Journal of Physiology (1988), **398**, *pp.* 423–440
With 9 text-figures
Printed in Great Britain

A DYNAMIC ANALYSIS OF THE VENTILATORY RESPONSE TO CARBON DIOXIDE INHALATION IN MAN

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(*Received 4 April 1986*)

SUMMARY

1. The dynamics of the ventilatory response to carbon dioxide inhalation were studied in ten healthy young men using four different inspired fractions of carbon dioxide (F_{I,CO_2}) in air (0·015, 0·030, 0·045 and 0·060) successively increasing and decreasing stepwise.

2. Seven such different progressions were performed for each subject and each of seven different durations of the steps (t) ranging between 0·1 (i.e. one ventilatory cycle) and 10 min ('steady-state' conditions). The overall duration of one test (T) was taken as the sum of the seven successive F_{I,CO_2} steps (t) plus one step, t, of air breathing. Thus, the values of T ranged between 0·8 (i.e. eight ventilatory cycles) and 80 min. Three subjects were tested twice.

3. We measured, as a function of T, the magnitude of the loops formed by the curves P_{A,CO_2}–$\dot{V}_E$ and the value of the highest ventilatory response ($\dot{V}_E$max) to each progression. For all ten subjects, both functions had two maxima, one for T values of 2·6 or 8·0 min and one for T values of 24 or 40 min, and one minimum at T equal to 12 min.

4. The same measurements were made on tidal volume–response curves (P_{A,CO_2}–V_T) and ventilatory frequency–response curves (P_{A,CO_2}–f) and yielded the same results except for the ventilatory frequency–response curves, for which we only found a statistically insignificant single maximum for T values of 24 or 40 min.

5. The locations of the maxima in loop magnitude and $\dot{V}_E$max were similar in duplicate tests in three subjects, whereas the quantitative values of these variables showed wide differences.

6. We compare our results with what is expected from the current linear dynamic model of ventilatory control submitted to the same forcing function: the first maximum in the loop magnitude is predicted by the model, but the second is not. The model shows no peak in the evolution of $\dot{V}_E$max.

7. We conclude that controlled system dynamics, which are the only ones included in dynamic models of ventilatory control, cannot by themselves account for our observations, and that one should take into consideration the dynamics of the controlling neuronal network.

INTRODUCTION

Ever since Gray's (1946) static model, the ventilatory control system has been extensively studied and modelled using the theory of linear control, which postulates a linear response curve in the steady state and smooth dynamics in the non-steady states. Mild non-linearities such as delays, thresholds or variable parameters have since been introduced in the dynamic models, but do not withdraw the basic assumption of a linear neural controller with no proper dynamics (Grodins, Gray, Schroeder, Noris & Jones, 1954).

Against this assumption, however, some authors have found the steady-state response curve to be non-linear, with a slope becoming steeper with increasing alveolar CO_2 pressure (P_{A,CO_2}) (Craig, 1958; Loeschcke & Gertz, 1958; Dejours, Puccinelli, Armand & Dicharry, 1965; Lefrançois, Gautier, Pasquis, Cevear, Hellot & Leroy, 1972; Smith, Jameson, Mitchell, Musch & Dempsey, 1984). Among them, Schaefer (1958) and Folgering, Bernards, Biesta & Smolders (1974) fitted an exponential function to their data while Kellogg, Pace, Archibald & Vaughan (1957) chose a hyperbolic function. Forster, Klein, Hamilton & Kampine (1982) distinguished between low CO_2 sensitivity below $P_{A,CO_2} = 42$ mmHg and higher sensitivity above this value.

Various dynamic stimuli have been used to test non-steady-state responses such as steps in inspired gas tension (Loeschcke, Katsaros, Albers & Michel, 1963; Lambertsen, Gelfand & Kemp, 1965) and in alveolar gas tension (Swanson & Bellville, 1975; Gardner, 1980), or sinusoidal variations of inspiratory (Thompson, 1962; Florentin, 1964; Stoll, 1969) and alveolar gas tension (Bellville, Fleischli & Defares, 1969; Guénard, Chambille & Loncle, 1973; Swanson & Bellville, 1975; Robbins, 1984) or pseudorandom testing (Sohrab & Yamashiro, 1980).

From these studies various parameters of gain, time constant and pure delay have been estimated using a simple mathematical model derived from the dynamic model of Grodins *et al.* (1954). With step stimuli and response averaging over several tests or subjects, the responses of the system seem to be in good agreement with model predictions. However, there have been discrepancies with the model when sinusoidal stimulations or pseudorandom testing have been used (Guénard *et al.* 1973; Sohrab & Yamashiro, 1980; Robbins, 1984).

Considering these discrepancies between experimental results along with theoretical studies concerning the dynamics of complex neuronal networks which predict major non-linearities (Thom, 1972; Wilson & Cowan, 1972; Feldman & Cowan, 1975; Bruter, 1976; Cleave, Levine, Fleming & Long, 1986), we decided to study individual ventilatory responses to dynamic stimulation by CO_2 over a wide temporal domain without any prior assumption as to the linearity of the system's behaviour.

We considered the influence of the rate of rise of the hypercapnic stimulus on the morphology of the curves of ventilatory response, a qualitative approach which gets around the problem of the well-known quantitative variability of the responses. When the direction of variation of a dynamic stimulus is reversed, the response curve forms a loop (Landmesser, Cobb, Peck & Converse, 1957; Bernards, Dejours & Lacaisse, 1966; Swanson, Carpenter, Snider & Bellville, 1971). These loops are

interesting to study because they can result from time constants, as well as from mild non-linearities originating in the controlled system such as delays or non-constant parameters (both of which have been included in the current model) or rather from major non-linearities originating from the controller.

We used a step-by-step stimulation allowing us to vary the duration of each step between 0·1 min (mean duration of one ventilatory cycle) and 10 min (quasi-static conditions). In this paper, we report the progression of the magnitude of these loops and of ventilatory response with the rate of change of the stimulus as compared with what is expected using a linear dynamic model.

METHODS

Apparatus

The experimental set-up is shown in Fig. 1. The subject was comfortably seated and listened to soft music with headphones. He breathed through a facial mask and a No. 3 Fleisch pneumotachometer (Gould, The Netherlands) both of which added a dead space of approximately 120 ml to the airways. The gas flow from which the subject breathed (1·5 s^{-1}) exceeded the instantaneous inspiratory flow of any subject during the tests in order to avoid rebreathing of the expired gas. Excess inspiratory and expired gases were ventilated to the exterior. This set-up minimized the mechanical load on the ventilatory system.

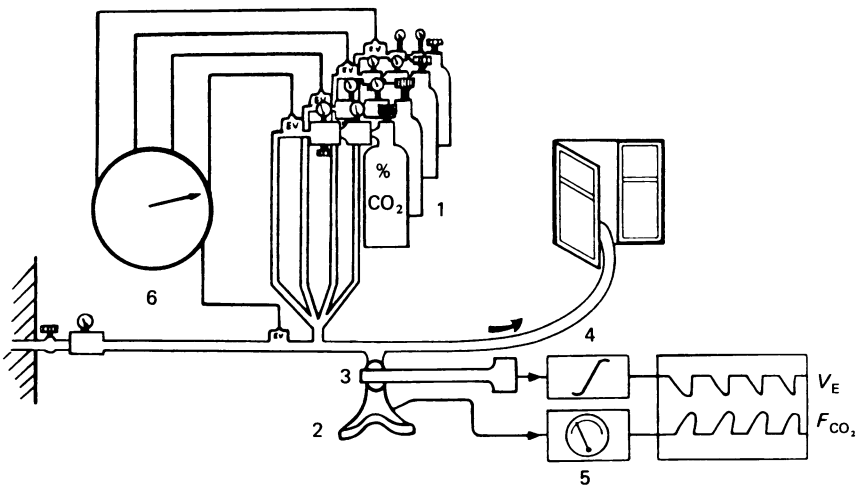


Fig. 1. Experimental set-up: (1) mixtures of CO_2 in air, (2) facial mask, (3) Fleisch pneumotachometer No. 3, (4) analog integrator, (5) fast CO_2 analyser and (6) electronic clock controlling solenoid valves (EV).

The stimulation was carried out by replacing the air flow by an equal flow of various inspired fractions of CO_2 (F_{I,CO_2}) in air. The sequence of stimulation was driven by an electronic clock which controlled the opening of solenoid valves.

A 200 ml min^{-1} flow of gas was sampled in the mask and sent to a fast CO_2 analyser (Beckman LB2, U.S.A.). Thus, the rise time of the gas analysing system was 230 ms, allowing an accurate measurement of end-tidal CO_2 partial pressures.

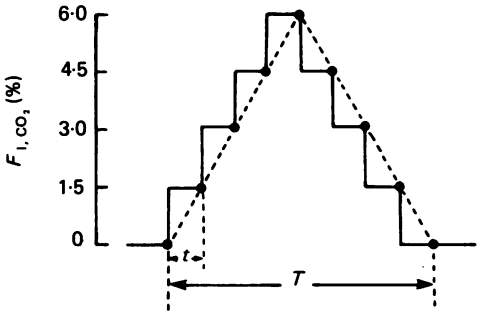
The instantaneous flow signal was given by the pneumotachometer coupled with a differential manometer (Schlumberger A1112, France) and a conditioning device (Auxiliaire CA 1065, Schlumberger, France) and then integrated to yield inspired and expired tidal volumes. The analog integrator was reset to zero between inspiration and expiration and a check for zero flow was periodically made during long tests by shunting the manometer in order to avoid any drift.

The volume measurement system was calibrated, before and after each test, directly in the BTPS conditions using a sinusoidal pump with 500 ml capacity and variable period. All volume and flow results are given in the BTP standard.

The electric signals from the analyser and the integrator were continuously recorded with a chart recorder (Siemens Oscillomink 8, F.R.G.).

Experimental design

The inspired fractions of carbon dioxide (F_{I,CO_2}) were respectively equal to 0·015, 0·030, 0·045 and 0·060. This last fraction is high enough to stimulate ventilation in all subjects without creating too much discomfort during long tests.



t (min)	T (min)	$\lvert dP_{I,CO_2}/dt \rvert$ (mmHg min^{-1})
0·1	0·8	114
0·3	2·6	35
1·0	8·0	11·4
1·5	12·0	7·6
3·0	24·0	3·8
5·0	40·0	2·3
10·0	80·0	1·14

Fig. 2. Experimental protocol with seven steps (t) of total duration T and the corresponding values of the rate of rise of the stimulus $|dP_{I,CO_2}/dt|$.

During each test we recorded 10 min of air breathing and then successively four steps up in F_{I,CO_2} and four steps down to air breathing again. The duration of each step (t) was varied for each of the seven different tests made with each subject. The values of t were: around 0·10 (i.e. one ventilatory cycle), 0·33, 1·00, 1·50, 3·00, 5·00 and 10·00 min. T was the total duration of the stimulation, equal to 8 t, and thus had the following values: around 0·80 (eight ventilatory cycles), 2·66, 8·00, 12·00, 24·00, 40·00 and 80·00 min. The rate of rise of the stimulus $|dP_{I,CO_2}/dt|$ was defined as the slope of the line joining the steps and had values between 114 and 1·14 mmHg min^{-1} (Fig. 2).

Data analysis

Calculation of the ventilatory parameters and of the P_{A,CO_2} was made from the recording chart with a digitizer connected to a microcomputer (Apple II, U.S.A.) in the following way: (i) on the unique cycle of each step t of 0·1 min, (ii) on the last two cycles of each step t of 0·3 min, (iii) on the last five cycles of each step t of 1 and 1·5 min, and (iv) on the last ten cycles of each step t of 3, 5, and 10 min. P_{A,CO_2}, in millimetres of mercury, was taken as P_{CO_2} at the end of expiration (P_{ET,CO_2}). The ventilatory response ($\dot{V}_E$) and stimulus (P_{A,CO_2}) values are given as: $\dot{V}_E/\dot{V}_{E,rest}$ and $P_{A,CO_2}/P_{A,CO_2,rest}$.

The magnitude of the loops was quantified in two ways: (1) By surface area measurement (S) using planimetry after closing the surface by linear interpolation between experimental points. Anticlockwise rotation gave positive areas, clockwise rotation gave negative areas and total area of the curve's surface was the algebraic sum of elementary areas when the limbs of the curve crossed. (2) By the largest difference (h) in ventilatory responses ($\dot{V}_E/\dot{V}_{E,rest}$) taken respectively on the upward and downward limbs of the curves for the same P_{A,CO_2}. Of these two parameters, the surface S is much less affected by the sudden variations in ventilation that can be observed in individual response curves during short tests and can lead to errors in the value of parameter h. On the other hand, S, but not h, is dependent on the length of the curve.

These parameters both show to what extent and in which sense the response of the system is influenced by what happened before. Their variation with the dynamics of the inputs in a multi-

compartment model shows maxima corresponding to the time constants of the compartments. Their value is null, both for very fast and very slow dynamics of stimulation.

The magnitude of the ventilatory response to each test was defined as the highest $\dot{V}_E/\dot{V}_{E,rest}$ reached during the test ($\dot{V}_E/\dot{V}_{E,rest}$max).

Statistical analysis

Comparisons of the results among tests for the ten subjects was performed using two-way variance analysis without replication and an F test using the remainder of the variance. This allowed elimination of the influence of inter-individual variability upon the effect of varying the stimulation period T. Multiple comparisons were made using the Student–Newman–Keuls (SNK) test (Zar, 1974).

Subjects

We studied ten healthy non-smoking male subjects aged 20–37. The tests were performed in the morning in a random order and with time intervals of at least 1 day to ensure that there would be no influence of the preceding test. The subjects were not informed about the purposes of the experiment but consented to the protocol. Three of these subjects had replicate tests.

Comparison with a dynamic model

The results are displayed together with those of the dynamic model of Bellville, Whip, Kaufman, Swanson, Aqleh & Wilberg (1979), taken as an example of current linear dynamic models. This model is modified from that of Grodins *et al.* (1954) by adding a compartment for the peripheral chemoreflex and dependence of the central chemoreflex time constant on the arterial P_{CO_2} level.

Results of this model were obtained using a computer simulation of the same protocol with the difference that the model's input was P_{A,CO_2} whereas we stimulated our subjects using manipulation of inspired CO_2 pressure (P_{I,CO_2}). Consequently, the steps in P_{A,CO_2} in our experiments are smooth compared to those of the model and the $|dP_I/dt|$ is slightly less during the shorter runs due to the dynamics of the P_{I,CO_2}–P_{A,CO_2} transfer (Robbins, Swanson & Howson, 1982). The P_{A,CO_2} values we chose as the model's inputs covered the range of P_{A,CO_2} observed in our experimentation, that is P_{A,CO_2} ranging from 40 to 60 mmHg in four steps with 5 mmHg increments.

As for model parameters, we chose the mean values found experimentally by Bellville *et al.* (1979) on seven normal subjects in normoxia. As the observed inter-individual differences were very large, we tried the extreme values of the parameters found in the literature but this did not change our results. The output has been modified in some Figures for a better fit with our mean results in order to show qualitative differences between the responses.

RESULTS

The experimental curves P_{A,CO_2}–$\dot{V}_E$ showed, as expected, an increased amplitude of ventilatory response when the dynamics of the stimulation became slower, but they displayed two maxima for ventilatory response and two maxima for loop magnitude as can be seen on Fig. 3*A* for one subject at t values of 1 and 5 min. At t equal to 1·5 min, there was a minimum for these parameters. This is more clearly shown in Fig. 3*C* displaying the relative variations of ventilatory response ($\dot{V}_E/\dot{V}_{E,rest}$max) and of loop magnitude (S and h) as a function of t for the same subject.

These singularities occurred for each of the ten subjects at t values of 0·3 or 1 min for the first maximum and of 3 or 5 min for the second. Their significance was statistically tested using individual values observed respectively at $t = 0{\cdot}1$ min, at $t = 0{\cdot}3$ or 1·0 min (i.e. first maximum), at $t = 1{\cdot}5$ min (i.e. minimum), at $t = 3{\cdot}0$ or 5·0 min (i.e. second maximum) and at $t = 10$ min.

Table 1 gives the results of the SNK multiple-comparison test performed after a two-way analysis of variance together with the mean results for each level of the stimulation duration.

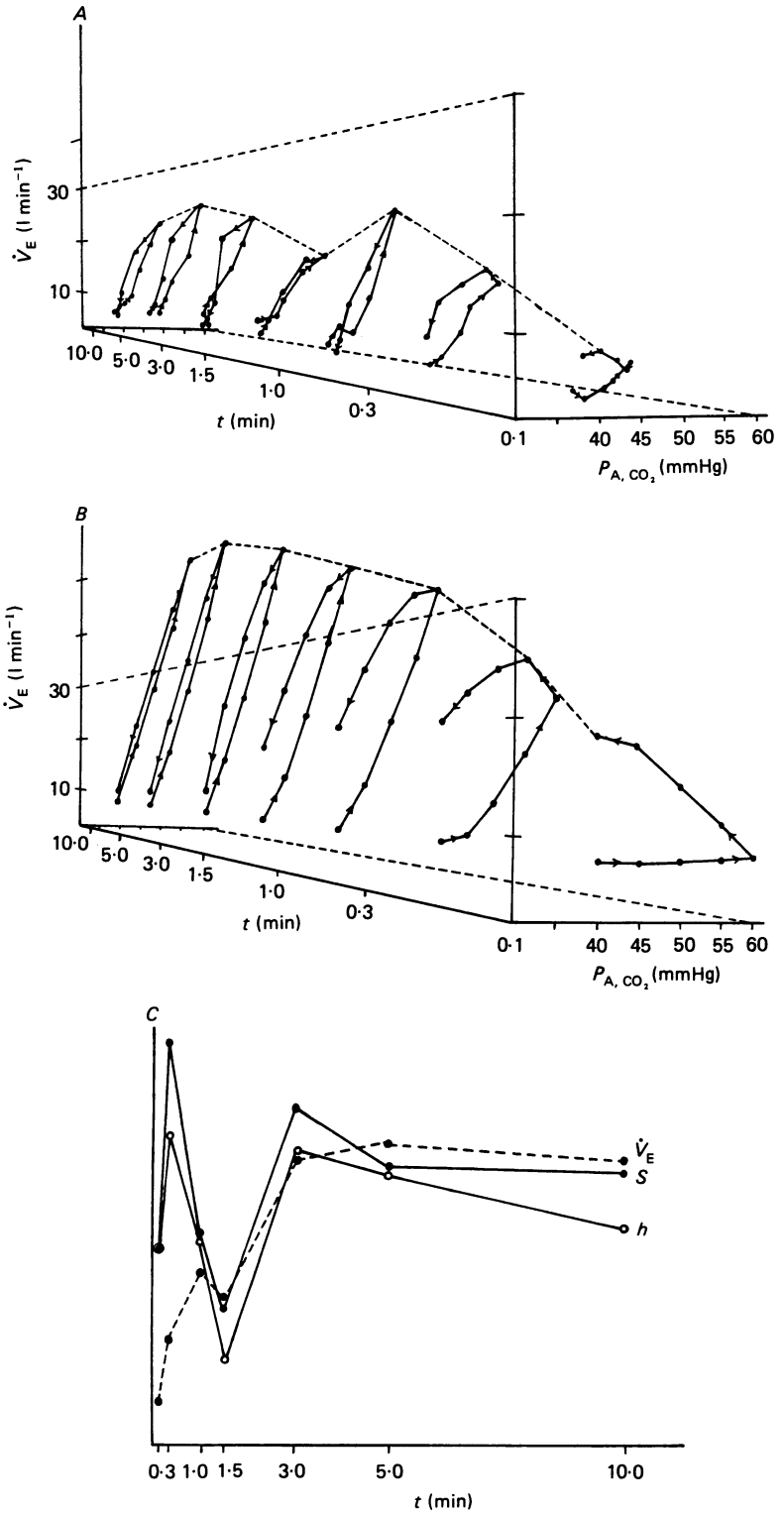


Fig. 3. For legend see opposite.

These results can be compared with the response curves produced by the model on Fig. 3*B* which shows: (i) A monotonic increase in ventilation which stabilizes at t around 5–10 min (i.e. near steady state). (ii) A variation in loop magnitude which increases until a maximum at t around 1 min and then decreases monotonously and disappears at t values over 10 min.

$\dot{V}_E/\dot{V}_{E,rest}$ max as a function of t

Figure 4 shows the progression with t of the highest ventilatory response reached during each test. It displays the average response of our ten subjects and standard deviations with superimposition of the results of the model in which the gain factors were so adjusted that its maximum output fitted our observations. The mean locations of the peaks – which are smoothed by the process of averaging – are 1 and 3 min on the t axis. None of these peaks is displayed by the model.

S and h as functions of t

Figure 5 shows that the mean variation in the magnitude of the loops as measured by $S(\dot{V}_E/\dot{V}_{E,rest})$ (Fig. 5*A*) and $h(\dot{V}_E/\dot{V}_{E,rest})$ (Fig. 5*b*) with increasing t for our ten subjects together with the results of the Bellville model with adjusted gains. The latter shows one maximum of S and h for a stimulation period T between 0·8 and 8 min related to the peripheral and central chemoreflex dynamics (time constant of the central chemoreflex between 1·3 min and over 6 min with a mean value of 3 min in the Bellville *et al.* study of 1979).

On the other hand, our subjects showed two maxima, at mean t values of 1 and 3 min. Here the first maximum is correctly predicted by the model, but the second is not.

Tidal volume (V_T) and ventilatory frequency (f)

The relative influences of V_T and f upon the progression of $\dot{V}_E$max, S and h were also studied. Frequency (f) mostly contributes to the second maximum in $\dot{V}_E$max, the first one being due only to the variations in V_T (Fig. 6*A* and *B*). This is coherent with many observations indicating that when total ventilation rises, f starts to increase only after a certain amount of V_T increase.

Figures 7 and 8 show the progression with t of parameters S (Fig. 7) and h (Fig. 8) of the loops in the V_T and f response curves. The first maximum involves only V_T and the second maximum involves both components of total ventilatory

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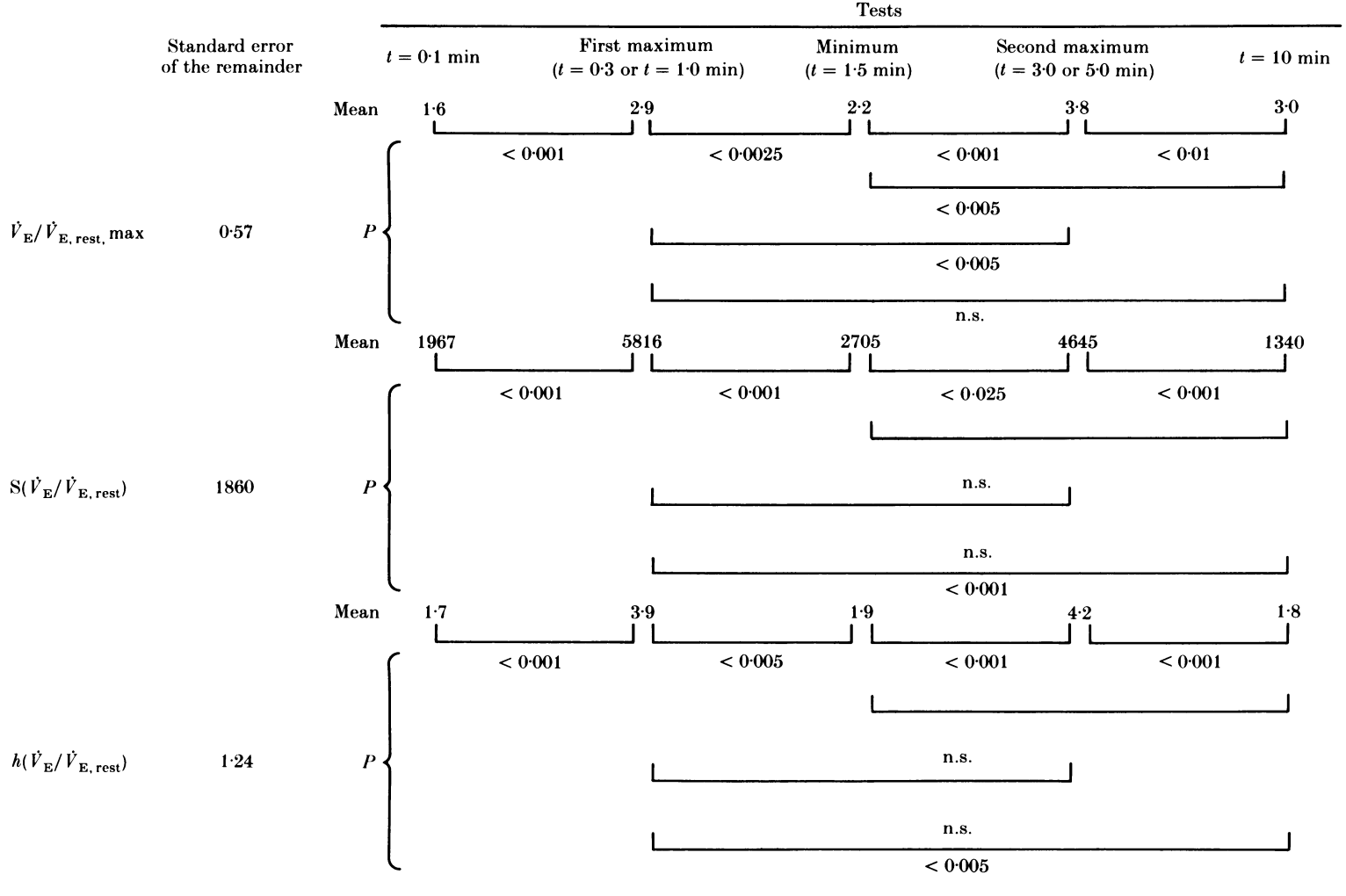
Fig. 3. *A* shows the results of the stimulation cycles for one subject in the space $P_{A,CO_2} \times \dot{V}_E \times t$. For convenience the curves are equally spaced on the t scale. The highest ventilatory responses to each test are linked by a dashed line. *B* shows the results of the Bellville *et al.* (1979) model with P_{A,CO_2} inputs of 45, 50, 55 and 60 mmHg. The experimental curves show a minimum of loop surface area and ventilatory response between two maxima; the model displays only one maximum in loop magnitude and its ventilatory response progressively rises towards a steady-state level reached for step durations of around 10 min. *C* shows, for the same subject as *A*, the variations with t of the loop magnitude as measured by $S(\dot{V}_E/\dot{V}_{E,rest})$ (●; continuous line) and $h(\dot{V}_E/\dot{V}_{E,rest})$ (○: continuous line), both in arbitrary units, and of the maximum relative ventilatory response $\dot{V}_E/\dot{V}_{E,rest}$max (dashed line).

TABLE 1. This Table gives, for each chosen parameter of the ventilatory response curves, the standard error of the remainder yielded by two-way variance analysis, the mean of the values for the stimulation durations defining the peaks and the significance levels for different pairwise comparisons made with the Student–Newman–Keuls test



n.s., not significant.

response. Statistical analysis was performed as described before and a high significance level was reached ($P < 0{\cdot}005$) for both peaks in V_T curves but the existence of the broad peak in f curves was not statistically established ($P > 0{\cdot}05$).

Reproducibility

Duplicate tests were made on three subjects, showing wide variations in ventilatory response for a given P_{A,CO_2} or in loop magnitude for a given t, but the

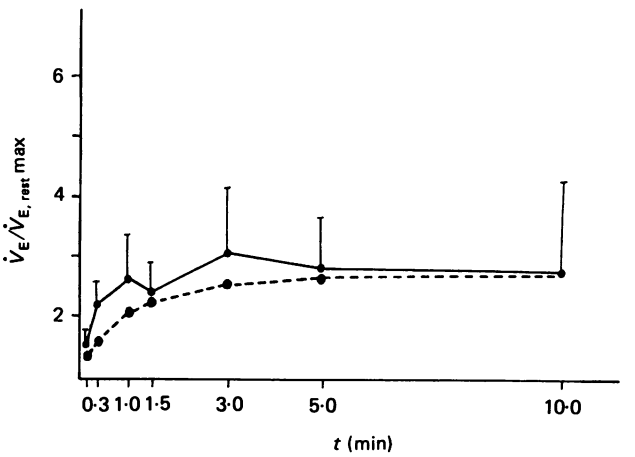


Fig. 4. Variations with t of the highest ventilatory response ($\dot{V}_E/\dot{V}_{E,rest}$ max) for the ten subjects (mean results with S.D.). The Bellville *et al.* (1979) model output (dashed line) was adjusted in such a way that its maximum was made equal to our experimental result (at 10 min) for an easier comparison.

locations of the maxima of ventilation and loop magnitude were found to be the same on the t axis. Figure 9 shows an example of these findings for one subject for whom the quantitative variations from one test to the other were particularly dramatic.

Regarding our results, we must point out that there is necessary imprecision in the location of the extremes since only a few chosen T periods were tested, and this imprecision is greater for the longer periods.

DISCUSSION

The variations in the ventilatory response curves observed in dynamic studies of the ventilatory control system using CO_2 stimulation have up to now been explained by the existence of circulatory delays and diffusion times of CO_2 towards the chemoreceptors, i.e. by the dynamics of the controlled system. However, they could just as well reflect the dynamics of the central neural controller, which is what the present study sought to bring out.

With a stimulus of triangular morphology and of increasing overall duration T, we made a qualitative study of the curves P_{A,CO_2}–$\dot{V}_E$ produced by ten healthy male subjects. We looked at the variations with increasing T of the magnitude of the

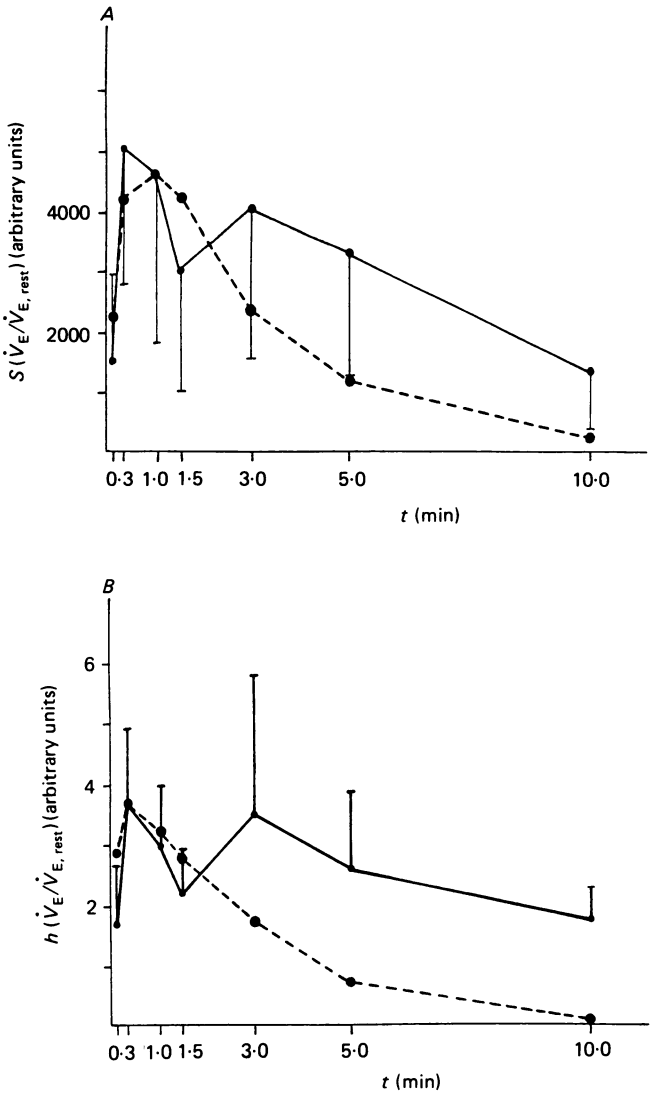


Fig. 5. *A*, variations with t of the surface area of the loops (S) in the curves $\dot{V}_E/\dot{V}_{E.rest} = f(P_{A,CO_2}/P_{A,CO_2,rest})$. *B*, variations with t of the maximum difference (h) in $\dot{V}_E/\dot{V}_{E,rest}$ between the downward limb and the upward limb of each loop $\dot{V}_E/\dot{V}_{E,rest} = f(P_{A,CO_2}/P_{A,CO_2,rest})$ for the same P_{A,CO_2}. Mean and S.D. for the ten subjects. S and h in arbitrary units. The model output (dashed line) was so adjusted that its maximum was made equal to our experimental result (at $t = 1{\cdot}0$ min for S and $t = 0{\cdot}3$ min for h).

ventilatory response to each test and of the loops formed by the curves. We found that these variables went through two maxima, one for T values of 2·6 or 8 min and the second for T values of 24 or 40 min. These results seem fairly stable as compared to the usual great inter- and intra-subject variability of the quantitative responses to this type of study if we consider that: (i) all ten subjects under study showed these two maxima, (ii) these maxima were not smoothed out by the process of averaging

and (iii) duplicate tests on three subjects showed the same maxima at the same location on the T axis.

Furthermore, we found that the first maximum was almost totally dependent on the variations in tidal volume (V_T) whereas ventilatory frequency (f) contributed, but insignificantly, only to the second maximum.

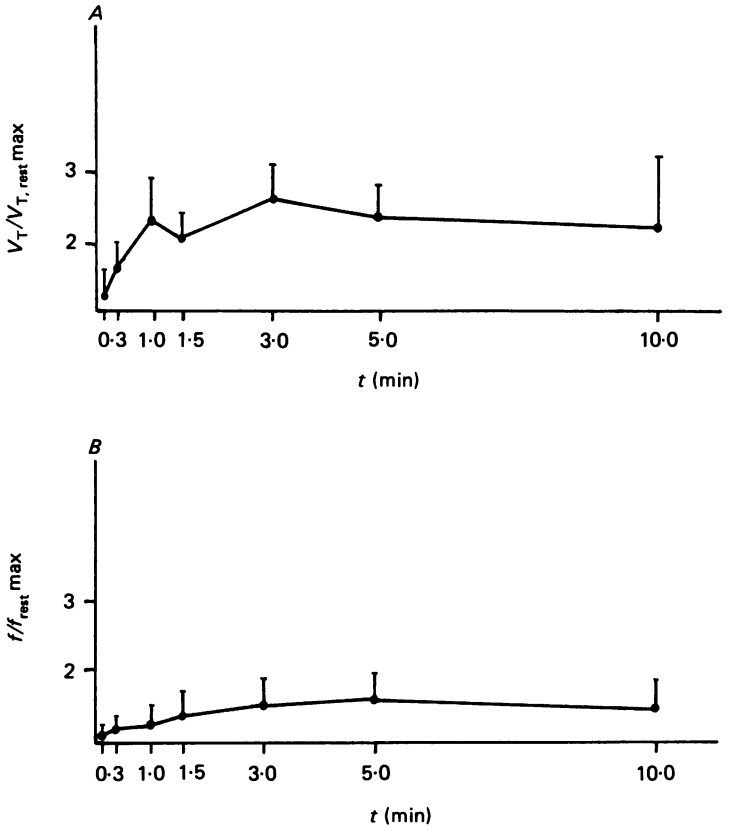


Fig. 6. Variations with t of the highest tidal volume ($V_T/V_{T,rest}$ max) (A) and respiratory frequency (f/f_{rest} max) (B) reached during each test (mean and S.D. of the ten subjects).

Magnitude of the loops in the stimulus–response curves

In classical dynamic analysis of the ventilatory control system, most authors have used models comprising two parallel subsystems (central and peripheral chemoreflexes) derived from the hydraulic and electric analog model of Grodins *et al.* (1954), with, in most cases, first-order dynamics and two time constants.

Using this approach, the existence of a loop in the stimulus–response curve $\dot{V}_E = f(P_{A,CO_2})$ can be the result of: (1) Pure delays represented by the circulation time between lungs and chemoreceptors. (2) Damping caused by the different mechanisms involved in the interreaction of the system with the stimulus: (a) chemical reactions, (b) transduction of the chemical stimulus into nervous discharges in the chemo-

receptors, (c) diffusion time of the CO_2 into interstitial bulbar fluid, and (d) integration of the stimuli and generation of the ventilatory drive by the bulbar centres and spinal motor nuclei. Among these, only the dynamics of the CO_2 stores have been considered to be slow enough to play a role in the generation of the loops in the response curves to dynamic stimulations.

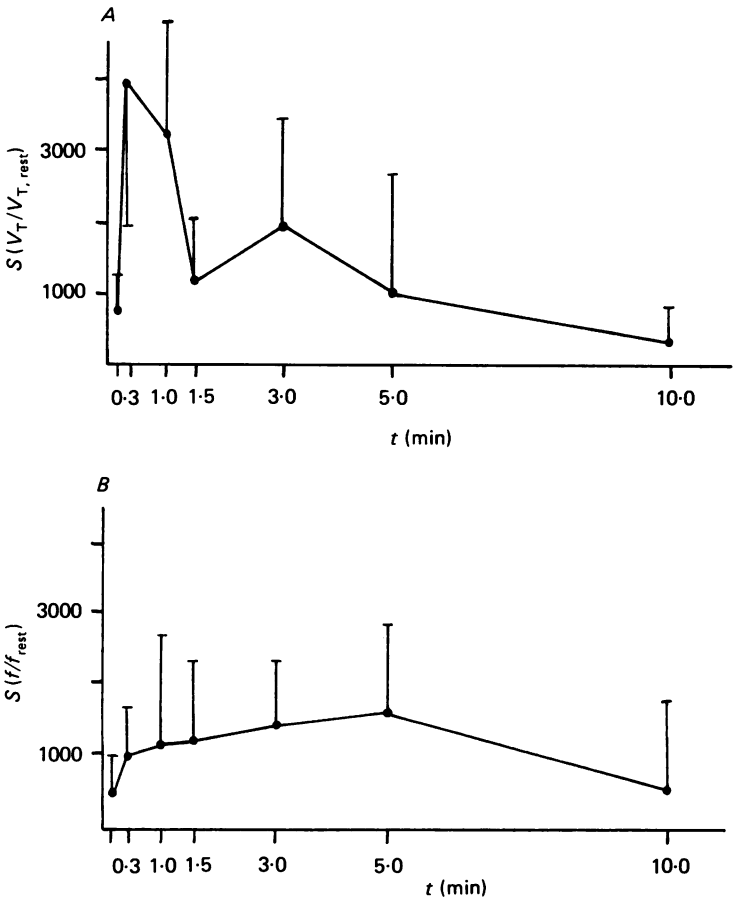


Fig. 7. Variations with t of the surface areas $S(V_T/V_{T,rest})$ (A) and $S(f/f_{rest})$ (B) of the loops formed by the curves $V_T/V_{T,rest} = f(P_{A,CO_2}/P_{A,CO_2,rest})$ and $(f/f_{rest}) = f(P_{A,CO_2}/P_{A,CO_2,rest})$ (mean of the ten subjects and S.D.).

Now, the circulation times to the peripheral chemoreceptors have been estimated at 4–13 s (Dejours, 1962; Edelman, Epstein, Lahiri & Cherniack, 1973; Gelfand & Lambertsen, 1973; Miller, Cunningham, Lloyd & Young, 1974; Milhorn, 1976; Bellville *et al.* 1979; Sohrab & Yamashiro, 1980) and at 10 to 20 s for the circulation to the central chemoreceptors (Bargeton, Barrès, Gauge & Durand 1961; Gelfand & Lambertsen, 1973; Miller *et al.* 1974; Swanson & Bellville, 1975; Bellville *et al.* 1979).

The values of the time constants have generally been estimated from recordings of averaged ventilatory responses to step stimulations by CO_2. A review of the

literature finds values between 3 and 26 s for the peripheral chemoreflex time constant (Gelfand & Lambertsen, 1973; Swanson & Bellville, 1975; Bellville *et al.* 1979; Gardner, 1980) and between 84 and 276 s for that of the central chemoreflex (Lambertsen *et al.* 1965; Swanson & Bellville, 1975; Bellville *et al.* 1979; Gardner, 1980).

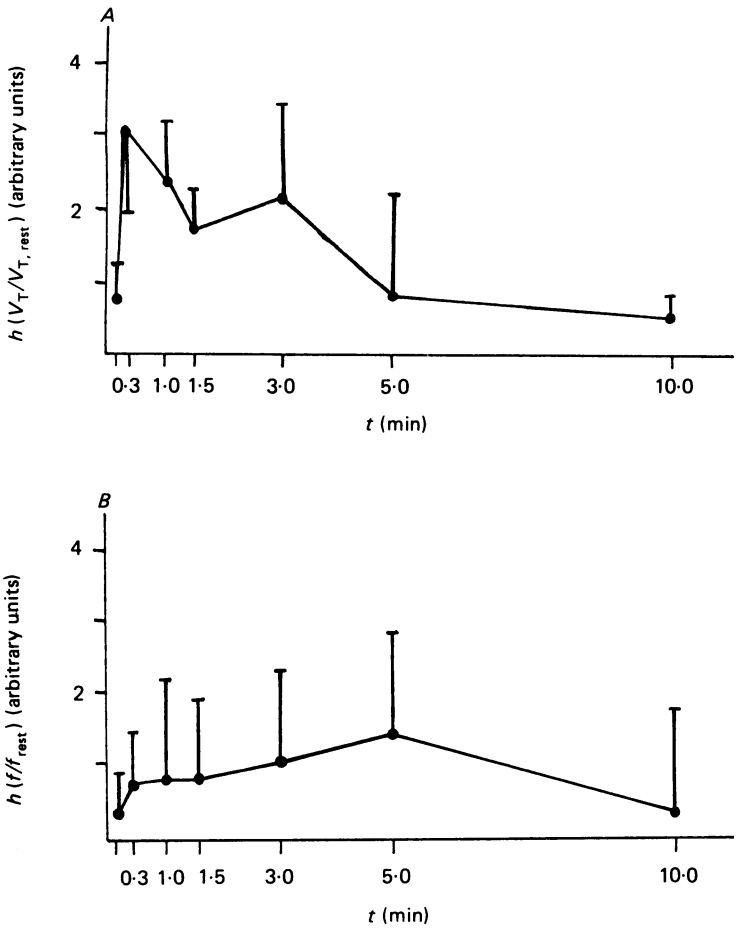


Fig. 8. Variations with t of the maximum difference between the downward and upward limbs $h(V_T/V_{T,rest})$ (A) and $h(f/f_{rest})$ (B) of the loops formed by the curves $V_T/V_{T,rest} = f(P_{A,CO_2}/P_{A,CO_2,rest})$ and $f/f_{rest} = f(P_{A,CO_2}/P_{A,CO_2,rest})$ (mean of the ten subjects and S.D.).

With the forcing functions we used in our experiments, such a linear model would produce a first maximum of surface S or height h of the loops for a T equal to the time constant of the peripheral chemoreflex system (maximum phase shift). Considering the values found in the literature, this maximum should thus be observed at T around 0·8 min, that is, for the fastest possible rate of rise of the stimulus in a model with alternate ventilation. Another maximum, corresponding to the central chemoreflex system, should be observed at T around 2·6 or 8 min. These maxima are

too close to be separated either in the experimental results or the model's responses (Fig. 5*A* and *B*).

In our study, the first observed maximum in loop magnitude involves the damping of the stimulus in both the central and peripheral chemoreflex systems but the

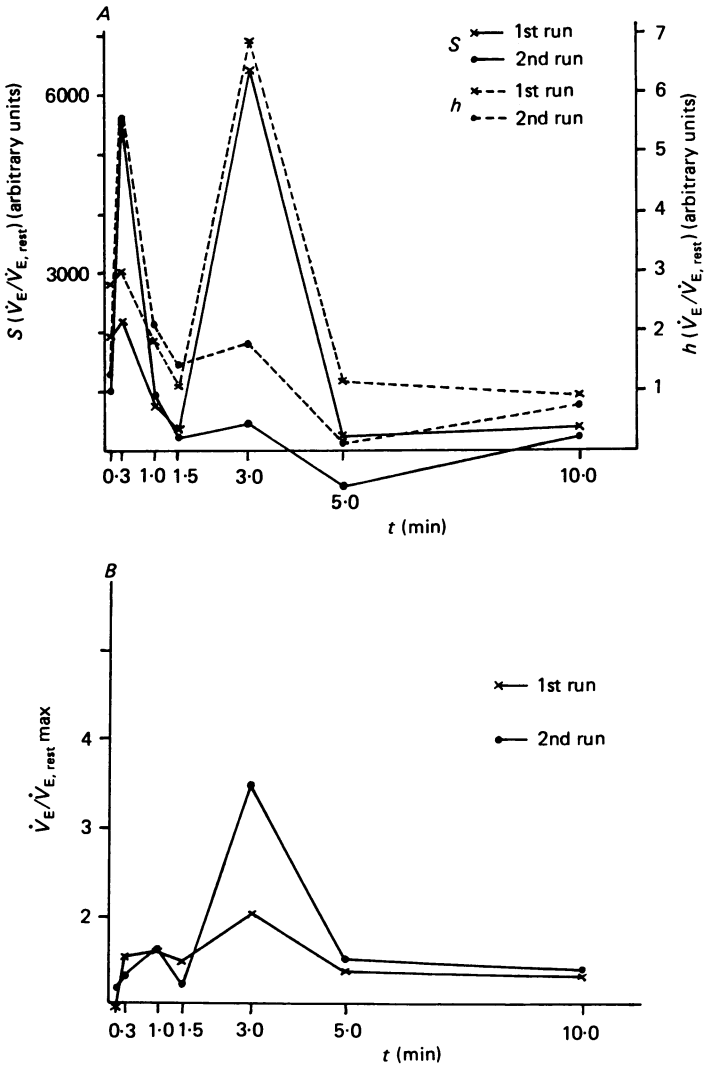


Fig. 9. Variations with t of S and h (A) and of $\dot{V}_E/\dot{V}_{E,rest}$ max (B) for the same subject for each of two series of tests. This subject shows particularly large differences in the values of the variables between the two series but the locations of the maxima are stable.

second maximum at T between 12 and 40 min remains totally unexplained by such a model unless we postulate the existence of a third and larger compartment with another chemoreceptor or a damping mechanism with a time constant larger than 12 min.

For instance, the hypothetical central venous CO_2 receptors and the very large

body tissue compartment could play this role, the time constant of this tissue compartment being of the order of 40 min (Cherniack & Longobardo, 1970).

Magnitude of ventilatory response

The classical model predicts a smooth rise in ventilatory response as a function of T. The response should stabilize for very slow dynamics of stimulation (steady-state conditions). Now, our subjects show two maxima of response at T values of 2·6 and 8·0 min for the first and 24 and 40 min for the second with a minimum of response for T equal to 12 min (Fig. 4).

There is no way to obtain such responses from a linear dynamic model by changing the parameters or adding another compartment. Furthermore, in our study the maxima of ventilation are found at the same locations on the T-axis as the maxima of loop magnitude whereas in a linear system the response would be maximum at minimum phase shift.

The existence of these peaks could be explained if the sensitivity of the central respiratory controller was rate dependent (differential sensitivity) with two preferential dynamics for the stimulus. This rate dependence cannot be caused by the differential sensitivity observed in the carotid chemoreceptors because the latter is observed for much faster dynamics of stimulation (Dutton, Hodson, Davies & Fenner, 1967). It must then be inherent in the neural controller dynamics which are not included in the classical model.

Experimentally, at least one specific observation of dynamics proper to the neuronal network has been reported in the ventilatory control centres' response, i.e. the central neural after-discharge, first observed by Gesell, Lapides & Levin (1940) and further studied by Eldridge, Gill-Kumar & Millhorn (1981): after a stimulation of the carotid sinus nerve has ceased, the central neural activity, taken as the discharge of the phrenic nerve, slowly decreases during some 5 min in decerebrate cats (Eldridge, 1976). This phenomenon can be related to the observation, on the downward limbs of some of our ventilatory response curves, of an otherwise unexplained persistence of increase in hyperventilation after the stimulus had been decreased. Such phenomena are memory effects in the ponto-medullar neuronal network.

On theoretical grounds (Thom, 1972), we propose, as a cause of both maxima of loop magnitude and maxima of ventilatory responses, a phenomenon of global excitation of the bulbo-pontine centres, caused by certain dynamics of stimulation, which leads to a higher ventilatory response to the same P_{A,CO_2} (resonance effect due to differential sensitivity of the centres). A lag in excitation and relaxation of the neural system would explain the concomitant maximum in loop magnitude and the persistence of the hyperventilation after the stimulus has been decreased.

This would also explain the relatively linear response curve obtained with the Read rebreathing test (Read, 1967) where the rate of rise of P_{CO_2} is of the same order as that which gives minima of loop magnitude and of ventilatory response in our study.

If such a global excitation could also be triggered by a threshold value of P_{A,CO_2}, the resulting sudden increase in gain of the controller would explain the observed non-linearity of the response curve in the steady state.

In summary, using a triangular dynamic stimulation by CO_2 over a long time range in ten subjects, we observed some important discrepancies with the current dynamic model of the ventilatory control system: (1) With short periods (T) of stimulation, the progression with T of the morphology of the stimulus response loops followed what was predicted by the model. This was not the case with the magnitude of the ventilatory response, which instead went through a maximum at a mean T of 8 min in each of our subjects. (2) With longer periods of stimulation, we observed a trough in the magnitude of the loops and in the ventilatory response at T equal to 12 min and a second peak in these variables for a mean T of 24 min. These results were not predicted by the model. Our hypothesis is that these discrepancies are caused by the dynamics of the controller's neural network.

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