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

SONIA MEZA, MANUEL MENDEZ, MICHELE OSTROWSKI, AND MAGDY YOUNES
Respiratory Medicine, University of Manitoba, Winnipeg, Manitoba, Canada R3A 1R8

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 (Ers,E) but that the actual level at which PB will develop [PSV(PB)] will be influenced by the ΔPCO2 (difference between eupneic P CO2 and CO2 apneic threshold) and by ΔRR [response of respiratory rate (RR) to PSV]. We also wished to determine the pressure 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 P CO2, 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 PAV 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 VT1 (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 VT1 + 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 conclude that 1) a P CO2 apneic threshold exists during sleep at 1.5–5.8 Torr below eupneic P CO2, 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 occurs 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.

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.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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).1

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 a parallel shift in unassisted relation, whereas PAV causes a change in slope. Different amplification factors with PAV are produced by applying volume- and flow-assist levels that are 0, 33, 50, 67, and 75% of R and E for amplification factors of 1.0, 1.5, 2.0, 3.0, and 4, respectively. See THEORY for explanation of arrows and circles. VTsp, spontaneous VT.

1 The driving force is a theoretical neural output waveform with a rising phase (T1), a peak (percentage of a theoretical maximum), a declining phase, and a cycle duration (Tc). The conversion of neural output to Pmus is determined by relating instantaneous neural output to inspiratory muscle strength (maximum inspiratory pressure at functional residual capacity = 100 cmH2O in normal subjects), which is a function of instantaneous lung volume (1). In the case of assisted ventilation, an additional driving force (Paw) is generated at the onset of inspiration with a form that fits the specific mode. In the case of PSV, Paw rises exponentially (time constant in the present simulation = 0.2 s) to a set level (PSV level), where it remains until flow decreases to a fixed value (0.1 l/s). In the case of PAV, Paw rises according to the PAV equation: Paw = V·VA + V·FA, where V and V are instantaneous volume and flow, respectively, and VA and FA are the desired magnitudes of volume and flow-related assist (29). The computer determines instantaneous V and V in an iterative fashion on the basis of the sum of the driving forces (Pmus + Paw) and the given values of E and R. Iteration continues over successive breaths until ventilatory output stabilizes.
is obtained by dividing both sides of Eq. 1 by VTsp. Thus

\[
\frac{V_{T_{min}}}{V_{Tsp}} = \frac{PSV}{V_{Tsp} \cdot E}
\]

(2)

It follows that the lower the product VTsp · E, the lower is the PSV level at which PB can potentially occur.

At PSV levels where \( V_{T_{min}} > V_{Tsp} \), a steady state can be reached if RR decreases such that the product \( V_{T_{min}} \cdot RR_{PSV} \) is approximately the same as \( V_{Tsp} \cdot RR_{sp} \). If RR does not decrease, several breaths with \( V_{T_{min}} > V_{Tsp} \) will force PCO2 below the CO2 set point. Central apnea must develop and continue until PCO2 rises again above the set point. Several breaths, all larger than VTsp, will then occur, forcing PCO2 below the set point again, and the cycle repeats. If RR actually decreases as PSV level increases, then a greater difference between VTmin and VTsp 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 PCO2 is the PCO2 set point? This \( \Delta PCO2 \) determines the extent to which the product \( V_{T_{min}} \cdot RR_{PSV} \) 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 \( V_{T_{min}} \) 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-cmH2O 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 VTsp · E? In our experience, VTsp during sleep in normal subjects varies considerably. This is due, in part, to differences in baseline VE and PCO2 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 VTsp, E, \( \Delta PCO2 \), 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 \( V_{T} \) intercept and, hence, no \( V_{T_{min}} \) (30). Regardless of the amplification factor, there is always a \( V_{T} \) that corresponds to VTsp. If the assist is increased, an initial increase in VT, with a consequent decrease in PCO2 and Pmus, will be followed by a gradual return of VT to near the spontaneous level. Accordingly, unlike the case of PSV where a \( V_{T_{min}} \) exists, a steady state is theoretically possible with PAV regardless of the level of assist (amplification factor). Whereas the lack of a \( V_{T_{min}} \) 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 PCO2 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, CO2 and O2 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 (Respirtrace, Ambulatory Monitoring, Airdsley NY), end-tidal 

PCO2 (PetCO2; Datex, Helsinki, Finland), and airway pressure; 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 subject flow and volume after allowing for leaks. The accuracy of the leak correction 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 until inspiration fails to terminate at the usual TI (see Fig. 2 in Ref. 16). Instead, inspiratory flow (Vi) remains above zero beyond the normal Ti. 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, expiratory 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) than E were entered in the ventilator. The percent of (dilated E and R) assist was then increased in the following steps: 20, 40, 60, 80, 90, and 95%. Each step lasted 3–5 min. Increases in 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⁻¹·s⁻¹</th>
<th>Resistance, cmH2O·l⁻¹</th>
<th>CPAP, cmH2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>M</td>
<td>68</td>
<td>170</td>
<td>23.5</td>
<td>20</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>M</td>
<td>60</td>
<td>160</td>
<td>24.4</td>
<td>21</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>F</td>
<td>52</td>
<td>163</td>
<td>19.4</td>
<td>25</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>M</td>
<td>73</td>
<td>170</td>
<td>25.4</td>
<td>11</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>F</td>
<td>47</td>
<td>158</td>
<td>18.9</td>
<td>23</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>F</td>
<td>72</td>
<td>170</td>
<td>25.0</td>
<td>17</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>M</td>
<td>72</td>
<td>180</td>
<td>22.2</td>
<td>15</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>F</td>
<td>61</td>
<td>168</td>
<td>21.6</td>
<td>16</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>M</td>
<td>56</td>
<td>177</td>
<td>17.9</td>
<td>12</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>M</td>
<td>81</td>
<td>180</td>
<td>25.0</td>
<td>17</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>25</td>
<td>F</td>
<td>61</td>
<td>168</td>
<td>22.6</td>
<td>21</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>F</td>
<td>60</td>
<td>163</td>
<td>21.5</td>
<td>18</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

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.
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.

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.

PSV during which stable breathing was observed (i.e., level immediately before onset of PB) ranged from 5 to 10 cmH$_2$O ($7.2 \pm 1.3 \text{ (SD) cmH}_2\text{O}$).

Figure 2 shows a response to progressively increasing PSV level in one subject. There were small changes in $V_t$ and $R$ 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 ± 0.13 vs. 0.402 ± 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 ± 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 ± 8.5 vs. 21.2 ± 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 $V_{T satire}$ (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). In the other subjects the changes were small and bidirectional. On average, the change in RR was not significant (13.8 ± 2.5 vs. 14.7 ± 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 $V_t$. $V_t$ at zero assist and at the pre-PB level was 5.31 ± 1.15 and 5.24 ± 1.15 l/min, respectively. The difference was not significant (paired t-test).

Figure 6 shows the changes in $P_{ET CO_2}$ between zero assist and the PSV level immediately before PB. Baseline $P_{ET CO_2}$ varied considerably with a range of 38.3–51.5 Torr (47.2 ± 3.7 Torr). All subjects sustained a reduction in $P_{ET CO_2}$ before the appearance of PB, but the range was from 1.5 (subject 11) to 5.8 Torr.
On average, $\text{PETCO}_2$ decreased $3.3 \pm 1.4$ 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 ($\text{VT}_{sp}, \Delta \text{PCO}_2$, and $\Delta \text{RR}$) as well as age, height, gender (1 man and 2 women), body mass index, spontaneous RR, and spontaneous $\text{PETCO}_2$. The only variables that significantly correlated with PSV(PB) in the final model were $\text{VT}_{sp}$ ($P \leq 0.001$), $\Delta \text{E}$ ($P \leq 0.00009$), $\Delta \text{PCO}_2$ ($P \leq 0.007$), and $\Delta \text{RR}$ ($P \leq 0.006$). The final regression equation was

$$\text{PSV(PB)} = 11.1 \text{VT}_{sp} + 0.3 \Delta \text{E} - 0.4 \Delta \text{PCO}_2 - 0.34 \Delta \text{RR} - 3.4 \quad (3)$$

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 $\text{Pmus}$ in the 12 subjects averaged $3.2 \pm 2.0$ cmH$_2$O and peak Paw averaged $6.1 \pm 2.1$ cmH$_2$O. PAF ranged from 1.5 to 7.6 ($3.6 \pm 1.7$).

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) cmH$_2$O PSV in a representative subject. $C_2/A_2$ and $C_4/A_2$, electroencephalogram channels; EOG, electrooculogram [right (R) and left (L)]; Paw, airway pressure; EMG, electromyogram; $\text{PETCO}_2$, end-tidal $\text{PCO}_2$. In flow tracing, inspiratory flow is negative. Note appearance of periodic breathing (PB) with central apneas at 8 cmH$_2$O PSV (D). Also in D, $\text{VT}$ does not show crescendo-decrescendo pattern typical of Cheyne-Stokes breathing but, rather, is constant.

Fig. 3. Effect of increasing PSV levels on $\text{VT}$ in individual subjects (numbers on right) and average results (heavy line). Leftmost point, $\text{VT}$ at 0 assist; middle point, $\text{VT}$ at PSV level immediately before PB; rightmost point, $\text{VT}$ during ventilatory phase of PB. $\text{VT}$ 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.
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 Leewers 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 V̇T and/or ventilation (12, 13). As PSV level is increased in small steps, there are only minor and insignificant changes in V̇T 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-V̇T ratio due to the different flow patterns (decelerating with PSV vs. near sinusoidal during spontaneous breathing).

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).
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)/PETCO2, 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 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 cmH$_2$O of pressure support (IPAP = 9–9.5 cmH$_2$O, EPAP = 2–2.5 cmH$_2$O). 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 $V_T$, including periodic apneas (no chest expansion), despite continued ventilator triggering and delivery of the same Paw. These occurred at a time when $PCO_2$ was forced down into the 20-Torr range on account of the obligatory high rate and high pressure. The fluctuation in $V_T$ and apneas were related to vocal cord narrowing and closure at these markedly hypocapnic levels (which were well below the apneic threshold). 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 Respirtrace 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 cmH$_2$O because of awakening. In this subject the critical PSV, calculated retrospectively from Eq. 3, was 7.0 cmH$_2$O.

The PSV level at which PB developed varied considerably (5.5–10.5 cmH$_2$O). The results (Eq. 3, $r = 0.98$) show that 96% of this variability is related to $V_T$, $E$, $\Delta RR$, and $\Delta PCO_2$, 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, $\Delta RR$ 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 $\Delta RR$ may be related to differences in response of respiratory centers to the following factors: 1) reduction in $PCO_2$, 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 ($\Delta Ti$) 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 $PETCO_2$, (factor 1) and unloading (factor 2) were comparable, but there is no subject-ventilator nonsynchrony, a comparison of $\Delta RR$ 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$^{-2}$). There were, however, individual differences, with $\Delta RR$ ranging from +1.7 to −2.6 min$^{-2}$. $\Delta RR$ (PAV) correlated significantly with $\Delta RR$(PSV), indicating that some of the variability in $\Delta RR$ with PSV is related to interindividual differences in RR response to unloading and hypocapnia, as reflected in $\Delta RR$(PAV). $\Delta RR$(PAV), however, accounted for only 40% of $\Delta RR$(PSV) ($r = 0.63, r^2 = 0.40$). In addition, mean $\Delta RR$ (PSV) was significantly lower than mean $\Delta RR$ (PAV) (−1.0 ± 1.6 vs. +0.2 ± 1.4 min$^{-2}$, $P < 0.02$). These observations suggest that subject-ventilator synchrony may play a role in determining $\Delta RR$, 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 $PETCO_2$ and the $PETCO_2$ set point, the more resistant one is to PB ($P = 0.006$). The range of $\Delta PETCO_2$ 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 $PCO_2$ threshold because of the nature of their $CO_2$ responsiveness, because of abnormal mechanics, or as a result of increased fraction of inspired CO$_2$ 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 $PETCO_2$, added dead space or increased fraction of inspired CO$_2$ would increase $V_T$. 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, $V_T$ 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 $PCO_2$. Thus, with PAV, peak Pmus decreased by two-thirds (from 9.3 ± 2.9 cmH$_2$O at 0 assist to 3.2 ± 2.0 cmH$_2$O at the highest assist). The corresponding $PETCO_2$ was −3.0 ± 1.3 Torr ($P < 0.0001$). Given that complete apnea (Pmus = 0) occurs when $PETCO_2$ decreases
by slightly >3.3 ± 1.4 Torr (see PB With PSV), the average two-thirds reduction in Pmus with PAV can readily be accounted for by the 3.0-Torr reduction in PETCO2.

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 P02, 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. This could mean 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, in 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 Vt, 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.

We thank W. Thompson and C. Leslie for technical assistance and K. Foster for manuscript preparation. This research was supported by the Medical Research Council of Canada.

Address for reprint requests: M. Younes, Respiratory Hospital, 810 Sherbrook St., Winnipeg, MB, Canada R3A 1R8.

Received 25 February 1998; accepted in final form 2 July 1998.

REFERENCES


1940

PERIODIC BREATHING WITH PSV AND PAV DURING SLEEP


