Cardiac and respiratory activity at arousal from sleep under controlled ventilation conditions

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Cardiac and respiratory activity at arousal from sleep under controlled ventilation conditions. J. Appl. Physiol. 90: 1455–1463, 2001.—Arousal from sleep is associated with elevated cardiac and respiratory activity. It is unclear whether this occurs because of homeostatic mechanisms or a reflex activation response associated with arousal. Cardiorespiratory activity was measured during spontaneous arousals from sleep in subjects breathing passively on a ventilator. Under such conditions, homeostatic mechanisms are eliminated. Ventilation, end-tidal Pco2, mask pressure, diaphragmatic electromyograph, heart rate, and blood pressure were measured in four normal subjects under two conditions: assisted ventilation and a normal ventilation control condition. In the control condition, there was a normal, sleep-related fall in ventilation and rise in end-tidal PCO2. Subsequently, at an arousal, there was an increase in respiratory and cardiac activity. In the ventilator condition, a vigorous cardiorespiratory response to a spontaneous arousal from sleep remained. These results indicate that sleep-related respiratory stimuli are not necessary for the occurrence of elevated cardiorespiratory activity at an arousal from sleep and are consistent with the hypothesis that such activity is at least in part due to a reflex activation response.

Arousal from sleep is associated with higher levels of cardiac and respiratory activity than during both sleep before the arousal and relaxed wakefulness subsequent to the arousal (4, 7–9, 14, 28, 30). Enhanced cardiorespiratory activity at an arousal is of considerable interest because, in disorders of sleep that are characterized by frequent arousal, the elevated activity associated with each arousal results in considerable variability in cardiac functioning. Some authors have speculated that this variability may be associated with heart disease (23). There are several hypotheses to account for the heightened cardiorespiratory activity immediately after an arousal (14). The first hypothesis suggests it is a consequence of the presence at awakening of sleep-induced respiratory stimuli (16). Sleep is permissive of hypoventilation and elevated chemical and mechanical stimuli. This occurs as a consequence of two related processes: the loss of a tonic input to respiratory drive (the wakefulness stimulus) and reduced responsiveness of ventilation to respiratory and mechanical stimuli. Thus respiratory stimuli rise during sleep, but they have a blunted effect on ventilation. It is then argued that, with an arousal, the wakefulness stimulus and waking respiratory responsiveness return, resulting in augmented respiratory activity. Cardiac activity is also elevated, either because respiratory stimuli directly stimulate cardiac activity (21, 22) or because cardiac activity is stimulated by respiratory activity (12, 26). Cardiorespiratory activity then falls during subsequent relaxed wakefulness as a consequence of the hyperventilation-induced reduction in respiratory stimuli (17).

As noted above, it is possible to conceptualize this model as consisting of two components, both of which vary as a function of sleep-wake state: a homeostatic process and a tonic wakefulness component. With respect to the homeostatic component, evidence showing that sleep is associated with hypoventilation and a rise in respiratory stimuli, and that arousal is associated with the reinstatement of waking regulatory control, is compelling (17). Furthermore, arousal-related cardiorespiratory activity is even further exaggerated when the degree of sleep-related hypoventilation, and thus the level of respiratory stimulation at an arousal, is extreme, such as occurs in patients with obstructive sleep apnea (OSA) (15, 22, 29). However, it is also possible that mechanical factors also contribute to cardiac activity in OSA (18, 22).

A second hypothesized mechanism is that arousal from sleep is associated with a reflex activation of the cardiorespiratory system (4, 7–9, 14). Such reflex acti-
vation could be considered to be the return of the tonic respiratory component, i.e., the wakefulness stimulus. Alternatively, it could be considered as a more general activation response encompassing a number of physiological systems and being functionally related to preparation for action in the event of a threatening situation (these alternatives will be considered in more detail in the discussion section). Irrespective of the specific mechanisms, the magnitude of the reflex response would be expected to be independent of respiratory stimuli, although it could be dependent on the level of threat experienced by the organism.

The major evidence for reflex activation of the cardiorespiratory system on arousal from sleep comes from studies in which an arousal has been elicited in normal sleepers by external stimulation (4, 6, 8, 14, 20). The rationale for these studies has been that the development of respiratory stimuli during sleep is negligible in normal sleepers and that any effects are due to the arousal. Unfortunately, such studies are inconclusive because normal sleepers still experience significant sleep-related hypoventilation (28) and increases in negative airway pressures (10, 11) and because external stimuli have independent effects on respiratory and cardiac activity during sleep (4, 27).

The two mechanisms (homeostatic control vs. reflex activation) are difficult to disentangle because both are hypothesized to be activated by an arousal from sleep. Furthermore, a method has not been devised to eliminate the hypothesized reflex activation while retaining the effect of reintroducing waking regulatory control of respiration. However, it should be possible to eliminate sleep-induced respiratory stimuli by artificial ventilation. One study has used this methodology in dogs, showing that cardiorespiratory activity increased at arousal from sleep when ventilation and respiratory stimuli were maintained at waking levels, suggesting the presence of reflex activation at arousal from sleep (8).

The aim of the present study was to assess respiratory and cardiac activity in humans after spontaneous arousal from sleep. The subjects were studied under two conditions: during normal sleep and during sleep while being ventilated via nasal mask by a volume-cycle ventilator. In the ventilator condition, the subjects went to sleep while being ventilated via nasal mask by a volume-cycle ventilator and while they maintained passive ventilation. In the control condition, subjects breathed unassisted through a nasal mask in each of the two conditions in the study, the data of interest were subjects’ cardiac and respiratory responses to spontaneous arousal from sleep. The study was approved by Human Ethics Committees of the University of Melbourne and the Austin and Repatriation Medical Centre. Participants gave written informed consent before their participation in the study.

Laboratory procedures. On data collection days, subjects were requested to abstain from consuming caffeine or alcohol. Subjects arrived at the laboratory 2 h before their normal bedtime for the attachment of recording equipment. They then retired between 10:00 PM and midnight and, after the lights were turned out, were allowed to go to sleep undisturbed. The events of interest were spontaneous arousals that occurred during the sleep-onset period from the onset of stage 1 sleep until stage 2 sleep had been firmly established. When 10 min of uninterrupted stage 2 sleep had occurred, or if they entered stage 3 or 4 sleep, subjects were aroused by the experimenter. After a period of wakefulness sufficient to ensure a reasonable level of alertness, they were allowed to return to sleep. These procedures were repeated until 4 h of data had been collected.

Respiratory circuit. On the ventilator nights, subjects were maintained on intermittent positive-pressure ventilation with constant volume. The intent of the artificial ventilation was to maintain each subject’s ventilation at a constant level throughout sleep and wakefulness and so prevent the rise in mechanical and chemical stimulation normally associated with sleep. The ventilator was set at a level sufficient to produce mild hypocapnia. In addition, subjects were required not to have any active respiratory activity while being ventilated. This was achieved by the hypocapnia suppressing spontaneous respiratory activity and by training the subjects to be allowed to be ventilated passively. Passive ventilation was identified during both the training and data collection sessions from a mask pressure (Pmask) tracing and diaphragmatic electromyograph (EMGsub) recording.

Intermittent positive-pressure ventilation was provided by a Life Care PLV 100 volume-cycle ventilator (Lafayette, Colorado). Subjects were connected to the ventilator by a 0.8 m of 22-mm-diameter tubing. An unheated pneumotachograph (PK Morgan) was located in the inspiratory line to determine airflow. The line was attached to the subject by a Sullivan nasal mask system and a two-way breathing valve, the mask being individually fitted to suit each subject. Subjects’ mouths were taped to prevent mouth breathing. Air was sampled from the mask to assess CO2 levels, and Pmask was measured.

End-tidal PCO2 pressure (PETCO2) (Datex, Helsinki, Finland) was recorded both for analysis purposes and to ensure that the level of hypocapnia attained was not excessive. In addition, as a safety precaution, percentage of arterial O2 hemoglobin saturation from pulse oximetry (Spo2) was measured and a respiratory specialist physician was always present on ventilator nights.

On control nights the subjects wore the nasal mask connected to the two-way breathing valve, tubing, and pneumotachograph, although the ventilator was not attached. Dead space was identical in the two conditions. To reduce inspiratory resistance the 22-mm inspiratory line was replaced with 40-mm-diameter tubing, resulting in a resistance of 2.5
cmH₂O·l⁻¹·s measured at a flow rate of 40 l/s. Because the system was effectively an open circuit in this condition, \( P_{\text{mask}} \) was not available.

As noted, airflow was measured by a pneumotachograph located in the inspiratory line. The system was calibrated over the range 0–100 l/min against a precision rotometer. Airflow was used to calculate tidal volume (VT) and inspiratory minute ventilation (V̇I). PETCO₂ was measured using a Datex end-tidal CO₂ monitor. Air was sampled from the mask via 2-mm tubing at the rate of 7 ml/s. The monitor was calibrated by using a two-point calibration procedure, a calibration gas (7% CO₂), and room air. \( P_{\text{mask}} \) was measured by a Validyne differential pressure transducer (model DP45), exposed to \( P_{\text{mask}} \) on one side and atmospheric pressure on the other. The \( P_{\text{mask}} \) transducer was calibrated over 0–20 cmH₂O against a water-filled manometer. EMG₄ was measured by Grass gold-plated surface electrodes placed on the right hand side of the chest wall at the mid clavicular line, between the eighth and ninth intercostal space. \( \text{SpO}_2 \) was measured by a Radiometer Copenhagen oximeter using a finger probe. The signal was filtered above 200 and below 10 Hz.

An example of a subject breathing passively and then arousing in the ventilator condition during stage 2 sleep is shown in Fig. 1. The passive ventilation is indicated by the absence of phasic activity in the EMG₄ and by the morphology of the \( P_{\text{mask}} \) tracing. Phasic diaphragmatic activity characteristic of normal breathing in the control condition is shown in Fig. 2. Stage 2 sleep in the first half of the figure is followed by an arousal.

**Identification of arousals and sleep-wake state.** Sleep-wake state was identified from electroencephalogram (EEG) (C₃/A2, O₁/A2 sites), submental electromyograph (EMG), and electrooculogram (EOG) recordings, according to standardized procedures (19). EEG and EOG signals were passed between 0.3 and 30 Hz and the EMG between 10 and 100 Hz. Arousals from sleep were identified by an experienced scorer (J. Trinder, who was blind to the respiratory and cardiac data) according to the following criteria. 1) A minimum of 22 s of continuous sleep, as defined by EEG 8 activity, with or without sleep spindles and K complexes, had to have occurred before an arousal could be scored. 2) Consistent with the American Sleep Disorders Association criteria (1), an arousal was defined as at least 3 s of continuous EEG 8 activity. 3) The point of onset of each arousal was defined by the first occurrence of either the onset of 3 s of 8 activity or the onset of another activity (an awake eye movement, submental EMG activity, a K complex) that resolved into at least 3 s
Arousal from Sleep during Controlled Ventilation

Cardiac activity. Two indexes of cardiac activity were measured, heart rate (HR) and blood pressure (BP). HR was assessed from the ECG as measured through Meditrace Ag/AgCl spot electrodes. Electrodes were placed over the lower left and right rib cage and right clavicle. The signal was passed between 0.3 and 30 Hz. BP was monitored by means of a Finapres BP monitor (Ohmeda).

Data analysis. The recordings for all measures were acquired, digitized, and stored for off-line analysis using a Compumedics (Abbotsford, Victoria, Australia) Sleep Watch system. EMG and ECG recordings were sampled at 500 Hz; EEGs, BP, PetCO2, airflow, and Pmax at 125 Hz; EOGs at 50 Hz; and the remaining respiratory variables at 25 Hz. The respiratory and cardiac recordings were analyzed by computer using analysis algorithms developed within the laboratory. For all measures, detection algorithms were visually verified and edited as necessary on a breath-by-breath or a beat-by-beat basis. Vi and Vr were calculated by integration of inspiratory flow after identification of inspiration by a breath-detection algorithm. PetCO2 was defined as the asymptote of an exponential function fitted to the expiratory CO2 recording. This procedure was introduced because, under conditions of low VT, such as occurs during sleep, CO2 may be underestimated. This occurs because the level of CO2 in expired air does not reach an asymptote. The estimated asymptote, compared with the maximum value, is less dependent on VT. Pmax was defined as the peak positive pressure during inspiration. EMGd was analyzed by integrating the raw EMG signal using a 100-ms moving-time average. Before integration, 100- to 160-ms sections of the raw EMG containing QRS complexes were removed and replaced by the data in the 50- to 80-ms periods before and after the QRS complex. The measure of EMG activity used was phasic inspiratory activity, which was defined as the integrated activity during inspiration minus average tonic activity during expiration. The latter was obtained by dividing the previous expiration into 10 equal time periods, with tonic activity for that breath being defined as the mean EMG amplitude of the period with the lowest mean amplitude. Because of wide variation in, and arbitrary nature of, the amplitude of EMG recordings, the values for all breaths analyzed as part of the spontaneous arousals within a night were converted to z scores. As a consequence, the breaths making up each night’s data had a mean of zero and the same variance from night to night and subject to subject. The computation of HR was based on the ECG R-R interval, and systolic, diastolic, and mean arterial BP were obtained from the Finapres record using software developed in the laboratory. Because the Finapres device has an internal calibration procedure, absolute BP values are unreliable. Thus BP values were rescaled within each night’s recording to a mean of zero. The variables analyzed were Vi, Vr, PetCO2, Pmax, EMGd, HR, and systolic, diastolic, and mean arterial BP.

To assess the effect of arousal from sleep on each variable, up to 5 breaths or 20 heartbeats before and after an arousal were analyzed. The number of postarousal breaths or heartbeats was independent of when the arousal terminated and the participant returned to sleep. Breaths, or heartbeats, were then numbered backward and forward from the point of arousal and averaged over arousals within each numbered position for each condition. The sequence of values were then graphically presented.

Arousal were statistically analyzed by averaging over positions within pre- and postarousal for each variable (up to 5 breaths or 10 heartbeats). For HR and BP the average of the last 10 prearousal heartbeats was also compared with the peak postarousal value (within the first 10 postarousal heartbeats). The resulting analyses consisted of a series of two-by-two ANOVAs. The factors were condition (ventilator vs. control) and time with respect to the arousal (prearousal vs. postarousal). Importantly, participants were analyzed as independent experiments with arousals being used as replicates. As a consequence, condition was treated as a between-groups factor, whereas pre- vs. postarousal was treated as a repeated-measures factor.

In addition to arousals, sustained periods of quiet wakefulness were identified, both at the beginning of the recording session before sleep had occurred and during subsequent periods of wakefulness between periods of sleep. In the latter case, the periods of wakefulness had to be at least 30 s in duration. Respiratory activity during periods of wakefulness was compared with activity during sleep, as represented by the period preceding an arousal. Thus this difference represented the effect of sleep on respiratory activity immediately before an arousal occurred.

The prearousal values were defined as the second and third to last breaths before each arousal. The last breath before an arousal was not included because the assignment of breaths to pre- or postarousal at the transition can be uncertain. The prearousal values were compared with an equivalent number of two breath averages obtained from the sustained periods of quiet wakefulness. The comparisons were conducted using independent conditions t-tests with each subject being treated as a separate experiment. Significance was set at P < 0.05 for all analyses.

RESULTS

The number of arousals obtained for subjects DB, RP, KC, and CN were 148, 150, 43, and 102 for the ventilator nights and 147, 145, 31, and 122 for the control nights, respectively. Data comparing quiet wakefulness with prearousal sleep values are shown in Table 1, and the results of statistical analyses of the arousals are summarized in Table 2.

Ventilation and CO2. As shown in Table 1, in the control condition all subjects showed a substantial fall in ventilation and a small increase in PetCO2 levels during sleep compared with quiet wakefulness (the effects were significant for all subjects, except Vi for subject KC). In contrast, ventilation was, as expected, unaffected by sleep in the ventilator condition, whereas PetCO2 was reduced during prearousal sleep compared with wakefulness in three of the four subjects (the significant effects for ventilation in 2 subjects was due to the low variance associated with the controlled ventilation). The reduction in PetCO2 presumably reflects a sleep-related reduction in CO2 production, combined with the maintenance of constant ventilation. Thus, as illustrated in Figs. 3 and 4, ventilation was substantially higher and PetCO2 substantially lower in the ventilator condition at the time of an arousal. Finally, as indicated in these figures, the ventilator eliminated the effect of an arousal on Vi and PetCO2. Thus, whereas the normal effects of sleep and arousal on ventilation were apparent in the control condition, both were eliminated in the ventilator condition. After an arousal in the control condition, Vi did not reach the...
a level of the ventilated condition, a result consistent with the absence of an increase in ventilation in the ventilator condition, despite an increase in respiratory effort (see Pmask and EMGdi). Although not shown graphically, the data for VT showed essentially identical results.

Statistically the arousal effects were significant in all subjects (see Table 2). Thus the main effect of condition and the interaction between condition and pre- vs. postarousal were significant for both V˙I and VT, reflecting the higher ventilation in the ventilator condition and the larger effect of arousal in the control condition, respectively. The large ventilation response to arousal in the control condition also caused a significant main effect of arousal for both V˙I and VT.

In accord with the intent of the controlled ventilation in the ventilator condition, PETCO2 levels were significantly lower in all subjects during this condition. As indicated in Fig. 4, the PETCO2 achieved in the ventilator condition was sufficiently low to permit passive ventilation. Furthermore, as indicated by the significant interaction effects, there was a significant change

Table 2. Cardiorespiratory response to arousals

<table>
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<th>Variable</th>
<th>Subject</th>
<th>Effect</th>
<th>Pre-Post</th>
<th>Condition</th>
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Values are F ratios for each variable, subject, and effect. Pmask, mask pressure; EMGdi, diaphragmatic EMG; HRavg, average heart rate; HRmax, maximum heart rate; BPavg, average blood pressure; BPmax, maximum blood pressure. *P < 0.05.
in PetCO2 after an arousal in the control condition, compared with the ventilated condition.

Pmask and EMGdi. Although ventilation did not change after an arousal in the ventilated condition, respiratory effort did. Thus Pmask fell significantly (reduction in peak positive pressure as a consequence of negative pressure generated by the subject) in the ventilated condition, indicating active respiration immediately after the arousal (see Fig. 5). Furthermore, after an arousal, phasic EMGdi activity increased significantly in all participants in both conditions (see Fig. 6 and Table 2). There was a slight tendency for the effect of an arousal to be greater in the control condition; however, the interaction effect was only significant for subject RP (Table 2). Thus, in the ventilated condition, all subjects actively inspired after an arousal despite an absence of negative intrathoracic pressure and chemical stimulation.

HR and BP. As shown in Figs. 7 and 8, both HR and systolic BP significantly increased in association with an arousal, as assessed by both the average level over the first 10 postarousal heartbeats and the peak response. The magnitude of the response was somewhat affected by condition, with a tendency to be larger in the control condition. Thus, for average HR, maximum HR, average systolic BP, and peak systolic BP, several of the subjects showed significant interaction effects for each variable (see Table 2). However, as can be seen in Figs. 7 and 8, the most salient aspect of the data was how small the difference was between the two conditions. The results for diastolic and mean arterial BP were the same as for systolic and as a consequence have not been presented. Sleeping baseline HR was slightly lower in the ventilated compared with the control condition.

DISCUSSION

In the present study, subjects were trained to be ventilated passively under positive-pressure ventilation. Under these conditions, ventilation was the same during wakefulness and sleep, and PetCO2 was, if anything, lower during sleep than wakefulness. In contrast, during a control condition, in which subjects breathed spontaneously, the normal sleep-related fall in ventilation and the rise in PetCO2 were observed.
Despite an absence of the sleep-related elevation in chemical and negative upper airway pressure stimuli when subjects were passively ventilated, there was a vigorous cardiac response, as assessed by HR and BP, and respiratory response, as assessed by $P_{\text{mask}}$ and EMG$_{di}$ measures, to a spontaneous arousal from sleep. This response was virtually as large as the response in the control condition, during which the chemical and upper airway stimuli were present. This finding indicates that sleep-related respiratory stimuli are not necessary for the occurrence of elevated cardiorespiratory activity at an arousal from sleep, although the presence of such stimuli did augment the magnitude of the response in some subjects. These results are consistent with an earlier report in dogs (8), with studies that have produced auditory arousals in OSA patients maintained on continuous positive airway pressure (6, 20), and with one study that reported that the magnitude of the ventilation response to auditory-induced arousals was independent of the ongoing level of hypercapnia (3). The data are also consistent with the hypothesis that increased cardiorespiratory activity at an arousal from sleep is in part due to a reflex activation response (4, 7–9, 14).

Whereas the presence of a reflex activation response is clearly indicated, the specific nature of the mechanism remains uncertain. There are several possibilities. The most parsimonious, with respect to current concepts in the literature, is that with an arousal cardiorespiratory activity is stimulated by the return of the wakefulness stimulus. The wakefulness stimulus is conceptualized as a tonic excitation of the respiratory system that is present during wakefulness, but absent during sleep (17). During wakefulness this component of respiratory drive is sufficient to maintain ventilation in the absence of metabolic stimuli (5), thus the need to train subjects to suppress respiratory activity during wakefulness while being passively ventilated. However, this explanation cannot account for the large cardiac response also observed at an arousal, because there is evidence to suggest that the wakefulness stimulus is specific to the respiratory system. Thus the wakefulness stimulus becomes inactive during sleep onset at the transition from $\alpha$ to $\theta$ EEG activity, producing a number of changes in respiratory activity, including a fall in ventilation (24, 28, 30). In contrast, cardiac activity, as reflected in HR, does not show an equivalent change at this time (2). Therefore, the return of the wakefulness stimulus is unlikely to be a direct cause of cardiac changes at an arousal (transition from $\theta$ to $\alpha$ EEG activity).

Although increases in cardiac activity at an arousal are not likely to be a direct consequence of the return of the wakefulness stimulus, it is possible that they are secondary to increases in respiratory activity. Thus it has been shown that respiratory activity is sufficient to cause an increase in both HR and BP (12, 26). In the present study, ventilation did not change at an arousal in the ventilator condition, although respiratory effort, as indicated by changes in $P_{\text{mask}}$ and EMG$_{di}$ activity, increased. Thus it is possible that cardiac activation at an arousal is secondary to increases in respiratory effort produced by the return of the wakefulness stimulus.

An alternative explanation is that increases in both respiratory and cardiac activity at an arousal are, in part, due to a reflex activation response specifically associated with arousal from sleep (9, 14). Such a response could have had evolutionary advantages in preparing individuals in the event that the arousing stimulus was threatening (9). The generalized arousal that occurs in both the respiratory and cardiovascular, and possibly other, systems is consistent with this perspective. Indeed, whereas some authors have suggested that the response is either an orienting (4) or startle (13) reflex, a recent study (25) has shown substantial differences in the pattern of physiological activity after arousal from sleep compared with that in response to orienting or startle stimuli. Consistent with its proposed adaptive role, the pattern of cardiorespiratory activity at an arousal is more one of energy mobilization than the other reflexes (25). Thus it has been suggested that the response on arousal from sleep is a specific, or unique, reflex associated with, and elicited by, an arousal. The term “the waking reflex” has been proposed to describe it (25).

The evidence for a vigorous respiratory response after an arousal in the absence of sleep-induced chemical and mechanical stimuli rests on the observation that respiratory effort increased, as indicated by changes in $P_{\text{mask}}$ and EMG$_{di}$ activity. There was, however, no evidence of a change in $V_{i}$ or PET$_{CO_2}$. Although this is understandable in terms of the control exerted over ventilation in the ventilated condition, it should be noted that the evidence for nonhomeostatic increases in respiratory activity was perhaps not as strong as for cardiac activity.

In evaluating respiratory responses in the ventilator condition, we considered the possibility that active ventilation occurred out of phase with the respirator. Indeed, it was noted that this did occasionally occur after a spontaneous arousal. However, these events

![Graph](https://example.com/graph.png)
consisted almost entirely of the subject anticipating the ventilator, such that the active inspiration became continuous with the inspiratory phase of the ventilator. As a consequence, the breath-detection algorithm incorporated the active component into its estimate of the inspiratory phase. Because the inspiratory phase identified by the airflow breath detection algorithm was used to define the interval to be analyzed for the other measures (e.g., EMGdi), these measures also include total inspiratory activity.

In summary, the data indicate that homeostatic mechanisms are not able to account for the increase in cardiorespiratory activity that occurs at an arousal from sleep. However, the specific mechanism responsible is unclear. One possibility is that respiratory activity is augmented by the return of the wakefulness stimulus, which in turn stimulates cardiac activity. The alternative is that a reflex activation response is specifically elicited by an arousal. The present data do not allow a distinction between these hypotheses.

The data are somewhat equivocal with respect to the role of sleep-related respiratory stimuli in the normal breathing condition. It was anticipated that both the respiratory and cardiac responses to an arousal would have been larger in the control condition, because in this condition both homeostatic and reflex activation responses would have been expected to be present. However, only one subject showed a significantly larger respiratory response in the control condition, as indicated by EMGdi. Furthermore, whereas significantly larger responses in the control condition were more common in the cardiac measures, significant effects were not uniform across subjects and the additional effect was only small in magnitude.

A possible explanation for the small impact of homeostatic components is that the homeostatic stimuli were themselves small in magnitude. Thus, in this study, spontaneous arousals were collected from stage 1 and early stage 2 sleep, when changes in chemical (28) and mechanical (11) stimuli are smaller than during established sleep. Indeed, as shown by the data of the present study, the increase in PetCO2, although significant, was relatively small in magnitude. However, it also has to be borne in mind that, despite the use of procedures to avoid the problem, PetCO2 values may still have been underestimated under conditions of low Vt. Thus the difference in chemical stimulation between quiet wakefulness and the prearousal sleep state may have been underestimated.

Another interpretation of the small homeostatic response in the control condition is that homeostatic mechanisms are briefly suspended immediately after an arousal from sleep. Consistent with this, Horner et al. (9) have suggested that the period of wakefulness immediately after an arousal may be a qualitatively different state than wakefulness at other times. In a similar vein, it has been suggested central arousal effects may override peripheral chemical and mechanical effects (20). Empirical evidence for this possibility has been provided by Carley and colleagues (3). They demonstrated that hypercapnia sufficient to increase sleeping minute ventilation by 35% had no effect on the magnitude of the ventilation response to auditory evoked arousals from sleep.

A final possibility is that the small effect attributable to homeostatic factors in the present data may reflect a nonadditivity in the relationship between the two stimuli. Thus, under conditions when sleep-related respiratory stimuli would be relatively weak, as during sleep onset, they may add little to respiratory and cardiac activity after an arousal.

In designing the present study, more intrusive measures of CO2 levels and of airway negative pressure were rejected on the grounds that the instrumentation of subjects was already substantial. It is argued that this has not compromised the establishment of conditions necessary to test the central hypothesis. It has, however, compromised the capacity to determine the level of respiratory stimuli present at an arousal and, therefore, to evaluate the small homeostatic response present in the control condition.

In conclusion, under conditions in which metabolic and mechanical respiratory stimuli were held below threshold, arousal from sleep was associated with significant increases in respiratory and cardiac activity. This is interpreted to indicate that a reflex activation response is elicited at sleep onset, although the data do not permit speculation on whether this response reflects the return of the wakefulness stimulus, or a more generalized activation response specifically elicited by the act of arousing. It was tentatively suggested that the absence of a significant homeostatic response in the control condition may indicate that the homeostatic system is inactive immediately after an arousal from sleep.

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