Modulation of the corticospinal control of ventilation by changes in reflex respiratory drive

D. R. CORFIELD, C. A. ROBERTS, A. GUZ, K. MURPHY, AND L. ADAMS
National Heart and Lung Institute, Imperial College School of Medicine, London W6 8RP, United Kingdom

Corfield, D. R., C. A. Roberts, A. Guz, K. Murphy, and L. Adams. Modulation of the corticospinal control of ventilation by changes in reflex respiratory drive. J. Appl. Physiol. 87(5): 1923–1930, 1999.—We have determined whether changes in P\textsubscript{CO\textsubscript{2}} above and below eucapnia modulate the precision of the voluntary control of breathing. Twelve trained subjects performed a compensatory tracking task in which they had to maintain the position of a cursor (perturbed by a variable triangular forcing function) on a fixed target by breathing in and out of a spirometer (ventilatory tracking; at 10 l/min). Before each task, subjects hyperventilated for 5 min, and the end-tidal P\textsubscript{CO\textsubscript{2}} (PET\textsubscript{CO\textsubscript{2}}) was controlled; tracking was then performed separately at hypocapnia, eucapnia, and hypercapnia (PET\textsubscript{CO\textsubscript{2}} ~25, 37, and 43 Torr, respectively). Ventilatory tracking error was unchanged during hypocapnia (P > 0.05) but was significantly worse during hypercapnia (P < 0.003), compared with eucapnia; arm tracking error, performed as a control, was not significantly affected by PET\textsubscript{CO\textsubscript{2}} (P > 0.05). In conclusion, ventilatory tracking performance is unaffected by the eucapnic P\textsubscript{CO\textsubscript{2}}. From this, we suggest that resting breathing in awake humans may be independent of chemical drives and of the prevailing P\textsubscript{CO\textsubscript{2}}.

IN HUMANS IT IS PROBABLE that, during sleep, breathing is maintained and controlled reflexly via respiratory-related neurons located in the brain stem. Chemical stimuli are clearly important in maintaining this reflex breathing because experimentally induced reductions in the partial pressure of arterial CO\textsubscript{2} (P\textsubscript{aCO\textsubscript{2}}) consistently produce apnea in anesthetized patients (9) and in normal sleeping subjects (7, 26). In awake humans, breathing appears to be less dependent on the chemical stimulus to breathe. Support for this concept comes from observations that experimentally induced hypocapnia does not consistently result in posthyperventilation apneas during wakefulness (2, 8, 17, 26, 27) and that breathing during a period of hypocapnia is markedly irregular and independent of P\textsubscript{aCO\textsubscript{2}} (6). Fink’s (8) original observations led him to propose the concept of a wakefulness stimulus to breathe that maintains respiratory rhythm when the chemical stimulus to breathe is reduced or absent. Moreover, more recent evidence suggests that the P\textsubscript{aCO\textsubscript{2}} during wakefulness may be insufficient to maintain breathing during sleep. Skatrud and Dempsey (26) showed that, during non-rapid-eye-movement sleep, apnea occurred when end-tidal P\textsubscript{CO\textsubscript{2}} (PET\textsubscript{CO\textsubscript{2}}) was lowered to 1–2 Torr below the awake resting PET\textsubscript{CO\textsubscript{2}} level in 37 of 40 trials. Datta et al. (7) showed that apnea occurred, even during light sleep, when PET\textsubscript{CO\textsubscript{2}} was at, or even slightly above, the wakefulness PET\textsubscript{CO\textsubscript{2}}. Thus it is not clear whether the level of ventilation awake and at rest is determined by the chemical stimulus related to the level of P\textsubscript{aCO\textsubscript{2}} or whether the level of PET\textsubscript{CO\textsubscript{2}} is determined by the level of ventilation itself determined by the wakefulness stimulus. The neural basis for the wakefulness stimulus to breathing has not been identified. However, we have observed posthyperventilation apnea in a patient who was awake but had lost all corticomotor control of movement (14). This observation leads us to suggest that an important component of the wakefulness stimulus may be an input from the motor cortex.

It is difficult to assess directly the relative importance of chemical and wakefulness stimuli in determining the level of resting ventilation. The aim of the present study was to investigate the importance of the CO\textsubscript{2} stimulus to breathe by characterizing the precision with which a standardized voluntary respiratory control task was modulated by changes in chemical stimulation around the eucapnic level. To do this, a motor tracking task was used to assess the accuracy of the volitional control of breathing at different levels of P\textsubscript{aCO\textsubscript{2}} (here using PET\textsubscript{CO\textsubscript{2}} as an index of P\textsubscript{aCO\textsubscript{2}}). The task was performed during hypocapnia (when the chemical stimulus to breathe was presumably minimal or absent), eucapnia (the spontaneous resting P\textsubscript{aCO\textsubscript{2}} level), and hypercapnia (in the presence of an increased chemical stimulus to breathe). Our hypothesis was that any reduction in the accuracy of the volitional control of breathing during hypercapnia, compared with during eucapnia, would be due to a conflicting interaction between the chemical and volitional control systems. If the accuracy of the volitional control of breathing was also decreased at eucapnia, compared with that during hypocapnia, this would indicate that such a conflicting interaction still existed at the resting P\textsubscript{aCO\textsubscript{2}} level. If this were the case, this would suggest that the eucapnic P\textsubscript{aCO\textsubscript{2}} level does influence resting breathing during wakefulness. To account for any nonspecific effects of changes in CO\textsubscript{2} on motor performance, the effect of these changes in P\textsubscript{aCO\textsubscript{2}} on the accuracy of the voluntary control of arm movement (a manual tracking task) was also studied.

METHODS

Subjects

Twelve healthy subjects were studied (age 23–44 yr; 4 women and 8 men) with approval from the Ethics Committee.
of Charing Cross Hospital. Subjects had no history of respiratory or neurological disease, and all had normal lung function as determined by forced spirometry. Three subjects were light smokers; two of the subjects were authors of this paper.

Motor Control Task

Each subject was required to undertake a compensatory motor control tracking task (4, 15). To do this, the subject was seated in front of a computer monitor on which was displayed a stationary target and a cursor. The cursor could move in only one dimension, up and down the screen. The subject was instructed to maintain the position of the cursor on the target by compensating for imposed perturbations of the cursor from the target. The subject could control the position of the cursor in two ways: 1) by breathing in and out of a spirometer (ventilatory task) or 2) by moving a joystick backward and forward (manual task). Each type of tracking task lasted for 90 s.

For the ventilatory task, each subject breathed through a mouthpiece attached to a dry rolling seal spirometer (Spiroflow, PK Morgan) by a nonrebreathing valve and wide-bore tubing. The valve and tubing minimized rebreathing of expired gases during the task. The total volume of the closed tubing consisted of a metal rod attached to a rotary potentiometer; movement of the joystick was confined to a single plane, toward and away from the body.

The volume in the spirometer (during the ventilatory task) and the position of the joystick (during the manual task) were each sampled (at 20 Hz) by a computer [British Broadcasting Corporation (BBC) Master, Acorn Computers] that then controlled the movement of the screen cursor appropriately. Signals from the joystick and the spirometer were amplified so that a deflection of 4 cm on the screen was produced by a horizontal movement of 15 cm of the subject's arm or by a 1-liter volume displacement of the spirometer. Forward movement of the arm or exhalation produced upward movement of the cursor on the screen.

During each tracking task, the perturbations of the cursor from the target were created by using a triangular forcing function. The amplitude of each perturbation was selected from four possible values corresponding to 500, 750, 1,000, or 1,250 ml for breathing movements and 7.5, 11.25, 15, or 18.75 cm for of the joystick movements; the duration of each perturbation was either 4, 5, or 6 s. From these, four patterns of forcing function were chosen, such that the number of triangular waves and the sum of their amplitudes were the same over 90 s for each of the patterns; the forcing function for the ventilatory task was equivalent to 10 l/min. An example of one pattern of forcing function and the subject's response during a ventilatory task is shown in Fig 1.

Manipulation of Steady-State PETCO2

To establish controlled levels of steady-state PETCO2 levels before performing the tracking task [hypercapnia, eucapnia, and hypocapnia; see Protocol (Days 3 and 4)], each subject hyperventilated on a flow-past circuit for 5 min during which time the fraction of CO2 in the inspired air (FICO2) was adjusted to manipulate the subject's PETCO2. The level of hyperventilation before each task was designed to be constant; the subject breathed in and out in time to an auditory cue (resulting in 20 breaths/min) while being given verbal instructions to take larger or smaller breaths as their tidal volume (VT) was targeted to 1 liter. This level of hyperventila-

![Graph](http://jap.physiology.org/)

Fig. 1. Example of one pattern of triangular forcing function (top) and one subject's breathing response (middle, inspiration up) during a ventilatory tracking task. Forcing function has been inverted to allow easier comparison with breathing response; it represents the amplitude (liter) and duration (s) of the cursor movement from the target during the 90-s task. Accuracy of the subject's tracking performance is determined by how closely the subject's breathing response matches the pattern of the forcing function. Continuous error signal (bottom) shows the instantaneous difference between the forcing function and the subject's breathing response. Root mean square (RMS) error over 90 s was calculated to give a single measurement of the subject's tracking performance.

Control of PETCO2 and End-tidal PO2 (PETO2) Within the Spirometer Circuit

To minimize changes in the subject's PETCO2 from the desired level during the tracking tasks, the starting composition of the gas in the spirometer circuit was modified before each tracking run. Before the hypercapnic and eucapnic tracking tasks, predetermined amounts of 100% CO2 were titrated into the spirometer circuit. Approximately 250 ml of 100% O2 were added to the circuit before the eucapnic and hypocapnic tracking tasks to prevent any falls in arterial oxygen saturation (SaO2) that might occur during the manual tasks should the level of spontaneous ventilation fall.

Practice Tracking Runs (Days 1 and 2)

On day 1, each subject practiced four manual tasks and four ventilatory tasks with ~2 min of rest between each practice run; six of the subjects practiced the manual tasks
first and six of the subjects practiced the ventilatory tasks first. On day 2, the subjects practiced another four manual and four ventilatory tasks, in the reverse order from day 1.

Experimental Tracking Runs (Days 3 and 4)

On each of days 3 and 4, the subject performed six tracking tasks; only one type of task (i.e., ventilatory or manual) was performed on each day. The tracking task (run 1) was started at three different levels of PCO2: 1) hypocapnia (−25 Torr), 2) eucapnia (the resting PETCO2 level), and 3) hypercapnia (−5–6 Torr above the resting PETCO2 level). The order of the three PETCO2 levels was randomized; the task was then repeated (run 2) at each level of PETCO2, the order of which was again randomized.

Protocol (Days 3 and 4)

A measurement of the subject’s resting PETCO2 was made over 10 min while the subject was seated and reading; the mean level of PETCO2 over the last 2 min of this period was referred to as the subject’s eucapnic level. The subject then started to hyperventilate for 5 min, during which time the PETCO2 was held at the desired level for performing the first experimental tracking run. After 5 min of hyperventilation, if the subject was to perform a ventilatory task, they were asked to “hold their breath at the end of a normal breath out”; on their signal, they were switched into the spirometer circuit and immediately began the tracking task. Subjects had previously been familiarized with this procedure of relaxing their breathing at functional residual capacity so that the cursor would be stationary on the target at the start of the task before the perturbations began. If they were going to perform a manual task, they were asked to hold the joystick and move the cursor to its start position on the target. When they had done this, they were switched into the spirometer circuit and immediately performed the task. During the manual tasks, the subjects breathed spontaneously on the spirometer circuit. They had been instructed that the movement of the cursor was controlled only by the joystick and was completely independent of their breathing.

After performing the tracking task, the subjects remained seated at rest and read for 5 min after having removed the mouthpiece. They then began the hyperventilation period associated with the next experimental run.

Measurements

PCO2 and PO2 in respired air were measured, by using a mass spectrometer (QP 9000, Case Medical), from gas sampled at the mouthpiece. SaO2 was estimated by using pulse oximetry with an ear probe (Biox 3200, Ohmeda). When subjects were breathing on the flow-past circuit, airflow was measured with a pneumotachograph placed between this circuit and the three-way tap; airflow was integrated to give volume.

Recording of Data

Airflow, VT, end-tidal PCO2, PETCO2, SaO2, and the voltage outputs from the spirometer and the joystick were recorded using a computer-based data-acquisition system (1401 and Spike 2, Cambridge Electronic Design). In addition, during each tracking task, the forcing function and the subject’s response (the voltage output from either the joystick or spirometer) were sampled at a frequency of 10 Hz and stored on the BBC computer.

Data Analysis (Days 3 and 4)

For each period of hyperventilation, the inspired ventilation (Vi), and the mean PETCO2 and PETO2 levels were calculated from breath-by-breath measurements made over the last minute of the period. These are reported as the steady-state levels at time 0 (i.e., at the start of the tracking task). During the task, breath-by-breath measurements of PETCO2 and PETO2, and their mean values were calculated over three successive 30-s periods of the task (period 1: 0–30 s, period 2: 30–60 s, and period 3: 60–90 s). A mean level was calculated only if there were three or more end-tidal measurements that reached a satisfactory plateau during the 30-s time period. The accuracy of each tracking performance was assessed by determining the difference between the ideal response (as determined by forcing function) and the subject’s response sampled every 50 ms throughout the task (continuous error; Fig. 1). The average error [root mean square (RMS) error] for the 90 s of the task was calculated as follows:

\[
\text{RMS error} = \sqrt{\frac{\sum_{i=1}^{n} (\text{continuous error})^2}{n}}
\]

where i is the instantaneous measurement and n is the total number of measurements in the 90-s period.

Statistical Analysis

All data are presented as group means ± SE unless otherwise stated. Statistical comparisons were made by using repeated-measures one-way analyses of variance; for each test, overall statistical significance was determined by using a threshold of \( P < 0.05 \); further post hoc comparisons of individualwithin-factor differences were determined, as appropriate, by using Fisher’s least significant difference (LSD; \( P < 0.05 \); Ref. 10).

RESULTS

Training and Tracking Performance

The accuracy of both tracking tasks, assessed from the RMS error, improved significantly during the eight practice runs performed over the 2 days from 77 ± 7 (practice 1; RMS, arbitrary units) to 47 ± 3 (practice 8) for the arm tracking and from 71 ± 4 (practice 1) to 54 ± 3 (practice 8) for the ventilatory tracking.

Ventilation and PETCO2 Before the Tracking Tasks (Days 3 and 4)

The mean levels of Vi and PETCO2 achieved before each task are shown in Table 1. There were no significant differences between the levels of Vi achieved before run 1 or run 2 (\( P = 0.39 \)) or between the levels of Vi achieved before the manual or ventilatory tasks (\( P = 0.45 \)). Vi was slightly but significantly higher before the hypercapnic tasks compared with the periods before the eucapnic or hypocapnic tasks. For the three PCO2 levels (i.e., hypocapnia, eucapnia, and hypercapnia), there were no significant differences between the steady-state PETCO2 levels achieved before runs 1 or 2 (\( P = 0.85 \)) or between the steady-state PETCO2 level achieved before a manual or ventilatory task (\( P = 0.07 \)).

PETCO2, PETO2, and Breathing Pattern During the Tracking Tasks

Examples of a ventilatory and a manual tracking task performed at eucapnia are shown for one subject in
Table 1. Ventilation and PETCO2 before the tracking tasks performed on days 3 and 4

<table>
<thead>
<tr>
<th>PCO2 Level</th>
<th>Tracking Task</th>
<th>V̇I (l/min) Run 1</th>
<th>V̇I (l/min) Run 2</th>
<th>PETCO2, Torr Run 1</th>
<th>PETCO2, Torr Run 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocapnia</td>
<td>Manual</td>
<td>20.5 ± 0.5</td>
<td>21.0 ± 0.7</td>
<td>25.2 ± 0.7</td>
<td>24.5 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Ventilatory</td>
<td>21.3 ± 0.7</td>
<td>20.4 ± 0.5</td>
<td>24.9 ± 0.5</td>
<td>25.2 ± 0.4</td>
</tr>
<tr>
<td>Eucapnia</td>
<td>Manual</td>
<td>21.1 ± 0.3</td>
<td>21.0 ± 0.2</td>
<td>36.2 ± 0.7</td>
<td>36.0 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>Ventilatory</td>
<td>21.3 ± 0.7</td>
<td>20.8 ± 0.5</td>
<td>36.9 ± 0.6</td>
<td>36.9 ± 0.8</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>Manual</td>
<td>22.7 ± 0.1</td>
<td>23.0 ± 0.8</td>
<td>40.8 ± 0.9</td>
<td>41.8 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Ventilatory</td>
<td>23.5 ± 0.6</td>
<td>23.3 ± 0.7</td>
<td>42.9 ± 0.6</td>
<td>42.6 ± 0.7</td>
</tr>
</tbody>
</table>

Values are means ± SE of levels of inspired ventilation (V̇I) and end-tidal PCO2 (PETCO2) achieved before each tracking task. Level of V̇I and mean PETCO2 were calculated from measurements made over the last minute of the hyperventilation period immediately before the start of each tracking task. Mean values of V̇I and PETCO2 were calculated for 11 and 10 subjects, respectively (measurements not possible in 2 subjects for technical reasons). Mean spontaneous eucapnic PETCO2 level (calculated for all 12 subjects) was 34.9 ± 0.7 (SE) and 35.8 ± 0.6 mmHg before the manual and ventilatory tracking tasks, respectively.

Fig. 2. During the ventilatory task (Fig. 2A), the PETCO2 was maintained at the targeted eucapnic level as the task began and fell slightly in the middle of the task before increasing again over the last 30 s. The PETO2 remained above 100 Torr throughout the task. During the manual task (Fig. 2B), the PETCO2 fell slightly below the targeted PCO2 level after the subject took a large breath at the beginning of the task, but then it in-
increased as breathing became more shallow. The PETCO₂ fell gradually throughout the task to a minimum of 94 Torr after 90 s.

The group mean levels of PETCO₂ before, and during, each 30-s period of the manual and ventilatory tracking tasks are shown in Fig. 3. PETCO₂ level increased significantly (P < 0.001) with time (i.e., during periods 1–3) for both the manual and ventilatory tasks at all three levels of PETCO₂. During hypocapnia, the PETCO₂ level for period 2 was significantly lower during the ventilatory task (LSD, P < 0.05). During hypercapnia, PETCO₂ was slightly but significantly lower at all times during the manual task (i.e., during periods 1–3; LSD, P < 0.05)

PETO₂ and SaO₂ were maintained above 100 Torr and 95%, respectively, during all periods of ventilatory tracking. For the manual tracking, PETO₂ fell below 90 Torr during one of the two tasks performed at hypocapnia in four subjects (minimum PETO₂ 87 Torr). In a fifth subject, PETO₂ fell below 90 Torr during both of the manual tracking tasks performed at hypocapnia (minimum PETO₂ 79 Torr). In two of these subjects, the fall in PETO₂ was accompanied by a fall in SaO₂ to below 95% (minimum SaO₂ for the 2 subjects: 92 and 93%).

Tracking Performance

The RMS errors for both the manual and ventilatory tracking tasks at each level of PCO₂ are shown for the group in Fig. 4. Overall, there was a similar level of error for the two tasks. However, the RMS error for both tasks was significantly less for run 2 when compared with run 1 (P = 0.019, manual tasks; P = 0.002, ventilatory tasks) at all three levels of PCO₂ level.

There was no significant effect of PCO₂ level on the RMS error during the manual tasks (P = 0.434). For the ventilatory tasks, there was a significant difference in RMS error with changes in PCO₂ level for both run 1 (P < 0.001) and run 2 (P < 0.003). In each case, comparison of the means by using the LSD statistic (P < 0.05) revealed that the RMS error for the ventilatory tracking was significantly greater during hypercapnia compared with during eucapnia or hypocapnia; there was no significant difference in the errors during eucapnia compared with hypocapnia. These findings are illustrated for one individual in Fig. 5. The magnitude of the continuous error (the difference between the forcing function and the subject's response) is similar during the hypocapnic and eucapnic tracking tasks; however, during hypercapnia, the magnitude of the continuous error is visibly greater throughout the task.

Subjective Comments

All subjects were asked to report their subjective assessment of their performance in the tasks. Ten subjects reported that the ventilatory tracking tasks had varied in difficulty; only two felt that this was the case with the manual tasks. In every case, the ventilatory tasks were reported to have been more difficult in the hypercapnic state.

DISCUSSION

The principal findings of the study are 1) the accuracy of the volitional control of arm movement was the...
Experimental Approach

Motor control task. In the present study, the tracking task required subjects to compensate for imposed movements of a cursor from a stationary target. During the task, the subjects could see the stationary target (which represented zero error) and the position of the cursor (which represented the current error), but they could not see the triangular forcing function (i.e., the tracking task itself). This design means that subjects are unable to predict the task and the accuracy of motor control can be assessed independently from the subject's cognitive abilities. Such compensatory tracking tasks are used for the assessment of many types of motor control performance, and their use has been reviewed by Poulton (21).

The compensatory tracking task used in the present study was developed and used by Heywood et al. (15) to assess the precision of the voluntary control of breathing. They showed that for a slow tracking task, similar to that used in the present study, the voluntary control of breathing was as accurate as the volitional control of arm movement in normal healthy subjects; this finding was also confirmed by Cohen et al. (4). Hence in the present study, the control of arm movement was used as a condition with which to assess the effects of Pco2 per se on motor control. Clearly, such motor control was unaffected by the levels of hypo- and hypercapnia used here.

This form of voluntary breathing, tracking a target with visual feedback, is clearly not a natural form of breathing even for respiratory behaviors, including speech, that employ the voluntary motor control system (5, 18, 23). It does have the substantial advantage over speech in that the performance of the breathing task can be unambiguously quantified. However, it remains a caveat for the interpretation of this study that the neural basis for, and therefore the behavioral correlate of, the interaction between this task and the chemical control of breathing may be different from other breathing tasks that employ the voluntary motor system.

Practice runs. The aim of the practice runs was to minimize any confounding effects that learning might have on the experiment. Despite eight periods of training for each task, tracking performance continued to improve during the experimental runs on days 3 and 4, with the RMS error for run 2 being less than for run 1 at each Pco2 level for both tasks. This improvement was, however, slight compared with the learning achieved on days 1 and 2, and the study design means that the improved learning will not in itself confound our interpretation.

Measurement of resting PETCO2. The resting PETCO2 levels, referred to throughout the study as eucaopia, were made while the subjects were seated and concentrating on reading material. Despite the consistency between the measurements over the 2 days (34.9 and 35.8 Torr), these mean levels of resting PETCO2 appear low in comparison to the widely accepted view that the normal resting PETCO2 level is around 40 Torr (13). However, it has been argued more recently that the normal resting PETCO2 is lower than 40 Torr (25) and that resting measurements of PETCO2 are sensitive to changes in sensory stimulation and experimental conditions (1, 25). For example, Shea et al. (25) showed that the mean resting PETCO2 level, calculated for 41 healthy subjects, was 37.6 Torr (range for all subjects 29–42 Torr) when measured under strictly defined conditions of unstimulated rest (subject lying supine and blindfolded with sound muffled). Hence the mean resting PETCO2 levels measured in the present study may reflect the conditions of measurement, which were chosen to reflect a normal stimulated condition (i.e., eyes open and concentrating on reading material).
Interactions Between the Chemical and the Volitional Control of Breathing

Hypercapnia and voluntary control. To our knowledge the present study is the first to investigate the effect of changes in PCO₂, above and below eucapnia, on the accuracy of a task that requires explicit voluntary control of breathing. Lansing et al. (16) have reported that the ability to voluntarily target inspiration is impaired after the inhalation of 11% CO₂. The results of the present study have extended those of Lansing et al. by showing that the accuracy of the volitional control of breathing is reduced even during mild hypercapnia, when subjects are unaware of breathing inhaled CO₂. Hence, it would seem that precise voluntary control of breathing is affected by even small increases in PCO₂.

A number of studies have assessed the effect of increasing the chemical stimulus to breathe on the behavioral modifications of breathing that occur during speech (3, 20). Bunn and Mead (3) showed that speech is associated with an increase in ventilation (because the flows required exceed that of resting ventilation) and a decrease in PETCO₂. However, when the chemical stimulus to breathe was increased, speech quality was maintained at the expense of ventilation such that the ventilatory response to inhaled CO₂ during speech was reduced by 73% compared with the spontaneous response (3, 20). In the studies of Phillipson et al. (20), the behavioral control of breathing needed for speech appeared to override the chemical stimulus to breathe up to a PETCO₂ level of 70 Torr. The results of these studies appear at odds with the results of the present study and with those of Lansing et al. (16). However, it is not clear how the preservation of speech quality was assessed, and the fine control of ventilation was not assessed. It is possible that speech quality may not be impaired until ventilatory control is substantially compromised.

Eucapnia and voluntary control. The most important, and novel, observation of the present study is that the precision of the voluntary control of breathing was the same during eucapnia as during hypocapnia, both of these being more accurate than during hypercapnia. Had we observed that the accuracy of the volitional control of breathing was decreased at eucapnia, compared with during hypocapnia, we would have concluded that a conflicting interaction between voluntary and reflex breathing existed at the resting PaCO₂ level; this would have suggested that the eucapnic PaCO₂ level did influence resting breathing during wakefulness.

Our observation that the precision of the voluntary control of breathing was the same during eucapnia as during hypocapnia appears to have two potential explanations. First that any potentially confounding chemical drive is the same at these two levels of PCO₂, or, second, that the chemical drive is below that necessary to modulate the voluntary control task performed in this experiment.

The first explanation, that the chemical drive is the same at eucapnia and at hypocapnia, would be consistent with our previous observation that breathing at a low PCO₂ appears independent of the prevailing PCO₂ (6) and that immediate posthyperventilation apnea is rarely present in awake subjects during hypocapnia (2, 8, 17, 26, 27) but is easy to elicit in subjects who are asleep (7, 26). It would also be consistent with the widely reported “dogleg” shape of the ventilatory response to inhaled CO₂ first reported by Nielsen and Smith (19). This dogleg implies that there is no or minimal sensitivity to changes in CO₂ below the observed level of PCO₂ at which the bend in the dogleg is observed, this usually being at or around eucapnia. However, these concepts appear inconsistent with recent evidence that respiratory sensitivity to PCO₂ does exist below eucapnia in awake humans (11, 24). The response to a fixed peripheral chemoreceptor stimulus during volume-cycled mechanical ventilation has been assessed in this laboratory by using the modulation of inflation pressure and respiratory electromyographic activity as indexes of respiratory motor output (24). With these indexes, we observed that the response to the fixed peripheral chemoreceptor stimulus was modulated by changes in steady-state PETCO₂ (acting at the central chemoreceptors) below eucapnia, indicating that CO₂-related chemosensitivity persisted in the hypocapnic state. Georgopoulos et al. (11) induced hypocapnia with pressure-support ventilation and reported modulation of respiratory motor output by changes in PCO₂ during hypocapnia as low as 25 Torr. Significantly, both Roberts et al. (24) and Georgopoulos et al. (11) maintained hypocapnia independently of respiratory motor output, which was either slight or absent. This allowed CO₂ sensitivity to be assessed in terms of the neural output to the respiratory muscles during hypocapnia without other confounding effects being present; in particular, respiratory motor output related to wakefulness stimuli, which would presumably produce a level of ventilation typified by the dogleg phenomenon, would not have been present.

The second potential explanation for our observations is related to the level of ventilation at which the voluntary breathing was performed. We can expect that the level of spontaneous ventilation that would be associated with the levels of hypocapnia and eucapnia (6) used in the present study would be less than the level of ventilation associated with the ventilatory tracking task (10 l/min); similarly, the level of spontaneous breathing associated with hypercapnia would be greater than the level of ventilation during the tracking task. Therefore, it is possible that the observations in the present study do not reflect an absence of CO₂ drive at eucapnia per se. They may reflect a relationship in which voluntary ventilation (here determined by the tracking task) is independent of PCO₂ when the level of voluntary ventilation exceeds the level of spontaneous ventilation that would otherwise be associated with the prevailing PCO₂. This explanation would also be consistent with the data of Roberts et al. (24) and Georgopoulos et al. (11) discussed above. If this is the case, increasing the level of voluntary ventilation should increase the level of hypercapnia at which tracking error is increased. Similarly, if voluntary ventilation is reduced to a level below that present during eupnea, we
would expect an increased error associated with tracking during eucapnia. It is, however, not clear what components of the overall level of ventilation (i.e., timing, Vt, or airflow) might be important in this regard; Rafferty and Gardner (22) propose that maintenance of Vt may be more important than other aspects of respiratory pattern for, in the steady state, subjects are unable to voluntarily reduce Vt below that determined during free breathing at rest (22). In contradiction, it is clearly possible to take voluntarily breaths smaller than a resting Vt; the characteristics of the interaction between voluntary and reflex control may therefore depend on the duration of any given targeting period. Such questions remain unanswered at present.

Spontaneous ventilation and PaCO2 level. The results indicate that either a chemical stimulus to breath is absent during spontaneous eucapnic breathing or that, if ventilation exceeds that which the prevailing PaCO2 would determine, then breathing will be independent of PaCO2. We suggest that, during wakefulness, the chemical stimulus to breathe, related to PaCO2, is not a significant influence on breathing and that the wakefulness stimulus to breathe determines ventilation and hence the eucapnic PaCO2 level. However, the wakefulness stimulus is unlikely to be constant and eucapnic PaCO2 is labile; therefore, at times, the chemical stimulus to breathe may predominate. It is possible to speculate that the role of the wakefulness stimulus to breathe may be to maintain resting PaCO2 at a level at which breathing can be modified for the many volitional/behavioral acts without conflicting with the reflex chemical control of breathing. The neural basis for the integration of the reflex and voluntary control of breathing, as exemplified in the present study, remains speculative and a subject for further investigation; readers are referred to a recent review of this subject (12).

This work was supported by the Wellcome Trust. C. A. Roberts held a Wellcome Trust Prize Studentship.

Address for reprint requests and other correspondence: D. R. Corfield, Dept. of Respiratory Medicine, Imperial College School of Medicine, Charing Cross Campus, St. Dunstan’s Rd., London W6 8RP, UK (E-mail: d.corfield@ic.ac.uk).

Received 10 August 1998; accepted in final form 6 July 1999.

REFERENCES