown in Fig. 5. Two features to note are the way the control system turns the inspired CO_2 down and O_2 up as the ventilation falls in order to maintain the end-tidal gases constant, and the general high quality of control over the end-tidal gases that a computer-controlled system can obtain.

The results for the three subjects (711, 713 and 714) are shown in Figs 6, 7 and 8 respectively. The general quality of the end-tidal gas profiles is high. However, there is a slight hypocapnia at the onset of the hypoxic step in eucapnia in subjects 711 and 714. Furthermore the hypoxic step is not quite as square in the step type C protocols as in the step type A protocols.

In subjects 711 and 713, the pooled ventilatory responses to step types A and B show that hypoxia is clearly more effective during the transient than at the end of the step when approaching the steady state. For subject 714, however, this is much

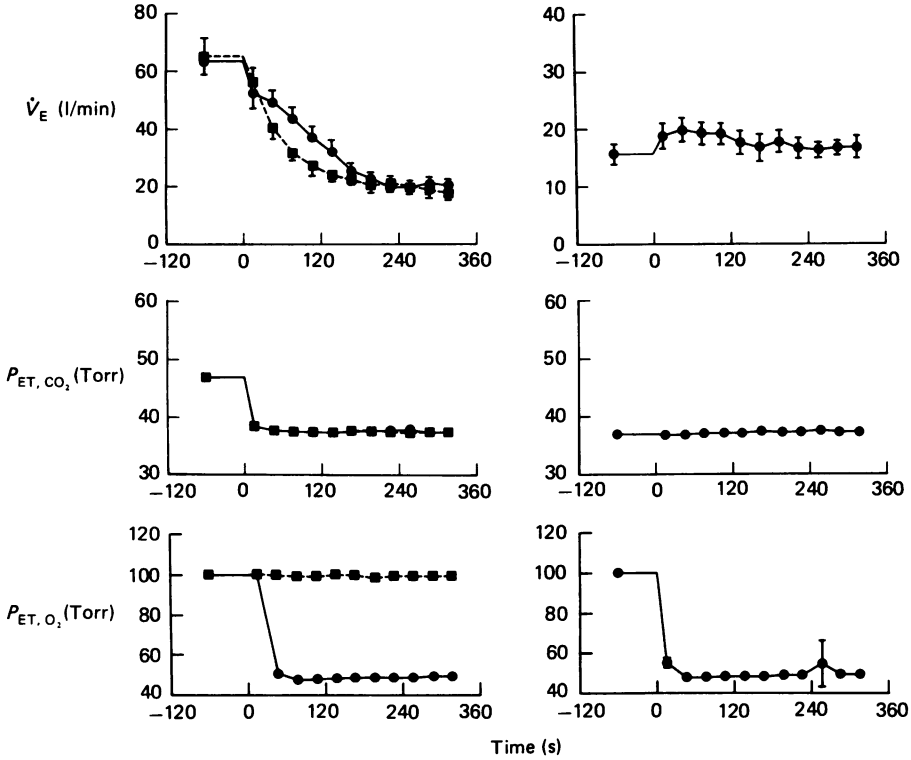

Fig. 7. Experimental results for subject 713. Rest of legend as for Fig. 6.

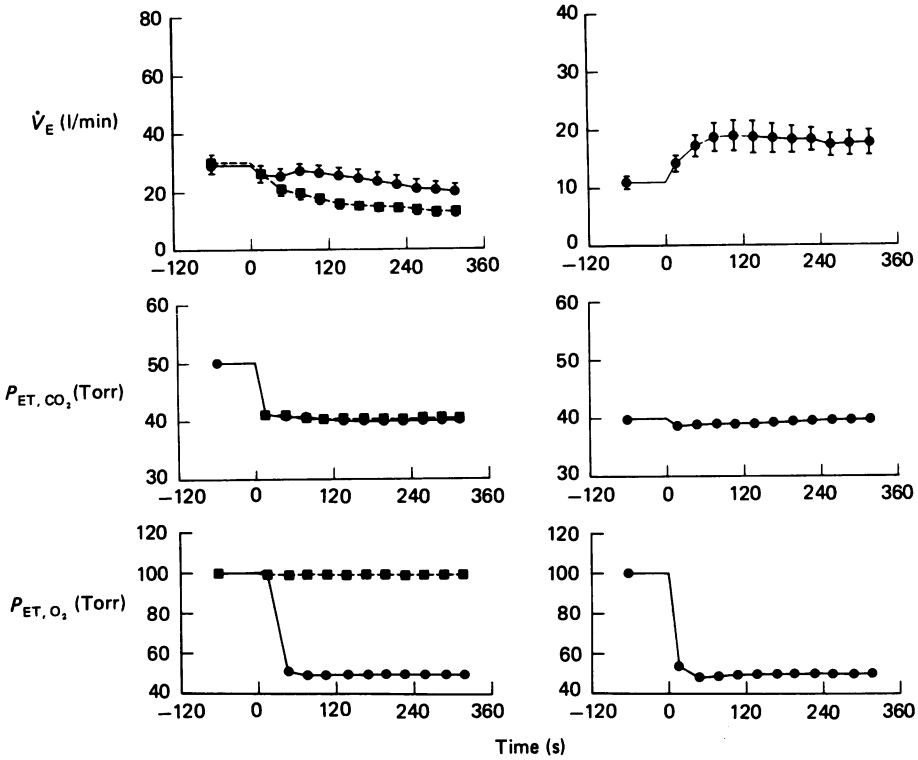

Fig. 8. Experimental results for subject 714. Rest of legend as tor Fig. 6.

less marked. The response to a hypoxic step in eucapnia (step type C) appears biphasic for all three subjects. To allow for this, the effect of hypoxia during the CO_2 transient was compared with the effect of hypoxia during eucapnia at corresponding times after the onset of hypoxia. This was done by subtracting the

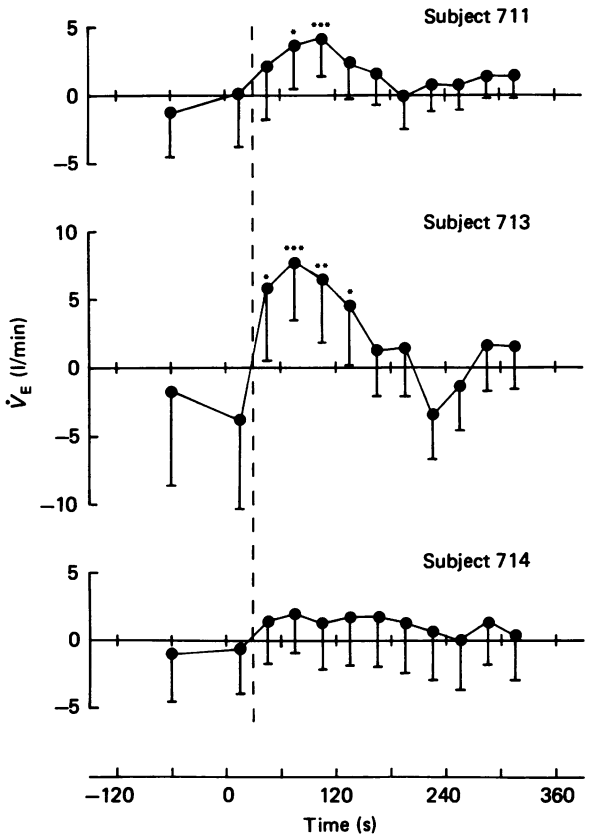

Fig. 9. Plots of the difference between the hypoxic response 30 s after a step decrease in P_{ET,CO_2} and the hypoxic response during steady-state eucapnic breathing. Top, subject 711; middle, subject 713, and bottom, subject 714. Error bars show 95% confidence interval. * $P < 0{\cdot}05$, ** $P < 0{\cdot}02$ and *** $P < 0{\cdot}01$.

latter from the former, and the results are shown in Fig. 9. For subjects 711 and 713 the effect of hypoxia is clearly still greater during the ventilation transient in step type A than in step type C. For subject 714, however, this was not the case.

DISCUSSION

The discussion of the results is divided into two parts. The first part deals with alternative interpretations of the findings, and the second with some of the predictions and consequences of central–peripheral chemoreceptor interaction in man.

Other interpretations

The possibility that the results could be explained by imperfections in the input stimuli needs to be considered. Noticeable imperfections were that the O_2 step was less square in step type C than in step type A and that there was a slight transient hypocapnia in subjects 711 and 714. The former imperfection was caused by the longer time taken to wash O_2 out of the lungs in step type C than in step type A; and the latter by the large increase in inspired CO_2 pressure P_{I,CO_2} required to hold P_{ET,CO_2} constant for even a modest increase in $\dot{V}_E$ when the initial $\dot{V}_E$ is low. Although both of the errors are in the direction required to explain the results, neither error seems of sufficient size to produce the effects observed.

An important alternative explanation for the greater effect of hypoxia during the CO_2 transient than in the ensuing steady state is that the response to a hypoxic step is, in itself, biphasic. This was controlled for by performing a step into hypoxia during steady-state eucapnia. The response to hypoxia did appear biphasic, and this may reasonably be explained by the phenomenon of central hypoxic depression (Easton, Slykerman & Anthonisen, 1986). However, the biphasic response was quantitatively insufficient to explain the enhanced hypoxic sensitivity during the CO_2 transient. Furthermore, for central hypoxic depression to explain the findings, it is necessary to propose that central hypoxic depression is in itself interactive with CO_2. This was not found to be the case in a study in anaesthetized cats (van Beek, Berkenbosch, de Goede & Olievier, 1984).

Another explanation of the results is that the CO_2 at the peripheral chemoreceptor was raised for the duration that the hypoxic sensitivity was augmented. For this explanation to be correct, however, the peripheral chemoreflex response to CO_2 steps would have to be much slower than that described directly in the cat (Black, McCloskey & Torrance, 1971) and indirectly in man (Swanson & Bellville, 1975; Bellville, Whipp, Kaufman, Swanson, Aqleh & Wiberg, 1979; Gardner, 1980).

A further alternative explanation of the results resides in the difference between the *in vivo* and *in vitro* blood dissociation curves (Michel, Lloyd & Cunningham, 1966). On inspiring CO_2 the bicarbonate in the arterial blood is raised along the *in vitro* blood dissociation curve. However, the bicarbonate then distributes itself across the extracellular fluid causing a slight metabolic acidosis of the blood. It is this effect that causes the difference between the *in vivo* and *in vitro* dissociation curves. If the CO_2 is now removed from the inspirate and the arterial P_{CO_2} returns to its initial value, the arterial blood will be slightly more acid than initially until the bicarbonate rediffuses into the blood. This could account for an augmentation of hypoxic sensitivity at the peripheral chemoreceptors. To deal with this possibility fully requires a study involving arterial samples of blood. It appears, however, that the onset of the effect is considerably faster than the offset (Michel *et al.* 1966) for reasons which are somewhat obscure. From these data the expectation is that the metabolic acidaemia would be maintained for the whole of the time period following the CO_2-off step. A consequence of this is that, if the metabolic acidaemia is significant, the hypoxic response should be augmented for the whole of the time period. This is not, however, what was actually observed.

One final alternative to consider is that the increased hypoxic sensitivity is related

to the increased CO_2 production. After a step down in alveolar P_{CO_2}, the CO_2 production at the lung goes up as the extra CO_2 stored in the tissues is eliminated. This causes an increase in the amplitude of the naturally occurring oscillations of P_{CO_2} in the arterial blood. The oscillations are sensed by the peripheral chemoreceptors, and it has been suggested that the magnitude of the oscillations provides a drive to breathe (Yamamoto, 1960; Robbins & Swanson, 1984). If this is the case, then it is certainly possible that hypoxia could augment the process. This would appear as an increased hypoxic sensitivity whilst the CO_2 oscillation amplitude is increased. Although this alternative is impossible to refute, it should be noted that the amplitude of oscillation in the discharge of the carotid sinus nerve in the cat is relatively independent of hypoxia (Band & Wolff, 1973; Goodman, Nail & Torrance, 1974) as indeed is the dynamic response to CO_2 of the carotid body generally when compared with the static responses.

Consequences of interaction

The independence of the peripheral and central chemoreceptor contributions to ventilation has been assumed in many studies, particularly those involving parameter estimation in humans (Swanson & Bellville, 1975; Bellville *et al.* 1979; Gardner, 1980; Ward & Bellville, 1983). If there is a significant interaction between the peripheral and central chemoreceptors, then the models used to describe the responses are, in structural terms, incorrect. However, to assess whether this is significant in modelling terms will require further experiment.

The studies listed above were concerned with modelling the human ventilatory response to step changes in P_{ET,CO_2} in one form or another. The interactive model has an interesting property in that it predicts the on and the off transients in ventilation to be asymmetric in response to step increases and decreases of P_{ET,CO_2}. Let us assume that the response of the peripheral and central chemoreceptors to a step change in P_{ET,CO_2} may be considered monoexponential. For a step increase of P_{ET,CO_2} the equations for their outputs may be written

$$i_c = a_c + k_c(1-\exp(-t/\tau_c)),$$

and

$$i_p = a_p + k_p(1-\exp(-t/\tau_p)),$$

where, for the central and peripheral chemoreceptors respectively, i_c and i_p are the outputs, k_c and k_p the gain terms, τ_c and τ_p the time constants, and a_c and a_p the steady-state discharge at the lower P_{ET,CO_2}. The interactive component may be written as the product of these two, which on multiplying out gives

$$a_c a_p + a_c k_p(1-\exp(-t/\tau_p)) + a_p k_c(1-\exp(-t/\tau_c)) + k_c k_p(1-\exp(-t/\tau_c))(1-\exp(-t/\tau_p)).$$

Multiplying out the last term gives, for that term

$$k_c k_p(1-\exp(-t/\tau_p)-\exp(-t/\tau_c)+\exp(-t/\tau_p)\exp(-t/\tau_c)).$$

Now if the peripheral chemoreceptor response is considerably faster than the central chemoreceptor response, i.e. $\tau_p \ll \tau_c$, the term involving both exponentials approxi-

mates to $\exp(-t/\tau_p)$ and the expression reduces to $k_c k_p(1-\exp(-t/\tau_c))$. The entire interactive component may now be written

$$a_c a_p + a_c k_p(1-\exp(-t/\tau_p)) + a_p k_c(1-\exp(-t/\tau_c)) + k_c k_p(1-\exp(-t/\tau_c)).$$

The important point to note is that the last term represents a slow exponential rise with a time constant τ_c.

For a step down of P_{ET,CO_2} the equations for the central and peripheral chemoreceptor outputs are

$$i_c = a_c + k_c \exp(-t/\tau_c),$$

and

$$i_p = a_p + k_p \exp(-t/\tau_p).$$

The product is

$$a_c a_p + a_c k_p \exp(-t/\tau_p) + a_p k_c \exp(-t/\tau_c) + k_c k_p \exp(-t/\tau_c)\exp(-t/\tau_p).$$

If $\tau_p \ll \tau_c$, then the term involving the product of the exponentials approximates to $k_c k_p \exp(-t/\tau_p)$. The entire interactive component may be written

$$a_c a_p + a_c k_p \exp(-t/\tau_p) + a_p k_c \exp(-t/\tau_c) + k_c k_p \exp(-t/\tau_p).$$

The last term represents a fast exponential decay with time constant τ_p.

Comparing the equations for the time course of the interactive component, the response may be seen to be symmetrical with the exception of the last term (of magnitude $k_c k_p$). This has central chemoreceptor kinetics when increasing and peripheral chemoreceptor kinetics when decreasing. This leads to the prediction that the apparent central chemoreceptor gain will be greater for a step increase in P_{ET,CO_2} than for a step decrease in P_{ET,CO_2}, and the apparent peripheral chemoreceptor gain will be greater for a step decrease in P_{ET,CO_2} than a step increase. Unfortunately, the gain terms in the literature have in general been estimated from the on and off transients combined and so it is impossible to test the prediction against the literature adequately.

However, a further prediction can be made from examining the expressions for the time course of the interactive component. The time course for both the on and the off transient contains a term with central chemoreceptor dynamics, but whose gain depends on the initial peripheral chemoreceptor discharge, a_p. Thus, if the respiratory control system shows interaction, the gain of the term with central chemoreceptor dynamics should increase with increasing hypoxia. Examining the data of Bellville *et al.* (1979) this is the case for six out of seven of their subjects. Furthermore, the authors found the central chemoreceptor gain of subjects who had undergone carotid body resection to be approximately half that of their normal subjects. The study of Ward & Bellville (1983), however, showed no significant reduction of the central chemoreceptor gain term with infusions of dopamine despite a significant reduction in peripheral chemoreceptor gain.

One of the features the model study revealed was a marked quantitative difference in the degree of interaction between CO_2 and O_2 at the peripheral chemoreceptor. In the multiplicative model, because there is interaction between central CO_2 and the peripheral input, less interaction between CO_2 and hypoxia is required at the level of the peripheral chemoreceptor itself. Extrapolating using the additive model, the prediction is that the peripheral chemoreceptor is silenced at a CO_2 pressure equal to

parameter value B in the Lloyd equation, typically around 37 Torr (Lloyd *et al.* 1958). Clearly this extrapolation is incorrect in man, since in many subjects it is possible to use hypoxia to drive the P_{ET,CO_2} to below 37 Torr. Consequently it is necessary to postulate that, in man, the relation between carotid sinus discharge and P_{CO_2} shows a dog-leg characteristic similar to that observed in the $\dot{V}_E$–P_{A,CO_2} relationship. No such behaviour is observed in the carotid sinus nerve discharge of the cat (Lahiri & Delaney, 1975). Furthermore the degree of interaction between O_2 and CO_2 at the carotid body of the cat is very much less than that observed in the ventilatory response to P_{CO_2} and P_{O_2} in intact man (Torrance, 1968). It is possible that a multiplicative model may help to integrate the responses of the peripheral chemoreceptor to CO_2 and O_2 in the cat with the overall ventilatory response to CO_2 and O_2 observed in man.

In conclusion, the results have shown hypoxic sensitivity near eucapnia is increased if a subject has been subjected to a period of hypercapnia prior to the test of hypoxic sensitivity. Although other explanations need to be considered, these results provide evidence for an interaction between the central and peripheral chemoreceptors in man.

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