Correlation between ventilation and EEG-defined arousal during sleep onset in young subjects

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Trinder, John, John A. Van Beveren, Philip Smith, Jan Kleiman, and Amanda Kay. Correlation between ventilation and EEG-defined arousal during sleep onset in young subjects. J. Appl. Physiol. 83(6): 2005–2011, 1997.—In studies of elderly individuals, ventilation and EEG-defined arousal have been shown to vary periodically and synchronously. Such results have been interpreted as indicating the primacy of sleep/wake state in causing ventilatory instability during sleep onset. However, because the elderly individuals studied were periodic breathers, the results do not unequivocally support this conclusion. In this study the relationship between ventilation and EEG-defined arousal was assessed in a group of 21 young, healthy men in whom ventilatory instability during sleep onset was not periodic. Ventilation and EEG (O1-A2) recordings were collected, and the longest uncontaminated periods from early and late in sleep onset were selected for subsequent analysis. The 84 time series (21 subjects, 2 variables, and 2 occasions in sleep onset) were subjected to spectral analysis to identify periodicity, and the relationship between the two variables was determined by cross-correlational methods. The results indicated that the time series were nonperiodic, yet significant correlations were observed between the two variables. The data support the view that during sleep onset ventilatory instability is driven primarily by variations in sleep/wake arousal level.

ventilation is unstable in most individuals during the process of getting to sleep [stage 1/2 non-rapid-eye-movement (NREM) sleep] (3, 14). Under particular conditions such as hypoxia (15, 21), or in particular groups of individuals such as elderly subjects (13, 16, 20), the variations in ventilation are periodic with a cycle time of ~40–60 s over individuals (the term “periodic” will be used to refer to variations in a variable such that the cycle of hyper- and hypoactivity has a constant duration within a subject). In other individuals, for example young and healthy individuals, the variation is not periodic (3, 7). Early hypotheses as to the mechanism underlying instability in the respiratory system during sleep onset focused on the observed periodicity and attributed the instability to the operation of feedback mechanisms in which feedback delay and overall loop gain are the critical concepts (4, 11).

Other explanations for periodic breathing have emphasized the effect of sleep/wake state on ventilation (3, 10, 14, 17). The effect is typically modeled as an abrupt change in the gain of the system in association with changes in state, with higher gain in wakefulness than sleep. The higher gain has been conceptualized as a tonic input to central respiratory drive that is specific to the awake state. It is frequently referred to as the “wakefulness stimulus.” The state change, as identified by the transition between dominant alpha (wakefulness) and theta (light sleep) activity in the electroencephalogram (EEG), is associated with abrupt alterations in ventilation. Indeed, changes in state as brief as single breaths are associated with changes in ventilation (3, 5, 18).

In an attempt to demonstrate the critical role of state changes in the occurrence of respiratory instability during sleep onset, Pack et al. (12) showed that, during periodic breathing in elderly individuals, changes in ventilation were correlated with zero lag with changes in arousal state. Hyperventilation was shown to occur in association with relative high-frequency EEG activity, indicative of arousal, whereas hyperventilation or apnea was shown to occur in association with relative low-frequency EEG activity, indicative of light sleep. This relationship was interpreted as being consistent with the view that changes in state play a critical role in producing respiratory instability during sleep onset. However, studies of the relationship between sleep/wake state and ventilation during periodic breathing may not fully elucidate the role of state changes. This is because the existence of periodicity in the range of ~40–60 s indicates a contribution from respiratory control mechanisms as there is not an intrinsic periodicity in sleep/wake oscillations during sleep onset. Thus, because the periodicity of changes in ventilation in these elderly individuals was due to respiratory mechanisms, it seems hazardous to conclude that the actual changes in ventilation were due to changes in state.

A more definitive test of the hypothesis that changes in state contribute to respiratory instability during sleep onset would be to investigate the relationship between ventilation and arousal state in individuals in whom ventilation was variable, but not periodic. Some evidence suggests respiratory instability during sleep onset in young adults is nonperiodic (3, 7). This is consistent with our informal observations over a number of studies of such subjects (5, 17, 18). The purposes of the present experiment were, first, to assess the periodicity of ventilation during sleep onset in young healthy men, and second, to assess the relationship between ventilation and EEG-defined arousal level in those subjects shown to have nonperiodic breathing.

METHODS
Subjects

The data from 21 young male subjects between the ages of 18 and 24 yr (average = 20.3 yr) are reported in this study.
The subjects were nonsmokers with an average height of 179 cm (167–192 cm) and weight of 71.7 kg (60–84 kg) and had no known history of sleep or respiratory pathology. The subjects were originally run in two studies by using identical laboratory procedures. Their data were selected for inclusion in this analysis if they contained two periods of at least 50 consecutive breaths in which there were no major movements, other disruptions of the recordings, or sustained changes in state. A further requirement was that one of the periods occur early in the sleep onset process, during what will be referred to as “phase 2” of sleep onset, and the other later in the sleep onset process, or phase 3 of sleep onset (8). The studies from which the subjects were selected were approved by the University of Melbourne’s Human Ethics Committee, and subjects gave written informed consent before their participation in the studies.

General Laboratory Procedures

Subjects spent two nonconsecutive nights in the sleep laboratory of the School of Behavioural Science, the University of Melbourne. They were required to refrain from consuming caffeine and alcohol on the day of the experimental sessions. Subjects arrived at ~2100, prepared for bed, and then the recording equipment was attached. Data collection commenced at ~2230. The equipment consisted of surface electrodes for the assessment of sleep/wake state, a full face mask to allow for the measurement of airflow and, in 17 subjects, a Millar catheter, which was introduced transnasally to the level of the epiglottis, to measure upper airway resistance. The variables of interest for the present analysis were sleep/wake state and ventilation, the latter being derived from the rate of airflow measurement.

Subjects were required to maintain a supine position during the experiment. The purpose was to record respiratory and sleep/wake state variables during sleep onset. Accordingly, subjects were instructed to go to sleep after lights out, but they were then awakened as soon as they had attained ~10–15 min of stage 2 NREM sleep. After subjects were awakened, the experimenter ensured that subjects were alert before instructing them to return to sleep. These procedures were repeated until data collection terminated (0300–0400). On average, four to five sleep onsets were obtained each night. The two data sets, one early and one late in a sleep night. The two data sets, one early and one late in a sleep onset process, during what will be referred to as “phase 2” of sleep onset, and the other late in the sleep onset process, or phase 3 of sleep onset (8). The studies from which the subjects were selected were approved by the University of Melbourne’s Human Ethics Committee, and subjects gave written informed consent before their participation in the studies.

Sleep/Wake State Recording Procedures

The EEG was recorded from central (C3-A2) and occipital (O1-A2) sites, the electrooculogram from two electrodes placed ~1 cm above and slightly lateral to the outer canthus of one eye and the same position but slightly below the other eye, and the electromyogram was recorded from the submental muscles. Grass gold cup electrodes were used, with the C3 and O1 electrodes being secured with collodion, and the remaining electrodes were attached with surgical tape.

Respiratory Measurements

Subjects wore either a modified Vital Signs “Downs Continuous Positive Airway Pressure (CPAP)” or a Commonwealth Industrial Gases (CIG) anesthetic face mask that covered the mouth and nose and was held tightly in place by a head strap. Route of breathing was not controlled. A heated Morgan pneumotachograph was attached to the mask. For subjects using the Downs CPAP mask, the pneumotachograph was attached directly to a port in the mask so that inspiratory and expiratory flow were obtained. For subjects using the CIG mask, the pneumotachograph was attached to the expiratory side of a two-way nonrebreathing valve so that expiratory flow was obtained. The total dead space of the mask and pneumotachograph varied as a function of facial configuration and was ~155 ml for the Downs CPAP mask and 120 ml for the CIG mask. For measurement of airflow the pneumotachograph was connected to a differential pressure transducer (Validyne DP45–14), the output of which was converted to a voltage signal by using a carrier demodulator (Validyne CD15). Airflow was calibrated by using a Shorete flowmeter (3355). For the subjects who originally participated in a study in which upper airway resistance was measured, a transducer-tipped catheter was inserted transnasally and positioned visually ~1 cm below the tongue base, 16–18 cm from the nares. The measurements from this device are not relevant to this study.

All sleep/wake and respiratory measurements were recorded by using a model 7D Grass polygraph. The occipital EEG and rate of airflow were also recorded and stored on an IBM-compatible 486 PC via a 16-bit analog-to-digital converter sampling at 100 Hz. Automated off-line analysis was used to compute expiratory tidal volume (VT) and respiratory timing information.

Statistical Procedures

The steps in the statistical analyses are summarized in Table 1.

<table>
<thead>
<tr>
<th>Step 1: Initial preparation of data</th>
<th>Step 2: Data analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determination of phase of sleep onset</td>
<td>Estimation of variability of ventilation</td>
</tr>
<tr>
<td>Identification of time series</td>
<td>Spectral analysis of each series</td>
</tr>
<tr>
<td>Conversion of analog EEG into a weighted ratio EEG</td>
<td>Correlations between tidal volume and weighted ratio</td>
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</table>

Table 1. Steps in statistical analysis

<table>
<thead>
<tr>
<th>Step 1: Initial preparation of data</th>
<th>Step 2: Data analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determination of phase of sleep onset</td>
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<tr>
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<tr>
<td>Conversion of analog EEG into a weighted ratio EEG</td>
<td>Correlations between tidal volume and weighted ratio</td>
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</tbody>
</table>

EEG, electroencephalogram.
with the assumptions of time series analyses and because previous work has indicated that changes in ventilation at transitions between states are a consequence of changes in VT (18). To identify the time series, the raw data from the two nights were inspected, and the longest segment of continuous artifact-free data in both phases 2 and 3 was selected. An artifact was defined as any disruption of the record that prevented the computation of VT or obscured the EEG tracing. The lengths of the identified time series for each phase and subject are shown in Table 2.

**Table 2. Time series length and periodicity in ventilation and EEG for phases 2 and 3**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>TS Length, s</th>
<th>Fisher test</th>
<th>Cycle time, s</th>
<th>Fisher test</th>
<th>Cycle time, s</th>
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<th>Cycle time, s</th>
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<td>20.3*</td>
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</table>

*Significant periodicity (periods between 20 and 90 s). Fisher test values with an asterisk, but without a corresponding cycle time, indicate significant periodicity outside interval 20–90s. Phase 2, sleep period with alternating alpha and theta activity; phase 3, later sleep period with alternating alpha and theta activity but with first appearance of sleep spindle and K complexes and repeated arousals.

Thus R could vary from −1, indicating predominantly higher frequency activity, to 0, indicating predominantly lower frequency activity.

In summary, these procedures allowed the EEG to be represented as a time series that expressed changes in the frequency content of the EEG and that corresponded in time with the time series for VT.

**CONVERSION OF THE IRREGULARLY SAMPLED TIME SERIES TO A REGULARLY SPACED TIME SERIES.** The statistical procedures subsequently applied to the data required that the time series had constant intervals. Thus the irregularly sampled time series for VT and R were resampled at intervals of 4 s by using the method described by Waggener et al. (19). The term “time series” as used in the remainder of the study refers to these evenly spaced (4-s) values for VT and R.

**TEST FOR STATIONARITY AND DETRENDING OF EACH TIME SERIES.** An additional requirement of subsequent statistical procedures was that each time series be stationary. That is, its mean and variance do not change with time. Each series was tested for stationarity by testing the autocorrelation coefficients obtained from the series by using the formula $r^2 < 1/lag$ (6), where lag refers to the number of adjacent values within the time series for which the series itself is correlated. If a series was not stationary, linear trends were removed, and in all cases this was sufficient to achieve stationarity. Of the 84 time series (21 subjects × 2 phases × 2 variables), 75 were initially stationary.
Spectral analysis. The analysis was to determine whether variations in \( V_T \) and \( R \) were periodic. The range of acceptable periodicities was restricted to between 20 and 90 s because periodicities outside this range were unlikely to occur as a function of respiratory mechanisms. The power spectral density of each time series was estimated by using periodogram methods (1). The periods of \( V_T \) and \( R \) were extracted from the relevant spectral estimate by testing for periodicities by using the Fisher test (2). The frequency values of periodicity identified by the Fisher test were determined by examination of the periodogram.

Correlation between \( V_T \) and \( R \). The final stage of the analysis was to examine the correlation between \( V_T \) and \( R \). This was done by fitting appropriate ARMA (autoregressive/moving average) models individually to both the \( V_T \) and \( R \) time series in the manner previously described (2, 6). The ARMA model is a linear filter that removes the autocovariance structures within a series (2). Mathematically, the value of the series at any time is represented as the sum of two components, one predictable from the history of the series before that time and one that is not. The predictable part is represented as a linear combination of previous values of the series and random statistical fluctuations. The residual series obtained after the predictable structure has been estimated and removed is uncorrelated. In the second part of the analysis, the two residual series obtained in this way were cross-correlated.

The third part of the analysis investigated whether ventilation was predictable from the EEG, under the assumption that the \( V_T \) and \( R \) series are, respectively, the input and output of a linear system. To do this, the Box-Jenkins “prewhitening” procedure was used (2, 6). Residuals were obtained for both series by fitting the \( R \) ARMA model to both the \( R \) and \( V_T \) series. The latter series is the output that would be obtained from an unknown (black box) linear system if it were given an uncorrelated series as input. To determine whether such a representation was appropriate, the coherence spectrum was calculated between the two series. This function is a measure of the squared correlation between the frequency components of the two series. If a correlation exists, it is appropriate to attempt to estimate the transfer function of the linear system that relates the two series. In such cases, the \( R \) residuals were entered into the transfer function modeling program (1) as the input series, and the \( V_T \) residuals, obtained by fitting the \( R \) ARMA model to \( V_T \), were entered as the output series. The predicted output series obtained from the transfer model were then cross-correlated with the actual \( V_T \) series to assess the quality of the linear system representation.

RESULTS

The CVs averaged over subjects for wakefulness and early (phase 2) and late (phase 3) in sleep onset were 25.6 (SD = 15.2), 24.3 (SD = 14.8), and 31.2 (SD = 26.3), respectively. The values for each phase did not differ significantly from each other. These values are comparable with those reported for elderly subjects in two studies (7, 16) and for equivalently aged young subjects in one of these (16) but were greater than those reported for young subjects in one other study (7). Of note were the large differences between subjects in CV values, as indicated by the SDs.

The results of the spectral analysis of the time series are shown in Table 2. Of the 84 series, 34 showed significant periodicity. Fourteen of the 34 were outside the range of periods that might reflect periodicity generated by the respiratory system (20–90 s). Of the 20 time series that showed significant periodicity with periods between 20 and 90 s, 9 were from the ventilation series (5 from phase 2 and 4 from phase 3) and 11 were from the EEG series (5 from phase 2 and 6 from phase 3). However, only one of the 21 subjects (subject 9) had significant ventilatory periodicity with approximately the same period for both phases 2 and 3. This subject also had significant periodicity in the EEG time series but at different periods from those observed for ventilation and at different periods for phases 2 and 3. No subject had significant periodicity with the same period length in both ventilation and the EEG within a phase, although in three cases (S1, S9, and S16) both time series were significant such that the ventilatory period was approximately double the EEG period.

In summary, within subjects neither the presence of periodicity, nor the cycle time of any periodicity, was consistent between \( V_T \) and \( R \), or between phases 2 and 3. The unsystematic pattern of the observed significant periodicities suggests the test is particularly sensitive and likely to produce type 1 errors. Thus the data are consistent with a previous report (3) and with our informal observations, suggesting that in young healthy individuals instability in both ventilation and sleep/wake state during sleep onset is essentially nonperiodic.

The finding that neither ventilation nor changes in sleep/wake state were periodic, despite substantial variability in ventilation, provided the appropriate preconditions for assessing the hypothesis that variations in ventilation need not be periodic for changes in ventilation and arousal state to be synchronous.

The relationship between ventilation and the EEG measurement of arousal level is shown in Table 3. The data presented are the maximum correlation coefficients between series for lags between ±3 (\( V_T \) phase delayed/advanced with respect to \( R \) by ±12 s). Values were considered only within this restricted range because Pack et al. (12) have indicated that ventilation and arousal level oscillate with an approximately zero lag, and also to reduce the likelihood of type 1 errors given the length of the time series, and thus the number of coefficients computed between any two series.

Consider, first, columns A and B, for phases 2 and 3, in Table 3. The results indicate that the removal of sequential dependencies (column B) from the original series (column A) slightly reduced the magnitude of the
Table 3. Cross-correlations between EEG measurements of arousal and ventilation

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Phase 2 Coefficient Lag</th>
<th>Phase 2 Coefficient Lag</th>
<th>Phase 3 Coefficient Lag</th>
<th>Phase 3 Coefficient Lag</th>
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<td>0.09</td>
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<td>0.12</td>
<td>0.03</td>
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</tr>
<tr>
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<td>0.09</td>
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<td>0.17</td>
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<td>11</td>
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<td>0.49*</td>
</tr>
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<td>0.21*</td>
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</tr>
</tbody>
</table>

A, equal interval raw data; B, residuals after fitting autoregressive/ moving average (ARMA) models; C, transfer-function analysis. Lag units, 4-s intervals; negative lags, weighted ratio lagged tidal volume. *Significant, P < 0.01.

Finally, as noted above, there were marked individual differences in the variability of ventilation. The magnitude of the relationship between VT and R tended to be lower in subjects who exhibited relatively low ventilatory variability. Thus, of the five subjects in whom there was no relationship between the two time series during phase 3, three had very low ventilatory variability.

DISCUSSION

The present data are consistent with an earlier report (12) showing a synchronous and positive relationship between ventilation and arousal during periods of unstable ventilation characteristic of sleep onset. Furthermore, the data suggest that the level of arousal, as defined by EEG frequency in the 3- to 13-Hz range, predicts the level of ventilation. However, it should be noted that despite the general similarities between the results of this study and the previous study (12), there were three notable differences between the two.

The first was that although the younger subjects in this study exhibited respiratory variability during sleep onset, neither ventilation nor EEG activity was periodic. This contrasts with the clear periodicity in ventilation characteristic of the elderly subject sample studied previously (12). Second, the magnitude of the relationship between arousal level and ventilation was greater in the older subjects. Finally, the phase relationship...
The positive relationship between arousal level and ventilation provides strong support for the view that in normal young adults the instability in ventilation that characterizes sleep onset is determined primarily by instability in sleep/wake state. Three aspects of the data support this conclusion. First, the absence of periodicity in ventilatory fluctuations suggests that respiratory mechanisms do not make a major contribution to these ventilatory oscillations. This is because fluctuations in the output of the respiratory control system are, by nature of the system, periodic. Second, the transfer function, in which the R residuals were entered as the input function, was significant in 15 of 21 subjects during phase 3 of sleep onset. The interpretation of this finding is that the level of arousal, as reflected in EEG activity, determines the level of ventilation. Third, the change in ventilation lagged behind the change in arousal such that maximum ventilation typically occurred, on average, one breath after the initiation of an increase in EEG frequency.

It may be questioned whether the lag in ventilation was significant and whether it might have occurred as an artifact of data processing and reduction. It is concluded that the effect is significant because it occurred in the vast majority of subjects in both phases of sleep onset. Furthermore, careful inspection of the data-reduction methods did not identify a systematic bias on either variable. Indeed, this seems unlikely because the variables were converted to a common time base early in the analyses and were treated identically from that point onward. Furthermore, both variables were maintained as continuous, avoiding artifacts associated with conversion to categorical data. Although it is not possible to entirely rule out an artifact, the data suggest a lag in changes in ventilation compared with changes in state in these young subjects, an effect that is possibly related to the absence of periodicity in their ventilation.

In the young subjects in this study the relationship between an EEG measurement of arousal level and ventilation was weaker than that reported for older subjects (12). Although this may reflect any number of differences between the two studies, it is also possible that the difference was a consequence of a greater contribution of respiratory mechanisms to respiratory instability in the older subjects. Thus in individuals who are prone to respiratory instability, such as elderly subjects, periodic instability in the respiratory system and instability in level of arousal, may, through mutual entrainment, become synchronous. The combined effect of these two sources of instability in elderly subjects might then result in a stronger relationship between ventilation and level of arousal than that observed in young individuals in whom ventilatory instability is driven solely by instability in level of arousal. Furthermore, such a mechanism could also account for the difference between the two age groups in phase relationship between EEG and ventilation.

The absence of periodic breathing in these young adult men was not due to lower levels of respiratory variability in these compared with older subjects because the average CV in all phases was comparable to that reported previously for older subjects (7, 16). There was, however, some evidence to suggest that in the younger individuals, in whom there was no relationship between arousal level and ventilation, there was low ventilatory variability. Such an effect would be anticipated on purely statistical grounds.

In this study the relationship between fluctuations in sleep/wake state and ventilation became stronger as sleep onset developed. In addition to the fact that more subjects showed statistically significant relationships between EEG and ventilation during phase 3 than during phase 2, 17 of the 21 subjects had higher transform functions in phase 3 than in phase 2. The cause of this is uncertain. There was no consistent change in the periodicity from phase 2 to phase 3. There was, however, a nonsignificant increase in the variability of ventilation during phase 3, and our laboratory has reported previously that changes in ventilation at state transitions between alpha and theta EEG activity are larger during phase 3 than phase 2 (17). Furthermore, by definition, the difference in arousal level between the wake and sleep states is greater in phase 3 because the sleep state is “deeper.” Thus the stronger statistical relationship between the two time series during phase 3 may have been due to greater variability in the variables during this phase.

The present study has not addressed the issue of the mechanism by which state changes might mediate changes in ventilation. It is widely accepted that state changes are associated with changes in central respiratory drive (14). However, it is likely that this effect is mediated through respiratory pump muscle activity and/or activity of the dilator muscles of the upper airway. Although it is known that airway resistance increases at state transitions from alpha to theta activity and decreases at transitions from theta to alpha (8, 9), this is not the only mechanism involved because there is only a weak relationship between the magnitude of the change in upper airway resistance and changes in ventilation (9). Furthermore, measurements of muscle electromyogram activity at these transitions indicate changes in both respiratory pump and upper airway muscles (22). Nevertheless, a significant relationship between changes in ventilation and airway resistance has been demonstrated during periodic breathing in healthy elderly subjects (7), suggesting that changes in ventilation in the present study are due, in part, to changes in resistance.

In conclusion, the data from this study support the view that fluctuations in arousal level play the major role in producing ventilatory instability during sleep onset in healthy young adults. In other groups, such as elderly subjects, this mechanism may be augmented by respiratory mechanisms.
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