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THE INFLUENCE OF OXYGEN ON THE VENTILATORY RESPONSE TO CARBON DIOXIDE IN MAN

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SUMMARY

1. The ventilatory response to isoxic square-wave challenges in end-tidal P_{CO_2} was investigated at three levels of end-tidal P_{O_2} (P_{ET,O_2}) in nine healthy male subjects.

2. Twenty-seven responses against a background of mild hypoxia ($P_{ET,O_2} \approx$ 10 kPa), sixty-seven against a background of normoxia ($P_{ET,O_2} \approx 14{\cdot}5$ kPa) and seventy-six against a background of hyperoxia ($P_{ET,O_2} \approx 70$ kPa) were collected.

3. The breath-to-breath data were partitioned into a fast and a slow ventilatory component using a two-compartment model.

4. In the normoxic and hypoxic experiments the CO_2 sensitivity of the fast component averaged to about 30 and 40% of the total CO_2 sensitivity, respectively. In the hyperoxic experiments three subjects had no fast component in their response while in three others the CO_2 sensitivity of the fast component averaged to about 24% of the total CO_2 sensitivity. In the remaining three subjects the presence of a fast component was doubtful.

5. We argue that the fast component is due to the peripheral chemoreflex loop and the slow component to the central chemoreflex loop.

6. The central CO_2 sensitivity and the apnoeic threshold (extrapolated end-tidal CO_2 at zero ventilation in the steady state) were 15% smaller in hyperoxia than those in normoxia and hypoxia. In normoxia and mild hypoxia the central CO_2 sensitivities were not significantly different.

7. We argue, that apart from peripheral oxygen–carbon dioxide interaction, there is evidence for central oxygen–carbon dioxide interaction in human subjects.

8. We conclude that in general there is a contribution to ventilation of the peripheral chemoreceptors during hyperoxia in man.

INTRODUCTION

The quantitative contribution of the peripheral and central respiratory chemoreceptors to ventilation is still subject to controversy. However, it is generally believed that during hyperoxia the peripheral chemoreflex loop is silent in resting man. This point of view is mainly based on the estimation of the latency of the onset of the ventilatory response to an abrupt change in inspired carbon dioxide and uses

the acknowledged differences in lung–receptor transit times. The technique of latency determination cannot estimate the quantitative contribution of the peripheral and central chemoreceptors. Therefore, Swanson and Bellville developed their non-invasive dynamic end-tidal CO_2 forcing (DEF) technique (Swanson & Bellville, 1975). In essence this DEF technique forces the end-tidal P_{CO_2} to follow a prescribed pattern in time against a constant background of O_2. The ventilatory response, measured on a breath-to-breath basis, is then partitioned into a fast 'peripheral' and a slow 'central' dynamic component using a two-compartment model, with the measured end-tidal CO_2 as input function. Bellville and co-workers applied this approach to study the ventilatory response to square-wave challenges of CO_2 during normoxia and hypoxia in human subjects (Bellville, Whipp, Kaufman, Swanson, Aqleh & Wiberg, 1979).

Using similar dynamic techniques Gelfand & Lambertsen (1973) came to the conclusion that the ventilatory response to abrupt changes in *inspired* CO_2 consisted of two central components and one peripheral component. During hyperoxia the peripheral component vanished.

The main aim of this study is to compare in detail the ventilatory response to CO_2 during normoxia and hyperoxia in resting man using the dynamic end-tidal forcing technique. To gain some more insight into the contribution of the peripheral and central chemoreflex loop to ventilation we also investigated the ventilatory response during mild hypoxia.

METHODS

Subjects

Nine male subjects, aged 20–26 years, who gave their informed consent, took part in the experimental protocol approved by the Leiden University Ethics Committee. All subjects were naive to respiratory physiology and unaware of the purpose of this study. They were healthy and had no history of cardiovascular or respiratory disease. Each subject was familiarized with the experimental procedure on the day before the first morning session. The subjects refrained from stimulant and depressant substances 12 h prior to the experiment.

Experimental design

In this study steps in end-tidal P_{CO_2} (P_{ET,CO_2}) with constant end-tidal O_2 (P_{ET,O_2}) were performed under normoxic conditions ($P_{ET,O_2} \approx 14{\cdot}5$ kPa) and hyperoxic conditions ($P_{ET,O_2} \approx 70$ kPa). Additional steps in P_{ET,CO_2} were applied at a mild hypoxic background ($P_{ET,O_2} \approx 10$ kPa). The experiments took place on four morning sessions, each three weeks apart. On the first two sessions three normoxic and three hyperoxic runs were obtained, in the third session four hyperoxic runs and finally in the last session three normoxic and three hypoxic runs.

After arrival at the laboratory the subjects rested for 30 min in a comfortable chair. Subsequently a face mask was fitted and the experiment started. The subjects were encouraged to read or listen to music through headphones. Each experiment started with a period of 'steady-state' ventilation of approximately 5 min during which the P_{ET,CO_2} was held slightly above resting P_{ET,CO_2}. The P_{ET,CO_2} was then elevated about 1 kPa within one or two breaths, maintained constant for approximately 8 min and then returned, stepwise, to the original value and maintained constant for a further 8 min. The P_{ET,O_2} was held constant at the hypoxic, normoxic or hyperoxic value. This technique has been described in detail by Swanson & Bellville (1975). Between the individual runs the subjects rested for 20 min.

Apparatus

The subjects were seated and an oronasal face mask was fitted. They were instructed to breathe through their mouths to prevent a change in airway resistance during the experiment. The airway

gas flow was measured with a Fleisch no. 3 pneumotachograph connected to a differential pressure transducer (Hewlett–Packard model 270, USA) and electronically integrated (Drummond & Goodenough, 1977) to yield a volume signal. The volume signal was calibrated with a motor-driven piston pump (stroke volume 1 l, at a frequency of 20 min^{-1}). Corrections were made for changes in gas viscosity due to changes in O_2 concentration of the inhaled gas mixture. The pneumotachograph was connected to a T-piece. One arm of the T-piece received a gas mixture with a flow of 40 l min^{-1} from a gas mixing system, consisting of three mass flow controllers (Bronkhorst High Tech BV-F202, The Netherlands) with which the flow of O_2, N_2 and CO_2 could be set individually at a desired level. A PDP 11/23 computer provided control signals to the mass flow controllers, so that the composition of the inspiratory gas mixture could be adjusted to force the P_{ET,CO_2} to follow a specific dynamic pattern in time and keep the P_{ET,O_2} constant. The CO_2 concentrations of the inspired and expired gases were measured with a fast response infra-red analyser (Gould Godart MK2 capnograph, The Netherlands) and the O_2 concentrations with a fast-response zirconium oxide cell (Jaeger O_2 test, FRG). All signals were recorded on a strip-chart recorder and also digitized and processed by the computer. The tidal volume, inspiratory time, expiratory time, respiratory frequency, expired ventilation ($\dot{V}_E$), end-tidal CO_2 and end-tidal O_2 tensions were stored on a breath-to-breath basis.

Data analysis

The analysis of the breath-by-breath data utilized a two-compartment model, describing the dynamics of the central and peripheral chemoreflex loop (Bellville *et al.* 1979):

$$\tau_c \frac{d}{dt}\dot{V}_c(t) + \dot{V}_c(t) = G_c[P_{ET,CO_2}(t-T_c) - B], \tag{1}$$

$$\tau_p \frac{d}{dt}\dot{V}_p(t) + \dot{V}_p(t) = G_p[P_{ET,CO_2}(t-T_p) - B]. \tag{2}$$

$\dot{V}_c(t)$ and $\dot{V}_p(t)$ are the outputs of the central and peripheral chemoreflex loops. $P_{ET,CO_2}(t-T_c)$ is the stimulus to the central chemoreflex loop delayed by the central transport delay time, $P_{ET,CO_2}(t-T_p)$ the input to the peripheral chemoreflex loop delayed by the peripheral transport delay time. The parameters G_c and τ_c are the CO_2 sensitivity and time constant of the central chemoreflex loop. The corresponding parameters of the peripheral chemoreflex loop are denoted by G_p and τ_p. B is the apnoeic threshold or extrapolated P_{ET,CO_2} of the steady-state $\dot{V}_E - P_{ET,CO_2}$ response at zero $\dot{V}_E$.

The noise corrupting the data is modelled through an external pathway with first-order dynamics:

$$\tau_n \frac{d}{dt}\dot{V}_n(t) + \dot{V}_n(t) = N(t). \tag{3}$$

$\dot{V}_n$ is the output of the noise pathway, $N(t)$ is a white noise source and τ_n is a time constant.

The inverse of the central time constant is made a linear function of P_{ET,CO_2} to allow for the possibility that the time constant (τ_{on}) of the ventilatory response to a step increase is different from that of the response to a step decrease (τ_{off}):

$$\frac{1}{\tau_c(t)} = m P_{ET,CO_2}(t-T_c) + b. \tag{4}$$

So at the cost of only one extra parameter the ventilatory 'on' and 'off' responses can be fitted simultaneously with different central time constants.

In most experiments a drift in the ventilation was present. We therefore decided to include a drift term in our model (Ct). The total ventilatory response is made up of the sum of the contributions of the central and peripheral chemoreflex loops, the external noise, the drift term and the measurement noise term ($W(t)$):

$$\dot{V}_E(t) = \dot{V}_c(t) + \dot{V}_p(t) + \dot{V}_n(t) + Ct + W(t). \tag{5}$$

For the sake of computer implementation for parameter estimation the continuous time

equations are 'discretized' at the measured times of exhale–inhale transitions. The estimation of the parameters of the two-compartment model was performed with a one-step prediction error method (Ljung, 1987). To obtain optimal time delays, a grid search was applied. All combinations between 1 and 22 s, with increments 1 s and with the constraint $T_c \geqslant T_p$ were used. When the residual sum of squares was minimal, with T_c equal to 22 s, the range of possible time delays was extended until a minimum in the residual sum of squares was found. The minimum time delays were, somewhat arbitrarily, chosen to be 1 s. The τ_p was constraint to be at least 0·3 s.

The estimated parameters of the normoxic and hyperoxic experiments were subjected to two-way analysis of variance. P values $< 0{\cdot}05$ were considered to be statistically significant.

RESULTS

A total of eighty-one normoxic, ninety hyperoxic and twenty-seven hypoxic runs were performed. Due to problems with the data acquisition six normoxic and eight hyperoxic runs were lost for analysis. Furthermore, eight normoxic and six hyperoxic runs were not included in the data analysis due to an irregular pattern of breathing or due to discomfort of the subject during the experiment. In Fig. 1 a plot of a normoxic run is shown. After a period of steady-state ventilation the P_{ET,CO_2} was increased stepwise from 5·5 to 6·5 kPa by elevating the inspired CO_2 concentration (F_{I,CO_2}). After approximately 8 min of hypercapnia the P_{ET,CO_2} was returned to its original level. During the run the inspired O_2 was regulated to maintain a constant P_{ET,O_2} in spite of changes in ventilation.

Hyperoxia vs. normoxia

Since we were not able to demonstrate a significant day-to-day difference in any of the estimated parameters (analysis of variance), we pooled the data of the different experiment days.

After inspection of the results of the hyperoxic runs we divided the subjects into three groups to facilitate the presentation of the results. In group I (three subjects), in only four out of twenty-eight hyperoxic runs a fast component was detected. The ratio of the CO_2 sensitivity of this fast component to the total CO_2 sensitivity averaged to 0·04. In all normoxic runs we found a fast component, with a ratio averaging to 0·32. Figure 2 shows an analysis of the breath-to-breath data of a normoxic run of a representative of this group (subject J.J.A.). The total $\dot{V}_E$ is separated into a fast component ($\dot{V}_p(t)$) and a slow component ($\dot{V}_c(t)$). Figure 3 shows a typical hyperoxic run of this same subject. The fitting procedure resulted in only one slow component. A fast component could not be found. The CO_2 sensitivity of this component was smaller than that of the slow component of Fig. 2. In group II (three subjects), a fast component was observed in fourteen out of twenty-four hyperoxic runs. The ratio of the peripheral to total CO_2 sensitivity was 0·12, compared to 0·30 in the normoxic experiments. In group III (three subjects), the analysis revealed a fast component in twenty out of twenty-four runs. The peripheral to total CO_2 sensitivity ratio was 0·24. This was 0·26 in normoxia. Figure 4 shows the analysis of a typical hyperoxic run of this group (subject E.V.W.), in which both a fast and a slow component was found.

The means of the estimated parameters for the groups and for all subjects for the normoxic and hyperoxic runs are collected in Table 1. In Fig. 5 the mean values per

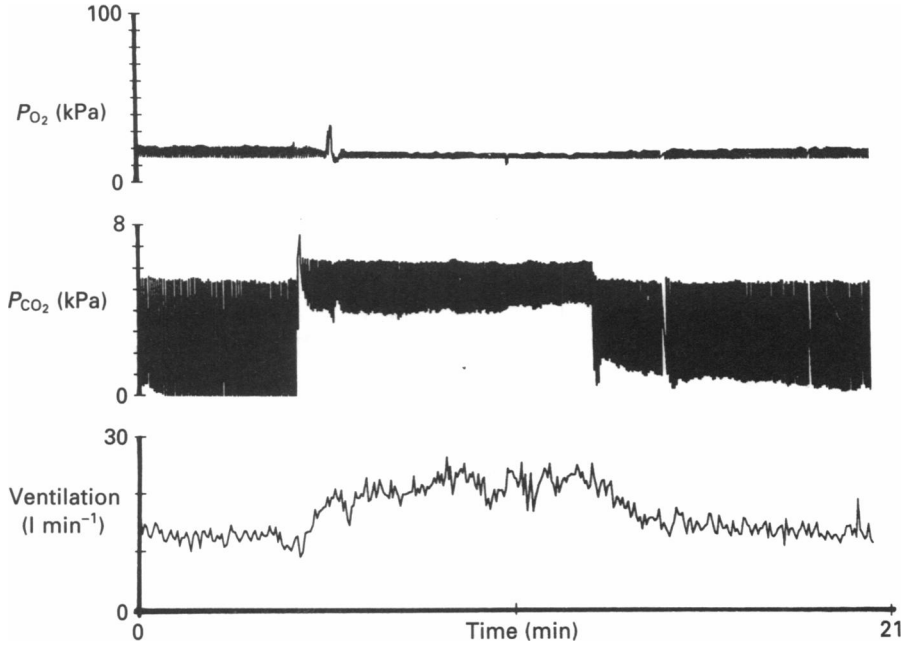

Fig. 1. Plot of an experiment at a background of normoxia of subject E.V.W.

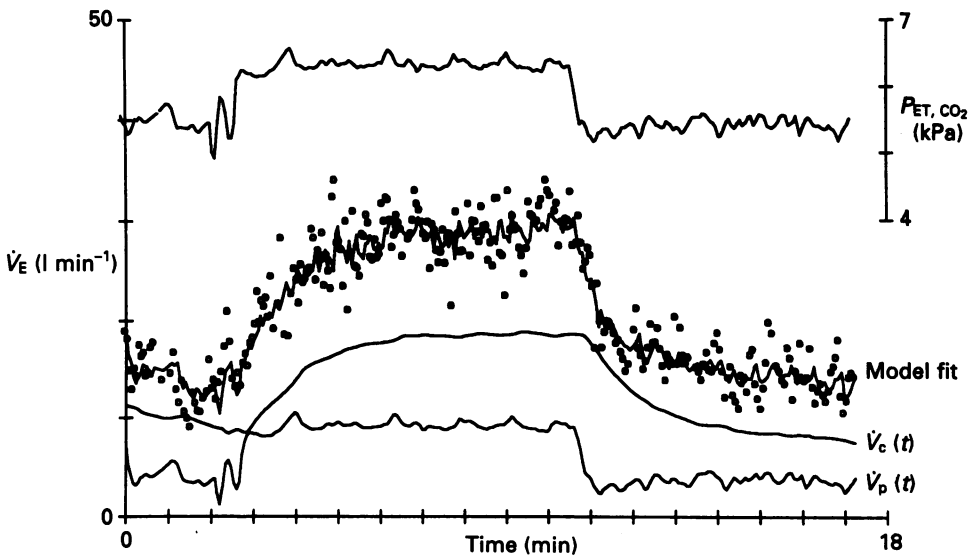

Fig. 2. Ventilatory response during normoxia and model fit (subject J.J.A.). Top panel shows the P_{ET, CO_2} stimulus. The dots represent the breath-to-breath ventilation. The curve through the data points is the model fit, $\dot{V}_E(t)$; it is the sum of the slow, $\dot{V}_c(t)$, and the fast, $\dot{V}_p(t)$, components, the output of the noise pathway and a drift term (not shown separately). The estimated parameter values are B 4·8 kPa, G_c 12·4 l min^{-1} kPa^{-1}, G_p 6·1 l min^{-1} kPa^{-1}, τ_{on} 75 s, τ_{off} 102 s, τ_p 3·5 s, τ_n 3·7 s, T_c 17 s, T_p 7 s and C 141 ml min^{-2}.

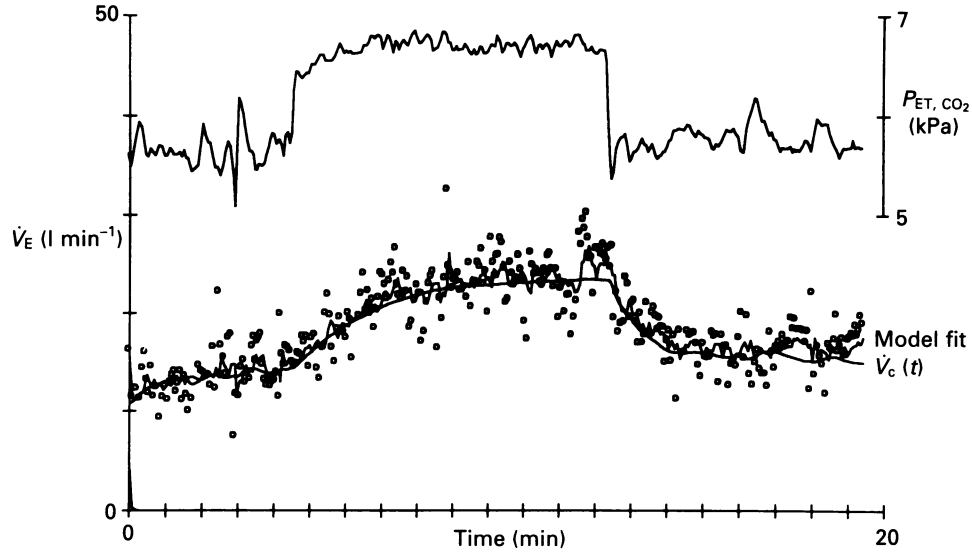

Fig. 3. Ventilatory response during hyperpoxia and model fit (subject J.J.A.). See legend Fig. 2 for an explanation of the panels. The estimated parameter values are B 4·1 kPa, G_c 8·9 l min^{-1} kPa^{-1}, G_p 0·0 = l min^{-1} kPa^{-1}, τ_{on} 123 s, τ_{off} 65 s, τ_n 5·7 s, T_c 6 s and C 51 ml min^{-2}.

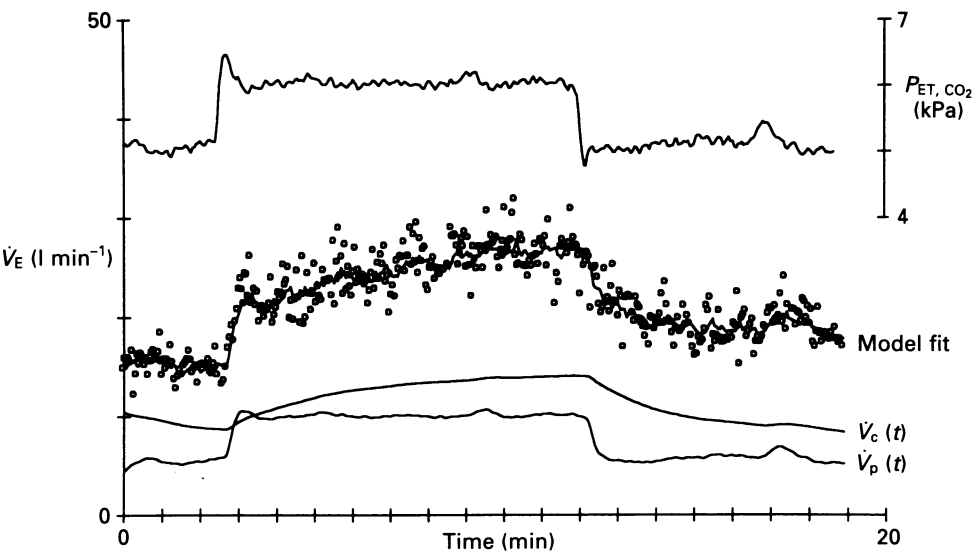

Fig. 4. Ventilatory response during hyperoxia and model fit (subject E.V.W.). See legend Fig. 2 for an explanation of the panels. The estimated parameter values are B 3·9 kPa, G_c 8·9 l min^{-1} kPa^{-1}, G_p 0·0 l min^{-1} kPa^{-1}, τ_{on} 123 s, τ_{off} 65 s, τ_n 5·7 s, T_c 6 s and T_p 16 s and C 232 ml min^{-2}.

subject of the threshold B, central CO_2 sensitivity and peripheral CO_2 sensitivity of the normoxic runs are plotted against their hyperoxic counterparts. The threshold decreased in all subjects, except one, yielding a 15% lower value in hyperoxia. Six of the nine subjects (two in each group) showed a decrease of the central CO_2

sensitivity during hyperoxia. Eight subjects had a lower peripheral CO_2 sensitivity in hyperoxia. It is interesting to note that in the subjects with a large peripheral CO_2 sensitivity in normoxia this sensitivity decreased the most in hyperoxia. On the average, going from normoxia to hyperoxia, the central CO_2 sensitivity decreased 15%, the peripheral CO_2 sensitivity 70%. The normoxic and hyperoxic ventilatory response curves have an intersection point at about the normal resting P_{CO_2}.

TABLE 1. Values of the estimated parameters of the normoxic, hyperoxic and hypoxic experiments (n, the number of runs; B, the apnoeic threshold in kPa; G_c and G_p, the central and peripheral gain terms in l min^{-1} kPa^{-1}; τ_{on} and τ_{off}, the central time constants of the 'on' and 'off' response in s; τ_p, the peripheral time constant in s; T_c and T_p, the time delays of the central and peripheral chemoreflex loops in s; C, the trend term in ml min^{-2})

	n	B	G_c	G_p	τ_{on}	τ_{off}	τ_p	T_c	T_p	C
					Group I (three subjects)					
Normoxia	22	4·53	11·02	5·60	128·6	123·2	9·7	9·9	7·2	36·3
		(0·18)	(3·67)	(0·71)	(29·1)	(63·6)	(1·4)	(0·1)	(1·0)	(50·1)
Hyperoxia	28	3·73	9·45	0·41	76·7	65·3	2·2	8·6	10·5	113·3
		(0·11)	(1·67)	(0·37)	(20·7)	(8·9)	(2·4)	(0·7)	(1·4)	(40·0)
					Group II (three subjects)					
Normoxia	20	4·29	10·06	4·30	119·7	134·9	13·5	13·6	10·9	32·0
		(0·61)	(3·47)	(1·36)	(24·5)	(28·2)	(1·0)	(2·6)	(0·7)	(35·7)
Hyperoxia	24	3·63	8·86	1·17	105·8	105·8	7·8	13·1	10·5	196·2
		(0·58)	(2·51)	(0·59)	(12·5)	(15·7)	(5·0)	(2·6)	(2·4)	(109·6)
					Group III (three subjects)					
Normoxia	23	4·26	9·05	3·19	190·9	168·4	6·2	13·9	9·8	32·5
		(0·04)	(2·92)	(0·88)	(59·8)	(19·7)	(2·4)	(0·9)	(1·1)	(77·0)
Hyperoxia	24	3·78	7·06	2·28	115·3	187·4	6·1	13·8	10·8	115·6
		(0·70)	(1·32)	(0·41)	(36·5)	(68·6)	(1·5)	(2·0)	(1·4)	(3·5)
					Means of all subjects					
Normoxia	67	4·36	10·04	4·36	146·6	142·1	9·8	12·5	9·3	33·6
		(0·34)	(3·04)	(1·37)	(48·8)	(41·4)	(3·5)	(2·4)	(1·8)	(49·3)
Hyperoxia	76	3·71	8·46	1·29	99·3	119·5	6·2	11·9	10·6	113·1
		(0·46)	(1·97)	(0·71)	(28·0)	(64·5)	(3·7)	(3·0)	(1·6)	(83·6)
P value		0·0001	0·0043	0·0001	0·0010	0·2115	0·0312	0·6397	0·3524	0·0001
Hypoxia	27	4·44	9·91	7·11	123·7	117·9	9·4	11·9	7·3	44·9
		(0·40)	(3·52)	(2·81)	(56·5)	(64·1)	(5·2)	(4·4)	(2·6)	(50·7)

Values are means (S.D.). Statistical analysis (hyperoxia *vs.* normoxia): two-way analysis of variance.

The time constant of the 'on' response was significantly shorter in hyperoxia compared to the time constant of the normoxic curves. The time constants of the 'on' response and 'off' response for both normoxia and hyperoxia were not significantly different. In normoxia the value of the trend term was as often positive as negative, whereas in the hyperoxic runs a consistent positive term was observed.

Hypoxia vs. normoxia

The mean peripheral CO_2 sensitivity during hypoxia almost doubled compared to the one estimated from the normoxic runs. This resulted in a ratio of the peripheral to the total CO_2 sensitivity of 0·42. The peripheral delay time decreased from 9·3 to

7·3 s. All other parameters are about the same as those obtained in normoxia (see Table 1). The normoxic and hypoxic response lines intersect close to the abscissa.

DISCUSSION

In this paper we studied the ventilatory response to square-wave challenges of end-tidal CO_2 at three levels of oxygen in man. The magnitude of the step was chosen

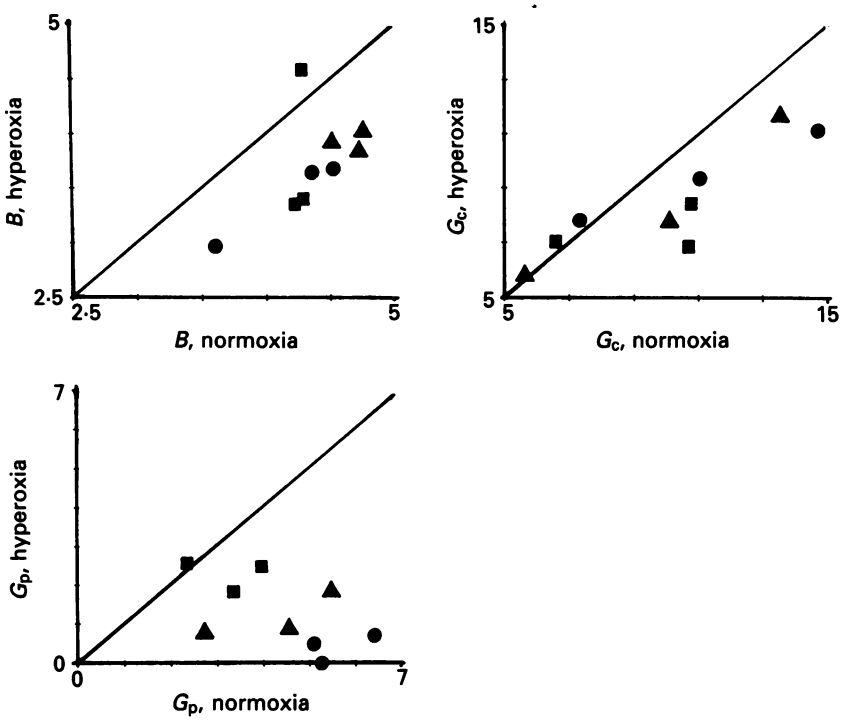

Fig. 5. Scatter diagram of the means of the threshold (B in kPa), central gain term (G_c in l min^{-1} kPa^{-1}) and peripheral gain term (G_p in l min^{-1} kPa^{-1}) of the subjects obtained in normoxia and hyperoxia. ●, subjects belonging to group I; ▲, group II; ■, group III.

to be about 1 kPa to minimize the effects on ventilation of changes in smell and taste of the gas mixture at the time of the transition. All subjects denied noticing any of the steps during the experiments. We tried to minimize possible cortical influences on breathing by familiarizing the subjects with the apparatus before the actual experiments started and by using a face mask instead of a mouthpiece and nose-clip arrangement. The mask allows normal movements of mouth and lips and is considered less disruptive to normal breathing than a mouthpiece (Gelfand & Lambertsen, 1983).

The two-compartment model

We analysed the breath-to-breath data using a two-compartment model introduced by Bellville *et al.* (1979). The analysis shows that in general the total ventilation can be broken up into a fast and a slow ventilatory component. It seems reasonable to attribute the fast component to the peripheral chemoreflex loop and

the slow component to the central chemoreflex loop (Bellville *et al.* 1979). The results of this paper support this point of view. Inspection of Table 1 reveals that on the average the dynamic characteristics of the fast component (time constant and time delay) during hypoxia, normoxia and hyperoxia are similar while a decrease in CO_2 sensitivity is found, as expected for a peripheral ventilatory component due to the well-described positive interactive effect of oxygen and carbon dioxide at the site of the peripheral chemoreceptors (Miller, Cunningham, Lloyd & Young, 1974; Ward & Bellville, 1983*a*; Cunningham, Robbins & Wolff, 1986). Furthermore, the peripheral time delay is about 3 s shorter than that of the slow component, reflecting the difference between the peripheral and central lung–receptor transit time.

Absence of central–peripheral interaction

A major assumption in the two-compartment model we used is that there is no interaction between the dynamic components. In the work of Bellville *et al.* (1979) there are some indications for such an interaction in the human respiratory control system. They found in normal subjects an increased central CO_2 sensitivity in hypoxia compared to normoxia, and in subjects who had undergone carotid body resection a decreased CO_2 sensitivity was obtained. On the other hand, Ward & Bellville (1983*b*) found no significant reduction of the central CO_2 sensitivity after intravenous infusion of dopamine, which caused a large decrease of the peripheral CO_2 sensitivity. The results of Robbins (1988) may also point in the direction of an interaction. He compared hypoxic steps against a background of normocapnia at the peripheral chemoreceptors and initial hypercapnia at the central chemoreceptors with hypoxic steps against a background of normocapnia at both sets of chemoreceptors. Two of his three subjects showed an increased ventilatory response to steps into hypoxia when central P_{CO_2} was high.

To get some insight into the existence of an interaction we analysed all normoxic curves using the two-compartment model in which eqn (5) was extended (cf. Robbins, 1988) into:

$$\dot{V}_E(t) = \dot{V}_c(t) + \dot{V}_p(t) + G_m \dot{V}_c(t) \dot{V}_p(t) + Ct + W(t), \quad (6)$$

in which G_m is an interaction parameter. In this analysis we only took measurement noise ($W(t)$) into account. We obtained convergence in only 70 % of the curves, which suggests overparametrization of the interaction model with regard to the information content of the experimental data. Moreover, the interaction which we characterized by $G_m G_c G_p$, was not significantly different from zero ($-0{\cdot}5 \pm 2{\cdot}5$ l min^{-1} kPa^{-2}; $n = 47$). So we could not demonstrate any significant central–peripheral interaction in the data sets of our subjects. Furthermore, the fit to the data using the additive two-compartment model is good, the residual function 'white' and the cross-correlation between residuals and input function small so that it is unwarranted to use a more complex model (Swanson & Bellville, 1975; Milhorn & Reynolds, 1976; Ljung, 1987). Nevertheless, an entirely convincing validation of the two-compartment model remains a challenging issue for further research.

The results of the breath-to-breath analysis of the hyperoxic experiments indicate that there is a great diversity between subjects with regard to the magnitude of the peripheral component. As can be seen from Table 1 some subjects showed almost no

peripheral ventilatory response to carbon dioxide (group I), some had a response similar in magnitude to that found during normoxia (group III) and in some subjects a decision about the existence of a peripheral component could not be made (group II). In a simulation study we found that a fast component could be identified with confidence only if its magnitude exceeded the 'noise level' which was about 1·5 l min^{-1} (mean of the residual sum of squares of the fit) in our subjects. This was the case in group III but generally not in group II.

Our demonstration of two components during hyperoxia is in agreement with the results of Olievier, Berkenbosch & DeGoede (1989) in cats, Berger, Krasny & Dutton (1973) in dogs and Gelfand & Lambertsen (1973) in man. In cats Olievier *et al.* (1989) attributed the fast component to the peripheral chemoreflex loop and the slow one to the central chemoreflex loop. Berger *et al.* (1973) and Gelfand & Lambertsen (1973) argued that both components originated from the central chemoreceptors as they had the same time delay. The time constants of the components were 20 and 118 s in the experiments of Berger *et al.* (1973) and 10 and 89 s in the experiments of Gelfand & Lambertsen (1973). Gelfand & Lambertsen (1973) applied the technique of exponential peeling in their analysis. We used the breath-to-breath ventilation and the measured end-tidal CO_2 and estimated the model parameters with a one-step prediction error method. We therefore accounted for the imperfection of the square-wave input. The parameter estimation technique we used is an extension of the technique of exponential peeling. It is therefore reasonable to give a meaning to the difference we estimated between the time delay of the fast and slow component in both normoxia and hyperoxia. The value of the time delay of the fast component we found was the same in normoxia and hyperoxia. We therefore believe that this fast component is of peripheral rather than of central origin. Recently Berkenbosch, Ward, Olievier, DeGoede & VanHartevelt (1989) showed that the ventilatory response to step changes in CO_2 of the blood perfusing the brain stem of the cat consists of one (central) component only. Furthermore, a peripheral component in terms of ventilation during hyperoxia has also been demonstrated in cats using the technique of artificial brain stem perfusion (VanBeek, Berkenbosch, DeGoede & Olievier, 1983). Olievier *et al.* (1989) were able to reproduce these results with the dynamic end-tidal forcing technique. Moreover, DeGoede, Berkenbosch, Ward, Bellville & Olievier (1985) showed good correspondence between the central and peripheral CO_2 sensitivities obtained with the technique of artificial perfusion of the brain stem and the technique of dynamic end-tidal CO_2 forcing in the same but 'intact' cat using the two-compartment model, as has been done in this study, in anaesthetized cats. These results in cats add to the confidence we have that the two-compartment model correctly estimates the central and peripheral component to ventilation in human beings.

Our findings of a peripheral component during hyperoxia are not at variance with those of Miller *et al.* (1974) and Ward & Bellville (1983*a*) who measured latency times which are defined as the period between the switch in P_{ET,CO_2} and the first *significant* change in ventilation. In three hypercapnic subjects Miller *et al.* (1973) performed transients into hypocapnia at a background of normoxia and hyperoxia. They found a difference of two to three breaths in the latencies. Similar results were obtained by Ward & Bellville (1983*a*), who performed step increases in P_{ET,CO_2}. The difference of

the latency times of the response to CO_2 during normoxia and hyperoxia has been interpreted as evidence that the peripheral chemoreceptors do not contribute to the ventilation in hyperoxia (Cunningham *et al.* 1986; Cunningham, 1987). Using eqns (1), (2), (4) and (5) we simulated the ventilatory response to a step increase of 1 kPa

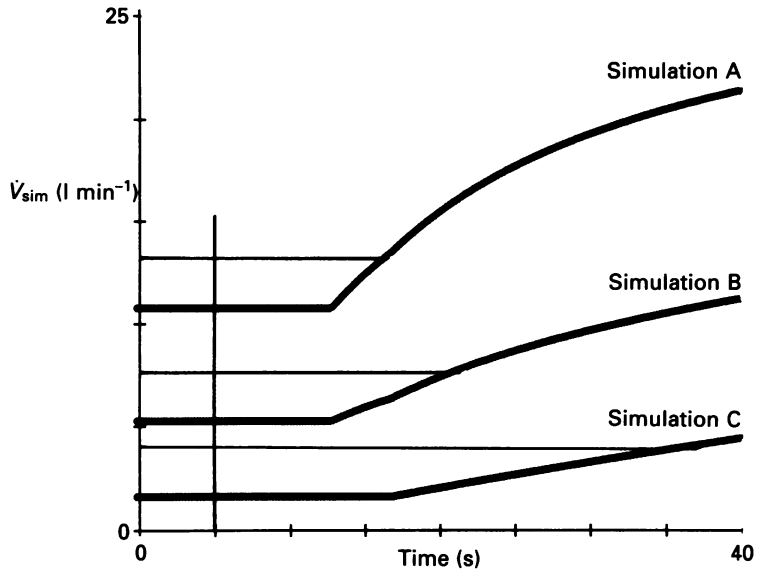

Fig. 6. Three simulations performed using eqns (1), (2), (4) and (5). A 1 kPa step increase in P_{ET,CO_2} was used as input function (from 5·6 to 6·6 kPa). Parameters used for simulation A: B 4·5 kPa, G_c 10·0 l min^{-1} kPa^{-1}, G_p 5·0 l min^{-1} kPa^{-1}, m 0·0 s^{-1} kPa^{-1}, b 0·008 s^{-1} (τ_{on} 125 s), τ_p 10 s, T_c 12 s, T_p 8 s and C 0 ml min^{-2}; simulation B: same parameter values as in simulation A except for G_p which was made 2·0 l min^{-1} kPa^{-1}; simulation C: same parameter values as in simulation A, G_p was made 0 l min^{-1} kPa^{-1}. At time $t = 5$ s the transition in P_{ET,CO_2} occurred. The latency time was determined by the time the ventilation ($\dot{V}_{sim}$) crossed the horizontal line (2 × S.E.M. = 1·5 l min^{-1}). The latency times found were: simulation A, 11 s; simulation B, 16 s; simulation C, 30 s.

in P_{ET,CO_2} with several parameter values for the peripheral CO_2 sensitivity (see Fig. 6). The latency was set at the time that the ventilation ($\dot{V}_{sim}$) exceeded the resting $\dot{V}_{sim}$ by 1·5 l min^{-1}. This value is about twice the standard error of the mean of the run-in period as estimated from the ensemble average of the ventilation of our subjects and close to the value used by Miller *et al.* (1974) and Ward & Bellville (1983*a*). A decrease in peripheral CO_2 sensitivity from 5 to 2 l min^{-1} kPa^{-1} increased the latency by about two breaths (5 s). Silencing the peripheral chemoreceptors increased the latency time by another 14 s. We observed especially in the group that showed no peripheral component in hyperoxia a shortening of the central time constant in hyperoxia. A central time constant of 80 s yielded a latency time of 26 s with the remaining parameters as in simulation C of Fig. 6. In the absence of peripheral input we thus expect a latency time of at least 26 s. It is interesting that Bouverot, Flandrois, Puccinelli & Dejours (1965) found a latency time of 5–10 s in dogs after a step increase in F_{I,CO_2} (background F_{I,O_2}) but 20–25 s in chemodenervated dogs. However, Ward & Bellville (1983*a*) and Miller *et al.* (1974) found a value of

about 15 s during hyperoxia suggesting that a peripheral component was present in their subjects. Although our experiments were not designed for this purpose we determined latency times of the 'on' responses in a similar fashion as has been done by Ward & Bellville (1983*a*) as a further consistency check for our estimated model parameters. A reduction of the latency time of about two breaths was estimated

TABLE 2. Mean latencies (in s) of the 'on' response of the hyperoxic, normoxic and hypoxic experiments determined from the ensemble average of the ventilatory data (*n* is the number of runs)

Subject	Hyperoxia (*n*)	Normoxia (*n*)	Hypoxia (*n*)
		Group I	
P.V.E.	19·0 (10)	12·5 (7)	8·8 (3)
J.J.A.	20·2 (9)	16·8 (8)	22·7 (3)
G.L.Y.	24·6 (9)	15·5 (7)	9·3 (3)
		Group II	
M.T.O.	21·8 (9)	18·7 (7)	10·7 (3)
E.V.D.	22·9 (8)	14·9 (7)	9·3 (3)
M.G.I.	30·0 (7)	20·8 (6)	14·4 (3)
		Group III	
E.V.W.	20·3 (8)	18·7 (8)	16·0 (3)
E.V.H.	28·0 (9)	24·5 (8)	15·2 (3)
R.R.A.	19·8 (7)	14·0 (7)	8·8 (3)

going from hyperoxia to normoxia and hypoxia (see Table 2). The agreement between the latency times obtained from the estimated model parameters and those directly determined from the experimental data was good. The above discussion shows that it is not possible, using the technique of latency time determination, to conclude that the peripheral chemoreceptors do not contribute to the ventilation during hyperoxia, unless the standard error of the mean of the run-in period is very small. If a peripheral component is then not present the latency is about equal to the time delay of the central chemoreflex loop.

Characteristics of components

The estimated values of the threshold B and the ratio of the peripheral over the total carbon dioxide sensitivity in normoxia are in good correspondence with the results of Bellville *et al.* (1979) and Ward & Bellville (1983*b*).

Going from normoxia to hyperoxia the central CO_2 sensitivity decreased by 15% (see Table 1). It is important to note that this decrease occurs in all three groups. It is therefore unlikely that the decrease of the central CO_2 sensitivities in group II and III is due to an overestimation of the peripheral component. Also, Gelfand & Lambertsen (1973) found evidence for a decreased (total) central CO_2 sensitivity. Since we could not find evidence for an interaction between the peripheral and central chemoreflex it is unlikely that the diminished central CO_2 sensitivity is due to the average decrease of peripheral chemoreceptor input. A central O_2–CO_2 interaction seems to be more plausible. This interpretation is not necessarily at variance with the results of Robbins (1988) since he could not exclude a period of central hypoxia together with central hypercapnia shortly after the step into hypoxia.

The decreased value of the threshold B may be due to a diminished cerebral blood flow together with a reduction of the Haldane effect in hyperoxia (Dautrebande & Haldane, 1921; Kety & Schmidt, 1948).

The central time constants in normoxia reported by us are not supported by those obtained by Bellville *et al.* (1979) and Ward & Bellville (1983*b*), who estimated a faster 'on' than 'off' transient. On the other hand the observations of Gardner (1980) are in good correspondence with our findings, showing no difference in the time constants of the 'on' and 'off' response of the central component. The magnitude of the normoxic central time constants is roughly three times larger than would be expected from the magnitude of the cerebral blood flow (cf. Dahan, Berkenbosch, DeGoede, Olievier & Bovill, 1990). This may be due to the existence of neuronal dynamics (Eldridge, 1977; Eldridge, Kiley & Paydarfar, 1987; Teppema, Vis, Evers & Folgering, 1982). The shortening of the central time constants in hyperoxia especially in the group that showed no peripheral component is unexpected. We have no satisfactory explanation for this finding.

The estimated trend term in hypoxia was as often positive as negative. This suggests that a slow on-going hypoxic decline at this degree of hypoxia was absent (Easton, Slykerman & Anthonisen, 1986) and that the 20 min interlude between our hypoxic experiments was sufficient to warrant no effect of the previous experiment on the following one (Easton, Slykerman & Anthonisen, 1988). From Table 1 we see that we estimated a much larger trend term from the hyperoxic experiments. Although there may be several factors which contribute to this trend, it is probably best explained by a *slow* excitatory effect of hyperoxia on ventilation (cf. Easton *et al.* 1988). This slow increase in ventilation cannot be detected from the strip-chart recording in the time period prior to the CO_2 transition as the noise level of the ventilation is appreciable.

This study of the influence of hyperoxia on the ventilatory response to carbon dioxide in awake human beings has shown that often a fast ventilatory component is present. We have advanced arguments that this fast component is of peripheral origin. During normoxia and hypoxia there is, besides a peripheral component, only one central component, so that we disagree with the findings of two central components by Gelfand & Lambertsen (1973). It is perhaps worth stressing that there seems to be no qualitative difference between the ventilatory response to carbon dioxide of the peripheral chemoreflex loop during hyperoxia between anaesthetized cat and awake man. On the other hand a decreased central CO_2 sensitivity with respect to normoxia has not been observed in the anaesthetized cat. It would be interesting to investigate whether this is related to the use of anaesthetics.

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