Control of breathing during sleep assessed by proportional assist ventilation

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Meza, S., E. Giannouli, and M. Younes. Control of breathing during sleep assessed by proportional assist ventilation. J. Appl. Physiol. 84(1): 3–12, 1998.—We used proportional assist ventilation (PAV) to evaluate the sources of respiratory drive during sleep. PAV increases the slope of the relation between tidal volume ($V_t$) and respiratory muscle pressure output (Pmus). We reasoned that if respiratory drive is dominated by chemical factors, progressive increase of PAV gain should result in only a small increase in $V_t$ because Pmus would be downregulated substantially as a result of small decreases in $P_{CO_2}$. In the presence of substantial nonchemical sources of drive [believed to be the case in rapid-eye-movement (REM) sleep] PAV should result in a substantial increase in minute ventilation and reduction in $P_{CO_2}$ as the output related to the chemically insensitive drive source is amplified severalfold. Twelve normal subjects underwent polysomnography while connected to a PAV ventilator. Continuous positive air pressure (5.2 ± 2.0 cmH$_2$O) was administered to stabilize the upper airway. PAV was increased in 2-min steps from 0 to 20, 40, 60, 80, and 90% of the subject’s elastance and resistance. $V_t$, respiratory rate, minute ventilation, and end-tidal CO$_2$ pressure were measured at the different levels, and Pmus was calculated. Observations were obtained in stage 2 sleep (n = 12), slow-wave sleep (n = 11), and REM sleep (n = 7). In all cases, Pmus was substantially downregulated with increase in assist so that the increase in $V_t$, although significant (P < 0.05), was small (0.08 liter at the highest assist). There was no difference in response between REM and non-REM sleep. We conclude that respiratory drive during sleep is dominated by chemical control and that there is no fundamental difference between REM and non-REM sleep in this regard. REM sleep appears to simply add bidirectional noise to what is basically a chemically controlled respiratory output.

PAV is, therefore, a useful tool to study the contribution of nonchemical factors to respiratory drive and the CO$_2$ gain in the hypocapnic range.

It is generally believed that control of breathing during non-rapid-eye-movement (NREM) sleep is dominated by chemical factors, whereas in rapid-eye-movement (REM) sleep, particularly in phasic REM, it is dominated by behavioral factors (20). According to present understanding, therefore, PAV should result in small changes in $V_t$ and $P_{CO_2}$ in NREM sleep while causing large changes in $V_t$ and $P_{CO_2}$ in REM sleep.

Methods

Twelve normal subjects (7 nonsnorers and 5 snorers) underwent full polysomnography while connected by a nose
mask to a PAV research prototype (Respironics). Six subjects were patients who were initially referred for suspected sleep apnea but proved not to have it. The other six subjects were recruited from a pool of students and technical personnel working within the hospital. Subjects were free of cardiopulmonary disease, and all had had at least one overnight polysomnography in the past, either for suspected apnea or as subjects in other research projects. None of the subjects had sleep apnea, as evident from the results of previous polysomnography. Four subjects were smokers, one was a former smoker, and seven had never smoked. The mean age of subjects was 33.3 yr, and the mean body mass index was 28.46 (Table 1). None of the subjects was receiving any medication. The protocol was approved by the institutional committee for human experimentation.

Three-channel electroencephalography (C3/A2, C4/A1, O2/A1), right and left electrooculography, and submental electromyography were monitored. Sleep stages were scored by the Rechtschaffen and Kales method (23). Electrocardiography and chest wall movements (Respirac; Ambulatory Monitoring, NY) were also monitored. O2 saturation was measured using a finger oximeter (Nellcor, N-200). End-tidal CO2 partial pressure (PetCO2) (Datex) was measured through a port in the mask and transcutaneous P CO2 (Kontron gas analyzer; Microgas 7640 MKZ) was also obtained. All signals were simultaneously recorded on a model 78G polysomnograph (Grass Instruments, Quincy, MA). Signals for flow, volume, and mouth pressure obtained from the ventilator were also recorded on the polygraph. The ventilator used was equipped with algorithms to estimate leak from all sources (including mouth), and the magnitude of the leak was continuously displayed. The nose mask was tightened enough to ensure that leaks around the nose were minimal. When necessary (leak still high despite a tightly fitting nose mask), a chin strap was applied; if that failed to control the leak, the mouth was taped. Observations were carried out only when the subject was in NREM sleep. We calculated respiratory E and R. These measurements were carried while the subject was in NREM sleep. We calculated respiratory R of each subject by using a pulse technique. Brief pressure pulses, with an amplitude of 3 cmH2O and a duration of 400 ms, were given by using a pulse generator connected to the ventilator system. Pulses were delivered at the beginning of inspiration, when the elastic recoil of the respiratory system is least (Fig. 1).

To set the level of VA and FA, we measured respiratory system E and R. These measurements were carried while the subject was in NREM sleep. We calculated respiratory R of each subject by using a pulse technique. Brief pressure pulses, with an amplitude of 3 cmH2O and a duration of 400 ms, were given by using a pulse generator connected to the ventilator system. Pulses were delivered at the beginning of inspiration, when the elastic recoil of the respiratory system is least (Fig. 1). To calculate R, the increase in pressure above the CPAP level was divided by the increase in flow measured at the time of peak flow. Peak flow invariably occurred very early during the pulse (Fig. 1).

The E of the respiratory system was obtained by using the runway method that has been described previously (30). Briefly, with FA set at zero, the VA gain on the ventilator is gradually increased until inspiration fails to terminate at the usual inspiratory time (Ti; Fig. 2). Instead, inspiratory flow does not decrease to zero and rises progressively, along with volume, until the cycle is terminated by a set pressure limit on the ventilator (Fig. 2). As described elsewhere (30), this occurs when VA just exceeds the respiratory system E. Thus the value of VA at this point (in cmH2O/l) is taken as E.

Calculated respiratory E and R were entered in the ventilator. Once the subject reached a stable stage of sleep, we applied different levels of proportional assist in the following order: 0, 20, 60, 80, and, when possible (i.e., no arousal), 90%. Each level was maintained for at least 2 min. PAV was applied in stage 2, slow-wave sleep (SWS) and, when possible, in REM. If an arousal occurred, the assist was removed, and data collection did not resume until the subject was again in a stable stage of sleep. If a change in sleep stage occurred during the increasing levels of assist process, the data were discarded. The results given here are from the single trial during which the highest level of assist (80 or 90%) was reached without arousals or change in sleep stage.

Data analysis was made in the 30- to 40-s interval preceding a change in level of assist. Respiratory rate, VT, Vl, and PetCO2 were analyzed from chart records on a breath-by-breath basis. To calculate the Pmus generated by inspiratory muscles, we measured instantaneous flow (V˙) and volume above end-expiratory level (Vl) at 100-ms intervals in 3–5 representative breaths at each level of assist. The corresponding values of airway pressure above CPAP (Pawtot) were also determined. Instantaneous Pmus (Pmus t) was calculated from the equation (29)

\[ Pmus_t = E \cdot Vl + R \cdot Vl - Paw_{tot} \]

Table 1. Clinical and respiratory characteristics of subjects

<table>
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<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Height, m</th>
<th>BMI, kg/m²</th>
<th>Elastance, cmH2O/l</th>
<th>Resistance, cmH2O·l⁻¹·s</th>
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Average ± SD 33.3 ± 8.5 84.0 ± 26.0 1.71 ± 0.06 28.5 ± 7.7 11.4 ± 2.4 3.7 ± 1.3 5.2 ± 2.0

BMI, body mass index; CPAP, continuous positive air pressure; M, male; F, female.
where respiratory E and R are determined during sleep (see Protocol). The highest Pmus value within each breath was noted (peak Pmus).

For the statistical analysis, we used one-way analysis of variance (ANOVA) and two-way interaction when required. Differences were considered significant if the null hypothesis was rejected at a level of \( P < 0.05 \). The analysis performed is included in the text where appropriate.

RESULTS

The demographic characteristics of the subjects are detailed in Table 1. We had reliable data for stage 2 sleep in 12 subjects, for SWS in 11 subjects, and for REM sleep in 7 subjects.

Respiratory E and R values (Table 1) were: E = 11.4 ± 2.4 cmH₂O/l and R = 3.7 ± 1.3 cmH₂O·l⁻¹·s. These values were within normal limits (2, 17).

It was possible to reach 90% assist without arousal during NREM sleep in at least one test in each subject. Arousals and even full awakenings occurred with 90% assist during REM sleep. The highest level reached in REM was 80% assist.

Figure 3 is an example of response to high-level (90%) assist in one subject during stage 2 sleep. At 90% assist (Fig. 3B) \( V_T \) was slightly larger and PETCO₂ was slightly lower than at 0% assist (Fig. 3A). Respiratory rate was not affected. Figure 4 provides the average results for stage 2 sleep and SWS. The tendency for \( V_T \) and \( V_I \) to increase and for PETCO₂ to decrease is evident for the whole group. Significant changes from 0% assist were observed only at high levels of assist (one-way ANOVA for repeated measures). There was no difference in response between stage 2 sleep and SWS (two-way ANOVA). For the combined data of stage 2 sleep and SWS, \( V_T \) increased from 0.441 ± 0.09 to 0.527 ± 0.14 liter between 0 and 90% assist (\( P < 0.05 \)). Respiratory rate did not change significantly, whereas \( V_I \) increased over the same range of assist from 6.11 ± 1.56 to 7.44 ± 2.16 l/min (\( P < 0.05 \)). PETCO₂ decreased from 44.3 ± 4.2 at 0% assist to 41.8 ± 3.81 mmHg at 90% assist (\( P < 0.001 \)).

Figure 5 compares the responses in REM sleep with those in NREM sleep in the same seven subjects for whom REM data were available. The maximum level of assist was 80% in both cases. There was no significant difference in response to PAV between the two states (two-way interaction ANOVA). The changes in \( V_I \) and PETCO₂ as a result of the assist were also comparable.

Because it is thought that phasic REM differs from tonic REM and NREM in the extent of behavioral influences (20), we further specifically assessed the response in phasic REM. In six subjects, there were fairly lengthy periods (>20 s) of phasic REM near the highest level of assist. The average \( V_T \) in these periods was compared with average \( V_T \) during phasic REM at 0% assist. The results are shown in Fig. 6. This figure also shows the results in tonic REM and NREM in the same six subjects over a comparable range of assist. There was no significant difference in response to the assist between the three sleep states (three-way interaction ANOVA). The changes in \( V_I \) and PETCO₂ as a result of the assist were also comparable.

The main conclusions from this study are that in normal subjects substantial unloading of the respir-
tory muscles during sleep is met with downregulation of respiratory motor output, so that there is little change in ventilation and PCO₂ and there is little difference in these responses among NREM, phasic REM, and tonic REM sleep. Some of these conclusions are substantially at variance with contemporary concepts.

Technical Considerations

Extent of unloading/amplification of motor output. In theory (29), when the ventilator provides 50% of elastic and resistive pressure, the system is 50% unloaded and the combined pressure output of subject plus ventilator is twice what it would be without the assist (i.e., subject alone). A pressure-amplification factor of 2 is then to be expected [amplification factor = 100/(100 – %assist)]. For 80% assist, the pressure-amplification factor should be 5, and for 90% assist it should be 10 (ventilator provides 9 cmH₂O for each 1 cmH₂O developed by the subject). In reality, these theoretical targets cannot be expected because of ventilator-response delays. Even small delays can appreciably reduce the pressure-amplification factor, particularly at high levels of assist. For example, if, at 90% intended assist, the delivered pressure is 10% less than intended as a result of the response delay, actual assist is 81%, and the amplification factor is degraded from 10 to 5.3 (1/0.19 instead of 1/0.10). With the same 10% error, the amplification factor at an intended 50% assist would be 1.8 instead of 2.0.

Apart from the above technical confounding factor, the actual amplification factor that is applied to Pmus during the assist need not translate into similar volume amplification. The conversion of pressure to volume is complex (31, 32) and is influenced by nonlinearities in the pressure-volume and pressure-flow relationships (passive properties) as well as by the intrinsic properties of the respiratory muscles.¹ A true pressure amplification factor is 5, but the volume amplification factor is only 3.0. The ventilator may thus be amplifying Pmus during the assisted breath by a factor of 5, as intended (6/1.2). However, at the same neural output, V̇t has increased only threefold. It is the latter relation (V̇t per unit neural activation) that is relevant to loop gain.

¹ Assume that at a given neural activity the inspiratory muscles generate a pressure of 2 cmH₂O near functional residual capacity. In the absence of assist (e.g., first unassisted breath, Fig. 8), this may produce a V̇t of 100 ml. We dial an assist of 80%. With the assist, flow and volume are greater. Because pressure output for a given neural activation decreases as a function of flow and volume (force-velocity and force-length relationships; for review see Ref. 31), Pmus in the assisted breath is <2 cmH₂O. Assume that, as a result of these intrinsic muscle properties, Pmus is decreased to 1.2 cmH₂O. Given the amplification factor of 5 (at 80% assist), the total pressure is now 5 × 1.2 or 6.0 cmH₂O. For the same mechanics (respiratory system R and respiratory system E), V̇t increases only 3.0 times (6.0/2.0). The ventilator may thus be amplifying Pmus during the assisted breath by a factor of 5, as intended (6/1.2). However, at the same neural output, V̇t has increased only threefold. It is the latter relation (V̇t per unit neural activation) that is relevant to loop gain.
fication of 5 (80% assist) will produce less than fivefold increase in Vt. Although the percent unloading (or pressure-amplification factor) is the relevant index from the energetic standpoint, it is the Vt amplification (i.e., ratio of unloaded to loaded Vt at the same muscle activation) that is relevant to the objectives of the present study (see INTRODUCTION).

An estimate of the actual Vt amplification can be obtained by stopping the assist for one breath and noting the ratio of the assisted to the nonassisted Vt (Fig. 8). This estimate takes into account both the technical factor (related to ventilator-response delay) and the physiological factors involved in pressure-to-volume conversion. Because the time difference between the assisted and nonassisted breath is too short for chemical responses, and because of lack of neural responses to load changes during sleep (see Downregulation of Respiratory Output), it can be reasonably assumed that respiratory muscle activation is similar in the first unassisted breath to the immediately preceding assisted breaths. From observations such as those shown in Fig. 8, we conclude that the Vt amplification factor at the highest level of assist (90%) is between 3.0 and 4.0. This still represents a substantial augmentation of ventilatory response to respiratory muscle activity.

Use of CPAP. All our subjects received CPAP (Table 1). This was necessary to stabilize UAR, thereby making it possible to target a certain resistive unloading. Had UAR been allowed to vary, as it normally does within and between breaths during sleep (10), a given flow-related assist setting on the ventilator would have meant a highly variable amplification factor. Nonetheless, the control of breathing in our subjects was altered from its usual state by the lack of variability in UAR, and this may have affected the results. Thus, to the extent that part of sleep-related hypoventilation is due to the increase in UAR (11), our subjects likely did not hypoventilate as much as they usually do during sleep.

Downregulation of Respiratory Output

Had there been no downregulation, Vt would have increased three- to fourfold at the highest level of assist used (see Technical Considerations). The fact that Vt increased <20% indicates that downregulation was so
Fig. 4. Average results of tidal volume (A), respiratory rate (B), minute ventilation (C), and end-tidal PCO₂ for stage 2 (ST 2, ●; n = 12) and slow-wave sleep (SWS, ○; n = 11). Bars, SE. Significantly different from zero assist in same stage by 1-way analysis of variance (ANOVA) repeated measures: *P < 0.05, **P < 0.01, + P < 0.001. No significant difference between stage 2 and SWS by ANOVA 2-way interaction.

Fig. 5. Responses to different levels of assist for 7 subjects with data in non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) sleep. Bars, SE. *Significantly different from zero assist in same stage P < 0.05. There was no significant difference in response to proportional assist ventilation (PAV) between 2 stages (2-way interaction ANOVA).
effective as to almost completely cancel out the effect of unloading; the observed increases in VT and V̇I were, 10% of the expected increases had there been no downregulation. Downregulation was also documented more objectively by calculating Pmus (Fig. 7).

There are three possible mechanisms for this pressure downregulation: mechanical, load compensatory neural reflexes (including upper airway reflexes), and chemical. The impact of mechanical feedback is almost certainly trivial. This feedback works via the force-length and force-velocity relationships of the respiratory muscles. The gain of this feedback (31) is such that the steady-state changes in flow and volume observed during the assist (relative to steady state on no assist) could not have decreased pressure output by more than a few percentage points. For example, an increase in flow of 1 l/s decreases pressure output by 6% (1). In the present study, inspiratory flow increased by <0.1 l/s at the highest assist. Similarly, the steady-state increase in V̇I (0.08 liter on average; Fig. 4) could not have reduced pressure output by >1–2% (31).

There are no discernible immediate (i.e., first breath) changes in respiratory muscle activity on addition of R or even on complete airway occlusion during sleep (3, 12–14). Neural load-compensatory mechanisms appear, therefore, to be inoperative during sleep. Downregulation, accordingly, cannot be related to altered relation between muscle activation and spirometric output.

The mechanism of downregulation is almost certainly chemical. This is not only because other mechanisms are unlikely but also because the extent of downregulation is totally compatible with what we know about the gain of chemical feedback. Thus Fig. 7 shows that Pmus decreased to one-third of its initial value as PETCO₂ decreased by 1.5 Torr. The corresponding ventilatory response to this 65% reduction in Pmus, in the absence of assist, would have been about two-thirds of the baseline V̇I (see Figs. 4 and 5), or 4 l/min. This gives a ventilatory response of 2.6 l·min⁻¹·mmHg⁻¹ (4.0/1.5), which is the normal ventilatory response to CO₂ (22).

Sources of Respiratory Drive During Sleep

NREM sleep. Until recently, the control of breathing during NREM sleep was believed, unequivocally, to be dominated by chemical feedback (7, 20). This was based primarily on the observation that lowering PaCO₂ by artificial ventilation in this state readily results in apnea (6, 25). Thus Skatrud and Dempsey (25) demonstrated that reducing arterial PCO₂ (PaCO₂) by 3–6 Torr...
resulted in 5- to 10-s apnea, and the duration of apnea was linearly related to the degree to which $P_{aCO_2}$ is lowered during passive hyperventilation. More recently, this notion has been questioned, because reports from the same laboratory indicated that apnea occurred during and after artificial ventilation during sleep even when $PETCO_2$ was held constant at, or even slightly above, its eupneic sleep level (15). Thus, according to these recent data, apnea after hypocapnic mechanical ventilation (6, 25) may be due to active inhibition related to excessive volume during artificial ventilation and does not necessarily represent dependence on chemical feedback during NREM sleep. The present results, in which substantial downregulation occurred despite minimal increases in $VT$ and $Vi$, and in which the gain of this downregulation is quantitatively consistent with $CO_2$ responses, seem to reaffirm the original belief that respiratory drive in NREM sleep is dominated by inputs from chemoreceptors. The reason for the occurrence of apnea after isocapnic artificial ventilation (15) is not clear. Perhaps a strong inhibitory input, with memory, is generated with very high volumes of ventilation (15, 16). It must be pointed out, however, that the relation between $PETCO_2$ and brain $PCO_2$ during artificial ventilation with supplemental fractional inspired $CO_2$ is not known so that isocapnia at the same end-tidal level need not reflect isocapnia at the brain level.

REM sleep. Unlike the case in NREM sleep, in REM sleep (at least in phasic REM) breathing is believed to be dominated by behavioral factors (20). This belief is based on the erratic pattern of breathing and the fact that this pattern is not altered by hypoxia (5, 19, 21), hyperoxia (18, 26), or hypercapnia (27). Furthermore, the ventilatory response to $CO_2$ was reported to be quite depressed in humans (8) and dogs [particularly in phasic REM (27)]. The periodic breathing typical of NREM sleep at high altitude [which is chemically mediated (7)] was noted to disappear with the onset of REM sleep (4, 24).

If respiratory drive during REM included an important component that is unrelated to chemoreceptor inputs, then downregulation of respiratory motor output, as a result of unloading induced hypocapnia, should be less pronounced (in view of the presence of substantial inputs that are impervious to $CO_2$). Therefore we fully expected to find substantial hyperventilation in REM sleep, at least in phasic REM, on amplify-
ing respiratory motor output with PAV. This was not observed. The slope of Pmus vs. PCO₂ was not different (Fig. 7), and average V₁ did not increase any more with the assist whether we measured the response in phasic or tonic REM (Fig. 6). Our results, therefore, suggest that control of the average respiratory motor output continues to be dominated by input of chemoreceptors both in phasic and in tonic REM sleep and that the gain of chemical responsiveness is similar in REM and NREM sleep. Phasic REM sleep simply introduces nonchemical biphasic “noise” that is superimposed on a basically similar, chemically controlled, average motor output. An alternative explanation for the similarity of the PETCO₂/Pmus slope in REM and NREM sleep (Fig. 7) is that such similarity is fortuitous and related to two opposing differences between the two states. Thus the slope of the PETCO₂/Pmus at constant load may be lower in REM sleep, but this is offset by greater load-related, mechanoreceptor-mediated response in REM sleep. With this scenario, only part of the downregulation of Pmus in REM sleep is related to hypocapnia, while the other part is caused by load-related reflexes. Our results do not permit a distinction between the two possible interpretations of the similar slope. It is to be noted that studies showing lack of important nonchemical, load-related responses in sleep (3, 12–14) were carried out in NREM sleep. On the other hand, we have recently shown (9) that there is no appreciable downregulation of respiratory motor output during unloading under isocapnic conditions in awake humans. Whitelaw et al. (28) also demonstrated earlier, in anesthetized humans, that when CO₂ is controlled, addition of R elicits no additional motor responses subsequent to the first loaded breath. Given the demonstrated lack of nonchemical load responses in humans while awake (9), anesthetized (28), or in NREM sleep (3, 12–14), it is unlikely that such responses are important during REM sleep. Our conclusion, that respiratory drive in REM sleep is principally chemical in origin, but with superimposed bidirectional noise, is not inconsistent with most of the previous evidence used to arrive at the theory of behavioral control of respiration during REM sleep. This conclusion is thus consistent with the persistence, referred to earlier, of erratic breathing during hypoxia, hyperoxia, and hypocapnia in REM. Furthermore, in the presence of substantial noise in respiratory output, it would be difficult to elicit sustained, chemically induced apnea, because the occasional large, behaviorally mediated breath would break through. Perhaps a more profound hypocapnia, whereby even large sporadic excitation fails to elicit phasic motor response, is needed to produce sustained apnea in REM sleep.

The relationship between Pmus and PCO₂ was shifted to the left in REM. This shift suggests an extra tonic drive to breathing in REM which is equivalent to 1.5 Torr in PCO₂. We cannot be sure, however, that this shift is real, because the relation between PETCO₂ and Pmus may be different in REM and NREM sleep because of the different breathing pattern and shorter expiratory time in REM.

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