

Effect of Ventilator Mode on Sleep Quality in Critically Ill Patients

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To determine whether sleep quality is influenced by the mode of mechanical ventilation, we performed polysomnography on 11 critically ill patients. Because pressure support predisposes to central apneas in healthy subjects, we examined whether the presence of a backup rate on assist-control ventilation would decrease apnea-related arousals and improve sleep quality. Sleep fragmentation, measured as the number of arousals and awakenings, was greater during pressure support than during assist-control ventilation: 79 ± 7 versus 54 ± 7 events per hour ($p = 0.02$). Central apneas occurred during pressure support in six patients; heart failure was more common in these six patients than in the five patients without apneas: 83 versus 20% ($p = 0.04$). Among patients with central apneas, adding dead space decreased sleep fragmentation: 44 ± 6 versus 83 ± 12 arousals and awakenings per hour ($p = 0.02$). Changes in sleep-wakefulness state caused greater changes in breath components and end-tidal CO_2 during pressure support than during assist-control ventilation. In conclusion, inspiratory assistance from pressure support causes hypocapnia, which combined with the lack of a backup rate and wakefulness drive can lead to central apneas and sleep fragmentation, especially in patients with heart failure.

Keywords: arousal; artificial respiration; critical illness; mechanical ventilator; sleep

Mechanical ventilation is used primarily to improve gas exchange and achieve respiratory muscle rest (1). To achieve this goal, it is important that a patient does not make respiratory efforts out of synchrony with the cycling of the ventilator (2, 3). Because behavioral stimuli are decreased during sleep, respiratory muscle rest might be greater during sleep as compared with wakefulness. The operation of a ventilator, however, including its alarms, may disrupt sleep (4). Although disruptions of sleep may adversely affect critically ill patients, little information is available about the interplay between patient-ventilator synchrony and sleep. Studies of healthy volunteers and animals suggest that sleep disruption could result in negative energy balance (5, 6), reduced host immunity (7), and decreased ventilatory responses to hypoxemia and hypercapnia (8, 9). These deleterious effects might prolong the duration of mechanical ventilation in critically ill patients.

Cooper and coworkers (10) have shown that mechanically ventilated patients arouse repeatedly from sleep. In patients

free of critical illness, arousals can result from a derangement of arterial blood gases or an increase in respiratory effort (11–13), and both are common occurrences in critically ill patients. Patient-ventilator dyssynchrony or a particular ventilator mode might also lead to sleep disruption (10). Pressure support predisposes to an abnormal breathing pattern, specifically central apneas with consequent hyperpnea (14). Meza and coworkers (14) demonstrated that healthy subjects develop central apneas during pressure support when their carbon dioxide tension (Pco_2) decreases by a few torr below the apnea threshold. Whether pressure support causes apneas in critically ill patients and whether the apneas lead to disruption of sleep are unknown. Disruption of sleep secondary to central apneas, however, can cause cardiopulmonary abnormalities in ambulatory patients (8, 9, 15–20), and these effects may be magnified in critically ill patients.

Unlike pressure support, assist-control ventilation delivers a fixed tidal volume on every breath, and it can be set to deliver breaths when a patient fails to make an effort. The backup rate will prevent the development of apneas, and perhaps decrease arousals. If pressure support causes central apneas by lowering arterial Pco_2 below the apnea threshold, then adding dead space to the ventilator circuit might also decrease both the apneas and arousals.

The purpose of our study was to determine whether the mode of mechanical ventilation influences sleep consolidation in critically ill patients. We hypothesized that sleep would be more fragmented during pressure support than during assist-control ventilation, primarily because of the development of central apneas. A second goal was to determine whether adding dead space during pressure support would decrease sleep fragmentation as a result of decreasing the frequency of central apneas. Some of the results of these studies have been previously reported in the form of abstracts (21, 22).

METHODS

Additional details are provided in the online data supplement.

Patients

Eleven mechanically ventilated patients were recruited (Table 1) after obtaining informed consent from surrogates. Patients were excluded if they were comatose; receiving vasopressors; recovering from general anesthesia, drug overdose, or alcohol intoxication; or were considered unstable by their primary physician.

Experimental Setup

Patients were ventilated through an endotracheal tube or tracheostomy connected to a Puritan-Bennett 7200 ventilator (Mallinckrodt, Hazelwood, MO). End-tidal CO_2 was measured at the distal end of the endotracheal or tracheostomy tube. Airflow and airway pressure were measured in the inspiratory limb of the ventilator circuit, close to the Y-piece. The signals were measured between the end-tidal CO_2 connector and the Y-piece when dead space (100 ml) was introduced. Ribcage and abdominal motion, pulse oximetry, electroencephalography,

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TABLE 1. CHARACTERISTICS OF PATIENTS

Patient No.	Diagnosis	Age (yr)	Days of Ventilator Support
1	ARDS, CHF	90	26
2	ARDS, CHF	65	7
3	ARDS	75	16
4	ARDS	54	31
5	CHF	67	3
6	CHF	49	4
7	CHF	72	50
8	Pneumonia	66	7
9	Pneumonia	59	2
10	Pneumonia, CHF	85	34
11	Pulmonary hemorrhage	58	4

Definition of abbreviations: ARDS = adult respiratory distress syndrome; CHF = congestive heart failure.

All patients were male and were receiving sedatives.

right and left electrooculography, submental electromyography, and electrocardiography were recorded (see online data supplement).

Determination of Settings

The ventilator was initially set in the assist-control mode with a backup rate of 4 breaths per minute and tidal volume (V_T) of 8 ml/kg. Over 5 to 10 minutes of quiet wakefulness, the patient's respiratory rate on the ventilator was measured. The backup rate on assist-control ventilation was then set at 4 breaths below the patient's respiratory rate and kept at that setting for the rest of the study. Pressure support was adjusted to achieve a V_T equivalent to that during assist-control ventilation, namely 8 ml/kg. Patients were randomized to receive at least 2 hours each of the following three modes: assist-control ventilation, pressure support alone, and pressure support with dead space.

Physiologic Measurements

All studies were performed between 10:00 P.M. and 06:00 A.M. Apneas, and electroencephalogram (EEG) arousals and awakenings were manually scored (23). EEG arousals were defined as an abrupt shift in EEG frequency consisting of theta, α , and/or frequencies greater than 12 Hz lasting 3 seconds or longer and suggestive of a return toward wakefulness (24). Awakenings were defined as EEG features compatible with wakefulness and lasting more than half of a 30-second epoch (23). Arousals and awakenings were classified as apnea related if they occurred within 3 breaths of the end of an apnea (25, 26).

Elastance and resistance of the respiratory system were measured as described previously (27). Mechanical inspiratory time (T_I), expiratory time (T_E), total respiratory cycle time (T_{tot}), end-tidal CO_2 , and V_T were measured on a breath-by-breath basis. Apnea threshold was determined from the end-tidal CO_2 of the breath immediately before the onset of an apnea (28) (see online data supplement).

Data Analysis

Number of apneas, arousals, and awakenings that occurred per hour of sleep and the coefficient of variation of end-tidal CO_2 were calculated for each mode of ventilation and compared by one-way analysis of variance (ANOVA). For a given mode, breath components during wakefulness were quantified as percentage change from sleep to wakefulness, and vice versa. This approach was used to assess the effect of a state (sleep or wakefulness) on breathing pattern while still accounting for differences in breath components among patients. During a given state (sleep or wakefulness), the differences in magnitude of breath components between ventilator modes are expressed in absolute numbers. Two-way ANOVA was used to compare breath components during different ventilator modes and sleep-wakefulness states. For ANOVA results, Newman-Keuls multiple range tests were applied.

RESULTS

Sleep Recordings

All 11 patients achieved sleep while receiving each mode of ventilation. Total durations of sleep were as follows: 90 ± 6

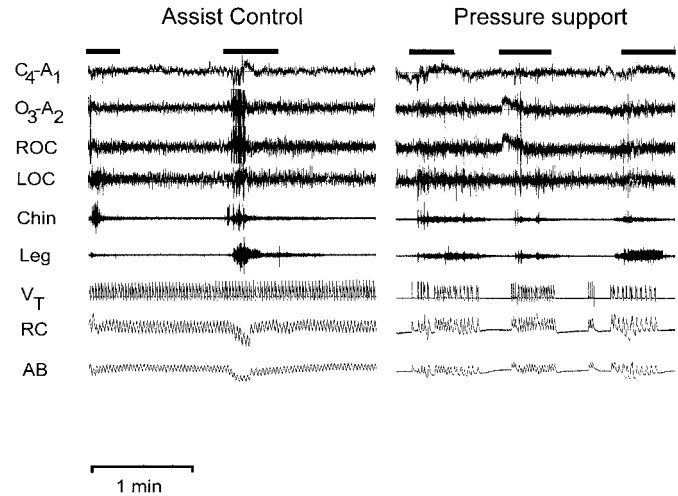


Figure 1. Polysomnographic tracings during assist-control ventilation and pressure support in a representative patient. Electroencephalogram (C_4-A_1 , O_3-A_2), electrooculogram (ROC, LOC), electromyograms (Chin and Leg), integrated tidal volume (V_T), rib-cage (RC), and abdominal (AB) excursions on respiratory inductive plethysmography are shown. Arousals and awakenings, indicated by horizontal bars, were more numerous during pressure support than during assist-control ventilation.

minutes during assist-control ventilation, 75 ± 6 minutes during pressure support alone, and 82 ± 7 minutes during pressure support with added dead space. Rapid eye movement sleep was observed in 4 of the 11 patients, but only 1 patient achieved rapid eye movement sleep with all three modes. Slow wave sleep was not seen in any patient. Five patients had features of Stage 2 sleep (spindles and K complexes), and the other six patients had features of only Stage 1 sleep. The efficiency of maintaining sleep (time asleep divided by duration of the study arm, 2 hours) was $63 \pm 5\%$ during pressure support alone; efficiency was higher with the addition of dead space, $81 \pm 7\%$ ($p < 0.05$), or with assist-control ventilation, $75 \pm 5\%$ ($p < 0.05$).

Apneas. Six of the 11 patients developed apneas during pressure support but not during assist-control ventilation by virtue of the backup rate ($p < 0.05$; Figure 1 and Figure 2, top). Among the six patients who developed apneas, adding dead space decreased the frequency: 4 ± 2 versus 53 ± 8 apneas/hour ($p < 0.01$; Figure 2, bottom). Heart failure (defined as a left-ventricular ejection of less than 50% or a history of congestive heart failure) was more common among the patients with apneas than among the patients without apneas: 83 versus 20% ($p = 0.04$; χ^2 test).

Sleep fragmentation. In the 11 patients, the frequency of arousals was equivalent during pressure support and assist-control ventilation: 39 ± 6 and 35 ± 7 arousals/hour, respectively ($p = 0.8$). Awakenings were more frequent during pressure support than during assist-control ventilation: 39 ± 7 versus 19 ± 3 awakenings/hour ($p < 0.01$). Total sleep fragmentation, measured as the sum of arousals and awakenings, was greater during pressure support than during assist-control ventilation: 79 ± 7 versus 54 ± 7 arousals and awakenings/hour ($p < 0.05$). During pressure support, apnea-related sleep fragmentation consisted of 10 ± 4 arousals/hour, 13 ± 6 awakenings/hour, and 23 ± 7 arousals and awakenings/hour as contrasted with rates of zero during assist-control ventilation ($p < 0.05$).

In the six patients who developed apneas during pressure support, arousals and awakenings were more frequent during

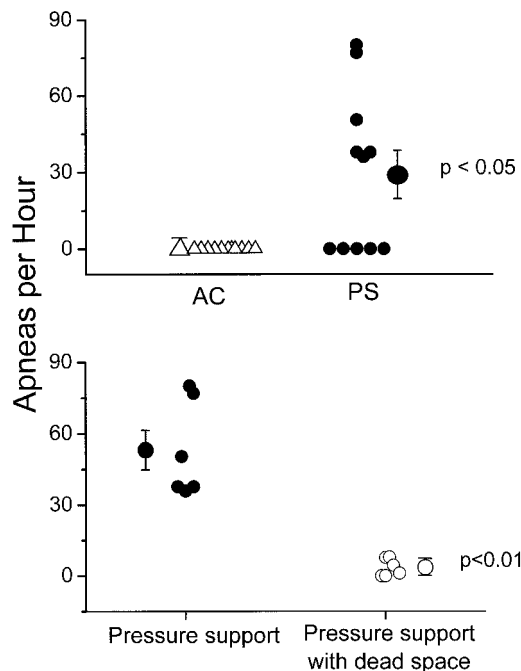


Figure 2. Number of apneas per hour during assist-control ventilation (AC; open triangles), pressure support (PS; closed circles), and pressure support with added dead space (open circles). Six of 11 patients developed apneas during pressure support as compared with none during assist-control ventilation (top). In the patients who developed apneas, the number of apneas decreased with the addition of dead space (bottom). Individual and group mean values are shown. Bars represent the SE.

pressure support than during assist-control ventilation: 83 ± 12 versus 43 ± 7 events/hour ($p < 0.05$). In the five patients who did not develop apneas during pressure support, the frequency of arousals and awakenings was not different during pressure support and assist-control ventilation: 74 ± 6 and 68 ± 12 events/hour, respectively ($p = 0.9$). In the six patients who developed apneas during pressure support, the addition of dead space decreased the frequency of arousals and awakenings from 83 ± 12 to 44 ± 6 events/hour ($p < 0.01$).

Breath Components and Respiratory Mechanics

Compared with wakefulness, respiratory rate was $14.9 \pm 3.2\%$ lower ($p = 0.0001$; Figure 3, top right) during sleep in patients receiving assist-control ventilation; mechanical T_I and T_E did not differ between sleep and wakefulness ($p > 0.2$; Figure 3, top middle). Compared with wakefulness, T_E was $126.0 \pm 30.2\%$ longer ($p = 0.0001$; Figure 3, top left), mechanical T_I was $23.1 \pm 4.6\%$ longer ($p = 0.0001$; Figure 3, top middle), and respiratory rate was $32.6 \pm 6.1\%$ lower ($p = 0.0001$; Figure 3, top right) during sleep in patients receiving pressure support.

Minute ventilation (V_I) was lower during sleep as compared with wakefulness: $17.3 \pm 3.9\%$ during assist-control ventilation ($p < 0.05$) and $24.0 \pm 8.0\%$ ($p = 0.003$) during pressure support (Figure 3, bottom left). By design, V_T during wakefulness was equivalent during assist-control ventilation and pressure support: 0.57 ± 0.03 versus 0.64 ± 0.05 L ($p = 0.3$; Figure 3, bottom middle). During assist-control ventilation, V_T did not change between wakefulness and sleep ($p = 0.4$). During pressure support, however, V_T was greater during sleep as compared with wakefulness ($p = 0.001$; Figure 3, bottom middle). The differences in respiratory rate, T_I , and T_E between sleep and wake-

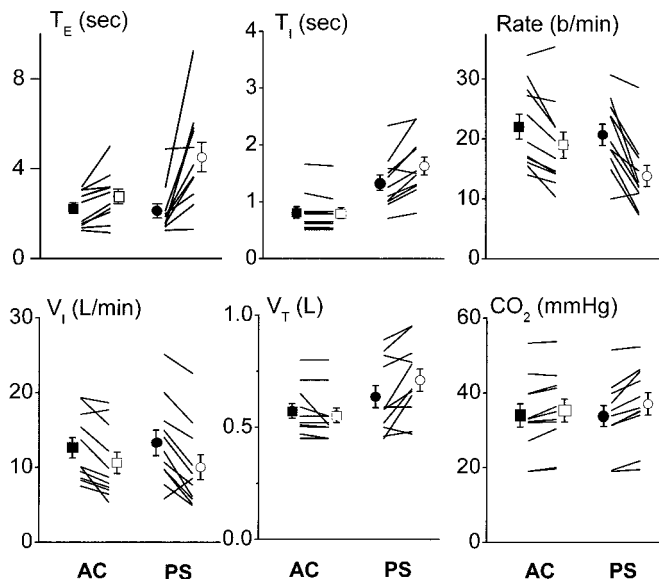


Figure 3. Mechanical expiratory time (T_E ; top left), mechanical inspiratory time (T_I ; top middle), respiratory rate (top right), minute ventilation (V_I ; bottom left), tidal volume (V_T ; bottom middle), and end-tidal CO_2 (CO_2 ; bottom right) during assist-control ventilation (AC) and pressure support (PS). For each mode, the lines connect the mean value of each patient during wakefulness (left) and sleep (right). The group mean values are shown for wakefulness (closed symbols) and sleep (open symbols). Compared with wakefulness, T_E , V_T , and P_{CO_2} were greater and respiratory rate and V_I were less during sleep. The differences between sleep and wakefulness for respiratory rate, T_I , and T_E were greater for pressure support than for assist control.

fulness were greater during pressure support than during assist-control ventilation ($p < 0.05$; Figure 3).

During wakefulness while receiving pressure support, the five patients without apneas had a greater V_T , 0.75 ± 0.08 versus 0.54 ± 0.02 L ($p = 0.02$), and a greater V_I , 17.2 ± 2.5 versus 10.0 ± 1.3 L/minute ($p = 0.03$; Figure 4), than did the six patients who developed apneas. During sleep while receiving pressure support, the patients who did not develop apneas had a greater V_I , 11.82 ± 1.81 versus 6.73 ± 0.89 L/minute ($p = 0.02$; Figure 4), and a greater V_T , 0.83 ± 0.06 versus 0.61 ± 0.05 L ($p = 0.02$), than did the patients who developed apneas.

Mean inspiratory flow, a measure of respiratory drive, was higher in patients without apneas than in patients with apneas: 642 ± 104 versus 359 ± 48 ml/second ($p < 0.05$) during sleep; and 690 ± 128 versus 402 ± 55 ml/second ($p < 0.05$) during wakefulness.

The patients with apneas and without apneas had equivalent respective levels of pressure support, 16.8 ± 1.5 and 19.6 ± 2.6 cm H_2O ($p = 0.6$), static elastance, 25.9 ± 4.1 and 29.7 ± 5.7 cm H_2O/L ($p = 0.3$), and respiratory resistance, 13.5 ± 2.0 and 14.1 ± 1.6 cm H_2O/L per second ($p = 0.8$; unpaired t tests). The doses of sedatives did not differ between the patients with and without apneas.

Gas Exchange

End-tidal CO_2 was greater during sleep than during wakefulness: by $4.6 \pm 1.8\%$ during assist-control ventilation ($p = 0.01$) and by $11.0 \pm 2.3\%$ ($p = 0.0001$) during pressure support (Figure 3, bottom right). The extent of change in end-tidal CO_2 was greater during pressure support than during assist-control ventilation ($p = 0.02$; Figure 3, bottom right). The coefficient of variation

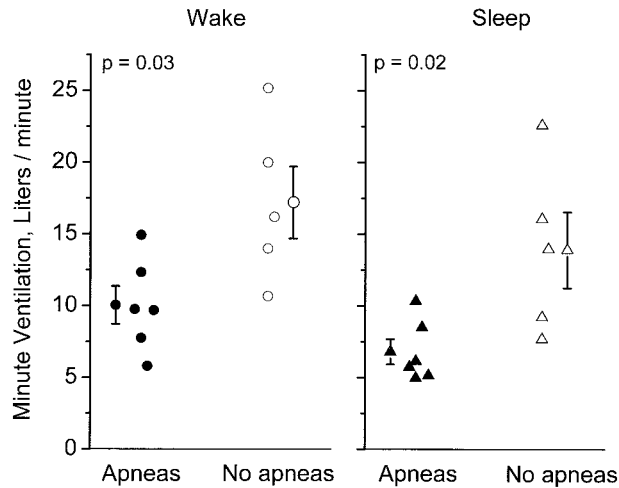


Figure 4. Minute ventilation during pressure support while awake (left) and asleep (right) in six patients with apneas (closed symbols) and five patients without apneas (open symbols). Minute ventilation during sleep was greater in patients who did not develop apneas than in patients who developed apneas ($p = 0.02$), suggesting that increased respiratory drive protects against the development of central apneas.

of end-tidal CO_2 levels was greater during pressure support than during assist-control ventilation: 8.7 ± 1.4 versus $4.7 \pm 0.7\%$ ($p = 0.03$). In the six patients who developed apneas, the addition of dead space resulted in a 4.3 ± 1.4 mm Hg increase in end-tidal CO_2 ($p = 0.01$) and it tended to decrease the coefficient of variation in end-tidal CO_2 to $5.6 \pm 0.6\%$ ($p = 0.06$). In all patients, oxygen saturation was never below 93%, and it was not affected by differences in sleep-wakefulness state or the mode of ventilation.

Relationship between Central Apneas and P_{ETCO_2}

The number of central apneas was significantly related to the difference between end-tidal CO_2 and the apnea threshold point during wakefulness ($r = -0.6$; $p = 0.02$; Figure 5), and during a mixture of sleep and wakefulness, which included the transitions ($r = -0.83$, $p < 0.001$; Figure 5); the relationship was not significant during sleep on its own ($r = -0.52$; $p = 0.08$; Figure 5). The number of central apneas was also correlated with the level of pressure support ($r = 0.35$, $p = 0.04$), compliance of the respiratory system ($r = 0.34$, $p = 0.04$), and the number of awakenings per hour ($r = 0.57$, $p = 0.02$). In a multiple regression model, however, the only factor that significantly predicted the number of central apneas was the difference between the level of end-tidal CO_2 and the apnea threshold point ($\beta = -0.67$, $p = 0.01$).

DISCUSSION

The study provides several insights into the effect of ventilator mode on sleep quality of critically ill patients: (1) patients receiving mechanical ventilation have severely fragmented sleep, but pressure support may further aggravate the fragmentation in susceptible patients; (2) at commonly used ventilator settings, central apneas occur during pressure support but not during assist-control ventilation. These apneas can worsen sleep fragmentation; (3) adding dead space decreases the frequency of central apneas and sleep fragmentation during pressure support; and (4) in critically ill patients, the patterns of breathing and gas exchange during sleep differ from those during wakefulness,

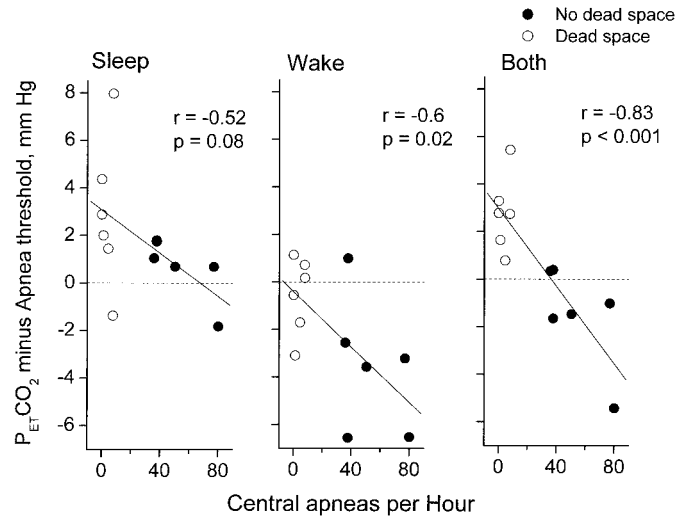


Figure 5. The difference between the average end-tidal CO_2 and the apnea threshold plotted against the number of central apneas per hour of pressure support alone (closed symbols) and pressure support with added dead space (open symbols) in six patients. The average end-tidal CO_2 was measured during sleep (left), wakefulness (middle), and during both sleep and wakefulness (right). The mean number of central apneas per hour was strongly correlated with the end-tidal CO_2 during a mixture of both sleep and wakefulness (including the transitions between sleep and wakefulness) ($r = -0.83$, $p < 0.001$), but not during sleep alone ($r = -0.52$, $p = 0.08$).

and these differences are greater with pressure support as compared with assist-control ventilation.

Sleep Fragmentation and Consequences

Cooper and coworkers (10) studied sleep quality in mechanically ventilated patients. In eight patients with electrophysiological features of sleep, 42 arousals and awakenings occurred per hour of sleep. This level of sleep fragmentation is similar to that seen in patients with obstructive sleep apnea who have excessive daytime sleepiness and impaired cognition (29). It is also comparable to the fragmentation we observed during assist-control ventilation. Unlike the current study, Cooper and coworkers (10) did not investigate the effect of ventilator mode on sleep quality.

Central apneas can cause hypoxia and hypercapnia with consequent increase in respiratory effort, and all three factors can cause arousal from sleep (25, 30, 31). The patients who developed central apneas did so more frequently during pressure support than during pressure support with added dead space, and, in turn, more frequently than during assist-control ventilation (Figure 2). Sleep fragmentation followed a similar trend. Compared with assist-control ventilation, the increase in apneas during pressure support, with and without dead space, was associated with a proportional increase in the number of awakenings ($r = 0.66$; $p = 0.01$). These data suggest that central apneas during pressure support may worsen sleep quality.

Sleep fragmentation during pressure support resulted from an increased frequency of awakenings rather than arousals; indeed, arousals did not differ between the two modes. These data suggest that not only the frequency, but also the degree, of sleep fragmentation was greater during pressure support. Changes in sleep depth are thought to be more important than the mere frequency of disruptions in causing daytime sleepiness in patients with obstructive sleep apnea (32). Although daytime sleepiness may not be a concern in critically ill patients, sleep fragmentation

can adversely affect the cardiorespiratory and autonomic nervous systems (16, 17, 19, 20).

To delineate the influence of central apneas on sleep fragmentation, we divided arousals and awakenings into those that did or did not occur within 3 breaths of the end of an apnea. A substantial number of apnea-related arousals and awakenings occurred during pressure support. These events were decreased by adding dead space and completely eradicated with assist-control ventilation. At first glance, it might seem that categorizing arousals and awakenings as apnea or nonapnea related would lead to predictable results (because the backup rate on assist-control ventilation should prohibit apnea-related arousals). The classification, however, highlights that all other (non-apnea-related) arousals and awakenings were equally frequent during assist-control ventilation and pressure support. This observation suggests that critically ill patients have a background level of sleep disturbance, probably secondary to nonrespiratory factors such as pain, medications, staff interruptions, noise, and light (10, 33, 34). Nevertheless, a change in the ventilator mode from assist-control ventilation to pressure support can further aggravate sleep disruption.

To minimize the effect of variations in environmental factors (33–35), pain, acuity of illness, and medications (36) on sleep fragmentation, the patients were randomized to three arms on a single night. Visits from staff were minimized and data during such visits were excluded from analyses.

Control of Breathing

This is the first study to assess whether critically ill patients develop central apneas while receiving mechanical ventilation (Figure 1). During pressure support, six patients developed apneas and five patients did not (Figure 2). Heart failure was more common among the patients with apneas than among the patients without apneas: 83 versus 20% ($p = 0.04$). This finding suggests that mechanisms similar to those seen in patients with Cheyne–Stokes respiration could be involved (37). Occurrence of central apneas during pressure support is not unique to patients with heart failure. Central apneas can occur in healthy subjects receiving pressure support (14, 38). Moreover, pressure support has inherent oscillatory behavior that predisposes to substantial variations in tidal volume even when patient effort is constant (39, 40). This instability combined with higher levels of pressure support (14) predisposes to central apneas and consequent sleep fragmentation in patients without heart failure, and may explain the occurrence of apneas in our patient who did not have heart failure.

If pressure support predisposes to apneas in healthy subjects, it might appear puzzling that five of our patients did not develop apneas during pressure support. The lack of apneas may have resulted from dampening of the chemical control system secondary to abnormal respiratory mechanics and elevated dead space (41); a low functional residual capacity and low levels of pressure support may have also contributed. The level of pressure support and the elastance of the respiratory system were not different in the six patients with apneas and the five patients without apneas ($p > 0.3$). During both sleep and wakefulness, minute ventilation was greater in patients without apneas than in patients with apneas (Figure 4). The higher ventilation in the patients without apneas suggests that a greater respiratory drive, intrinsic dead space, or both may have stabilized ventilation and prevented central apneas. Mean inspiratory flow, a measure of respiratory drive (42), was indeed higher in patients without apneas than in the patients with apneas during both sleep and wakefulness ($p < 0.05$). The elevated respiratory drive in these five patients may have stabilized ventilation and prevented apneas from occurring (43). An elevated drive may have also pre-

vented the occurrence of apneas during pressure support in one of our patients with heart failure.

Effect of Dead Space

The addition of dead space produced a mean increase in end-tidal CO_2 of 4.3 mm Hg, which resulted in a decrease in the frequency of central apneas (Figure 2, *bottom*) and sleep disruptions. Hypocapnia can trigger central apneas in patients with heart failure (44), and the correction of hypocapnia can abolish central apneas in patients with idiopathic central sleep apnea (44) and central sleep apnea due to heart failure (45). Adding dead space has not been previously shown to prevent central apneas during pressure support.

Inspiratory assistance, pain, discomfort, and sepsis can cause chronic hyperventilation (46, 47), which, in turn, may lower the Pco_2 below the apnea threshold and cause central apneas. Therefore, as expected, the level of pressure support and elastance of the respiratory system correlated with the frequency of central apneas (14). Similarly, acute hyperventilation due to awakenings from sleep can also lower Pco_2 , and thereby cause central apneas (48). As expected, the number of awakenings correlated with the number of central apneas. In line with the preceding conceptual framework, a smaller difference between the end-tidal CO_2 and the apnea threshold point would result in more numerous central apneas. In the current study, the frequency of central apneas correlated most strongly with the difference between the end-tidal CO_2 (during both wakefulness and sleep) and the apnea threshold point ($r = -0.83$, $p = 0.01$; Figure 5). In a multiple regression model, however, the only factor that significantly predicted the frequency of central apneas was the difference between the level of end-tidal CO_2 (during both wakefulness and sleep) and the apnea threshold point.

The relative importance of hyperpnea during sleep, wakefulness, and the transition between wakefulness and sleep in causing central apneas is controversial. To address this issue, we measured end-tidal CO_2 during unequivocal sleep (Figure 5), during unequivocal wakefulness (Figure 5), and during a mixture of sleep and wakefulness (to include the transitions between the two states) (Figure 5). The frequency of central apneas was strongly correlated with values of end-tidal CO_2 that included a mixture of wakefulness and sleep ($r = -0.83$; $p < 0.001$; Figure 5) but was not significantly correlated with values of end-tidal CO_2 during sleep alone ($r = -0.52$; $p = 0.08$). This observation stresses that the level of CO_2 during sleep is not the sole determinant of central apneas. If a patient is chronically hyperventilating during wakefulness and then rapidly switches from wakefulness to sleep, not enough time will be available at the point of sleep onset for Pco_2 to increase. Consequently, central apneas will ensue.

Clinical Implications

When physicians set the ventilator during the daytime they do not base it on whether a patient is asleep or awake because they usually cannot tell what state a patient is in. In the current study, both the pattern of breathing and gas exchange differed between sleep and wakefulness during both assist-control ventilation and pressure support (Figure 3) and the state-dependent changes were greater during pressure support than during assist-control ventilation. In clinical practice, the level of pressure support is adjusted in accordance with a patient's respiratory rate, which provides reasonable guidance as to a patient's inspiratory effort (49). Respiratory rate was lower during sleep as compared with wakefulness (Figure 3, *top right*). If a physician adjusts pressure support according to patient's sleeping respiratory rate, patient effort will likely increase on awakening.

Changes in ventilator settings are commonly based on arterial

blood gas measurements. With pressure support, end-tidal CO₂ was up to 7 mm Hg higher during sleep as compared with wakefulness. The coefficient of variation for end-tidal CO₂ during pressure support was 8.1% (range, 1.5 to 10.3%). Differences of this magnitude between sleep and wakefulness, arising from variations in CO₂, may cause physicians to change ventilator settings when a change is not necessary. Consequently, under-ventilation or overventilation may result (50).

The changes in breathing pattern and gas exchange between sleep and wakefulness carry important implications for research. During pressure support, our patients experienced an increase in mechanical inspiratory time on moving from wakefulness to sleep (Figure 3, top middle). This change was associated with an increase in tidal volume, thereby inducing hypocapnia and apnea during pressure support. Research into patient-ventilator interaction also needs to carefully control for the sleep-wakefulness state because of its effect on breath components and gas exchange (51, 52).

It would be imprudent to disregard central apneas and the associated fragmentation of sleep as aberrations of little consequence. Central apneas can cause repetitive arousals that can, in turn, produce elevations in the levels of catecholamines (16) and blood pressure (15), and contribute to the progression of cardiac failure (17, 18) and arrhythmias (19). These deleterious consequences of central apneas might increase morbidity and mortality in critically ill patients. In summary, critically ill patients experience greater fragmentation of sleep during pressure support than during assist-control ventilation because of the development of central apneas, and this effect is especially prominent in patients with heart failure. In conclusion, selecting a ventilator mode has a marked influence on the quality of sleep in a critically ill patient, and a patient's response to ventilator settings can differ significantly between sleep and wakefulness.

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