Ventilation is unstable during drowsiness before sleep onset

Stuart Thomson,1 Mary J. Morrell,2 Jeremy J. Cordingly,2 and Stephen J. Semple1

1Department of Respiratory Medicine, Charing Cross Hospital Campus, and 2Clinical and Academic Unit of Sleep and Breathing, Royal Brompton Hospital, National Heart and Lung Institute, Imperial College, London, United Kingdom

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Ventilation is unstable during drowsiness before sleep onset. J Appl Physiol 99: 2036–2044, 2005. First published July 14, 2005; doi:10.1152/japplphysiol.01040.2004.—Ventilation is unstable during drowsiness before sleep onset. We have studied the effects of transitory changes in cerebral state during drowsiness on ventilation at sleep onset (25), which may prevent the occurrence of apneas and periodic breathing changes with changes in cerebral state. It is our hypothesis that the sleep-related rise in Pco2 does so by raising the Pco2 above the apneic threshold for CO2.

The purpose and design of our experiments was to determine the change in ventilatory motor output at the alpha-to-theta transition, independent of fluctuations in ventilation, Pco2, and upper airway resistance. We used assisted ventilation to clamp Pteco2 and Pteo2 constant during alpha activity and so determine the effect of a change in cerebral activity, independent of fluctuating chemical feedback or feedforward. To avoid changes in tidal volume (VT) from alterations in upper airway resistance, a volume-cycled ventilation was used, set at a predetermined volume. The ventilator was triggered by the subject (assist/control mode), and the assessment of ventilatory drive after the alpha-theta transition was made from the presence or absence of a breath triggered by the subject.

The development of a rapid-responding intra-arterial pH electrode in our laboratory enabled us, for the first time, to...
record changes in arterial Pco2 (Paco2) in two subjects during periods of ventilatory instability associated with an apnea, when PetCO2 cannot be used as a surrogate for Paco2.

We observed, at constant PetCO2, that the transition from alpha to theta activity produced a significant prolongation of breath duration (Tr), often with apneas lasting 10–20 s. A preliminary report on these findings has been presented (28).

METHODS

Subjects. Volunteers were recruited from the staff of the medical school. All were men with no history of snoring or ill health. The mean (SD) body mass index was 22.37 kg/m2 (SD 3.04). None of the subjects was aware of the purpose of the experiments. Ethical approval for the experiments was obtained from the local Research Ethics Committee, and full consent was obtained from each subject. The two subjects in whom an arterial record was obtained had normal spirometric lung function studies. Arterial cannulation was carried out under local anaesthetic with full aseptic precautions.

Measurements. The EEG was monitored using two EEGs (C3-A2, C4-A1), two electrooculograms (left and right eye), and electromyogram of submental muscle. These were recorded and calibrated via analog amplifiers (model 18c-P-23, Grass Instrument, Warwick, MA). Airflow was measured by using a Fleisch no. 2 pneumotachometer with a differential pressure transducer (MP 45 + 2 cmH2O Validyne, Northridge, CA) attached to a nasal mask. Expired air was sampled through a flexible tube placed within the nostril. From this, PetCO2, and PacO2 were measured by using a mass spectrometer (QP9000, P. K. Morgan, Kent, UK). During apneas and breathing at slow respiratory rates, there was occasional contamination of expired airflow from air within the mask. In these circumstances, PetCO2 was determined by extrapolation of the mid- to terminal part of the expired CO2 to the end of expiration. The dead space of the mask plus pneumotachygraph was ~60 ml.

Arterial pH and PacO2. PacO2 was continuously measured by using a fast-responding intra-arterial pH electrode, which has been described in detail elsewhere (5). Briefly, the sensor of the system consisted of a pH-sensitive plastic membrane adherent to the tip of a catheter, which was threaded down a radial artery catheter (gauge 18) protruding 2–3 mm into the arterial lumen. The internal reference electrode was Ag-AgCl, housed in a 2-ml syringe containing 0.9% NaCl, attached to the radial artery catheter. To avoid thrombus formation and deposition of protomaceous material on the pH sensor, a slow infusion of dilute heparin (2,500 units in 500 ml of 0.9% NaCl) was maintained by a flush device at a rate of 3 ml/h. The 10–90% response time of the electrode system has been determined with phosphate buffers and was 0.17 s (0.01) (n = 43) (6). The voltage output of the electrode system was recorded by using an optical isolated electrometer connected to a locally constructed high-impedance amplifier. The electrode system was calibrated in vivo in isolated electrometer connected to a locally constructed high-impedance amplifier. The electrode system was calibrated in vivo in absolute pH units (pHi) from measurement of arterial blood samples taken during the experiments. Changes in PacO2 were derived from the relationship between millivolts and pH units from the Nernst equation.

Derivation of PacO2 from the record of pH. Over short time periods at rest, pHi is determined solely by changes in PacO2 (1). The output of the electrode system was, therefore, calibrated in terms of PacO2 using pHi, the base excess of the blood sample, and the current hemoglobin level of the subject. A blood-gas calculator (29) was used to derive the PacO2, at intervals of 0.05 units over the full range of pHi covered during an experiment with linear extrapolation between these intervals. The pHi, PacO2, and PacO2 of the blood samples were measured on a blood-gas machine (CIBA-Corning 248), which also provided the base excess of the samples.

Assisted ventilation. This was provided by a volume-cycled ventilator (Life Care, PLV-100, Lafayette, IN), triggered by the subject at the start of an inspiratory effort (assist/control mode). The Vt, inspiratory-to-expiratory ratio, and flow rate were adjusted to those which the subject found most comfortable.

All signals were recorded on a digital computer via an analog-to-digital interface (model 1401 Plus, Cambridge Electronic Design, Cambridge, UK). Digital signals were then analyzed by using commercially written software (Spike 2, Cambridge Electronic Design).

Protocol. Subjects attended the laboratory on a day previous to the experiment to familiarize them with the equipment and assisted ventilation. The subjects were asked to restrict their sleep on the night before the experiment (3–5 h). No caffeine was taken for ≥4 h before the experiment and a light meal in the evening ≥2 h before the study.

Subjects arrived in the laboratory at 10:00 PM. The EEG electrodes were attached, and the catheter for sampling end-tidal gases was placed just inside the nostrils. Subjects then lay on a bed and were asked to relax but not encouraged to sleep. The waking PacO2 was taken over 15–20 breaths at the end of a 10–20 min period of relaxed wakefulness. In the two subjects in whom a record of pH was obtained, the radial artery catheter was then inserted under local anesthesia. The nasal mask was then attached and tested for air leaks. Following this, the assisted ventilation was started. Lights were turned off, and the subjects were asked to sleep. In four subjects, it was necessary to give 5 mg of zopiclone because they experienced no drowsiness, and no theta activity was recorded on the EEG. During the experiment, the presence of air leaks was monitored; if present, the magnitude was assessed from the ratio of expiratory Vt (VTe) to inspiratory Vt (Vti).

Analysis. All variables were analyzed during the period of drowsiness before sleep onset. Drowsiness was defined as occurring during intermittent theta activity on the EEG in the absence of stable stage I/II sleep, as defined by the criteria of Rechtschaffen and Kales (27). Theta activity was defined as a low-frequency activity (<10 Hz) in the absence of rapid eye movements and alpha activity as a frequency content of >10 Hz. During drowsiness, the breaths where theta activity occurred for all or part of the breath were defined as theta breaths. All theta breaths were analyzed if they were preceded and followed by breaths associated with continuous alpha activity on the EEG (alpha breaths) (Fig. 1).

Vt, inspiratory time (Ti), expiratory time (Te), Tr, and expiratory pause (Tp) were derived from the airflow signal; Tr was the period between cessation of expiratory airflow and the onset of the next inspiration. The end-tidal gas tensions, together with pHi and PacO2 in two subjects, were recorded at the end of expiration. The maximum pressure generated by the ventilator was recorded during inspiration. All measurements were made on the theta breaths and the two associated breaths before the theta breath (Pre-1 and Pre-2) and two post-alpha breaths (Post-1 and Post-2) (Fig. 1). The group mean (SD) for the five breaths was computed, and the differences between breaths were compared by using a one-way analysis of variance with repeated measures. When the analysis of variance was statistically significant, a post hoc analysis on the averages was carried out using Fisher’s least squares difference. P < 0.05 was considered statistically significant.

RESULTS

The volume of air delivered by the ventilator and the ratio of Ti to Tr were set where the subject felt most comfortable. The resulting PetCO2 on ventilatory support was significantly less compared with no support [when fully vigilant at the start of the experiment, no ventilatory support = 39.5 Torr (SD 2.3); ventilatory support = 38.0 Torr (SD 1.4); P < 0.05].

Figure 2 shows the effect of the transition from alpha to theta activity on ventilation. Two alpha breaths were followed by an apnea that was associated with theta activity. The record of
mask pressure (Pmask) showed the ventilator was triggered by a drop of 1 cmH2O or less; this was the trigger sensitivity used in our experiments.

The onset of theta activity usually occurred during TE (n = 33, 42%) or TP (n = 29, 37%), the remainder being during TI (n = 16, 21%). In the majority of the 78 theta breaths analyzed, alpha activity resumed during the inspiration of the first post-theta breath (Post-1); however, in 21 of the theta breaths (27%), alpha activity clearly resumed before the Post-1 breath, i.e., at the end of the theta breath.

Effect of changes in cerebral activity on components of TT, end-tidal gases, and maximum inspiratory pressure. The mean results for all eight subjects are included in Table 1. The number of five-breath analyses periods for each subject varied (mean 9.8, range 9–11).

There was no statistically significant difference in the mean values for all variables between Pre-1 and Pre-2 breaths. Throughout the five breaths, mean (SD) Ti remained constant [1.6 s (SD 0.5)], as did VTi [0.86 liter (SD 0.11)]. There was a significant prolongation of TE and TT during the theta breaths, with a 10-fold increase in TP. If an apnea is defined as a cessation of expiratory airflow for ≥10 s, there were 18 apneas, the mean per subject was 2.3 (SD 1.3); 23% of theta breaths analyzed. There was a small but nonsignificant decrease in TE, TT, and TP during the Post-1 breaths compared with Pre-2 and Post-2 breaths.
The mean PETCO2 of the theta and Post-1 breaths was significantly greater than that of the Pre-2 breaths but not the Post-2 breaths. However, the mean PETCO2 of the Post-2 breaths was not significantly different from that of the Pre-2 breaths. The mean PETCO2 of the Post-1 and Post-2 breaths was lower than the preceding three breaths, and this was significant. Maximum pressure was significantly greater in the Post-1 breath only (Table 1).

### Table 1. Effect of changes in EEG activity on breath duration, end-tidal gases, and peak mask pressure

<table>
<thead>
<tr>
<th>Breaths</th>
<th>Ti, s</th>
<th>Tr, s</th>
<th>Tv, s</th>
<th>PETCO2, Torr</th>
<th>PETO2, Torr</th>
<th>VTe, liter</th>
<th>Pmask, cmH2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1</td>
<td>2.9  (1.0)</td>
<td>0.7  (0.3)</td>
<td>5.3  (1.4)</td>
<td>38.0 (1.5)</td>
<td>104 (4.5)</td>
<td>0.72 (0.11)</td>
<td>14.6 (2.6)</td>
</tr>
<tr>
<td>Pre-2</td>
<td>3.1  (0.9)</td>
<td>0.7  (0.3)</td>
<td>5.2  (1.4)</td>
<td>37.9 (1.4)</td>
<td>105 (7.1)</td>
<td>0.73 (0.09)</td>
<td>14.5 (2.6)</td>
</tr>
<tr>
<td>Theta</td>
<td>3.8  (1.5)a</td>
<td>7.5  (2.2)a</td>
<td>13.0 (2.1)a</td>
<td>39.4 (1.4)b</td>
<td>106 (13.4)</td>
<td>0.77 (0.08)</td>
<td>15.1 (2.8)</td>
</tr>
<tr>
<td>Post-1</td>
<td>2.7  (0.9)</td>
<td>0.6  (0.2)</td>
<td>4.8  (1.3)</td>
<td>39.4 (1.6)</td>
<td>98 (2.3)c</td>
<td>0.66 (0.14)d</td>
<td>17.5 (4.0)e</td>
</tr>
<tr>
<td>Post-2</td>
<td>2.9  (0.9)</td>
<td>0.6  (0.2)</td>
<td>5.1  (1.3)</td>
<td>38.7 (1.6)</td>
<td>100 (3.5)c</td>
<td>0.73 (0.11)</td>
<td>14.3 (3.2)</td>
</tr>
</tbody>
</table>

Values are means with SD in parentheses for 8 subjects. The table covers 5 breaths: 2 before a theta breath (Pre-1 and Pre-2) and 2 after (Post-1 and Post-2). 

- TE, expiratory time; Tr, respiratory pause; Tv, breath duration; PETCO2, end-tidal CO2 tension; PETO2, end-tidal PO2; VTe, expiratory tidal volume; Pmask, mask pressure. 
- Ti, Tv, and Tr significantly longer than all other breaths; 
- PETCO2 significantly higher than all other breaths; 
- PETO2 significantly lower than preceding breaths; 
- VTe of Post-1 breath significantly smaller than all other breaths; 
- Pmask significantly higher than all other breaths: $P < 0.05$.

The mean PETCO2 of the theta and Post-1 breaths was significantly greater than that of the Pre-2 breaths but not the Post-2 breaths. However, the mean PETCO2 of the Post-2 breaths was not significantly different from that of the Pre-2 breaths. The mean PETCO2 of the Post-1 and Post-2 breaths was lower than the preceding three breaths, and this was significant. Maximum pressure was significantly greater in the Post-1 breath only (Table 1).

### Change in pHα, PαCO2 before, during, and after theta breaths

Figure 3 shows a record of pHα, EEG, VT, and PETCO2 in one of the subjects. The theta breath is associated with a change in EEG activity and an apnea. The arrow in the figure joins the VT to the pHα oscillation, which it generates in the lung. The delay is due to the circulatory time between lung and radial artery. The relationship between pHα and VT is maintained throughout the record, such that the fourth pHα oscillation is generated by the immediately preceding VT; thus the second oscillation is generated by the first VT shown on the extreme left of the figure (see arrow). The next breath has a slightly longer TV than the other alpha breaths so that the third oscillation has a slightly longer and deeper downstroke of the pHα. During the theta breath, the fall in pHα does not start until about halfway through TV. Thereafter, pHα rises following the return of ventilation to the same level that preceded the theta breaths. The vertical lines on the pHα record are the points at which pHα is measured, and PaCO2 is computed at the end of expiration. The values of pHα and PaCO2 from left to right are 7.415 and 41.0 Torr, 7.414 and 41.1 Torr, 7.413 and 41.3 Torr, 7.399 and 43.1 Torr, 7.393 and 44.2 Torr, 7.409 and 41.8 Torr, and 7.415 and 41.0 Torr, respectively. The PETCO2 of the Post-1 breath was less than the Pre-1 and the theta breath. However, the pHα fell from 7.399 to 7.393 and the PaCO2 rose from 43.1 to 44.2 between the end of the theta breath and the end of the Post-1 breath. The reason for this discrepancy between PETCO2 and PaCO2 is addressed in the DISCUSSION under Changes in lung volume and arterial to end-tidal PCO2 gradient. Due to the slow respiratory frequency on assisted ventilation and the low or absence of gas flow at the end of expiration, the expired CO2 is contaminated from gas within the mask. The PETCO2 was derived from extrapolation of the expired CO2, as described in METHODS.
tion, during the apnea, is generated by the theta breath. Measurements of pH and PaCO₂ were made at the end of expiration shown by the short vertical lines on the record of pH. It can be seen that there is little change in pH at the beginning of the apnea. Following the apnea, pH rises rapidly, returning to the preapnea level by the third post-theta breath.

Twelve apneas were measured in the subject shown in Fig. 3, and the mean results are presented in a stylized format in Fig. 4 and in Table 2 (subject A), together with a statistical analysis in the table. At the start of the apnea, there was no change in pH due to the delayed arrival in the radial artery of the oscillations in pH from breaths Pre-2 and theta. Thus there was no significant difference in the means of pH and PaCO₂ between breaths Pre-1, Pre-2, and the first missed breath during the apnea (MB-1: Table 2). For the second missed breath during the apnea (MB-2), only four data points were collected, because the apneas terminated before the second missed breath. However, using unpaired t-tests, there was no significant difference between the mean pH of MB-1 and MB-2, but there was a significant difference between the mean pH of MB-2 and that of the theta breaths (P < 0.05). The mean pH of the theta breaths were significantly lower, and the PaCO₂ was higher than Pre-2 breaths, being 0.008 units and 1.1 Torr, respectively. After the theta breaths, pH fell further. The mean pH of Post-1 breaths was significantly lower and PaCO₂ higher than all other means. However, by the Post-3 breaths, none of

Table 2. Arterial pH, PaCO₂, PETCO₂, and arterial-to-end-tidal PCO₂ gradient for 2 subjects, before, during, and after a theta breath

<table>
<thead>
<tr>
<th>Breaths</th>
<th>pHa, units</th>
<th>PaCO₂, Torr</th>
<th>PETCO₂, Torr</th>
<th>PaCO₂-PETCO₂, Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Pre-1</td>
<td>7.415 (0.007)</td>
<td>7.392 (0.006)</td>
<td>41.0 (0.9)</td>
<td>38.1 (0.9)</td>
</tr>
<tr>
<td>Pre-2</td>
<td>7.416 (0.006)</td>
<td>7.395 (0.008)</td>
<td>40.9 (0.9)</td>
<td>37.7 (0.9)</td>
</tr>
<tr>
<td>MB-1</td>
<td>7.414 (0.009)</td>
<td>7.392 (0.008)</td>
<td>41.1 (1.2)</td>
<td>37.9 (1.2)</td>
</tr>
<tr>
<td>MB-2</td>
<td>7.414 (0.008)</td>
<td>7.393 (0.008)</td>
<td>41.1 (0.4)</td>
<td>38.1 (1.0)</td>
</tr>
<tr>
<td>Theta</td>
<td>7.408 (0.007)</td>
<td>7.367 (0.008)</td>
<td>42.0 (1.0)</td>
<td>41.6 (1.4)</td>
</tr>
<tr>
<td>Post-1</td>
<td>7.400 (0.007)</td>
<td>7.364 (0.008)</td>
<td>43.0 (1.0)</td>
<td>42.2 (1.3)</td>
</tr>
<tr>
<td>Post-2</td>
<td>7.409 (0.009)</td>
<td>7.378 (0.011)</td>
<td>41.8 (1.2)</td>
<td>40.0 (1.5)</td>
</tr>
<tr>
<td>Post-3</td>
<td>7.416 (0.009)</td>
<td>7.390 (0.009)</td>
<td>40.9 (1.3)</td>
<td>38.4 (1.2)</td>
</tr>
</tbody>
</table>

Values are means with SD in parentheses of 12 breaths in each of 2 subjects, A and B. The measurements were made at end of expiration for 2 breaths before (Pre-1 and Pre-2) and for 3 breaths after a theta breath (Post-1 to Post-3). Missed breaths (MB-1 and MB-2) are measurements of arterial pH (pHa) and arterial Pco₂ (PaCO₂), where breaths were anticipated from respiratory frequency of preceding alpha breaths. There was no significant difference between the mean pH and PaCO₂ of Pre-1, Pre-2, and Post-3 breaths. The mean pH of the theta breaths was lower and PaCO₂ higher than the Pre-1, Pre-2, and Post-3 breaths for both subjects. Post-1 breaths: The mean pH was lower and the PaCO₂ higher than the theta breaths. This fall in mean pH was significantly different for subject A and was now significantly different from all other breaths, P < 0.05. However, in subject B, the fall was not significantly different from the theta breaths. Post-2 breaths: In both subjects, the mean pH rose and PaCO₂ fell compared with the Post-1 breaths. The means for subject A were now not significantly different from the theta breaths. The mean for subject B, however, was significantly different from all other breaths, P < 0.05. PaCO₂-PETCO₂: The mean gradient was significantly different from all other breaths for subject A, P < 0.05. The mean gradient for the Post-1 and Post-2 breaths was significantly different from all other breaths for both subjects, P < 0.05.
the means was significantly different from those of the Pre-2 breaths (the control value).

The mean results for the second subject in whom pH₈ was recorded are shown in Table 2 (subject B). In this subject, there was no significant difference in the means of Pre-1, Pre-2, MB-1, MB-2, and Post-3. Thus by the third post-theta breath, the mean pH₈ and PaCO₂ had returned to the Pre-2 breath values. Mean pH₈ of the theta breaths was significantly lower and the PaCO₂ higher than all other breaths, except the Post-1 breaths.

The constant pH₈ up to and including the two missed breaths in both subjects confirm that the prolongation of Tr of the theta breaths was solely due to a change in cerebral state, resulting in an altered ventilatory response to an unchanged chemical drive.

Relationship of pH₈ of the theta breath to that of the last preceding missed breath. If the termination of an apnea is due to a chemical stimulus, then the pH₈ of the theta breath (end expiratory) should be less than the last missed breath. Therefore, a comparison of the mean pH₈ and PaCO₂ of all theta breaths in both subjects with the corresponding means of the last missed breath was made. The mean pH₈ (SD) of the last missed breath was 7.392 (SD 0.023), and PaCO₂ was 41.2 Torr (SD 1.4), whereas that of the theta breaths was 7.388 (SD 0.028) and 41.9 Torr (SD 1.3), respectively. Although the mean differences are small (0.004 units and 0.7 Torr), the mean pH₈ of the theta breaths was significantly lower and the mean PaCO₂ higher than the mean of the last missed breaths.

PaCO₂-to-PETCO₂ gradient. The breath-by-breath record of PaCO₂ at the end of expiration allowed us to estimate this gradient (PaCO₂-PETCO₂ gradient) before, during, and after an apnea (Table 2). The gradient during the apnea could only be determined in one of the two subjects, because of contamination of expired CO₂ by air from the mask during the long apneas in subject B. There was a small decrease in the mean gradient in the subject in whom it was determined (Table 2). In contrast, in both subjects, there was a significant increase in the PaCO₂-PETCO₂ gradient following a theta breath for Post-1 and Post-2 breaths. By the Post-3 breaths, the gradient was close to the control means, and the difference was not significantly different (Table 2). The cause of the widening of the PaCO₂-PETCO₂ gradient was that the rise in PaCO₂ following an apnea was not reflected in the PETCO₂.

Changes in expired volume and lung volume with changes in cerebral activity. The mean VTₑ of the Post-1 breaths was significantly smaller than that of all other breaths (Table 1). Changes in VTₑ at constant VTₐ imply changes in lung volume. To determine from our data whether lung volumes had changed between breaths, we calculated the ratio of VTE/VT₁ for all subjects for all breaths. An increase in lung volume will lead to a reduction in VTₑ in relation to VT₁ and hence a decrease in the ratio. A decrease in lung volume will increase the ratio. The results are shown in Table 3. In seven of the eight subjects, the mean VTE/VT₁ of the Post-1 breaths for each of the seven subjects was less than that of all other breaths. The fall in the group mean from 0.85 to 0.74 was statistically significant. Although there was an increase in the VTE/VT₁ for the group mean of the theta breaths, this was not statistically significant, as an increase in the ratio occurred in only four subjects.

Air leaks around the mask. VTₑ was usually less than VT₁, pointing to an air leak between the exit of the Fleisch head and from around the nasal mask. To assess whether the leaks were constant, we used the ratio of VTE to VT₁ (Table 3). Because there was evidence of a change in lung volume in the Post-1 breath and possibly theta breath, Pre-1, Pre-2, and Post-2 breaths were used to assess the constancy or otherwise of air leaks through the five-breath analysis. It can be seen that the average ratio (0.85) for Pre-1, Pre-2, and Post-2 is constant, with the range of ratios between subjects varying from 0.70 to 1.0. In addition, the variation in the ratio within each subject for the three breaths ranged from 0.06 to 0.02, with a mean of 0.04 (SD 0.01).

DISCUSSION

Our results show that, at the transition between awake and asleep, there is an abrupt reduction of ventilatory motor output, which returned equally abruptly at the sleep-to-awake transition. These changes in ventilation at the alpha-theta transition were solely due to a change in cerebral state, independent of fluctuations in ventilation, PCO₂, and upper airway resistance. Our observations were made when the subjects were drowsy, before the attainment of stable stage I/II sleep.

The continuous record of PaCO₂ was in good agreement with that of PETCO₂ in showing that the PCO₂ was stable before the attainment of stable stage I/II sleep. In particular, it showed that the PCO₂ had fallen during the Post-2 breaths of the Post-1 breaths. This finding is in agreement with the observation that the PCO₂ had returned to preapnea levels.

Table 3. Changes in lung volume from the ratio VTE/VT₁

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Pre-1</th>
<th>Pre-2</th>
<th>Theta</th>
<th>Post-1</th>
<th>Post-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.68</td>
<td>0.72</td>
<td>0.99</td>
<td>0.50</td>
<td>0.68</td>
</tr>
<tr>
<td>2</td>
<td>0.93</td>
<td>0.96</td>
<td>0.91</td>
<td>1.03</td>
<td>0.96</td>
</tr>
<tr>
<td>3</td>
<td>0.82</td>
<td>0.84</td>
<td>0.83</td>
<td>0.78</td>
<td>0.85</td>
</tr>
<tr>
<td>4</td>
<td>0.90</td>
<td>0.84</td>
<td>0.91</td>
<td>0.77</td>
<td>0.86</td>
</tr>
<tr>
<td>5</td>
<td>0.94</td>
<td>0.96</td>
<td>0.96</td>
<td>0.68</td>
<td>0.95</td>
</tr>
<tr>
<td>6</td>
<td>1.00</td>
<td>1.00</td>
<td>1.03</td>
<td>0.94</td>
<td>0.96</td>
</tr>
<tr>
<td>7</td>
<td>0.84</td>
<td>0.89</td>
<td>0.98</td>
<td>0.71</td>
<td>0.87</td>
</tr>
<tr>
<td>8</td>
<td>0.72</td>
<td>0.71</td>
<td>0.72</td>
<td>0.49</td>
<td>0.69</td>
</tr>
<tr>
<td>Group mean</td>
<td>0.85</td>
<td>0.86</td>
<td>0.91</td>
<td>0.74</td>
<td>0.85</td>
</tr>
<tr>
<td>(SD)</td>
<td>(0.11)</td>
<td>(0.11)</td>
<td>(0.10)</td>
<td>(0.11)</td>
<td>(0.11)</td>
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</tbody>
</table>

Values are the means for the ratio of VTE/inspiratory tidal volume (VT₁) for each subject over 5 breaths, Pre-1 through to Post-2. The number of 5 breaths analyzed for each subject varied between 9 and 11 (mean 9.8). Also included in the table are the group means for the 8 subjects.

Critique of the methods. The mean PETCO₂ of our subjects was 1.5 Torr below that when awake, and it is possible that the hypocapnia due to assisted ventilation was responsible for the apneas observed. It could be argued that, if the subjects had been breathing spontaneously, then the PCO₂ would have been at or above that when awake, and no apneas would have occurred. This interpretation would be correct if our subjects had been in stable slow-wave sleep. Indeed, in this stable state, periodic breathing and apnea can only be produced by lowering the PCO₂ with assisted or mechanical ventilation (8, 18). Our subjects were not studied in stable sleep but at the start of the onset of non-rapid eye movement (NREM) sleep. Periodic
breathing and apneas have been consistently observed during the onset of NREM sleep (3, 25). Bulow (3) studied 75 normal subjects during drowsiness with alternating alpha and theta activity. He observed in more than two-thirds of subjects periods of periodic breathing, often lasting 10–20 min. Apneas were recorded lasting 10–20 s and occurred when the PetCO2 was “relatively low,” closer to that when awake than when asleep. Zhou et al. (35) induced central apneas in stable sleep in men by mechanical ventilation via a nasal mask. A mean reduction in PetCO2 of 3.54 Torr produced apnea at a PetCO2 equivalent to that when awake. The observations of Bulow (3) and of Zhou et al. (35) are consistent with the PCO2 awake being at or very close to the CO2 apneic threshold when asleep [see also the review by Dempsey (7)]. Thus, during drowsiness at the beginning of sleep onset, apneas can be anticipated until the fall in ventilation associated with sleep raises the PCO2 above the apneic threshold.

We conclude that the apneas observed in our studies were not solely a consequence of assisted ventilation and the associated hypocapnia. The reason that apneas are seen both in spontaneously breathing subjects and those on assisted ventilation at sleep onset is that, initially, in both conditions, the PetCO2 is at or below the apneic threshold.

We have chosen to describe the prolongation of Tr as an apnea, but it is appreciated that, if the definition of an apnea is cessation of breathing for ≥10 s, then we are including theta breaths, which do not meet that criterion. For the purpose of this paper, the term apnea has been retained.

**Derivation of Paco2**. This was determined continuously from the pH(4) record with the conversion of units to Torr using the hemoglobin and base excess of the blood samples (29). This relationship between pH and PCO2 in blood has been determined in vitro under steady-state conditions, and this might not hold under non-steady-state conditions in vivo as in our experiments, where there is a continuously changing pH. However, it has been observed that breath-by-breath oscillations in Paco2 in humans and animals, derived from continuous records of pH(4) (non-steady state), are equivalent to the corresponding fluctuations in alveolar PCO2 (1, 2). On this basis, it is considered that the derivation of Paco2 is justified.

**Air leaks around the mask**. From the analysis of VTe/VTi (Table 3), we conclude that air leaks were virtually constant between breaths and that the reported changes in VTe are valid. This constancy of air leak between breaths is important when considering the mean fall in VTe of the Post-1 breaths, where there was an increase in mean Pmask and hence a likelihood of a larger mask leak. This is unlikely in that three of the subjects had a rise in Pmask of <0.4 cmH2O, but there was still a fall in VTe. In addition, in subject 2 with the highest increase in Pmask (7 cmH2O), there was a small increase, not reduction, in VTe/VTi.

**Constancy of PCO2**. The design of the experiments was to hold Paco2 constant so as to observe the effect on Tr of a change in cerebral state. To determine whether the purpose of this design was achieved, it is necessary to show that the rise in PCO2 following an apnea had been eliminated by the control breaths of the next theta breath. As regards the peripheral chemoreceptors, we consider that the purpose of the design was achieved. There was no significant difference between mean PetCO2 of the Pre-1 and Pre-2 breaths and that of the Post-2 breaths for the group data. There was no significant difference in PaCO2 between Pre-1 and Pre-2 breaths and Post-3 breaths in the two subjects in whom it was measured. Where there were only four breaths between theta breaths, then Post-3 breaths would be the equivalent of the Pre-1 breaths of the following group of five breaths. Assuming the Paco2 in the radial artery approximates that at the peripheral chemoreceptors in time (14), then the constancy of the Paco2 at the chemoreceptors between theta breaths can reasonably be claimed to have been achieved.

While PCO2 at the peripheral chemoreceptors can be determined from that in the arterial blood, this is not so for the chemosensitive regions of the brain due to the relatively slow “wash-in” and “washout” of CO2 in these areas. The magnitude of the ventilatory effects of a brief disturbance of Paco2 at the central chemoreceptor sites has been estimated in experiments in which it was assumed that the contribution to ventilation from the peripheral chemoreceptors was small or nonexistent (13, 16, 19). For example, the ventilatory effect of the inhalation of CO2 for one to three breaths has been studied in humans in hyperoxia awake and asleep (20). The overall cumulative ventilatory response was the same between awake and asleep but was slower in sleep. The peak ventilatory response was 0.08 l/min for a 1-Torr rise in PetCO2; ~2% of expired volume (Ve) was due to a change in VT alone. Special techniques not used in the present experiments are required to detect such small changes in ventilation, such as pseudorandom binary CO2 stimulation (16, 19, 31) and ensemble averaging (13). The ventilatory response to a transient disturbance of CO2 has been shown to be predominantly, if not exclusively, due to the peripheral chemoreceptors in the dog (23) and human (31). We conclude that the effect of the transient rise in PCO2 in our experiments on the theta and subsequent breaths was mediated through the peripheral chemoreceptors, and for the reasons quoted above this effect was cleared by the control breaths of the next theta breath.

**Nonchemical inhibition of respiratory motor output**. There is evidence of a significant nonchemical inhibition of respiratory motor output in sleeping humans on assist-control mechanical ventilation (33). This inhibition may well have been present in our experiments during the theta breaths. The effect on Tr will have been to prolong Tr by 13–32% at the transition from alpha to theta activity on the EEG. However, this nonchemical inhibition of respiratory motor output has been shown not to lead to apnea (33) and, therefore, will have had little or no effect on Tr.

**Changes in lung volume and Paco2-to-Petco2 gradient**. These two changes have been discussed together because they may be causally related. Although we did not measure changes in lung volume directly, there was evidence of rapid changes in lung volume over one to two breaths between the alpha and theta transitions. Hudgel and Devadatta (12) measured lung volumes directly during wakefulness and stable sleep and observed a reduction in lung volume in sleep in 8 out of 10 subjects. They attributed this reduction to a loss of muscle tone of the chest muscles with an implied reduction in thoracic cage recoil, leaving the reduction in lung volume due to the unchanged elastic recoil of the lung. Our mean results for the changes in VT(4) at the alpha and theta transitions are compatible with these proposed mechanisms (Table 1). The reduction in VTe at the theta-to-alpha transition was consistent in all but one of the subjects and was presumably due to a return of muscle
tone with the onset of alpha activity and hence increase of lung volume. However, the expected increase of VT at the alphato-theta transition occurred in only four of the eight subjects. We cannot explain this discrepancy between the two transitions, but it could be due to the effect of continuous gas absorption during the theta breaths, an effect on VE opposite to that of the elastic recoil of the lung, thereby leaving VT unchanged in some subjects.

In both subjects in whom we had a record of PaCO2, there was a significant increase in the PaCO2-PETCO2 gradient in the two breaths following an apnea (Post-1 and Post-2, Table 2). During the apnea in one of the subjects (subject A), there was a small decrease in gradient, but, in subject B, it was not possible to determine the gradient because of contamination of expired air from within the mask. The cause of the increase in gradient after the apneas was not determined, and further research would be required to elicit the cause. However, the changes in lung volume and PaCO2-PETCO2 gradient were closely related in time, and we put forward the possibility that the contraction of lung volume during the apnea altered the ventilation-to-perfusion relationships within the lung, possibly due to airway closure. The effect of this change was manifest in the widening of the PaCO2-PETCO2 gradient in the two subsequent breaths. In addition, the mean Pmask of the first breath after the theta breath (Post-1; Table 1) was significantly higher than all other breaths for the same VT, indicating a change in compliance and/or resistance during the theta breath.

The contribution of the continuous measurement of pHm to the present experimental results. PETCO2, a discontinuous measurement, has been used in the present experiment as an indicator of changes in PaCO2. However, this correlate may fail when there is absent expiratory airflow, rapid changes in PaCO2, and a changing arterial-to-alveolar PaCO2 gradient. All of these factors operated in our experiments and hence the need for a continuous measurement of PaCO2 to determine when PETCO2 could be used as a surrogate for PaCO2. While the changes in PaCO2 during and after an apnea could be qualitatively predicted, on known physiological mechanism, we are unaware that they have ever been recorded before.

There was good agreement between record of PaCO2 with that of PETCO2, in showing PaCO2 was stable before the theta breaths. More importantly, PaCO2 remained unchanged during Ti, Te, and the beginning of the apnea (Tr) of the theta breaths. This is illustrated in Fig. 4 (missed breaths) and confirmed for both subjects in Table 2. Following an apnea, PETCO2 cannot be used to determine changes in PaCO2 because of a changing PaCO2-to-PETCO2 gradient. However, by the third post-theta breath, the relationship between PETCO2 and PaCO2 had been reestablished, and the rise in PaCO2 following the theta breath had been eliminated, thus preserving the constancy of PaCO2 before the next theta breath.

Resumption of breathing after a theta breath. We consider that the resumption of breathing after a theta breath was due to the increase of Pco2, either acting directly as a chemical stimulus to ventilation or indirectly by causing a change in cerebral state. In two-thirds of the theta breaths in this study, the onset of the Post-1 breaths preceded a return in the EEG to an alpha rhythm. In addition, in all subjects, there were occasions when theta activity persisted beyond the Post-1 breath, leading to irregular breathing with repetitive apneas (S. J. G. Semple, unpublished results). Following the theta breaths, the mean Tr and Tr (Table 2) were shorter than all other breaths, although this failed to reach statistical significance. If these mean changes are real, then it can be reasonably attributed to the rise in PaCO2, which continued after the theta breath (Table 2) and, for reasons given earlier, would be mediated primarily through the peripheral chemoreceptors.

Comparison of present findings with previous research. The results of the present experiments confirm the results of Trinder et al. (32) that ventilatory instability at sleep onset is predominantly due to alternating changes in cerebral state, with state being determined, as in our experiments, by alpha and theta activity in the EEG record. There were important differences in experimental design between the two studies. In the experiments of Trinder et al. (32), their subjects were breathing spontaneously, and there were 2–10 breaths or more between the changes in cerebral state. They observed a cyclical variation in VE and PETCO2, predominantly determined by hyperventilation, and fall in PETCO2, associated with the arousal at the theta-to-alpha transition, an increase in ventilation in excess of metabolic demand (11). The magnitude and duration of the cyclical variation in ventilation depended on a complex interaction between changes in state, their duration, and a fluctuating Pco2. In contrast, in our own experiments, VE and Pco2 were stable at the alpha-to-theta transition, whereas, at arousal, there was a transitory rise in Pco2, with no statistically significant change in Tr. Thus, in our experiments, at the alpha-to-theta transition, Tr was determined by a change in cerebral state alone.

The most important difference in experimental design and results between our experiments and those of Trinder et al. (32) was that, in their experiments, the subjects at sleep onset were breathing spontaneously, and no apneas were recorded. In the latter experiments, the anticipated rise in Pco2 between awake and as sleep had occurred (a mean rise of 2.0 Torr), and it is reasonable to assume that the Pco2 was now above the apneic threshold and hence the absence of apneas. In contrast, in our own experiments, a rise in Pco2 at sleep onset was prevented by the assisted ventilation at fixed volume. These findings illustrate the critical role of the rise in Pco2 at sleep onset in reducing or eliminating central apneas and thereby lessening ventilatory instability (28).

Apneic threshold and control of ventilation. We did not determine the apneic CO2 threshold directly in our subjects, but plainly the Pco2 at the alpha-theta transition was below the threshold. The mean Pco2 before the transition was 1.5 Torr (SD 1.8) below that awake, with a range of 0–3.6 Torr. In four subjects, the difference was under 2.0 Torr, being 0, 0.4, 0.5, and 1.8 Torr. If, at the start of drowsiness, the Pco2 is that when awake, then a small, augmented VT from whatever cause may precipitate an apnea (8).

The PETCO2 in the present experiments was below the eupneic Pco2 when awake, and this will have the effect of decreasing plant gain (the ventilatory increase required for a given reduction in Pco2) (9). This will render ventilation more stable during the theta breaths than in subjects breathing spontaneously at a higher Pco2. However, the PETCO2 of our subjects was slightly above the apnea/hypopnea CO2 threshold, and we predict that this would also have been the case if the subjects were breathing spontaneously because, for reasons given earlier, the Pco2 when awake is at or below the threshold. We do not think, therefore, that the predicted increase in ventilatory
stability in our experiments affected the conclusions drawn from the results.

**Conclusions and predictions.** At the start of sleep onset when drowsy, and when the PcO2 is close to or at that when awake, apneas and periodic breathing will occur with changes in cerebral state. The most ready explanation for these findings is that the PcO2 when awake is close to or at the apneic/hypopneic CO2 threshold (7). This explanation would also account for the apneas and periodic breathing frequently observed at the onset of NREM sleep and is likely to be most prevalent in subjects with a high-ventilatory sensitivity to CO2 (10). We have also shown that, when the sleep-related rise in PcO2 is prevented, this unstable ventilatory condition is likely to persist. Any condition that maintains PcO2 close to or below that when awake will render ventilation unstable. This phenomenon has been well documented in patients with heart failure and central sleep apnea where there is no rise in PcO2 from wakefulness to sleep and no proportional reduction in their apnea or hypopnea threshold. In contrast, patients with heart failure and no central sleep apnea do show a rise in PcO2 in stable sleep (34).

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