

The respiratory response to carbon dioxide in humans with unilateral and bilateral resections of the carotid bodies

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The acute hypercapnic ventilatory response (AHCVR) arises from both peripheral and central chemoreflexes. In humans, one technique for identifying the separate contributions of these chemoreflexes to AHCVR has been to associate the rapid component of AHCVR with the peripheral chemoreflex and the slow component with the central chemoreflex. Our first aim was to validate this technique further by determining whether a single slow component was sufficient to describe AHCVR in patients with bilateral carotid body resections (BR) for glomus cell tumours. Our second aim was to determine whether the slow component of AHCVR was diminished following carotid body resection as has been suggested by studies in experimental animals. Seven BR subjects were studied together with seven subjects with unilateral resections (UR) and seven healthy controls. A multifrequency binary sequence in end-tidal P_{CO_2} was employed to stimulate ventilation dynamically under conditions of both euoxia and mild hypoxia. Both two- and one-compartment models of AHCVR were fitted to the data. For BR subjects, the two-compartment model fitted significantly better on 1 out of 13 occasions compared with 22 out of 28 occasions for the other subjects. Average values for the chemoreflex sensitivity of the slow component of AHCVR differed significantly ($P < 0.05$) between the groups and were 0.95, 1.38 and 1.50 $\text{l min}^{-1} \text{Torr}^{-1}$ for BR, UR and control subjects, respectively. We conclude that, without the peripheral chemoreflex, AHCVR is adequately described by a single slow component and that BR subjects have sensitivities for the slow component that are lower than those of control subjects.

(Received 26 February 2003; accepted after revision 7 April 2003; first published online 25 April 2003)

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A recurring problem when investigating the chemoreflex responses to CO_2 in human studies has been our relative inability to separate the level of stimulation at the peripheral chemoreceptors from the level of stimulation at the central chemoreceptors. This has made it difficult to ascribe with any certainty a given response in expired minute ventilation (\dot{V}_E) to either the central chemoreflex or the peripheral chemoreflex. However, the central and peripheral chemoreflexes do differ in relation to their speed of response by about one order of magnitude, and consequently one approach to separating their contributions to \dot{V}_E has been to ascribe the fast component of the response to the peripheral chemoreflex and the slow component to the central chemoreflex (Swanson & Bellville, 1975; DeGoede *et al.* 1985). Early experiments using this approach tended to focus on modelling the ventilatory response to step changes in end-tidal partial pressure of CO_2 ($P_{\text{ET,CO}_2}$; Swanson & Bellville, 1975; Bellville *et al.* 1979; Gardner, 1980; Dahan *et al.* 1990). More recently, other patterns have been employed to produce dynamic stimulation in $P_{\text{ET,CO}_2}$ that have been devised to optimise the separation of the peripheral and

central chemoreflex components (Pedersen *et al.* 1999a,b; Fatemian & Robbins, 2001; Nieuwenhuijs *et al.* 2001; Fatemian *et al.* 2003). Pedersen *et al.* (1999b) demonstrated that a two-compartment model (i.e. with fast and slow components) was required to model the data, but a remaining concern has to be whether the fast and slow components can be accurately ascribed to the peripheral and central chemoreflexes, respectively. The first aim of this study was to assess whether a two-compartment model is still required to describe the responses of patients who have undergone bilateral carotid body resections and therefore lack a peripheral (carotid body) chemoreflex response to CO_2 .

One fundamental question concerning the chemoreflex responses to CO_2 is whether the peripheral and central components of the response are independent and additive with respect to their effects on \dot{V}_E . In relation to acute changes in the level of stimulation at the chemoreceptors, the majority of the data suggest that this is the case (van Beek *et al.* 1983; Clement *et al.* 1995). In relation to longer-term alterations, the picture is less clear-cut. For example,

in the goat, the data of Pan *et al.* (1998) suggest that the reduction in ventilatory sensitivity to CO₂ following bilateral carotid body denervation may become more marked in the first few days following surgery than it is immediately following denervation, although after day 4 the sensitivity increases again. The second aim of this study was to assess whether humans who have undergone bilateral carotid body resection exhibit a reduction in central chemosensitivity to CO₂.

METHODS

Patients and volunteers

Fourteen patients and seven volunteers were recruited. Seven of the patients had previously undergone bilateral resection of the carotid bodies and the other seven had undergone unilateral resection of the carotid bodies. The operations had been carried out between 1 and 26 years before the current experiments. All subjects were otherwise healthy. The control subjects were reasonably matched for age and sex with the patients.

Patients had undergone carotid body resection because they had developed tumours of one or both carotid bodies (glomus tumour or chemodectoma). These tumours were due to a mutation of the gene encoding for succinate–ubiquinone oxidoreductase subunit D (SDHD) on chromosome 11q23, as part of the syndrome of head and neck hereditary paraganglioma. SDHD is a small part of cytochrome b588 of the mitochondrial respiratory chain complex II. In the majority of Dutch patients (all patients arising from the Dutch founder families) a missense mutation of Asp⁹² → Tyr has been reported (van der Mey, 1992; Baysal *et al.* 2000; Jansen, 2001).

The study was approved by Leiden University Medical Centre ethics committee. All subjects gave their informed, written consent, and the experiments conformed with the guidelines laid down in the Declaration of Helsinki.

Study design

Each subject was studied in the laboratory on one occasion. After a 30 min period of rest, a 10 min measurement was made of the subject's natural P_{ET,CO_2} under air-breathing conditions. Following this, the subject's ventilatory response to CO₂ against a background of euoxia (end-tidal partial pressure of O₂, $P_{ET,O_2} = 100$ Torr) was measured. Finally, the subject's ventilatory response to CO₂ against a background of mild hypoxia ($P_{ET,O_2} = 75$ Torr) was measured.

The ventilatory responses to CO₂ were assessed by dynamic variation of P_{ET,CO_2} . The core stimulus was a multifrequency binary sequence (MFBS) in which P_{ET,CO_2} varied between +2 and +10 Torr above the subject's natural air-breathing value. The sequence lasted 1408 s, and included a total of 26 transitions between the two levels of P_{ET,CO_2} . The particular sequence employed had been optimised to separate the contributions of peripheral and central chemoreflex stimulation to overall \dot{V}_E (Pedersen *et al.* 1999b). The MFBS was imposed twice under conditions of euoxia and twice under conditions of hypoxia. For measurements under both euoxic and hypoxic conditions, the first MFBS was separated from the second MFBS by a 5 min period during which P_{ET,CO_2} was held at +2 Torr above the subject's natural air-breathing value. For the measurements made under hypoxic conditions, hypoxia was induced 20 min prior to

the start of the first MFBS to allow time for hypoxic ventilatory depression to develop before the MFBS began and so provide a more stable background against which to perform the MFBS. Isocapnia was maintained during the induction of hypoxia, and this allowed a measurement to be made of the ventilatory response to hypoxia.

Apparatus and technique

The subjects were seated comfortably in a hospital bed and breathed through a face mask (Vital Signs, Totowa, NJ, USA). Respired gases were sampled and analysed for P_{CO_2} and P_{O_2} using a Datex Multicap gas monitor (Datex-Engstrom, Helsinki, Finland). Arterial O₂ saturation (S_{O_2}) was monitored by pulse oximetry. Respired flows were measured with a pneumotachograph connected to a pressure transducer. The pressure signal was integrated to yield a volume signal. Corrections were made for the changes in gas viscosity due to changes in the oxygen content of the inhaled gas mixture. All data were logged and stored to a personal computer for further analysis.

Gas mixtures were supplied to the subject via a T-piece connected to the pneumotachograph. One arm of the T-piece received a gas mixture with a total flow of 50 l min⁻¹ from three mass flow controllers (Bronkhorst High Tech BV-F202, The Netherlands). These three mass flow controllers set the individual flows for O₂, CO₂ and N₂ in response to signals received from the computer. The P_{ET,CO_2} and P_{ET,O_2} of the subject were regulated using the technique of end-tidal forcing (Robbins *et al.* 1982). The data acquisition and control software were custom built (RESREG(c), E. Kruyt and E. Olofsen, Leiden University Medical Center).

Data analysis

Modelling. The purpose of fitting models to the data was twofold. First, it was to assess whether a separate peripheral chemoreflex component could be identified from the three subject groups, and the second was to compare parameter values for the ventilatory response to CO₂ between the three subject groups.

The two models fitted to the data were those of Pedersen *et al.* (1999b). These were closely related to the earlier models of Bellville *et al.* (1979) and Dahan *et al.* (1990). The first of these was a one-compartment model representing just the central chemoreflex response to CO₂, and the second was a two-compartment model representing both the central and the peripheral chemoreflex responses to CO₂.

The equations describing the two-compartment model are as follows:

$$\begin{aligned}\dot{V}_E &= \dot{V}_C + \dot{V}_P + Ct, \\ \tau_c(d\dot{V}_C/dt) + \dot{V}_C &= G_c(P_{ET,CO_2}(t - d_c) - B), \\ \tau_p(d\dot{V}_P/dt) + \dot{V}_P &= G_p(P_{ET,CO_2}(t - d_p) - B),\end{aligned}$$

where \dot{V}_C and \dot{V}_P are the slow (central) and fast (peripheral) components of the ventilatory response, respectively, and C is a trend term. In this model, \dot{V}_C and \dot{V}_P are determined by first-order differential equations in which P_{ET,CO_2} is the input at time t delayed by either d_c or d_p for the central and peripheral chemoreflex components, respectively. G_c and G_p are the sensitivities of the central and peripheral chemoreflex loops, and τ_c and τ_p their time constants. Parameter B is the extrapolated value for P_{ET,CO_2} for which steady-state \dot{V}_E is zero. The one-compartment model is obtained from this model by removing the fast component (i.e. G_p , and hence \dot{V}_P , are zero). Assuming that P_{ET,CO_2} remains constant during a single breath, these differential equations can be

Table 1. Physical characteristics of bilaterally carotid body-resected (BR), unilaterally carotid body-resected (UR) and control (C) subjects

Subject no.	Sex	Weight (kg)	Height (m)	Age (years)	P_{ET,CO_2} (Torr)	Date of surgery
002	M	80	1.96	48	45.8	06.06.96
004	M	82	1.93	28	45.0	15.06.90
005	M	87	1.78	49	42.0	21.07.90
BR 006	F	62	1.60	45	46.5	20.09.00
111	F	68	1.62	51	42.8	19.04.00
168	F	62	1.54	51	50.3	01.09.02
953	M	69	1.73	49	43.5	21.02.90
Mean \pm s.d.		73 \pm 10	1.74 \pm 0.16	46 \pm 8	45.1 \pm 2.8	
001	M	65	1.70	35	45.8	19.01.90
003	M	94	1.93	42	39.8	07.03.90
UR 004b	M	84	1.83	56	36.0	01.01.76
007	F	62	1.54	50	36.0	01.11.00
104	F	56	1.72	32	41.3	14.10.93
105	M	82	1.87	30	44.3	01.01.00
110	F	105	1.78	45	36.8	01.01.83
Mean \pm s.d.		78 \pm 18	1.77 \pm 0.13	41 \pm 10	40.0 \pm 4.0	
103	M	77	1.78	31	39.8	—
217	M	72	1.74	43	42.8	—
222	F	77	1.78	39	40.5	—
C 225	F	55	1.57	57	42.8	—
227	M	75	1.82	59	39.0	—
243	F	65	1.7	55	41.3	—
244	M	89	1.84	55	41.3	—
Mean \pm s.d.		73 \pm 11	1.75 \pm 0.09	48 \pm 11	41.0 \pm 1.4	

solved to form a set of difference equations that provide \dot{V}_E for breath $n + 1$ as a function of P_{ET,CO_2} at breath $n + 1$ and \dot{V}_E at breath n .

One complication associated with modelling respiratory data is that successive breaths are not independent observations, but show a degree of correlation with previous breaths. To address this issue, a parallel noise model that describes the correlation that exists between successive breaths (Liang *et al.* 1996) was fitted to the data simultaneously with the deterministic models described above.

The models were fitted to the data using a standard subroutine for the minimisation of a sum of squared residuals (Numerical Algorithms Group, Oxford, UK).

Model comparison. *F*-ratio tests were used to compare the goodness of fit between the two models for each group. The statistic is given by (Armitage & Berry, 1987):

$$F = \frac{(RSS_1 - RSS_2)/(df_1 - df_2)}{RSS_2/df_2} \sim F(df_1 - df_2, df_2),$$

where RSS_1 and df_1 are the residual sum of squares and the remaining degrees of freedom for the larger (two-compartment) model and RSS_2 and df_2 are the residual sum of squares and the remaining degrees of freedom for the smaller (one-compartment) model, respectively. This test indicates whether, after allowing for the different number of parameters, the two-compartment model is a significantly better fit to the data set than the one-compartment model. An important assumption of this test is that the residuals are uncorrelated. This assumption is provided for by

including the noise model, which ensures that the residuals are white (Pedersen *et al.* 1999b).

Comparison of model parameters between protocols and groups. Analysis of variance (ANOVA, SPSS statistical package) was used to compare model parameters. In the case of comparisons between protocols within a group, protocol was employed as a fixed factor and subjects as a random factor. In the case of comparisons between groups, group and protocol were employed as fixed factors. Statistical significance was assumed at $P < 0.05$.

RESULTS

Subjects

The physical characteristics of the subjects are given in Table 1. Of note, air-breathing P_{ET,CO_2} in the bilaterally resected group was significantly higher (by 4.6 ± 1.3 Torr, mean \pm s.d.) than for either the unilaterally resected group ($P < 0.005$) or the control group ($P < 0.05$). The unilaterally resected group and control group did not differ in this respect.

For each subject, the ventilatory response to hypoxia was calculated as the difference between \dot{V}_E during the second and third minutes of hypoxia and \dot{V}_E during the 2 min period immediately prior to the onset of hypoxia. The ventilatory response to hypoxia averaged 1.5 ± 1.7 ,

3.8 ± 3.0 and 7.3 ± 2.7 l min⁻¹ (mean \pm s.d.) for the bilaterally resected subjects, unilaterally resected subjects and controls, respectively. The value for bilaterally resected subjects did not differ significantly from zero. The apparent slight increase in \dot{V}_E in the bilaterally resected subjects may have been due to a small but significant increase in P_{ET,CO_2} of 0.9 ± 0.3 Torr between euoxia and hypoxia.

General observations and model fitting

An example of the ventilatory response to the MFBS in P_{ET,CO_2} together with an example of the fit of the two-compartment model to the data is shown in Fig. 1. The changes in ventilation clearly followed the variations in P_{ET,CO_2} . The response to the second MFBS was very similar to the first one. The fit of the model to data is illustrated both including and excluding the stochastic component of the model that was obtained as part of the overall fitting process. The residuals calculated without the stochastic component clearly show the presence of longer-term trends. These trends in the residuals are absent when the stochastic component is included in the calculation.

Model comparison

The residual sums of squares and *F*-ratio test results for both model fits for all subjects are shown in Table 2. There

was a clear distinction between the results for the bilaterally resected subjects compared with the unilaterally resected subjects and healthy controls. For the unilaterally resected subjects and the healthy controls, the two-compartment model fitted the data significantly better than the one-compartment model on 22 out of 28 occasions, with no distinction between data gathered against a background of euoxia and data gathered against a background of hypoxia. An *F*-ratio test conducted on the overall data from the unilaterally resected and control subjects indicated that the two-compartment model fitted the data significantly better than the one-compartment model against both background levels of oxygen tension.

The results from the bilaterally resected subjects contrasted markedly with those from the unilaterally resected subjects and healthy controls. For the bilaterally resected subjects, the two-compartment model fitted significantly better than the one-compartment model for only one out of the 13 data sets. For the bilaterally resected subjects overall, the two-compartment model did not fit the data significantly better than the one-compartment model for either the data gathered against a euoxic background or for the data gathered against a hypoxic background.

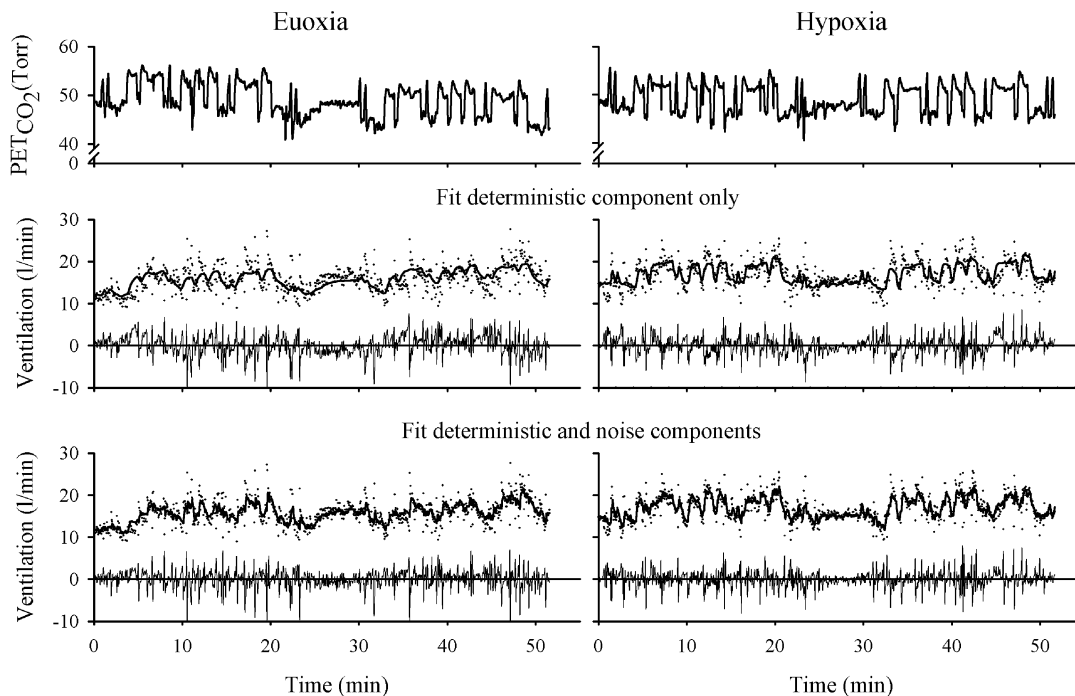


Figure 1. Example of data and model fits for a bilaterally carotid body-resected subject under conditions of euoxia (left) and hypoxia (right)

The top panel shows the multifrequency binary sequence (MFBS) in P_{ET,CO_2} . The two other panels show the ventilation data and model fits. Dots represent ventilation data and lines represent the model output; residuals are shown below each fit. The middle panel shows just the deterministic component of the model fit, i.e. the component that arises directly from the input stimulus. The model follows the pattern of variations in ventilation but the residuals remain correlated with many successive residuals being either all positive or all negative. The bottom panel shows the entire model fit. This includes the noise model, which models the intrinsic correlation between breaths. In this case the residuals are much less correlated, with no long runs of successive residuals being either all positive or all negative.

Table 2. Residual sum of squares (RSS) for both model fits for BR, UR and C groups

Subject no.	Euoxia				Hypoxia				
	<i>N</i>	RSS ₁ /df ₁ (1 min ⁻¹) ²	RSS ₂ /df ₂ (1 min ⁻¹) ²	<i>F</i>	<i>n</i>	RSS ₁ /df ₁ (1 min ⁻¹) ²	RSS ₂ /df ₂ (1 min ⁻¹) ²	<i>F</i>	
BR	002	709	6.71	6.70	n.s.	695	8.05	8.13	n.s.
	004	862	6.42	6.39	n.s.	444	6.44	6.54	n.s.
	005	828	4.92	4.93	n.s.	885	3.91	3.87	<i>P</i> < 0.005
	006	828	3.69	3.68	n.s.	903	2.94	2.97	n.s.
	111	722	1.37	1.37	n.s.	745	1.60	1.62	n.s.
	168	764	2.14	2.19	n.s.	—	—	—	—
	953	419	2.17	2.17	n.s.	438	2.70	2.74	n.s.
	Overall		4.08	4.08	n.s.		4.11	4.11	n.s.
UR	001	907	5.48	5.49	n.s.	929	7.90	7.91	n.s.
	003	863	18.99	18.71	<i>P</i> < 0.005	1004	11.58	11.32	<i>P</i> < 0.005
	004b	713	16.02	15.65	<i>P</i> < 0.005	321	19.47	19.28	<i>P</i> < 0.05
	007	843	2.40	2.04	<i>P</i> < 0.005	949	2.27	1.97	<i>P</i> < 0.005
	104	599	3.29	3.19	<i>P</i> < 0.005	759	0.81	0.81	<i>P</i> < 0.05
	105	736	1.67	1.65	<i>P</i> < 0.05	760	1.92	1.90	<i>P</i> < 0.005
	110	641	8.32	8.10	<i>P</i> < 0.005	750	5.01	4.98	<i>P</i> < 0.005
Overall		8.18	7.99	<i>P</i> < 0.005		6.03	5.87	<i>P</i> < 0.005	
C	103	804	3.93	3.81	<i>P</i> < 0.005	935	5.12	5.03	<i>P</i> < 0.005
	217	714	8.45	8.21	<i>P</i> < 0.005	655	9.74	9.29	<i>P</i> < 0.005
	222	866	7.58	7.50	<i>P</i> < 0.01	958	10.85	10.37	<i>P</i> < 0.005
	225	977	2.40	2.38	<i>P</i> < 0.005	1146	2.77	2.78	n.s.
	227	780	2.59	2.60	n.s.	802	2.11	2.13	n.s.
	243	737	5.05	5.05	n.s.	848	3.99	3.98	<i>P</i> < 0.05
	244	779	5.52	5.42	<i>P</i> < 0.005	832	5.67	5.53	<i>P</i> < 0.005
Overall		4.98	4.90	<i>P</i> < 0.005		5.57	5.39	<i>P</i> < 0.005	

N is the number of fitted data points, RSS₁ and RSS₂ are the residual sums of squares and df₁ and df₂ are the degrees of freedom (*n* minus number of model parameters) for the smaller and the larger models, respectively. Overall values are calculated as $\Sigma \text{RSS} / \Sigma \text{df}$.

Model parameters

The values of the parameters obtained by fitting the two-compartment model to the data are presented in Tables 3–5. Within each group of subjects, comparisons were drawn between the parameter values for the two protocols (euoxia vs. hypoxia). For the control subjects, there was a significant increase in G_p with hypoxia ($P < 0.05$, ANOVA). There was a similar-sized increase in G_p for the unilaterally resected subjects, but in this case the observation did not reach significance. For the bilaterally resected subjects, there was no increase in the magnitude of G_p with hypoxia.

There were no significant changes in any of the other parameters with hypoxia for any of the subject groups with one exception. The exception was that there was a significant increase in G_c with hypoxia in the control subjects ($P < 0.001$).

In order to determine the effect of carotid body resection on the parameters, comparisons were drawn across the three groups. There were significant differences in the values for G_p between subject groups ($P < 0.05$). *Post hoc* testing revealed that G_p was significantly lower in the

bilaterally resected subjects than in the controls ($P < 0.005$). Apart from the differences in G_p , there were also differences in the values for G_c ($P < 0.05$). *Post hoc* testing revealed that G_c was significantly lower in the bilaterally resected subjects than in the controls ($P < 0.05$).

Other differences included the observation that parameter B was significantly lower for both bilaterally and unilaterally resected subjects compared with the control group ($P < 0.05$). Finally, for the stochastic component of the model, the value for parameter F was significantly lower for the bilaterally resected subjects compared with the other two subject groups ($P < 0.001$) which suggests that there may be less correlation between successive breaths in the absence of peripheral chemoreceptors.

DISCUSSION

The major results from this study were, first, in the bilaterally carotid body-resected subjects, a two-compartment model of the ventilatory response to CO₂ failed to fit the data significantly better than a one-compartment model. Second, in the bilaterally resected subjects, the slow component of the ventilatory sensitivity

Table 3. Model parameters for control subjects

Subject no.	G_c ($l \text{ min}^{-1} \text{ Torr}^{-1}$)	τ_c (s)	d_c (s)	G_p ($l \text{ min}^{-1} \text{ Torr}^{-1}$)	τ_p (s)	d_p (s)	B (Torr)	C ($l \text{ min}^{-1} \text{ min}^{-1}$)	F	R_v/R_w
103	1.78	132.9	11.0	0.28	3.3	4.8	36.9	0.108	0.97	0.05
217	1.78	223.2	19.9	0.64	9.9	4.9	38.8	0.010	0.84	0.22
222	1.88	224.6	7.4	0.69	8.5	8.5	39.5	0.032	0.89	0.22
Euoxia 225	0.89	55.6	4.8	0.14	0.04	4.7	36.4	0.124	0.98	0.01
227	1.80	100.5	14.8	0.16	2.4	6.5	35.7	-0.005	0.90	0.09
243	0.80	97.1	11.2	0.15	0.7	6.0	35.3	0.131	0.97	0.01
244	0.64	204.9	11.7	0.82	19.8	5.0	37.4	0.025	0.91	0.02
Mean	1.37	148.4	11.5	0.41	6.4	5.8	37.1	0.061	0.92	0.09
\pm S.D.	0.558	68.8	4.89	0.294	7.01	1.39	1.55	0.0580	0.052	0.094
103	2.03	104.7	14.6	0.62	5.6	4.2	37.5	0.117	0.92	0.30
217	2.09	245.8	19.3	0.71	6.7	7.0	38.9	0.027	0.85	0.17
222	2.04	133.1	13.8	1.13	7.5	6.3	39.5	0.062	0.78	0.50
Hypoxia 225	1.13	54.5	10.4	0.20	1.5	5.5	34.8	0.132	0.97	0.04
227	2.05	98.6	19.5	0.35	4.6	6.3	37.0	0.124	0.99	0.03
243	0.99	105.9	8.0	0.43	10.9	3.7	36.0	0.092	0.84	0.27
244	1.09	165.9	4.7	0.85	12.7	5.2	37.0	0.055	0.85	0.07
Mean	1.63	129.8	12.9	0.61	7.1	5.4	37.2	0.087	0.88	0.20
\pm S.D.	0.527	61.39	5.56	0.318	3.78	1.19	1.61	0.0399	0.076	0.172

G_c , central chemoreflex sensitivity; G_p , peripheral chemoreflex sensitivity; τ_c , central chemoreflex time constant; τ_p , peripheral chemoreflex time constant; d_c , central chemoreflex delay; d_p , peripheral chemoreflex delay; B , extrapolated value for P_{ET,CO_2} at which $\dot{V}_E = 0$; C , trend term; F , system gain for noise component; R_v/R_w , variance ratio for process and measurement noise.

to CO_2 was smaller than in either the control subjects or the unilaterally resected subjects.

Subjects

There have been a number of studies of the control of breathing in humans who have undergone bilateral carotid body resection (for review see Honda, 1985). These resections were performed in an attempt to relieve symptoms of breathlessness associated with asthma. Thus, the results from these studies are likely to be complicated by the presence of some degree of pulmonary pathology. A second group of subjects that have been studied are those who have had bilateral carotid endarterectomy and this has resulted in bilateral denervation of the carotid bodies (Wade *et al.* 1970). These subjects lack the pulmonary pathology of the first group but have the disadvantage of having established cerebrovascular disease. The subjects of the present study now form a third group. They are relatively young and do not have established cardio-respiratory disease.

The P_{ET,CO_2} of the bilaterally resected subjects was significantly greater than that of the control subjects by 4.6 Torr. This is close to the value of 5.8 Torr reported by Wade *et al.* (1970) for the rise in arterial P_{CO_2} for the subjects who had undergone (staged) bilateral carotid endarterectomy and had lost their ventilatory response to hypoxia. These results show that the carotid bodies play a

significant role in setting normal levels of \dot{V}_E and blood gas tensions in humans.

Dynamic separation of peripheral and central contributions to \dot{V}_E

A number of studies in experimental animals have suggested that the fast component of the ventilatory response to CO_2 may be linked with the peripheral chemoreflex and the slow component of the ventilatory response to CO_2 may be linked with the central chemoreflex. Daubenspeck (1973) demonstrated that the rapid component of the ventilatory response to sinusoidal variations in P_{CO_2} could be abolished by denervation of the carotid bodies. In anaesthetised cats, DeGoede *et al.* (1985) compared the gains of the peripheral and central chemoreflexes obtained from the dynamics of the ventilatory response to CO_2 with the gains obtained by directly varying the P_{CO_2} at either chemoreceptor using their technique of artificial brainstem perfusion. They found that the gains obtained by the two techniques were similar. Berkenbosch *et al.* (1989) reported that a step change in the arterial P_{CO_2} of the blood perfusing just the brainstem resulted in a single slow exponential change in \dot{V}_E .

Bellville *et al.* (1979) studied the ventilatory response to step changes in P_{ET,CO_2} in carotid body-resected humans. Although they did not compare different models for the ventilatory response to CO_2 in these subjects, they did fit a

Table 4. Model parameters for unilaterally carotid body-resected subjects

Subject no.	G_c ($l \text{ min}^{-1} \text{ Torr}^{-1}$)	τ_c (s)	d_c (s)	G_p ($l \text{ min}^{-1} \text{ Torr}^{-1}$)	τ_p (s)	d_p (s)	B (Torr)	C ($l \text{ min}^{-1} \text{ min}^{-1}$)	F	R_v/R_w
001	1.48	55.4	6.7	0.04	1.1	11.2	39.0	0.146	0.89	0.27
003	1.58	46.9	16.5	0.56	2.0	6.4	33.1	0.239	0.95	0.03
004b	2.04	61.9	6.3	0.38	3.4	6.1	32.1	0.201	0.97	0.02
007	1.27	186.3	6.3	0.29	0.8	6.3	30.9	0.078	0.92	0.03
104	0.71	264.7	6.9	0.21	15.5	6.1	35.1	0.017	0.93	0.02
105	0.96	43.5	4.5	0.11	0.2	4.0	36.2	0.160	0.85	0.42
110	1.61	62.8	16.1	0.48	0.1	5.3	34.1	0.030	0.97	0.04
Mean	1.38	103.1	9.0	0.29	3.3	6.5	34.3	0.124	0.92	0.12
\pm S.D.	0.443	86.93	5.02	0.191	5.50	2.24	2.71	0.0850	0.044	0.161
001	2.04	86.3	9.9	0.34	6.7	5.8	40.9	0.013	0.88	0.17
003	2.01	164.3	5.5	1.12	16.3	3.7	34.8	0.092	0.83	0.13
004b	2.20	72.7	12.4	0.54	1.5	8.7	32.9	0.261	0.97	0.01
007	1.06	189.5	13.3	0.36	1.4	5.6	29.2	0.022	0.89	0.10
104	0.49	94.6	18.4	0.13	5.2	3.3	30.4	0.060	0.98	0.02
105	0.73	138.5	1.6	0.62	18.5	3.5	37.6	0.17	0.90	0.18
110	1.13	48.7	10.4	0.29	0.15	5.1	30.9	0.107	0.98	0.01
Mean	1.38	113.5	10.2	0.48	7.11	5.1	33.8	0.104	0.92	0.09
\pm S.D.	0.693	51.55	5.44	0.323	7.42	1.89	4.23	0.0877	0.059	0.075

Symbols as in Table 3.

Table 5. Model parameters for bilaterally carotid body-resected subjects

Subject no.	G_c ($l \text{ min}^{-1} \text{ Torr}^{-1}$)	τ_c (s)	d_c (s)	G_p ($l \text{ min}^{-1} \text{ Torr}^{-1}$)	τ_p (s)	d_p (s)	B (Torr)	C ($l \text{ min}^{-1} \text{ min}^{-1}$)	F	R_v/R_w
002	0.93	123.0	19.9	0.43	15.6	5.4	34.4	0.092	0.63	0.49
004	2.34	207.0	19.5	0.41	21.3	8.4	38.5	0.058	0.83	0.12
005	0.60	52.4	3.9	0.26	26.4	12.2	34.5	0.128	0.85	0.17
006	0.55	23.4	17.7	0.18	0.9	6.0	31.3	0.033	0.84	0.90
111	0.28	209.3	19.6	0.09	0.1	12.3	33.5	0.069	0.81	0.34
168	0.62	101.7	4.7	0.04	7.2	4.8	26.9	0.066	0.94	0.01
953	1.32	98.3	4.1	0.08	2.6	16.8	35.5	0.145	0.90	0.40
Mean	0.95	116.4	12.8	0.21	10.6	9.4	33.5	0.084	0.83	0.35
\pm S.D.	0.696	70.91	8.02	0.159	10.56	4.48	3.63	0.0399	0.098	0.296
002	0.80	73.9	18.5	0.33	13.6	4.8	33.2	0.087	0.92	0.03
004	1.29	47.7	9.2	0.07	3.9	4.2	29.4	0.098	0.68	0.59
005	1.05	190.0	16.1	0.64	13.4	14.5	39.2	0.024	0.80	0.23
006	0.76	79.3	16.9	0.09	3.1	8.5	33.4	0.008	0.73	5.44
111	0.50	282.8	4.7	0.03	16.0	4.8	37.0	-0.028	0.80	0.23
168	—	—	—	—	—	—	—	—	—	—
953	1.31	75.0	8.2	0.11	29.8	16.8	35.0	0.147	0.79	0.80
Mean	0.95	124.8	12.3	0.21	13.30	8.9	34.5	0.056	0.79	1.22
\pm S.D.	0.321	91.98	5.62	0.235	9.72	5.47	3.39	0.0654	0.081	2.086

Symbols as in Table 3.

two-compartment model to their data. With this model, they reported the fast (peripheral) sensitivity to average $0.16 \text{ l min}^{-1} \text{ Torr}^{-1}$ in euoxia and $0.20 \text{ l min}^{-1} \text{ Torr}^{-1}$ in hypoxia. These values are very similar to those obtained in the present study ($0.21 \text{ l min}^{-1} \text{ Torr}^{-1}$ in both euoxia and hypoxia). In the present study, we have shown that the

inclusion of this fast component in the overall model does not lead to a significant improvement in the fit of the model to the data. We suggest that the relatively small values for G_p in the bilaterally resected subjects arise through a combination of imperfections in the model of the dynamics of the central chemoreflex and noise.

Central chemoreflex sensitivity in bilaterally carotid body-resected subjects

Although not clearly significant, Bellville *et al.* (1979) reported that central chemosensitivity appeared to be lower, by about half, in the patients who had undergone carotid body resection than in the normal controls. The present study confirms that the magnitude of the slow component is smaller in the bilaterally resected subjects than it is in the other two groups. There are at least two possible interpretations of this result. The first is that there is a component of the peripheral chemoreflex response to CO₂ that is slow. The second is that there is interaction between the peripheral and central chemoreflexes such that the presence of peripheral input augments the sensitivity of the central chemoreflex.

One theoretical reason in favour of the first hypothesis is that, following a change in P_{ET,CO_2} , there should be a component of the change in pH of the arterial blood that is slow. For example, in the case of a step increase in P_{ET,CO_2} , there will be a rise in bicarbonate in the arterial blood which will then partially redistribute itself into the peripheral tissues during circulation of the blood through the systemic capillaries. If P_{ET,CO_2} remains constant, this redistribution will result in a progressive acidification of the arterial blood. Consequently, if the arterial chemoreceptors primarily respond to pH (Hornbein & Roos, 1963; Donnelly *et al.* 1982), then *in vivo* there should be a slow component within their response to changes in P_{ET,CO_2} . However, in anaesthetised cats in which the P_{ET,CO_2} of the central chemoreflex was maintained constant by artificial perfusion of the brainstem, a single fast time constant was found to be sufficient to describe the ventilatory response to a step change in P_{ET,CO_2} (Berkenbosch *et al.* 1988). This result tends to suggest that the magnitude of any slow component within the peripheral chemoreflex response is small.

If there were a slow component within the peripheral chemoreflex response to CO₂, then it might reasonably be predicted that there would be an immediate reduction in the slow component of ventilatory response to CO₂ following carotid body denervation. However, experimental studies in animals have found that it takes two or more days for the decline in the ventilatory sensitivity to develop fully (Pan *et al.* 1998; Rodman *et al.* 2001). This would seem to be more compatible with a slow regulation of central chemoreflex sensitivity by peripheral chemoreflex activity – i.e. a slowly developing central–peripheral chemoreflex interaction.

If part of the slow component of the response does arise at the carotid bodies, then it would be reasonable to predict that the magnitude of the slow component of the chemoreflex response to CO₂ would be increased in hypoxia. Although a degree of interaction between the

central and peripheral chemoreflexes could also give rise to this result, the absence of any increase in the magnitude of the slow component with hypoxia would make a peripheral chemoreflex origin for any of the slow component unlikely. Unfortunately, the data in relation to this are contradictory. Using step changes in P_{ET,CO_2} , Bellville *et al.* (1979) report a non-significant increase in central chemoreflex sensitivity of 0.31 l min⁻¹ Torr⁻¹ (compared with a non-significant increase of 0.09 l min⁻¹ Torr⁻¹ for the carotid body-resected subjects) and Dahan *et al.* (1990) report almost no change (fall of ~0.02 l min⁻¹ Torr⁻¹). Using MFBS, Pedersen *et al.* (1999b) report a non-significant fall of 0.31 l min⁻¹ Torr⁻¹. However, Fatemian *et al.* (2003) report a significant rise in G_c with hypoxia of 0.6 l min⁻¹ Torr⁻¹, and in the present study there was a significant increase of 0.26 l min⁻¹ Torr⁻¹ (compared with no change for the carotid body-resected subjects).

If part of the slow component of the response does arise at the carotid bodies and is incorrectly attributed to the central chemoreflex in the modelling process, then a further prediction that can be made is that the pure delay of the central chemoreflex in normal subjects will be intermediate between that measured for the bilaterally carotid body-resected subjects and the pure delay for the peripheral chemoreflex. Our data lend no support to this prediction.

In summary, it is clear from the present study that, in humans, there is a reduction in the magnitude of the slow chemoreflex response to CO₂ following carotid body resection. However, there must remain a degree of uncertainty as to whether this is caused by the loss of some tonic influence by the peripheral chemoreceptors on central chemoreflex sensitivity or whether it simply results from the loss of a slow component that exists within the peripheral chemoreflex response to CO₂.

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Acknowledgements

This study was supported by the Wellcome Trust.