Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects

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Meza, Sonia, Manuel Mendez, Michele Ostrowski, and Magdy Younes. Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects. J. Appl. Physiol. 85(5): 1929–1940, 1998.—Assisted ventilation with pressure support (PSV) or proportional assist (PAV) ventilation has the potential to produce periodic breathing (PB) during sleep. We hypothesized that PB will develop when PSV level exceeds the product of spontaneous tidal volume (VT) and elastance (VTsp ·E) but that the actual level at which PB will develop [PSV(PB)] will be influenced by the ΔPCO2 (difference between eupneic PCO2 and CO2 apneic threshold) and by ΔRR (response of respiratory rate (RR) to PSV). We also wished to determine the level at which PB develops to assess inherent ventilatory stability in normal subjects. Twelve normal subjects underwent polysomnography while connected to a PSV/PAV ventilator prototype. Level of assist with either mode was increased in small steps (2–5 min each) until PB developed or the subject awakened. End-tidal PCO2, VT, RR, and airway pressure (Paw) were continuously monitored, and the pressure generated by respiratory muscle (Pmus) was calculated. The pressure amplification factor (PAF) at the highest level was calculated from [(ΔPaw + Pmus)/Pmus], where ΔPaw is peak Paw – continuous positive airway pressure. PB with central apneas developed in 11 of 12 subjects on PSV. ΔPCO2 ranged from 1.5 to 5.8 Torr. Changes in RR with PSV were small and bidirectional (+1.1 to −3.5 min⁻¹). With use of stepwise regression, PSV(PB) was significantly correlated with VTsp (P = 0.001), E (P = 0.00009), ΔPCO2 (P = 0.007), and ΔRR (P = 0.006). The final regression model was as follows: PSV(PB) = 11.1 VTsp + 0.3E − 0.4 ΔPCO2 − 0.34 ΔRR − 3.4 (r = 0.98). PB developed in five subjects on PAV at amplification factors of 1.5–3.4. It failed to occur in seven subjects, despite PAF of up to 7.6. We concluded that 1) a PCO2 apneic threshold exists during sleep at 1.5–5.8 Torr below eupneic PCO2, 2) the development of PB during PSV is entirely predictable during sleep, and 3) the inherent susceptibility to PB varies considerably among normal subjects.

Pressure support ventilation (PSV) is extensively used for continuous or nocturnal support in ventilator-dependent patients. In addition, in combination with positive end-expiratory pressure, it is also extensively used in the treatment of obstructive sleep apnea (OSA; bilevel support) in patients who, apart from the sleep-related upper airway dysfunction, have generally normal respiratory mechanics. Proportional assist ventilation (PAV) is another form of synchronized pressure assist that potentially has the same spectrum of clinical applications as PSV (29, 31, 32).

In the absence of a mandatory back-up rate, neither method is capable of producing sustained arrest of respiratory efforts; if ventilation increases excessively and PCO2 decreases below the apnea point, no triggering and, hence, no ventilation occur until PCO2 rises again enough to reestablish spontaneous efforts. The result of excessive assist would, therefore, be periodic breathing (PB). It has been reported that some normal subjects develop PB during sleep while receiving PSV (18).

Because both methods are capable of boosting ventilation, both have the potential to produce PB when the drive to breathe is dominated by chemoreceptor input, such as during NREM sleep. However, because the factors that would promote PB with the two methods are, at least in theory, substantially different, it may be expected that the susceptibility to develop PB with PSV and PAV during sleep will differ according to a variety of prevailing background conditions and inherent responses of the respiratory control system (see THEORY).

The present study was carried out in normal subjects with the following objectives: 1) to confirm that the theoretical bases for predicting PB with PSV are valid in practice and to determine the normal responses relevant to these predictions; this could result in guidelines to minimize the chance of this abnormality in clinical practice; 2) to precisely determine the CO2 set point (apnea point) during sleep in normal subjects using the PSV model; and 3) to compare the susceptibility to PB with the two methods (PSV and PAV) in the same subjects under similar experimental conditions and where background conditions of respiratory mechanics and control are normal; this information should be relevant to the use of these methods in OSA, where, as indicated earlier, the mechanics of the respiratory system proper are usually normal.

THEORY

Figure 1 shows the theoretical relation between peak inspiratory pressure output (Pmus) and tidal volume (VT) in a subject with normal mechanics and inspiratory duration (TI) at different levels of assist with PSV.
and PAV. These results were obtained using a model described in detail earlier (27) and used extensively to model neuromechanical interactions under a variety of clinically relevant conditions, including mechanical ventilation (30).

Because in the PSV mode the ventilator develops the same inspiratory pressure assist with every triggered breath, regardless of the magnitude of inspiratory effort, the effect is to boost Vt by nearly the same amount at all levels of peak inspiratory Pmus (30). As a result, the relation between peak Pmus and Vt is shifted upward in a parallel fashion (i.e., no change in slope), with the magnitude of the shift being a function of the applied PSV level (Fig. 1, left) and the subject’s mechanics. An important consequence of this parallel shift is that a minimum Vt (Vtmin) will be delivered even if the subject’s effort is very small (barely enough to trigger). This is given by the Vt intercepts in Fig. 1, left. The magnitude of Vtmin is given by (28, 30)

$$V_{t\text{min}} = (PSV - V_{th} \cdot R - P_{DH})/E$$

where Vth is the ventilator specific flow threshold at which the assist is terminated, R and E are the subject’s resistance and elastance, and P DH is the elastic recoil pressure associated with any dynamic hyperinflation that may exist at the beginning of inspiration. In normal subjects, little dynamic hyperinflation should occur in view of the normal expiratory R [if it is assumed that upper airway R is normalized with continuous positive airway pressure (CPAP)] and the relatively long expiratory duration. Furthermore, because $V_{th}$ and $R$ are small (∼0.1 l/s and 4.0 cmH2O·l−1·s), the product $V_{th} \cdot R$ should be small. In normal subjects, therefore, VTmin should essentially be determined by PSV level and E. Thus

$$V_{t\text{min}} \approx \frac{PSV}{E}$$

(1)

Assume that a normal subject, on enough CPAP to normalize R, is generating a peak Pmus of 8 cmH2O. With no additional PSV, he has a spontaneous Vt (Vtsp) of 0.5 liter (Fig. 1, filled circle, 0-assist line). Assume further that respiratory rate (RR) is 12 breaths/min, giving him a spontaneous ventilation (Ve) of 6 l/min. At the same Pmus, VT rises immediately to 700 ml (Fig. 1, filled square, 3.0-cmH2O line). If RR does not decrease, Ve will increase commensurately with the increase in Vt (i.e., to 8.4 l/min) and PCO2 will begin to decline. In the course of this decline in PCO2, Pmus and Vt will decrease along the path dictated by the 3.0-cmH2O line. The progressive reduction in Vt will moderate the rate of decline in PCO2. When Vt reaches a point close to Vtsp, PCO2 will no longer decrease, since Ve is now close to Ve,sp. Although there may be some undershoot in PCO2 and transient oscillation due to circulatory delays, a steady state can be reached. If the PCO2 set point is, as suspected (25), only a few Torr lower than spontaneous PCO2, then Vt in the steady state can be only slightly higher than Vtsp (with the assumption of a constant RR). A prerequisite for the development of a steady state during PSV is, therefore, that a point must exist along the Vt-Pmus relation where Vt is similar to Vtsp. Stated differently, unless RR increases with PSV, PB cannot develop only when Vtmin exceeds Vtsp. In the case of our average normal subject whose Vtsp is 0.5 liter (Fig. 1, left), this can be seen to be the case for 3- and 6-cmH2O PSV but not for higher PSV levels. At higher PSV levels, Vtmin is greater or much greater than Vtsp. The relation between Vtmin and Vtsp
is obtained by dividing both sides of Eq. 1 by $V_{Tsp}$. Thus

$$\frac{V_{Tmin}}{V_{Tsp}} = \frac{PSV}{V_{Tsp} \cdot E}$$

(2)

It follows that the lower the product $V_{Tsp} \cdot E$, the lower is the PSV level at which PB can potentially occur.

At PSV levels where $V_{Tmin} > V_{Tsp}$, a steady state can be reached if RR decreases such that the product $V_{Tmin} \cdot RR_{PSV}$ is approximately the same as $V_{Tsp} \cdot RR_{sp}$. If RR does not decrease, several breaths with $V_{Tmin} > V_{Tsp}$ will force $PCO_2$ below the CO$_2$ set point. Central apnea must develop and continue until $PCO_2$ rises again above the set point. Several breaths, all larger than $V_{Tsp}$, will then occur, forcing $PCO_2$ below the set point again, and the cycle repeats. If RR actually decreases as PSV level increases, then a greater difference between $V_{Tmin}$ and $V_{Tsp}$ can be tolerated before PB develops.

According to this synthesis, the following should be the factors that determine whether PB develops during PSV and the PSV level at which it will develop in a given individual.

1) How much below spontaneous $PCO_2$ is the $PCO_2$ set point? This $\Delta PCO_2$ determines the extent to which the product $V_{Tmin} \cdot RR_{PSV}$ can exceed $V_{Tsp} \cdot RR_{sp}$ before central apnea develops. This is not known (see DISCUSSION).

2) How much does RR decrease as PSV level is increased (i.e., $\Delta RR$)? This will determine the extent to which $V_{Tmin}$ can exceed $V_{Tsp}$ before $VE_{PSV}$ exceeds $VE_{sp}$. In awake subjects RR does not fall as PSV is increased, despite the development of marked hypocapnia (5, 18, 23). Likewise, Morrell et al. (18) reported no change in average RR in six sleeping subjects on application of 8-cmH$_2$O PSV. There were differences in individual responses, however. These differences could, theoretically, affect the PSV level at which PB develops in individual subjects.

3) What is the product $V_{Tsp} \cdot E$? In our experience, $V_{Tsp}$ during sleep in normal subjects varies considerably. This is due, in part, to differences in baseline $VE$ and $PCO_2$, and, in part, to different breathing patterns ($Vt$ vs. RR) at the same $VE$. Likewise, $E$ may be expected to vary considerably, depending on anthropometric characteristics (1) and state of health of the respiratory system.

The present study was designed to assess the variability in $V_{Tsp}$, $E$, $\Delta PCO_2$, and $\Delta RR$ during sleep in normal subjects and the extent to which differences in these variables among individuals determine the PSV level at which PB occurs [PSV(PB)].

With PAV the ventilator provides pressure assist that is proportional to the subject’s instantaneous inspiratory effort (29). In essence, the ventilator amplifies the pressure generated by the subject. The net effect is an increase in the slope of the relation between inspiratory Pmus and the resulting $Vt$ (Fig. 1, right). There is, in this case, no $Vt$ intercept and, hence, no $V_{Tmin}$ (30). Regardless of the amplification factor, there is always a $Vt$ that corresponds to $V_{Tsp}$. If the assist is increased, an initial increase in $Vt$, with a consequent decrease in $PCO_2$ and Pmus, will be followed by a gradual return of $Vt$ to near the spontaneous level. Accordingly, unlike the case of PSV where a $V_{Tmin}$ exists, a steady state is theoretically possible with PAV regardless of the level of assist (amplification factor). Whereas the lack of a $V_{Tmin}$ with PAV is a stabilizing feature, the increase in slope of the Pmus-$Vt$ relation is not. With an increase in slope, a given spontaneous change in Pmus will result in a greater ventilatory response and a greater change in $PCO_2$ than would otherwise occur. This, in turn, would elicit compensatory responses via chemoreceptors, the effect of which on Pmus is opposite to the initial perturbation. In the presence of a high slope, the ventilatory response to these secondary and opposite Pmus responses will also be exaggerated. A situation may thus arise where a spontaneous perturbation in Pmus may result in self-perpetuating oscillations in ventilatory output (PB). Whether a given increase in $Vt$-Pmus response slope results in PB should, theoretically, depend on how susceptible the control system is to oscillations in the first phase. This susceptibility, generally referred to as loop gain, is related to many factors, e.g., circulatory delays, $CO_2$ and $O_2$ stores in gas and blood, dynamics and gain of chemoreceptor responses, cardiac output, respiratory mechanics, and arousal threshold. A review of these factors is beyond the scope of this account (for review see Refs. 3, 4, 9, 10, and 26). Because there is a wide variability in these characteristics among different patients and even among normal subjects, it may be expected that the innate susceptibility to PB (underlying loop gain) must vary considerably. One extreme of this range is represented by subjects who spontaneously develop PB. These subjects have a spontaneous loop gain of $>1$; a given perturbation results in a secondary perturbation of an equal or greater magnitude. In all other subjects, those with stable breathing, loop gain is $<1$, but the range could, theoretically, be between 0 and just $<1$. A given increase in $Vt$-Pmus slope, such as with the use of PAV, may be expected to increase overall loop gain by a corresponding amount, with the assumption that all other factors remain unchanged. Thus a subject in whom loop gain is 0.5 and whose spontaneous breathing is stable may be expected to develop PB if the amplification factor produced by PAV is 2.0 (Fig. 1, right). The less susceptible a subject is to PB (the lower the loop gain), the greater is the amplification factor required to elicit PB. As proposed earlier, PAV can be used to estimate loop gain and, hence, susceptibility to PB, in subjects whose breathing is stable (17).

Because loop gain in normal subjects is not known, the tendency for these subjects to develop PB during sleep while on PAV is difficult to predict. In a preliminary study on 12 sleeping subjects, none developed PB during PAV (17). The amplification factor was, however, not accurately quantified. In the present study we will extend these observations in additional subjects and will determine the amplification factor in effect during PAV application.
METHODS

Twelve subjects (6 men and 6 women) were recruited from among medical and technical personnel and from students of allied health schools. All subjects were free of cardiopulmonary disease and had a normal body mass index (Table 1). Their average age was 27.1 ± 3.8 yr. Three of the subjects gave a history of snoring. The protocol was approved by the institutional Committee for Research on Human Subjects.

The subjects underwent standard polysomnography while connected via nasal mask to a ventilator research prototype capable of delivering PAV and bilevel pressure support (Respironics, Murrysville, PA). We monitored electroencephalography (C3/A2, C4/A1, O2/A1), right and left ocularography, submental electromyography, chest and abdominal movements (Respitrace, Ambulatory Monitoring, Airdsley NY), end-tidal PCO2 (PetCO2; Datex, Helsinki, Finland), and airway pressure (Paw). Flow and volume signals, corrected for leaks (see below), were obtained from the ventilator. All signals were simultaneously recorded on a polygraph ventilator (model 78 G, Grass Instruments, Quincy, MA).

The ventilator prototype is equipped with algorithms to estimate total leak flow (including mouth leaks), and the magnitude of the leak was continuously displayed. The nose mask was tightened enough to ensure that leaks around the nose were minimal. Where necessary (leak still too high, despite tight-fitting nasal mask), a chin strap was applied. If that failed to eliminate mouth leaks, the mouth was taped.

The flow and volume outputs of the ventilator provided estimated subject flow and volume after allowing for leaks. The accuracy of the leak correction was previously verified by comparing ventilator output with independently measured flow and volume (using a pneumotachograph) when leaks were deliberately introduced between the ventilator and the pneumotachograph.

To facilitate sleep in the laboratory, subjects were sleep deprived the night before the study. In two subjects a small dose of lorazepam (0.5 mg) was necessary to induce sleep.

Protocol

Once the subject was in stable NREM sleep, we used the pulse technique (16) to determine R on the minimal CPAP setting provided by the ventilator (2 cmH2O). Brief (400-ms) pressure pulses with an amplitude of 3 cmH2O were given by using a pulse generator connected to the ventilator. Pulses were delivered at the beginning of inspiration, where elastic recoil is minimal and baseline flow is small. To calculate R, the increase in Paw above the CPAP was divided by the increase in flow, measured at the time of peak flow. The validity of this technique was independently established (34). CPAP was increased in steps of 1 cmH2O, and R was measured again. The increase in CPAP continued until R decreased no further (minimal R). The CPAP at which R first reached this minimal value was subsequently maintained throughout the study. This CPAP averaged 3.5 ± 1.5 cmH2O (Table 1).

We next determined E using the “runaway” method (16, 31). Briefly, while the ventilator is in the PAV mode and flow assist is zero, the volume-assist (VA) gain is increased in steps of 1–2 cmH2O/l until inspiration fails to terminate at the usual T1 (see Fig. 2 in Ref. 16). Instead, inspiratory flow (Vi) remains above zero beyond the normal T1. Volume and Paw continue to rise until the cycle is terminated by a set pressure limit on the ventilator. As described elsewhere (31), this occurs when VA just exceeds E. Thus VA (in cmH2O/l) at this point is taken as E. This technique estimates dynamic E at the prevailing Vr and RR and is to be distinguished from static E.

The subjects were randomized as to whether PSV or PAV will be tested first. For PSV, inspiratory positive airway pressure (EPAP) was maintained at the CPAP associated with minimal R. The inspiratory positive airway pressure (IPAP) was increased in steps of 1–2 cmH2O. Each step was maintained for 3–5 min. Step increases continued until PB developed or the subject awakened. In the former case, we attempted to continue monitoring for an additional 10 min. If the subject awakened before PB, the IPAP was reset to the EPAP, we waited until the subject slept again, and the sequence was repeated.

For PAV, the value of R and a value slightly less (1–2 cmH2O/l) than E were entered in the ventilator. The percent of (dialled E and R) assist was then increased in the following steps: 20, 40, 60, 80, 90, and 95%. Each step lasted 3–5 min. Incremental assist continued until the maximum assist (95%) was reached, PB developed, or the subject awakened.

2 In our experience, when the full value of E is entered, there is a tendency for high levels of assist (e.g., 80–95%) to be associated with occasional large breaths. These may result from occasional sighing efforts, which, at these very high assist levels, are greatly amplified, or from small transient changes in leak level, which, at high gain, may result in runaway, even though volume assist is less than E (31). Setting the maximum value of volume assist to be slightly below E minimizes the chances of this occurring inadvertently with the possible consequence of subject awakening and interruption of the study.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>BMI, kg/m²</th>
<th>Elastance, cmH2O/l</th>
<th>Resistance, cmH2O · l−1 · s−1</th>
<th>CPAP, cmH2O</th>
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<td>M</td>
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<tr>
<td>2</td>
<td>33</td>
<td>F</td>
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<td>160</td>
<td>22.4</td>
<td>21</td>
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<tr>
<td>3</td>
<td>27</td>
<td>F</td>
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<td>4</td>
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Mean ± SD 27.1 ± 3.8 63.6 ± 9.4 169 ± 7.0 22.1 ± 2.3 18.1 ± 3.8 4.3 ± 1.3 3.5 ± 1.5

BMI, body mass index. CPAP, continuous positive airway pressure required to normalize resistance.
In the last case, the assist level was reduced to zero and the sequence was repeated after the subject was asleep again. All the results to be reported here were obtained in NREM sleep. Although attempts were made to obtain data in rapid-eye-movement sleep in some subjects, most of the time the subject reverted to NREM sleep before the protocol could be completed.

Analysis

Analysis was performed on the single PAV and the single PSV sequence during which the highest level of assist was reached. Other sequences that were interrupted prematurely on account of subject awakening were discarded.

At each step we measured $V_t$, RR, and $P_{ETCO_2}$. $V_t$ was calculated. Values from the last minute of the step were averaged. The actual IPAP and EPAP delivered during PSV were determined from the paper record. For PAV, peak Pmus at different assist levels was calculated by measuring flow ($V$), volume ($V$), and Paw at discrete points (every 100 ms) near the end of inspiration in four to eight representative breaths and applying the following equation of motion (15, 29) at each point

$$P_{mus} = V \cdot E + V \cdot R - Paw$$

where Paw is instantaneous Paw during inspiration above the expiratory level. The highest value was taken as peak Pmus for that breath. For the four to eight breaths analyzed, we determined average peak Pmus and average peak Paw. The pressure amplification factor (PAF) was calculated from

$$AF = \frac{\text{peak Pmus + peak Paw}}{\text{peak Pmus}}$$

PSV (PB) was taken as the average of the value during which PB occurred and the immediately preceding value during which breathing was not oscillating. The correlation between PSV (PB) and various variables of interest was determined by stepwise regression with backward elimination. With this approach the first step was multiple linear regression between PSV (PB) and all the variables of interest. The variable with the least correlation was deleted, and the regression between PSV (PB) and all the variables of interest was repeated with deletion of the least significant variable at each step until all remaining variables showed a significant correlation ($P < 0.05$) with PSV (PB).

RESULTS

Table 1 shows the subject's anthropometric data along with the values of $E$, $R$, and the CPAP used during the study. The $R$ values ($4.3 \pm 1.3 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$) were normal for nose-breathing subjects (15). The CPAP required to minimize $R$ was $3.5 \pm 1.5 \text{ cmH}_2\text{O}$. Dynamic $E$ values ranged from 11 to 25 cmH$_2$O/l.

PSV

In 11 of 12 subjects it was possible to increase PSV to a level associated with PB and repetitive central apneas. One subject consistently awakened whenever PSV level (IPAP – EPAP) was increased above 5 cmH$_2$O, and this level did not result in PB. The PSV level that first resulted in PB in the 11 subjects was $8.63 \pm 1.14 \text{ cmH}_2\text{O}$ (range 7–11 cmH$_2$O). The highest PSV during which stable breathing was observed (i.e., level immediately before onset of PB) ranged from 5 to 10 cmH$_2$O ($7.2 \pm 1.3$ (SD) cmH$_2$O).

Figure 2 shows a response to progressively increasing PSV level in one subject. There were small changes in $V_t$ and RR as PSV increased from 0 to 6 cmH$_2$O (Fig. 2, A–C). PB developed at the next higher PSV level (8 cmH$_2$O). $V_t$ was considerably larger with the development of PB (Fig. 2D), and arousals occurred with each ventilatory phase. To facilitate the reporting of the ventilatory data, only results at zero assist (Fig. 2A), at the PSV level immediately preceding PB (pre-PB level, Fig. 2C), and at the first level associated with PB will be reported. Values between zero assist and the pre-PB level were invariably intermediate.

Figure 3 shows individual results of $V_t$ at the three PSV levels of interest. In each case, the middle point is the highest level associated with stable breathing and the leftmost point is average $V_t$ during the ventilatory phase of PB. Spontaneous $V_t$ varied considerably among subjects. With the exception of one subject who showed a considerable increase in $V_t$ between zero assist and the pre-PB level (Fig. 3, subject 8), the changes in $V_t$ between these two levels were small and bidirectional. On average, there was no significant increase in $V_t$ as PSV level increased before the appearance of PB (Fig. 3, heavy line). There was a step increase in $V_t$ at the PSV level that resulted in PB (0.508 $\pm$ 0.13 vs. 0.402 $\pm$ 0.09 liter at pre-PB level, $P < 0.001$). In five subjects, PSV was increased one further step beyond the level that first resulted in PB. In each case, there was a further step increase in $V_t$ during the ventilatory phase. $\Delta V_t$ per 1-cmH$_2$O additional increase in PSV was 69 $\pm$ 18 ml/cmH$_2$O ($P < 0.001$). The increase in $V_t$ during the ventilatory phase was associated with an increase in percentage of time spent in apnea (38.8 $\pm$ 8.5 vs. 21.2 $\pm$ 10.6%, $P < 0.001$).

In seven subjects, PSV was discontinued intermittently for one breath to assess the level of respiratory output in the absence of assist. In all cases, the $V_t$ obtained during such maneuvers at the pre-PB PSV level was barely measurable and was clearly <15% of $V_{T_{max}}$ (Fig. 4).

Figure 5 shows the individual changes in RR as PSV level increased from zero to the highest level during which breathing was regular. Only four subjects developed an important (>10%) reduction in RR (subjects 1, 2, 8, and 12, Fig. 5). In the other subjects the changes were small and bidirectional. On average, the change in RR was not significant (13.8 $\pm$ 2.5 vs. 14.7 $\pm$ 2.3 min$^{-1}$, $P = 0.09$). The small changes in RR were offset by small changes in $V_t$, so that there were no systematic changes in $V_e$. $V_e$ at zero assist and at the pre-PB level was 5.31 $\pm$ 1.15 and 5.24 $\pm$ 1.15 l/min, respectively. The difference was not significant (paired t-test).

Figure 6 shows the changes in $P_{ETCO_2}$ between zero assist and the PSV level immediately before PB. Baseline $P_{ETCO_2}$ varied considerably with a range of 38.3–51.5 Torr (47.2 $\pm$ 3.7 Torr). All subjects sustained a reduction in $P_{ETCO_2}$ before the appearance of PB, but the range was from 1.5 (subject 11) to 5.8 Torr.
On average, PETCO2 decreased 3.3 ± 1.4 Torr (P < 0.0001). The relation between PSV(PB) and several potentially relevant variables was examined by stepwise regression (see METHODS). The variables entered in the first step were the four predicted theoretically to be the most important (VTsp, E, ΔPCO2, and ΔRR) as well as age, height, gender (1 man and 2 women), body mass index, spontaneous RR, and spontaneous PETCO2. The only variables that significantly correlated with PSV(PB) in the final model were VTsp (P < 0.001), E (P < 0.00009), ΔPCO2 (P = 0.007), and ΔRR (P = 0.006). The final regression equation was

\[
\text{PSV}(\text{PB}) = 11.1 \text{VT}_{sp} + 0.3E - 0.4 \Delta \text{PCO}_2 - 0.34 \Delta \text{RR} - 3.4
\]

The correlation coefficient for this model was 0.98. Figure 7 is a scatterplot of the relation between model prediction and actual PSV(PB).

PAV

At the highest level of assist associated with stable breathing, peak Pmus in the 12 subjects averaged 3.2 ± 2.0 cmH2O and peak Paw averaged 6.1 ± 2.1 cmH2O. PAF ranged from 1.5 to 7.6 (3.6 ± 1.7).

One subject developed classic Cheyne-Stokes breathing with central apneas whenever PAV was increased to a moderate level (Fig. 8). The PAF at the time of development of PB in this subject was 2.3. Four other

Fig. 2. Polygraph tracings at 0 (A), 3 (B), 6 (C), and 8 (D) cmH2O PSV in a representative subject. C2/A2 and C3/A3, electroencephalogram channels; EOG, electro-oculogram [right (R) and left (L)]; Paw, airway pressure; EMG, electromyogram; PETCO2, end-tidal PCO2. In flow tracing, inspiratory flow is negative. Note appearance of periodic breathing (PB) with central apneas at 8 cmH2O PSV (D). Also in D, VT does not show crescendo-decrescendo pattern typical of Cheyne-Stokes breathing but, rather, is constant.

Fig. 3. Effect of increasing PSV levels on VT in individual subjects (numbers on right) and average results (heavy line). Leftmost point, VT at 0 assist; middle point, VT at PSV level immediately before PB; rightmost point, VT during ventilatory phase of PB. VT changes little before appearance of PB. Data for subject 6 are not included, because she did not develop PB.
subjects developed a waxing-and-waning pattern of VT without central apneas at the highest level of PAV. PAF in these subjects was 1.5, 2.8, 2.9, and 3.4. In the remaining seven subjects, PB was not observed. The PAF at the highest level of assist in these subjects ranged from 2.0 to 7.6 [4.4 ± 1.8 (SD)]. VT changed little between zero assist and the highest level associated with regular breathing (0.35 ± 0.08 vs. 0.34 ± 0.09 liter, P = NS). Likewise, RR did not change (15.1 ± 3.3 vs. 14.8 ± 2.4 min⁻¹, P = NS). PETCO₂ decreased in all subjects, with a range of −1.0 to −4.8 Torr [−3.0 ± 1.3 (SD), P < 0.00001].

DISCUSSION
In the present study we have determined the PETCO₂ apneic threshold in sleeping normal subjects, defined the factors that lead to PB with PSV during sleep, and, using PAV, demonstrated that normal subjects display a wide range of susceptibility to PB.

Fig. 4. Response to discontinuation of PSV for 1 breath (arrow) at PSV level immediately before PB developed. See Fig. 2 legend for definitions. VT of unassisted breath is <10% of that of assisted breaths.

Fig. 5. Effect of increasing PSV level on RR in individual subjects (thin lines numbers on right) and on average (heavy line). Only results at 0 assist and highest level associated with stable breathing are given. Changes in RR were bidirectional and relatively small.

Fig. 6. PETCO₂ at 0 assist and at highest level of PSV before onset of PB in individual subjects (thin lines) and on average (heavy line). All subjects sustained a reduction in PETCO₂, but change varied among subjects.
CO₂ Apneic Threshold

Skatrud and Dempsey (25) were the first to show that artificially reducing PETCO₂ by a few Torr during NREM sleep, using a volume-cycled ventilator, results in apnea. This has led to the conclusion that chemoreceptors provide the main drive to breathe during NREM sleep (21) and that the CO₂ apneic threshold is only a few Torr lower than eupneic PCO₂. More recent observations from the same laboratory have, however, cast doubt on this notion. Thus, Henke et al. (6) studied the effect of restoring isocapnia after apnea had developed in the course of hypocapnic mechanical ventilation. They found that inspiratory efforts returned in most subjects but the level of activity was significantly less than at the same PCO₂ during eupnea. These findings pointed to the presence of a nonchemical source of respiratory inhibition during mechanical ventilation, which may have contributed to the development of apnea. Because none of the subjects developed apnea after discontinuation of mechanical ventilation in the isocapnic trials, they concluded that the nonchemical inhibition is not enough to cause complete cessation of inspiratory effort and that hypocapnia must develop for apnea to occur (6). These conclusions were, however, later negated by the findings of Levers et al. (12) that isocapnic mechanical ventilation during sleep can indeed produce apnea that is sustained beyond the period of mechanical ventilation (neuromechanical inhibition; for review see Refs. 12 and 13). The apnea observed earlier during hypocapnic mechanical ventilation (6, 25) may thus have been, at least in part, the result of neuromechanical inhibition. Therefore, it is not clear whether a minimum PCO₂ is required to obtain a rhythmic respiratory output (CO₂ set point) and, if so, what is this value relative to eupneic PCO₂.

The present study has revealed certain characteristics of the response to PSV that makes this method of ventilatory support particularly suitable for addressing the issue of the CO₂ set point during sleep. This is so, because a possible contribution from neuromechanical inhibition to the development of apnea can readily be discounted. The mechanisms that have been (12, 13) or can be postulated to cause neuromechanical inhibition are as follows.

Mechanoreceptor feedback related to increased VT and/or ventilation (12, 13). As PSV level is increased in small steps, there are only minor and insignificant changes in VT and RR, so that there is no significant change in Ve. The small reduction in PCO₂, despite the same Ve, is likely related to near elimination of the work of breathing (with a small decrease in CO₂ production) and/or to a small reduction in dead space-to-VT ratio due to the different flow patterns (deceleraring with PSV vs. near sinusoidal during spontaneous

Fig. 7. Relationship between actual PSV level at which PB occurred (PSV(PB)) and value predicted according to Eq. 3. Each point refers to a different subject (numbers on right).

Fig. 8. Polygraph tracing showing PB in only subject who developed repetitive central apneas during PAV. See Fig. 2 legend for definition of abbreviations. In this subject, transdiaphragmatic pressure (Pdi) was also monitored. Note crescendo-decrescendo pattern of VT typical of Cheyne-Stokes breathing (cf. Fig. 2 on PSV). ECG, electrocardiogram.
breathing; Fig. 2, A vs. C or D, inspiratory flow down). When apnea finally occurs, it cannot be attributed to larger Vt or Ve.

Ventilator inflation cycles preempting the spontaneous breaths. In all studies demonstrating neuromechanical inhibition during sleep (apnea or respiratory inhibition despite isocapnia), the ventilator was not triggered by the subject but the rate was set by the experimenter (6, 12). In most cases, the ventilator rate was set to be higher than the subject’s spontaneous rate. Even when an effort was made to synchronize the ventilator and the subject by manually adjusting the ventilator’s rate, Ti, and expiratory time to match those of the subject (6), there was no assurance that the ventilator cycle would not start before the subject initiated the breath. The occurrence of an inflation just before the spontaneous effort could, theoretically (e.g., via the Hering-Breuer reflex), preempt the spontaneous breath or reduce its intensity, resulting in apnea or reduced activity at isocapnia. With PSV, ventilator breaths are delivered only if triggered by the subject; they always follow the onset of inspiratory effort. When apnea develops, it cannot be attributed to the ventilator preempting spontaneous breaths.

Disfacilitation due to unloading. It has been postulated that disfacilitation due to removal of load-related excitatory input may, in part, be responsible for neuromechanical inhibition (6, 12, 13). Disfacilitation can be discounted as a possible contributor to apnea with the current approach (i.e., gradually increasing PSV) for several reasons. 1) Several previous studies have established that an increase in load, up to complete airway occlusion, during sleep elicits no immediate compensatory increases in respiratory muscle electromyogram (2, 8, 11). Given these observations, it would be quite improbable that the normal load is associated with a sufficiently high load-related excitatory input that removal of the load results, per se, in apnea. 2) In the current experiments the load was progressively decreased between zero assist and the point when central apnea began to appear. There were no systematic changes in RR up to and including the level immediately preceding the appearance of central apnea. At this penultimate level, there was virtually complete unloading, as evident from no appreciable difference in Vt from the value predicted in a passive system [Vt(passive) = (PSV − Vth,R)/E, see Theory]. In the present study, estimated Vt(passive) at the pre-PB level was 0.386 ± 0.067 liter, whereas the actual Vt at this level was 0.413 ± 0.096 liter, indicating that the subject was contributing <10% of the total pressure [(0.413 − 0.386)/0.413 = 0.065]. It would be difficult to envision load-related reflexes resulting in no change in RR, inasmuch as the load is reduced by >90%, yet suddenly producing complete apnea with the further reduction of the minimum load remaining at this penultimate level. 3) When the normal load was reestablished at the pre-PB level by temporarily discontinuing PSV, the Vt generated by the subject was minimal (Fig. 4), indicating that downregulation of pressure output between zero assist and the pre-PB PSV level was largely unrelated to unloading.

We conclude, therefore, that the downregulation of Pmus in this experimental model and its final elimination (apnea) are the result of associated hypocapnia. That neuromechanical inhibition cannot be invoked as causing or contributing to the apnea in this model makes it likely that the PCO2 at which apnea first appears with PSV is a true CO2 apneic threshold.

It is difficult to determine the exact CO2 apneic threshold from PETCO2 once PB develops. Under these conditions, PETCO2 is unstable and can be measured only during the ventilatory phase, where it is above the apneic threshold by an indeterminate amount. On the other hand, PETCO2 in the pre-PB level is stable and is as close as possible to apneic threshold; respiratory output is minimal, and one small further increase in support results in apnea. For these reasons, we believe that PETCO2 at the pre-PB level is a very good estimate of PCO2 apneic threshold. Our results show that apneic threshold during NREM sleep in normal subjects varies considerably, with a range of 36–49 Torr (43.9 ± 3.1 (SD) Torr; Fig. 6). They also show that the difference between spontaneous PETCO2 and apneic threshold during NREM sleep is, on average, quite small (mean 3.3 Torr) but varies considerably among subjects (1.5–5.8 Torr; Fig. 6).

Our data further permit an assessment of the ventilatory response to CO2 in the range between spontaneous PETCO2 and apneic threshold. This is given by spontaneous Ve(no assist)ΔPETCO2, with ΔPETCO2 being the difference between PETCO2 during breathing with zero assist and the PCO2 apneic threshold. This slope ranged from 0.73 to 2.50 l·min⁻¹·Torr⁻¹ [1.87 ± 0.61 (SD) l·min⁻¹·Torr⁻¹]. These values are within the range established in awake normal subjects (22) and suggest that the ventilatory response to CO2 during sleep (with normalized upper airway R) does not decrease substantially as apneic threshold is approached. This behavior may seem to be different from the response in awake normal subjects on mechanical ventilation, where we recently showed that the respiratory motor response to CO2 progressively decreases as PCO2 is lowered below spontaneous PCO2 (5, 20). However, the PCO2 range during which CO2 responsiveness was determined in the current study on sleeping subjects (43.9–47.2 Torr) is substantially higher than the range over which determinations were made on awake subjects (26.0–41.0 Torr).

Another apparent discrepancy is the occurrence of apnea during sleep at a PCO2 that is, on average, much higher (43.9 ± 3.1 Torr) than the range over which chemoreceptors continue to influence respiratory output in awake humans (28–35 Torr) (5, 20). The likely explanation is that respiratory centers do not oscillate unless subjected to a critical level of excitatory input (7, 24). Evidently, during sleep the chemoreceptor activity associated with a PCO2 in the low-40-Torr range is not sufficient, in the absence of other inputs related to consciousness, to provide the critical excitatory input required for the respiratory centers to oscillate.
PB During PSV

Morrell et al. (18) were the first to document the occurrence of PB during PSV application in normal sleeping subjects; they observed PB in two of six subjects who received 7.0–7.5 cm H₂O of pressure support (IPAP = 9–9.5 cm H₂O, EPAP = 2–2.5 cm H₂O). The occurrence of PB is also a common observation in clinical sleep laboratories during titrations of bilevel support for the treatment of OSA. The present study is, to our knowledge, the first in which the factors that determine the development of PB during PSV in sleep were systematically examined and quantitated.

The PB examined in our study is to be distinguished from that reported by Parreira et al. (19). They used bilevel support (during sleep) in the controlled mode, where the ventilator triggered spontaneously at a fixed rate of 17 min⁻¹. Under these conditions they observed fluctuation in VT, including periodic apneas (no chest expansion), despite continued ventilator triggering and delivery of the same Paw. These occurred at a time when PCO₂ was forced down into the 20-Torr range on ventilation without PB. These apneas were, accordingly, obstructive apneas. Because in our study the ventilator was triggered only with subject efforts, apneas reflect cessation of respiratory effort. That the apneas were central was also evident from the Respitrace signals, which showed no efforts (Fig. 2D).

We found that PB could be induced in virtually all subjects (11 of 12) when sufficient pressure support was applied. In the only subject who did not develop PB we could not increase the PSV beyond 5 cm H₂O because of awakening. In this subject the critical PSV, calculated retrospectively from Eq. 3, was 7.0 cm H₂O.

The PSV level at which PB developed varied considerably (5.5–10.5 cm H₂O). The results (Eq. 3, r = 0.98) show that 96% of this variability is related to VTsp, E, ∆RR, and ∆PCO₂, the four variables expected on theoretical grounds to be the main determinants of PSV(PB).

The changes in RR with increasing PSV level were small and bidirectional (Fig. 5). This finding is in keeping with previous reports in awake (5, 14, 23) and sleeping (18) normal subjects. Notwithstanding these small responses, and in support of theoretical prediction, ∆RR emerged as a very significant determinant of PSV(PB) (P = 0.006). It follows that measures that promote a greater reduction in RR with PSV application during sleep may significantly reduce the susceptibility to PB.

The factors that determine the direction and magnitude of change in RR as PSV is applied are not known and are likely complex. In theory, interindividual ∆RR may be related to differences in response of respiratory centers to the following factors: 1) reduction in PCO₂, 2) unloading, and/or 3) differences in timing between the inflation phase of the ventilator and the subject’s neural inspiratory phase. In the PSV mode, the ventilator inspiratory phase may outlast neural Ti (30). Continued inflation into neural expiration may delay the onset of the next breath via the Hering-Breuer reflex (33) and, hence, result in slower breathing. The extent to which inflation outlasts neural Ti (∆Ti) is, in turn, a function of the flow threshold for terminating the ventilator cycle, respiratory E and R, and PSV level (for review see Ref. 30). Because with PAV the decrease in PETCO₂ (factor 1) and unloading (factor 2) are comparable, but there is no subject-ventilator nonsynchrony, a comparison of ∆RR response in the two modes could help distinguish between the various possible mechanisms. As shown in an earlier study (16), in the current study RR did not change significantly with PAV (15.1 ± 3.3 vs. 14.8 ± 2.4 min⁻¹). There were, however, individual differences, with ∆RR ranging from +1.7 to −2.6 min⁻¹. ∆RR(PAV) correlated significantly with ∆RR(PSV), indicating that some of the variability in RR with PSV is related to interindividual differences in RR response to unloading and hypocapnia, as reflected in ∆RR(PAV). ∆RR(PAV), however, accounted for only 40% of ∆RR(PSV) (r = 0.63, r² = 0.40). In addition, mean ∆RR(PSV) was significantly lower than mean ∆RR(PAV) (−1.6 ± 1.0 vs. +0.2 ± 1.4 min⁻¹, P < 0.02). These observations suggest that subject-ventilator synchrony may play a role in determining ∆RR, and in the PSV mode it tends to cause, on average, some respiratory slowing.

Our current findings also confirm the theoretical prediction that the greater the difference between spontaneous PETCO₂ and the PETCO₂ set point, the more resistant one is to PB (P = 0.006). The range of ∆PETCO₂ in normal subjects (−1.5 to −5.8 Torr) is such that the quantitative impact of this variable on PSV(PB) is small. Nonetheless, this observation indicates that patients who are operating well above their apneic PCO₂ threshold because of the nature of their CO₂ responsiveness, because of abnormal mechanics, or as a result of increased fraction of inspired CO₂ are likely to be more resistant to PB. A corollary of this is that addition of artificial dead space should increase the PSV level at which PB occurs during sleep. Apart from increasing PETCO₂ added dead space or increased fraction of inspired CO₂ would increase VTsp. This would provide an added stabilizing effect (according to Eq. 3) and would permit the use of greater PSV levels without PB.

PB During PAV

The ventilatory response to increasing PAV levels observed in this study is similar to the response reported earlier in another group of subjects (16). As PAV increases, VT and VE change very little as a result of downregulation of Pmus. The current PSV data support our earlier speculation (16) that this downregulation is largely related to the small decrease in PCO₂. Thus, with PAV, peak Pmus decreased by two-thirds (from 9.3 ± 2.9 cm H₂O at 0 assist to 3.2 ± 2.0 cm H₂O at the highest assist). The corresponding PETCO₂ was −3.0 ± 1.3 Torr (P < 0.0001). Given that complete apnea (Pmus = 0) occurs when PETCO₂ decreases.
The occurrence of PB on PAV in some subjects is not surprising and was predictable (29). In theory, every subject should develop PB if the pressure amplification is increased sufficiently (see THEORY). The present study demonstrates, however, that the susceptibility to develop PB in normal subjects varies considerably. One subject developed PB with very modest assist (PAF = 1.5), whereas others failed to oscillate, despite amplification factors that are >4.0 and extending up to 7.6.3 The reason for this wide range is not clear. On the basis of our current understanding of the mechanisms of PB (3, 4, 9, 10, 26), this could be due to interindividual differences in innate respiratory center sensitivity to CO2 and O2 in the operating range of PCO2 and PO2, lung volume, respiratory impedance, arousability, circulation time, thoracic blood volume, and potency of the respiratory afterdischarge mechanism, among other factors. The present study does not permit an assessment of the reasons for these interindividual differences. It also remains to be determined whether subjects who develop PB at relatively low levels of PAV would more easily develop PB under pathological and physiological conditions that promote PB (e.g., hypoxemia or high altitude).

Notwithstanding the interindividual variability, normal subjects appear to be, on average, quite resistant to developing PB with PAV. Despite an average PAF at the highest PAV of 3.6 ± 1.7, only five subjects developed PB and, of these, only one had PB with apneas. Thus the reason that loop gain in normal subjects is, on average, very low (i.e., <1/3.6 or <0.28). Alternatively, the increase in the gain of one segment of the loop (in this case, the relation between Pmus and VT) may be offset by a decrease in the gain at other segments, so that the overall loop gain is not increased as much as the PAF (17). Regardless of the mechanism, the finding that very high amplification factors are generally required before PB develops has practical implications. Thus, the treatment of OSA (as a substitute to bilevel support), it would be unnecessary and impractical to use PAF > 2.0. In awake subjects with normal mechanics, a 50% assist (PAF = 2.0) generally results in large increases in Paw during inspiration and is perceived as too much assist by the subject. At PAF < 2.0, only 1 subject in 12 [1 in 24 if the current and the previous study (17) are considered] developed PB. In critically ill, ventilator-dependent patients, higher levels of assist (up to 80% assist, PAF = 5) are often needed, particularly in the acute phase of the illness. However, in such patients, neuroventilatory coupling (relation between respiratory muscle activity and VT) is usually so poor that a PAF of 3–5 would barely normalize the slope of this relation (29, 30). Accordingly, unless there are strong independent reasons for PB, it may be expected that ventilator-dependent patients would tolerate even greater PAF than normal subjects before PB develops. Although a systematic study of the occurrence of PB on PAV in these patients is needed, it is our experience (with several hundred patients) that PB is extremely rare at the levels of support required to comfortably support ventilation.

The five subjects who developed PB on PAV were not more susceptible than others to develop PB on PSV. Thus the PSV level at which PB developed in these five subjects was 8.2 ± 1.5 cmH2O, not significantly different from the corresponding level in the other six subjects (7.7 ± 1.3 cmH2O). This is in keeping with theoretical considerations that point to different mechanisms by which the two modes promote PB (see THEORY). This observation also indicates that subjects who are particularly susceptible to PB with one mode may be successfully managed with the other.

In summary, we have explored some of the factors relevant to PB during sleep. Using PSV, we have identified a CO2 apneic threshold that is a few Torr below eupneic PCO2. We have shown that development of PB is predictable on PSV and that the PSV level at which PB develops is primarily related to respiratory E and VT0 with significant, but quantitatively small, dependence on the difference between eupneic PCO2 and apneic threshold and on the response of RR to application of PSV. Finally, using PAV, we have shown that normal subjects display a wide range of susceptibility to PB.

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