Physiological effects of alveolar, tracheal, and “standard” pressure supports

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Physiological effects of alveolar, tracheal, and “standard” pressure supports. J. Appl. Physiol. 87(1): 428–437, 1999.—Pressure support (PS) is characterized by a pressure plateau, which is usually generated at the ventilator level (PSvent). We have built a PS device in which the pressure plateau can be obtained at the upper airway level (PSaw) or at the alveolar level (PSa). The effect of these different PS modes was evaluated in seven healthy men during air breathing and 5% CO2 breathing. Minute ventilation during air breathing was higher with PSa than with PSaw and lower with PSvent (16 ± 3, 14 ± 3, and 11 ± 2 l/min, respectively). By contrast, there were no significant differences in minute ventilation during 5% CO2 breathing (25 ± 5, 27 ± 7, and 23 ± 5 l/min, respectively). The esophageal pressure-time product per minute was lower with PSa than with PSaw and PSvent during air breathing (29 ± 26, 44 ± 44, and 48 ± 30 cmH2O·s, respectively) and 5% CO2 breathing (97 ± 40, 145 ± 62, and 220 ± 41 cmH2O·s, respectively). In conclusion, during PS, moving the inspiratory pressure plateau from the ventilator to the alveolar level reduces pressure output, particularly at high ventilation levels.

control of breathing; positive inspiratory pressure; unloading of the upper airway

AMONG THE DIFFERENT FORMS of partial ventilatory support, pressure support (PS) ventilation is the most commonly used, both in the early phase of acute respiratory failure and during weaning from mechanical ventilation (7, 9, 23, 27). During PS, each spontaneous breath is assisted by a constant positive pressure applied by the ventilator all along each inspiration. In the early study by Kacmarek (21) of intensive care PS devices, some of the devices failed to reach the prescribed pressure before the end of inspiration or failed to maintain the PS level near the inspiratory peak flow (Vpeak), i.e., at onset of inspiration. To minimize pressure instability during inspiration, some manufacturers have developed devices in which pressure is servo controlled to obtain a square pressure wave. Usually, the pressure-measuring site used to servo control the PS device is inside the ventilator. Because the inspiratory line of the breathing circuit and the respiratory system generate substantial resistance to flow, a pressure gradient exists between the ventilator, the airway opening, and the alveoli (19). Therefore, when a square pressure signal is generated inside the ventilator, the pressure signal in the airways is far from being constant throughout inspiration and is even highly flow dependent at the alveolar level. We hypothesized that a PS device capable of providing a square pressure signal at the airway opening would reduce the work of breathing compared with a conventional PS device producing a square pressure signal in the ventilator and that this effect would be further increased if the PS device maintains the square pressure signal at the level of the alveol.

To test these hypotheses, we have built a ventilator in which the location of the inspiratory positive-pressure plateau can be moved from the ventilator to the alveoli. The site where the pressure is controlled and regulated was a plateau can be inside the ventilator, at the airway opening, or at the alveolar level. One of these three sites is selected after estimation of the overall airway pressure (Paw) drop. The effect of PS generated at the three different levels of the ventilator-patient system (PSvent, PSaw, and PSA) was physiologically evaluated by measuring ventilatory parameters and the esophageal pressure (Pes)-time product in normal subjects under normal conditions (air breathing) and during breathing of a gas mixture enriched with 5% CO2 to enhance ventilatory demand.

METHODS

Apparatus Tested

The PS device was similar (Fig. 1) to that used in several previous studies (2, 9, 18, 23, 24), except the generated pressure was servo-controlled. Total resistance of the inspiratory line (1 m long) was ~2.5 cmH2O·l−1·s−1. To generate a positive inspiratory pressure, a jet of pressurized gas (air or CO2-enriched gas mixture) was blown into a chamber that was open to the atmosphere or connected to a highly compliant balloon (100 liters) filled with the appropriate CO2 mixture. This fluid system created air entrainment and pressurization of the overall gas flow and constituted a low-impedance positive-pressure generator that was not limited within the physiological range of inspiratory flows (V) used by the study subjects (19). The balloon ensured that the compositions of the injected gas and the entrained gas were similar.

To maintain the pressure plateau in the various modes of PS tested, a servo valve was placed upstream of the jet injector, instead of the simple on-off electrovalve used in the previous system. The servo valve was programmed to open when V rose above 17 ml/s (1 l/min) and to remain open until V fell below 150 ml/s, as in conventional inspiratory PS systems. Contrary to these conventional systems, however,
servo valve opening was commanded by a computer that compared, at intervals of 2 ms, the measured pressure [corrected or not corrected for airway resistance (Raw)] with the desired plateau pressure. The difference between these two pressures was minimized by using a second-order control loop that was modified to take into account the constant delay due to dry friction in the servo valve and to the self-inductance of the magnetic coil. The loop regulation of the pressure, as described in the Appendix (11, 15). In practice, after a V cycle, the servo valve opening was progressively increased to compensate for 1) the pressure drop through the pressure generator in the PS vent mode, 2) the pressure drop through the PS device inspiratory line in the PS aw mode, and 3) a minimal estimated airway pressure drop in the PS a mode. With our computer-controlled PS device, the pressure plateau was generated at the site where the reference pressure was measured (or estimated), i.e., 1) inside the ventilator (PS vent), 2) at the airway opening (PS aw) when pressure was measured near the mouthpiece, or 3) at the alveolar level when alveolar pressure (P A) was estimated (PS a regulation). P A was estimated on the basis of the Paw, Raw, and V according to the following formula

\[
P_{A} = P_{aw} - (V \cdot Raw)
\]

Raw was taken to be constant and equal to 80\% of the resistance of the respiratory system (Rrs). Rrs was measured in each subject with use of the forced oscillation method (10).

Before using the above-described modified PS device in our study subjects, we tested it in vitro using a lung model simulating patient inspiratory effort (Fig. 2, top). The lung model was a two-chamber Michigan test lung. One chamber was connected to and powered by a motor ventilator with a flow-controlled mode in such way that the effort generated was not influenced by the connected system (Cesar, Taema, Antony, France) [driving chamber], whereas the other chamber (PS-pressurized chamber) was connected to the PS ventilator under test. The two chambers were physically connected to each other by a small metal piece that allowed the driving chamber to lift the PS-pressurized chamber, thus mimicking the patient’s inspiration contribution to inspiration. With this system, the generation of positive pressure in the driving chamber lowered the pressure in the PS-pressurized chamber to subatmospheric levels, just as inspiratory muscle contraction produces negative P A in vivo. This effect was detected by the triggering system of the PS ventilators under test. Because the metal component was not secured to the PS-pressurized chamber, the latter, once effectively pressurized, could rise above the driving chamber within a time interval dependent on the mechanical properties (resistance and compliance) of the PS-pressurized chamber. The compliance of this chamber was set at 80 ml/cmH2O. Positive end-expiratory pressure (PEEP) was applied to the driving chamber at a level that ensured synchronized motions between the two chambers at onset of inspiration. A resistance of 4 cmH2O at 1 l/s, connected between the device and the lung model, was used to mimic the patient’s Rrs. The motor ventilator was set to obtain a predetermined respiratory frequency of 15 cycles/min, an inspiratory time (TI) of 1.2 s, and a decelerating flow with a Vpeak of 1.1 l/s.

A Fleisch no. 2 pneumotachograph (Gould Electronic, Longjumeau, France) was inserted between the lung model and the circuit of the tested device. Pressure was measured inside the ventilator (Pvent), at the airway opening (Paw), or inside the pressurized chamber (P A) with a differential pressure transducer (model MP45, ±70 cmH2O, Validyne, Northridge, CA) used at each pressure site. Figure 2, bottom, shows the Pvent, Paw, and P A signals for a PS set at 7 cmH2O during simulated spontaneous breathing (SB) with the PS device disconnected and with each of the three PS regulation
Fig. 2. Top: experimental setup. Circuits of tested PS devices were connected to a 2-chamber Michigan test lung. One chamber (driving chamber) of test lung was attached to and powered by a ventilator; the other chamber (PS-pressurized chamber) was connected to PS device under study. Driving chamber was able to lift PS-pressurized chamber and induced an initial negative pressure until PS device contributed to expansion of freely moving PS-pressurized chamber. Pressure and flow were measured at end of PS device circuit. C, compliance. Bottom: pressures obtained inside ventilator (Pvent), at mouth (Paw), and inside pressurized chamber (PA) during simulated spontaneous breathing with PS device disconnected (SB) and during each condition of PS regulation: PSvent regulation, PSAw regulation, and PSA regulation.

**Clinical Study**

Experiments were performed in seven healthy men (age = 35 ± 5 yr, weight = 73 ± 8 kg, height = 173 ± 3 cm).

Measurements. The subjects were seated, wore a noseclip, and breathed via a mouthpiece. Flow was measured using a pneumotachometer (Fleisch no. 2) connected to a pressure transducer (model MP45, 6 cmH2O, Validyne) and integrated to yield tidal volume (VT). Paw (model MP45, 50 cmH2O, Validyne) and PCO2 in respiratory air [end-tidal PCO2 (PETCO2); infrared analyzer, Gould, Ballainvilliers, France] were measured in the breathing tube close to the lips. Pes and gastric pressure (Pga) were recorded using a catheter-mounted transducer (Gaeltec, Dunvegan, Isle of Skye, UK). The validity of the Pes measurements was checked by analyzing the shape of the Pes curve after swallowing and by using the occlusion technique (5).

All signals were digitized at 128 Hz and sampled for subsequent analysis using an analog-numeric system (MP100, Biopac System, Goleta, CA).

The Pes-time products per breath, per minute, and per liter of ventilation were calculated as previously described (23, 29). Briefly, it was measured as the area enclosed within Pes and the chest wall static recoil pressure (Pcw,st)-time curve over Ti, with inspiratory PEEP (PEEPi) taken into account. The Pcw,st-time curve was extrapolated to the predicted value of chest wall compliance (Ccw,st). Thus the slope of the Pcw,st-time relationship was (ΔVT/Ccw,st)/(ΔTi).

Inspiratory work of breathing (WOB) per breath, per liter, and per minute was computed from Pes-volume loops, as previously described (8). Briefly, WOB was calculated from a Campbell diagram by computing the area between the recorded Pes-volume curve during inspiration and the static Pes-volume curve of the chest wall. The values for Pes at zero flow instants were taken as the beginning and the end of inspiration. The theoretical value of chest wall compliance, which theoretically represents ~4% of the predicted value of the vital capacity per cmH2O, was used to trace the static Pes-Vt curve of the chest wall (8). This curve passed through the value for elastic recoil pressure of the chest wall at end expiration, which was assessed by measuring intrinsic PEEP on the Pes tracing. The beginning of inspiration was thus separated from the elastic recoil pressure by an amount equal to the intrinsic PEEP on the Campbell diagram.

Experimental protocol. Two sessions were performed in each subject with two successive inspired CO2 fractions: 0% CO2 and 5% CO2 to stress the respiratory system. Within each session, four 10-min measuring periods were performed, each with a different ventilatory mode: SB, PSvent regulation, PSAw regulation, and PSA regulation. The order of the different ventilatory modalities was different from one subject to another and was determined using a randomization table. For each PS ventilation mode, the level of plateau pressure was set at 7 cmH2O.

Data analysis. The variables were recorded, after stabilization, from the 7th to the 10th min of each period. The following variables were read breath by breath: Ti as the onset of V to the onset of the expiratory flow, TE as the remainder of the total breath duration, VT from the calibrated integrated flow signal, PETCO2 as the peak of the airway CO2 record, Pes, Pga, Paw, and Vpeak.

These variables were used to calculate the following values per breath, respiratory rate (RR = 1/Ti – TE), total ventilation (Ve = VT × RR), inspiratory fraction (Ti/(Ti – TE)), mean inspiratory flow rate (VT/Ti), Pes-time product per breath, Pes-time product per minute, Pes-time product per minute.
Table 1. Pattern of breathing

<table>
<thead>
<tr>
<th></th>
<th>Air</th>
<th>5% CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SB</td>
<td>PSₐₜ</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>10.1±2.3</td>
<td>13.0±3.4</td>
</tr>
<tr>
<td>Vₜ, ml</td>
<td>825±266</td>
<td>982±248*</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>8.0±2.2</td>
<td>11.1±2.2*</td>
</tr>
<tr>
<td>Ti, s</td>
<td>2.3±0.7</td>
<td>2.0±0.6</td>
</tr>
<tr>
<td>Ti/Tt, %</td>
<td>43±4</td>
<td>45±12</td>
</tr>
<tr>
<td>PETCO₂, Torr</td>
<td>41±4</td>
<td>35±6</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 men. SB, spontaneous breathing; PSₐₜ, pressure support at ventilator level; PSₐ, pressure support at airway; PSA, pressure support at alveolar level; RR, respiratory rate; Vₜ, tidal volume; VE, minute ventilation; Ti, inspiratory time; Tt, total cycle time; PETCO₂, end-tidal PCO₂.*P < 0.05 between PSₐₜ and PSA (Wilcoxon test). †P < 0.05 between PSₐₜ and PA (Friedman test). ‡P < 0.05 between PSₐₜ and PSₐ (Wilcoxon test). §P < 0.05 between PSₐₜ and PSA (Wilcoxon test).

During air breathing, VE was largest during PSA, followed by PSₐₜ, PSₐ, and SB. No significant differences were observed during 5% CO₂ breathing. Similarly, we found a trend to a decrease in PETCO₂ from PSₐₜ to PSA and PA (P = 0.07) during air breathing, whereas PETCO₂ was identical during 5% CO₂ breathing with all three PS modes. There was a tendency to a reduction in Ti during air breathing, with no significant variation in Ti/Tt. During 5% CO₂ breathing, Ti and Tt decreased significantly from PSₐₜ to PSA and PA.

Effects of PS Mode on Pes

Mean values of Pes-time product per breath, Pes-time product per liter, Pes-time product per minute, and WOB per breath, WOB per liter, and WOB per minute, and PEEPdyn, i are displayed in Table 2. During air and 5% CO₂ breathing, Pes-time product per breath, Pes-time product per minute, and Pes-time product per liter were significantly higher during PSₐₜ than during PSₐ or PSA. Similar results were observed with the WOB indexes; however, the significances were less systematically observed, except during 5% CO₂ breathing between PSₐₜ and PA.

The mean level of PEEPdyn, i was <1 cmH₂O with all ventilator modes during air and 5% CO₂ breathing. There were no significant differences among the four ventilatory modes. Also, the shape of the P menus did not suggest any significant abdominal expiratory activity (22).

Table 2. Indexes of inspiratory activity

<table>
<thead>
<tr>
<th></th>
<th>Air</th>
<th>5% CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SB</td>
<td>PSₐₜ</td>
</tr>
<tr>
<td>PTP/breath, cmH₂O·s⁻¹</td>
<td>14.9±8.3</td>
<td>4.3±3.4*</td>
</tr>
<tr>
<td>PTP/l, cmH₂O·s⁻¹</td>
<td>17±5</td>
<td>4±2*</td>
</tr>
<tr>
<td>PTPmin, cmH₂O</td>
<td>130±58</td>
<td>48±30*</td>
</tr>
<tr>
<td>WOB/breath, J/breath</td>
<td>0.61±0.32</td>
<td>0.27±0.22</td>
</tr>
<tr>
<td>WOBI, J/l</td>
<td>0.71±0.14</td>
<td>0.26±0.17*</td>
</tr>
<tr>
<td>WOB/min, J/min</td>
<td>5.8±2.3</td>
<td>3.0±2.1</td>
</tr>
<tr>
<td>PEEPdyn, i, cmH₂O</td>
<td>0.7±0.4</td>
<td>0.5±0.6</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 men. PTP, esophageal pressure-time product; WOB, work of breathing; PEEPdyn, i, dynamic intrinsic positive end-expiratory pressure. *P < 0.05 between PSₐₜ, PSₐ, and PSA (Friedman test). †P < 0.05 between PSₐₜ and Pₐ (Wilcoxon test). ‡P < 0.05 between PSₐₜ and PSₐ (Wilcoxon test).
Modifications in Paw, VT/TI, and V˙peak

Mean inspiratory Paw, VT/TI, and V˙peak are shown in Table 3. Figure 3 shows recordings obtained with all ventilatory modes tested and provides further evidence of the effectiveness of the regulation device. As expected, mean inspiratory Paw, VT/TI, and V˙peak differed significantly among modes during air and 5% CO2 breathing, with values higher during PSaw and PSA than during PSvent.

Responsiveness to CO2

With all modes, we found significant differences in V˙E between air breathing and 5% CO2 breathing mainly because of a rise in VT. A significant rise in RR, with a

Table 3. Mean inspiratory airway pressure, VT/Ti, and V˙peak

<table>
<thead>
<tr>
<th></th>
<th>SB</th>
<th>PSvent</th>
<th>PSA</th>
<th>PSaw</th>
<th>SB</th>
<th>PSvent</th>
<th>PSA</th>
<th>PSaw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paw, I, cmH2O</td>
<td>-0.8±0.2</td>
<td>3.2±1.2*</td>
<td>4.2±1.9†</td>
<td>5.5±1.9‡§</td>
<td>-3.0±1.1</td>
<td>2.8±1.0*</td>
<td>5.6±0.9†</td>
<td>7.5±1.0‡§</td>
</tr>
<tr>
<td>VT/TI, ml/s</td>
<td>363±55</td>
<td>488±153*</td>
<td>596±291</td>
<td>766±248†</td>
<td>817±207</td>
<td>998±199*</td>
<td>1,309±378†</td>
<td>1,410±243‡§</td>
</tr>
<tr>
<td>V˙peak, ml/s</td>
<td>656±122</td>
<td>1,727±296*</td>
<td>2,141±301</td>
<td>2,605±477†</td>
<td>1,276±284</td>
<td>2,216±184*</td>
<td>2,883±383†</td>
<td>3,499±644‡</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 men. Paw, I, mean inspiratory airway pressure; VT/TI, mean inspiratory flow; V˙peak, peak of inspiratory flow. *P < 0.05 between PSvent, PSA, and PSA (Friedman test). †P < 0.05 between PSvent and PSAaw (Wilcoxon test). ‡P < 0.05 between PSvent and PSAaw (Wilcoxon test). §P < 0.05 between PSaw and PSA (Wilcoxon test).
decrease in $T_i$, was observed only for $P_{S_{aw}}$. However, this rise did not exceed 23%, whereas the change in $V_T$ was 53%. Mean inspiratory $P_{aw}$ was lower during 5% CO$_2$ breathing than during air breathing with SB and $PS_{vent}$. The opposite occurred for $P_{S_{aw}}$ and $PS_A$, suggesting a more favorable partition between $Paw$ applied by the ventilator and Pes-time product. This is illustrated in Fig. 4, which shows the relationship between the patient’s inspiratory effort and the assistance provided by the machine.

**DISCUSSION**

PS ventilation is a pressure-targeted mode in which pressure is delivered in a square-wave pattern that begins with the patient’s inspiratory effort and terminates when a threshold of decreasing $V$ is reached. However, a discrepancy between the expected inspiratory plateau of pressure and the observed pressure waveform is frequently observed in clinical practice (21). This discrepancy is related to high $V$, high resistive properties of the open-valve demand system and of the tubing between the pressure generator and the patient, and/or differences in pressure rise profiles. In extreme situations the result can be a lack of positive-pressure assistance at the beginning of inspiration, which is the time when resistive WOB is greatest.

Our laboratory has developed a regulation system that takes into account Paw and Raw. We used this system to evaluate the physiological effects of moving the pressure plateau from the generator to the mouth and presumably to the alveolar level. The regulation system was incorporated into a ventilator designed for noninvasive PS ventilation in intensive care and currently used in clinical practice with good results (9, 23). The efficacy of our regulation system was first checked using a lung model, with satisfactory results.

Once a given inspiration is initiated, the PS ventilation device delivers a high $V$, which decreases gradually throughout the inspiration. Clearly, our servo-regulated system allows adjustment of the initial flow to the value needed to reach the appropriate preset pressure level at different sites in the airway between the ventilator and the alveoli. As expected, we found that when the system was set to produce a pressure plateau in the airways rather than in the ventilator, the initial ventilator-delivered pressure and flow increased to overcome the resistance of the ventilator circuit. When the system was set to produce a pressure plateau in the alveoli, further increases in ventilator-delivered flow and pressure were observed; this effect would theoretically improve the rate of alveolar pressurization without increasing peak $PA$.

WOB includes a predominant elastic component and a flow-resistive component. Breathing through circuit tubing, connectors, a humidifier, internal pneumatic circuitry, and ventilator valves necessarily increases the resistive component. This may be crucial at the beginning of inspiration, at the time where the prescribed inspiratory plateau pressure has not yet been reached and the inspiratory flow demand is the highest. Therefore, the pressure delivered by a conventional PS ventilator ($PS_{vent}$) at the beginning of inspiration may undervent the resistive loading imposed by the circuitry and airway even when the level of prescribed $PS$ is high. This may result in a zero or negative $PA$ at the beginning of inspiration, and therefore the elastic and resistive load imposed by the respiratory system on the inspiratory muscles may not be reduced by PS during a crucial part of inspiration. This phenomenon can theoretically be minimized by prescribing higher levels of PS. However, these high levels can cause respiratory system overdistention and barotrauma as a result of high pressures being delivered at the end of inspiration (17). Also, high levels of PS can produce desynchronization between the patient’s SB and the ventilator (12). Alternatively, regulating the pressure at the alveolar level offers two advantages: 1) compensation for the resistive load due to the circuitry and airway at any level of ventilatory demand, resulting in positive $PA$ from the very beginning of inspiration, and 2) minimization of the risk of barotrauma or patient-ventilator desynchronization, since in theory there is no increase in peak $PA$.

Before discussing the possible advantages of this approach, we will address several potential limitations or negative consequences.

The proposed approach, in which we apply a constant pressure at the alveolar level, produces an abnormal flow pattern with an elevated early peak flow. This very rapid flow acceleration is not necessarily well tolerated at a subjective level, and the impact of this very high shear force at the beginning of inspiration may be significant when the $R_{rs}$ and/or the level of plateau pressure is high. Moreover, if the total Raw is completely compensated during $PS_{aw}$ with the assumption that gas inertance is negligible, the time constant of the respiratory system would decrease to zero. In this case, unless the subject is making a substantial crescendo effort to maintain flow, flow will essentially consist of a very brief spike, and the cycle will be immediately terminated. This pattern, which should clearly not be

![Fig. 4. Relationship between Pes-time product per breath (PTP/b), which represents inspiratory effort, and Paw-time product during inspiration per breath (PawTP/b), which represents assistance by machine during air breathing (●) and 5% CO$_2$ breathing (◆).](image-url)
an acceptable outcome, was not observed in our study. In fact, extreme shortening of T judge did not occur in our study, possibly because we have compensated for only 80% of the Rrs during PS. Furthermore, the forced oscillation resistance is estimated in the linear range and tends to underestimate the actual resistance that is flow dependent during breathing.

Another limitation is the increase in the peak pressure at the upper airway level, induced by regulating the pressure at the alveolar level, which may facilitate a possible gastric inflation. To prevent this gastric inflation during noninvasive ventilation, we voluntarily limited the maximal Paw induced by our apparatus to 25 cmH2O. Thus our ventilator should fail to maintain a Paw or PA if the Rrs and/or the setting of the level of plateau pressure is too high. In addition, we do not know the effect of PS in patients with airflow obstruction in which pulmonary heterogeneities exist, but it is probable that regional PA differs with differences in regional time constants.

Therefore, the findings from this study cannot be generalized, and the results may have been different at a higher level of the Rrs, at a higher setting of the plateau pressure, and/or when pulmonary heterogeneities predominate.

Previous studies have demonstrated that the site of pressure regulation during continuous positive airway pressure (CPAP) influences the imposed WOB (1, 3, 4, 13, 28). To eliminate the WOB imposed by the breathing circuit and ventilator, many CPAP devices have been designed with the goal of controlling the pressure level at the Y piece (1). More recently, attempts have been made to overcome the work imposed by the endotracheal tube, which is an additional resistive component of the breathing apparatus, by relocating the site of pressure regulation to the tracheal end of the endotracheal tube (3, 4, 28) or by estimating the tracheal pressure from the Paw and the endotracheal tube resistance (13). These studies consistently found that for a given CPAP level the WOB decreased when the pressure-controlling site was physically moved closer to the ventilatory muscles. In keeping with these studies, we observed that during PS ventilation inspiratory activity decreased when the site of the preset pressure was moved from the ventilator to the alveoli.

Varying the initial flow rate may interact with the breathing pattern and/or the patient’s effort. The respiratory control system has options: 1) it can maintain the central respiratory output, utilizing the additional unloading to produce more ventilation, or 2) it can maintain ventilation at the baseline level and use the assist to reduce respiratory muscle work. Any combination of these two extremes is also possible, and the result may vary with the ventilatory demand.

During air breathing in the resting condition, PS ventilation is known to induce hyperventilation and hypocapnia as a result of an increase in VT and also to decrease the inspiratory drive (2, 18, 24, 30). Our results confirmed this phenomenon and demonstrated that it was accentuated when the initial flow rate was further increased by moving the site of regulation of the appropriate preset pressure from the ventilator to the alveolar level.

The literature suggests that in acute conditions the additional unloading is used primarily to reduce inspiratory activity (6, 23). In a study of intensive care unit patients, Bonmarchand et al. (6) found that an initial flow rate increase during PS was associated with a decrease in diaphragmatic activity, although arterial PCO2 and minute ventilation remained unchanged over a broad range of flow rate variation. Similarly, we recently compared several PS devices in critically ill patients undergoing weaning from mechanical ventilation. We did not observe any differences in arterial PCO2 and minute ventilation, but we found that the inspiratory PS device that provided the highest initial flow rate was more efficient in reducing inspiratory activity than the inspiratory PS device that provided the lowest initial flow rate (23). These findings suggest that intubated patients with respiratory failure used the additional unloading afforded by the increase in the initial flow rate to reduce respiratory muscle work rather than to produce more ventilation.

Noncontradictory results were observed in normal subjects when inspiratory activity was constrained by CO2 inhalation. During PS ventilation and CO2 inhalation, subjects have full control over the onset of inspiration. TI and VT were dependent on the level of PS and the activity of inspiratory muscles. TE was determined to be the time when the subject triggered the next inspiration. Therefore, a respiratory response to inhaled CO2 is possible during conventional PS, and we previously found that PS shifted to the left the relationship between VE and PETCO2 and reduced inspiratory activity at any given PETCO2 (14, 18, 30). Therefore, these studies suggested that conventional PS induced a nonchemical inhibition of inspiratory activity. Our study confirms the findings of these previous studies and suggests that the nonchemical inhibition is influenced by the shape of the initial flow rate induced by the ventilator, since we observed that moving the site of regulation of the appropriate preset pressure from the ventilator to the alveoli was associated with a significant decrease in the inspiratory effort indexes with no statistically significant differences for VE and PETCO2. It is noteworthy that the reduction of inspiratory activity is not only due to the reduction in duration of inspiratory effort, since significant reductions were also observed for WOB indexes, which do not depend on Ti.

Previous studies have shown correlations between the Pes-time product and measurements of O2 utilization and CO2 production by the contracting respiratory muscles (8, 29). This led us to expect a decrease in CO2 production with a reduction in arterial PCO2 at a given level of alveolar ventilation during PSaw and PSA compared with PSvent. However, although VE was similar during CO2 and air breathing, PETCO2 values were virtually identical under all the PS ventilation conditions. This is probably ascribable to the fact that a number of phenomena have opposite effects on arterial PCO2. First, although a diminution in the work of breathing can lead to a diminution in CO2 production,
the magnitude of this effect is probably limited. Second, the increase in peak inspiratory pressure in the upper airways that occurs when the site of pressure regulation is moved from the ventilator toward the alveoli (Fig. 3) may increase the distension of the upper airways, leading to an increase in the anatomic dead space. Third, variations in the physiological dead space related to variations in Ti/Ti have been reported during controlled mechanical ventilation in different circumstances, although their mechanism remains unclear (16, 25, 26). Rebreathing can probably be excluded on the basis of the continuous analysis of the PETCO2 records (Fig. 3). Finally, some variation in Ve was observed among the three PS modes; although the differences were not statistically significant in such a small group of subjects, we cannot rule out variations in alveolar ventilation.

Despite similarities between CO2 stimulation in our study and that observed in most patients in clinical practice in terms of elevated inspiratory drive, major differences exist because of differences in respiratory resistance and compliance. For example, Jubran et al. (20) observed that although PS ventilation reduced respiratory frequency in patients with chronic obstructive pulmonary disease, several of these patients displayed expiratory activity. The patients with expiratory activity were those with long Ti, which facilitated expiratory muscle activity during lung inflation or shortened the time available for lung emptying. Because our servo-regulated system allows Vt/Ti to increase by moving the site of preset pressure regulation from the ventilator toward the alveoli, it also reduces Ti (as observed in our study) and may therefore reduce the occurrence and/or the importance of expiratory activity in these patients. Unfortunately, we were unable to demonstrate this potential beneficial effect, because we did not logically observe in our normal subjects any expiratory activity as detected from the shape of Pga recordings in all studied conditions.

In conclusion, we have built a PS device allowing inspiratory pressure regulation to be moved from the ventilator toward the alveolar level. The efficacy of this

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Fig. 5. A: block diagram of pressure support ventilation (PSV) device in which delivered pressure is computer controlled. V, mouth flow; Paw, airway pressure, which is compared with reference (desired) pressure each 2 ms; Cmd, command signal of servo valve. Gas source is at high pressure (p0). B: loop regulation circuit. In circuit (a), structure of C1 controller was actually modified to simulate structure of a controller (circuits b, bottom) that isolates time delay (τ) externally to loop feedback (P1). C: final structure of C1 controller, which allows effects of time delay (τ) and time constant (T) to be separated by means of a corrector called "Smith predictor." See APPENDIX for definitions of other abbreviations.
system has been confirmed during experiments first in a lung model, then in humans at rest and during stimulation with a 5% CO₂-enriched mixture. We observed a noticeable decrease in inspiratory activity when the site of the preset pressure was moved from the ventilator to the alveolus. This beneficial effect was particularly marked when ventilation was stimulated by CO₂. These data established in normal humans warrant a clinical evaluation.

APPENDIX

Loop regulation of the pressure assistance device. The outline of the loop regulation used to control the pressure is presented in Fig. 5A. Preliminary experiments in the open-loop configuration have shown that the delay between the command signal (Cmd) of the servo valve (PSV) and the Paw had the same magnitude as the time constant (τ) of the overall system. This allowed us to describe the system with an equation that approximates its response on the basis of the combination of a constant delay (τ) and a first-order mode of time constant T (Broı́da model)

\[ G(p) = \frac{\text{Paw}}{\text{Cmd}} = \frac{\text{Gs} e^{-\frac{p}{T}}} {1 + Tp} \]

where \( p = j \omega \) (\( j^2 = -1 \); \( \omega = \) pulsation) and Gs is direct-current gain between Paw and the command signal of the servo valve.

Both τ and T have a magnitude of 15 ms (sampling period: TE = 2 ms). The desired performances of the system consisted of a global time response <100 ms with an accuracy of the generated pressure within ±0.5 cmH₂O. The ratio of τ to T being close to unity, we could not use a simple proportional-integral (PI) corrector, because the gain of the closed-loop regulation could not be high enough to guarantee the imposed global time response (circuit a in Fig. 5B).

Definition of the feedback controller. We used a classic strategy to increase the gain of the loop regulation, which consists of looking for a structure of the controller (C₁ in Fig. 5B, top) that artificially isolates the τ externally to the loop feedback (PI), as in circuit b in Fig. 5B. Imposing identity of transfer functions between circuits a and b, we obtained the following relationship between C₁ and C₂

\[ C₁ = \frac{C₂}{1 + C₂ \text{Gs}(1 - e^{-\frac{p}{T}})} \]

The final structure of the C₁ corrector is given in Fig. 5C. This corrector is classically known as a “Smith predictor” (11, 14).

Such a structure greatly simplifies the numerical procedure, since differential equations describing the transfer function G(p) are expressed in terms of difference equations. Thus, taking the transfer function that simulates the first-order part of the model

\[ G(p) = \frac{\text{Sm}}{\text{Cmd}} = \frac{\text{Gs} e^{-\frac{p}{T}}} {1 + Tp} \]

where Sm is the value model output without delay. The corresponding time-domain equations (t) can be expressed as

\[ \text{Sm}(t) + T \frac{d\text{Sm}(t)}{dt} = \text{Gs} \times \text{Cmd} \]

and the difference equation becomes

\[ \text{Sm}(k) + T \frac{\text{Sm}(k) - \text{Sm}(k-1)}{\text{TE}} = \text{Gs} \times \text{Cmd}(k) \]

where k is sampling number and TE is sampling period. The recurrent function of the model is

\[ \text{Sm}(k) = \frac{\text{Gs} \times \text{Cmd}(k) + \text{TE} + \text{Sm}(k-1) \times T}{\text{TE} + T} \]

In Fig. 5C the simulation of τ is performed by selecting from a list of the last values (Sm) of model output. Moreover, the corrector C₂ uniquely considers a transfer function G(p), but without time delay. Therefore, the model reduces to a simple PI corrector and takes into account the pure delay with sufficient stability and fast response. The classic PI equation is given by

\[ C₂ = \frac{\text{Cmd}(t)}{\text{Ecart}(t)} = \left(1 + \frac{1}{T_1} p\right) Kp \]

where KP is the direct-current gain of the PI controller. The time domain equation is

\[ \text{Cmd}(t) = \left[\text{Ecart}(t) + \frac{1}{T_1} \int \text{Ecart}(k) \, dk\right] Kp \]

Using a simple algorithm to integrate

\[ \text{Integ}(t) = \text{Integ}(k-1) + \text{Ecart}(k) \times \frac{\text{TE}}{T_1} \]

The recurrent expression of the PI corrector becomes

\[ PI(k) = \left[\text{Ecart}(k) + \text{Integ}(k)\right] Kp \]

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