Physiologic Response of Ventilator-dependent Patients with Chronic Obstructive Pulmonary Disease to Proportional Assist Ventilation and Continuous Positive Airway Pressure

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To investigate the physiologic effects of proportional assist ventilation (PAV) in difficult-to-wean, mechanically ventilated patients with advanced COPD, we measured in eight ICU patients the breathing pattern, neuromuscular drive ($P_{0.1}$), lung mechanics, and inspiratory muscle effort (PTPdi and PTPpl) during both spontaneous breathing (SB) and ventilatory support with PAV, CPAP, and CPAP + PAV (in random sequence). PAV (volume assist [VA] and flow assist [FA]) was set as follows: dynamic lung elastance and inspiratory pulmonary resistance were measured during SB; then VA and FA were set to counterbalance the elastic and resistive loads exceeding the normal values, respectively, the inspiratory muscles bearing a normal elastic and resistive workload. CPAP was set close to dynamic intrinsic PEEP (8.3 ± 3.4 cm H_2O). We found significant reductions in $P_{0.1}$ and PTPdi during both CPAP (−45 and −37%, respectively) and PAV (−50 and −48%, respectively). However, only the combination of PAV and CPAP brought $P_{0.1}$ (1.69 ± 0.97 cm H_2O) and PTPdi (100 ± 68 cm $H_2O \cdot s$) within normal values, and ameliorated the breathing pattern compared with SB (tidal volume: 0.69 ± 0.33 versus 0.33 ± 0.14 L; breathing frequency, 14.6 ± 4.6 versus 21.0 ± 6.5 breaths/min, respectively), without generating ineffective inspiratory efforts. We conclude that in difficult-to-wean COPD patients, (*1*) PAV improves ventilation and reduces both $P_{0.1}$ and inspiratory muscle effort; (*2*) the combination of PAV and CPAP can unload the inspiratory muscles to values close to those found in normal subjects. Appendini L, Purro A, Gudjonsdottir M, Baderna P, Patessio A, Zanaboni S, Donner CF, Rossi A. Physiologic response of ventilator-dependent patients with chronic obstructive pulmonary disease to proportional assist ventilation and continuous positive airway pressure.

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In certain patients with acute respiratory failure due to exacerbation of chronic obstructive pulmonary disease (COPD), the early institution of noninvasive mechanical ventilation may reverse the acute episode without the need for endotracheal intubation (1). Nevertheless, other COPD patients with acute or chronic respiratory failure may need endotracheal intubation either because they are poor candidates for noninvasive support (e.g., lack of cooperation, severe cardiac arrhythmias) (2, 3) or because noninvasive ventilation fails (3). These patients are often the most severe and can be at risk of difficult weaning and even of tracheostomy for chronic ventilatory assistance (4). Among other reasons, poor patient–ventilator interaction may be a factor leading to prolonged mechanical ventilation (5). On the one hand, high levels of ventilatory support may be associated with ineffective efforts and patient–ventilator dyssynchrony; on the other hand, insufficient support causes the patient's inspiratory muscles to continue to contract under load, preventing adequate rest needed to resume spontaneous ventilation (4–6). It has been suggested that proportional assist ventilation (PAV) could improve the patient–ventilator interaction (7).

PAV is a new mode of mechanical ventilation (7), used in patients with acute respiratory failure also due to COPD (8). With PAV, the ventilator generates pressure in proportion to the patient's effort, allowing the patient to attain whatever ventilation and breathing pattern seems to fit the ventilatory control system, on a breath-by-breath basis. Because there is no target flow, volume, or pressure, the responsibility of guiding the ventilatory pattern is shifted completely from the caregiver to the patient. The working hypothesis of PAV is that the patient–ventilator interaction should thus be optimized. However, in ventilator-dependent patients with COPD a variety of different mechanisms may give rise to patient–ventilator dyssynchrony, namely (*1*) high levels of intrinsic positive

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end-expiratory pressure ($PEEP_i$) (5), (*2*) excessive tidal volume (9), and (*3*) reduced expiratory time due to disproportionate inspiratory flow duration with respect to inspiratory effort during assisted modes of mechanical ventilation such as pressure support ventilation (PSV) (4, 7). Theoretically, PAV should prevent the second and third causes whereas application of either positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) is needed to counterbalance $PEEP_i$. Hence, we reasoned that in ventilator-dependent patients with COPD, who commonly exhibit high levels of $PEEP_i$ (4, 8), application of CPAP during PAV should provide a better quality of ventilatory assistance and patient–ventilator interaction than either mode in isolation as was the case, for example, during pressure support ventilation (PSV) (4, 10).

Therefore, the aim of this study was to assess the physiologic response of ventilator-dependent patients with COPD to PAV and to the application of CPAP during PAV in terms of breathing pattern, respiratory drive, and inspiratory muscle effort.

METHODS

The study protocol was approved by the Institutional Ethics Committee, and informed consent was given by the patients or by their next of kin.

Patients

Eight mechanically ventilated patients with COPD were recruited for this study. Basically, in the ICU of our institution, we receive two kinds of patients: (*1*) patients with COPD who are periodically followed in our Respiratory Division, when the exacerbation of COPD is severe enough to require mechanical ventilatory support (either noninvasive or invasive); and (*2*) patients who were intubated, then tracheostomized in other institutions, and finally transferred to our institution for a variety of reasons, including weaning difficulties. The patients in this study belong to the latter group. Hence, they were not in the acute, early phase of respiratory failure, but in the late phase of the decision-making process leading to the assessment of chronic ventilator dependency as described in a 1995 American Thoracic Society (ATS) report (11). Nasotracheal intubation and mechanical ventilation (Evita2; Dräger, Lübeck, Germany) were instituted because of acute respiratory failure due to exacerbation of COPD. The diagnosis of COPD was confirmed by clinical history and pulmonary function tests (Table 1). On average, the patients had been ventilated for 41 ± 27 d before the study, having failed several weaning attempts during this period. In six of the patients a tracheostomy had been performed 32 ± 23 d before the study (cuffed tracheostomy cannula, 8- to 10-mm internal diameter; Shiley, Irvine, CA). The remaining two patients were on mechanical ventilation through a nasotracheal tube (8-mm i.d.; Portex, Hyte, Kent, UK) because they had denied consent for tracheostomy and asked for withdrawal of therapy, eventually. Pharmacological treatment (antibiotics, low daily doses of methylprednisolone [4.0 mg, intravenous], theophylline [0.6 mg/kg/h, intravenous], inhaled bronchodilators, etc.) as well as oxygen administration were prescribed by the primary physician in the ICU and remained unaltered throughout the procedure. Inspiratory fraction of oxygen ($F_{I_{O_2}}$) and arterial blood gases during mechanical ventilation just before the start of the study are provided in Table 2. The mode of ventilatory assistance as well as ventilatory settings were established by the primary physician according to conventional criteria and his/her judgment. In general, patients were on pressure support ventilation (PSV). At the time of the study the primary physician considered all patients ready to undergo a further trial of weaning.

Measurements

Flow, volume, and pleural and gastric pressures were measured as previously described (4). Flow (V) was measured with a heated Lilly pediatric-type pneumotachometer connected to a differential pressure transducer (Screenmate; Jaeger, Würzburg, Germany) inserted between the proximal tip of the tracheal cannula and the Y connector of the ventilator. Volume (V) was calculated from the numerical integration of the flow signal. Changes in pleural (Ppl) and abdominal (Pab) pressures were estimated from changes in esophageal (Pes) and gastric (Pga) pressures. Both Pes and Pga were measured using two balloon-tipped catheter systems connected to two differential pressure transducers (Micro Switch, Honeywell, Freeport, IL). The catheters were 80 cm in length and 1.7 mm in internal diameter; the balloons were 10 cm in length and 2.4 cm in circumference. Another, similar catheter and pressure transducer (Micro Switch, Honeywell) was used to sample the pressure at the airway opening (Pao) via a side port inserted between the tracheostomy tube and the pneumotachometer. Transpulmonary (P_L) and transdiaphragmatic (Pdi) pressures were obtained by subtracting Pes from Pao and Pga, respectively. Minute ventilation ($\dot{V}_E$), tidal volume (V_T), inspiratory (T_I) and expiratory time (T_E), total cycle duration (Ttot), respiratory frequency (f), mean inspiratory flow (V_T/T_I), and the "duty cycle" ($T_I/Ttot$) were calculated as average values from 1-min continuous recordings of flow and volume. In line with Barnard and Levine (12), the timing of the inspiratory effort was based on the Pdi tracing (Tdi). As shown in a representative record from Patient 5 (Figure 1), Tdi is the sum of three components: Tlead, T_I, and Ttrail (12). Tlead is the time interval between the start of the inspiratory effort (indicated by the onset of the positive Pdi swing above baseline) and the transition from expiratory to inspiratory flow; T_I is the common inspiratory time computed on the flow tracing; and Ttrail is the time after the cessation of inspiratory flow in which Pdi remains above baseline.

Transpulmonary pressure was used to calculate dynamic lung elastance ($E_{L_{dyn}}$) and pulmonary resistance at midinspiratory volume (R_L) according to the Neergaard–Wirtz elastic subtraction technique (13).

Dynamic intrinsic positive end-expiratory pressure ($PEEP_{i,dyn}$, i.e., the lowest regional value of $PEEP_i$ in a dishomogeneous lung) was

TABLE 1

PATIENT CHARACTERISTICS

No.	Age (*yr*)	Sex	FVC* Liters	FVC* %	FEV_1* Liters	FEV_1* %
1	65	M	0.944	21	0.315	10
2	66	F	0.588	16	0.152	7
3	67	M	1.252	40	0.409	18
4	60	F	NA	NA	NA	NA
5	68	M	1.917	48	0.450	16
6	75	F	0.753	25	0.145	7
7	72	F	NA	NA	NA	NA
8	74	M	1.803	36	0.447	14
Mean	68.4		1.209	31	0.320	12
SD	5.0		0.551	12	0.141	5

Definition of abbreviations: FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; NA = not available.

*At the time of study.

TABLE 2

PRESTUDY ARTERIAL BLOOD GASES DURING MECHANICAL VENTILATION

No.	$F_{I_{O_2}}$ (%)	Pa_{O_2} (*mm Hg*)	Pa_{CO_2} (*mm Hg*)	pH
1	40	89.0	47.0	7.412
2	50	102.8	77.4	7.354
3	40	139.5	54.7	7.386
4	40	135.7	56.0	7.341
5	35	70.4	55.5	7.412
6	40	101.8	72.0	7.399
7	50	59.6	51.9	7.365
8	50	97.4	58.3	7.374
Mean	43	99.5	59.1	7.380
SD	6	27.9	10.3	0.026

Definition of abbreviations: $F_{I_{O_2}}$ = fraction of inspired concentration of oxygen; Pa_{CO_2} = arterial carbon dioxide tension; Pa_{O_2} = arterial oxygen tension.

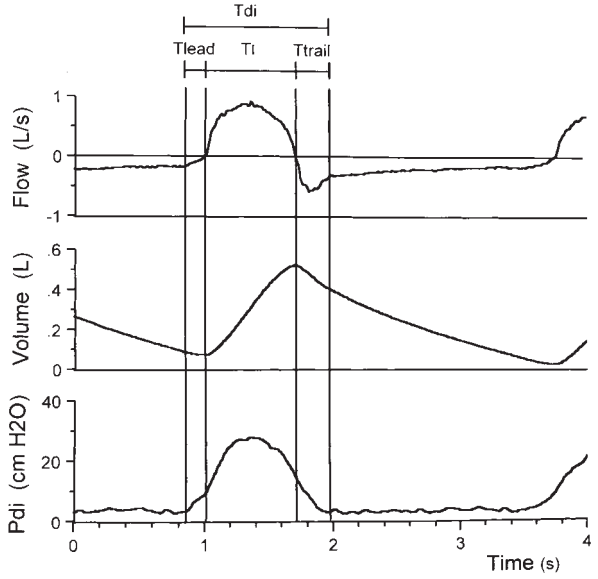

Figure 1. Representative record from patient 5, showing the partitioning of the Pdi swing into its three timing components. From top to bottom: inspiratory flow, tidal volume, and transdiaphragmatic pressure (Pdi). From *left* to *right*: *first vertical line*, start of inspiratory effort; *second vertical line*, start of inspiratory flow; *third vertical line*, end of inspiratory flow; *fourth vertical line*, point at which the Pdi swing returns to baseline. Tdi = time interval during which Pdi remains above baseline; Tlead = time interval from the start of inspiratory Pdi swing to the start of inspiratory flow; T_I = time interval between the start and end of inspiratory flow; Ttrail = time interval between the end of inspiratory flow and the point at which Pdi returns to its baseline value.

measured as the decrease in Ppl preceding the start of inspiratory flow and, where necessary, this measurement was corrected for overestimation due to expiratory muscle activity by subtracting the decrease in Pab from the drop in Ppl when both were present in the interval between the onset of inspiratory effort and the point of zero flow (4). Static intrinsic positive end-expiratory pressure ($PEEP_{i,st}$, i.e., the average end-expiratory elastic recoil of the respiratory system) was measured as the difference between maximum airway pressure (MIP) and maximal esophageal pressure (Ppl,max) obtained during a Mueller maneuver started from the end-expiratory lung volume (14).

The pressure–time product for the inspiratory muscles (PTPpl) and the diaphragm (PTPdi) were estimated from changes in Ppl and Pdi over time, respectively. PTPpl and PTPdi were obtained by measuring the area under Ppl and Pdi within a 1-min time interval as previously described (15). We used the pressure–time product as an index of inspiratory muscle energy expenditure, because this has been shown to be correlated to oxygen consumption (16).

Maximum transdiaphragmatic pressure (Pdi,max) was obtained in each subject from maximum inspiratory efforts against occluded airways. We are well aware of the limitations of this procedure, i.e., the Mueller maneuver, in measuring Pdi,max (17), particularly in ICU patients. However, our patients could not perform a sniff, nor had sufficient coordination to perform the combined maneuver suggested by Laporta and Grassino (18). MIP was obtained from the negative deflection in Pao during the same maneuvers performed to generate Pdi,max. Other procedures (19) were tried, too, but values were always lower than those obtained with maximum voluntary inspiratory efforts against occluded airways. Pdi,max was subsequently used to express the mean inspiratory Pdi($\overline{Pdi}$) as a fraction of Pdi,max ($\overline{Pdi}$/Pdi,max ratio) (20, 21).

Respiratory center output was estimated during spontaneous breathing (SB) by the decrease in tracheal pressure developed at 100 ms ($P_{0.1}$) after onset of an occluded inspiration, as previously described (22). The measuring equipment during SB was composed of a connector for airway pressure sampling, the pneumotachometer, and a T-tube circuit with the same resistive characteristics as the ventilator tubings. The inspiratory and expiratory lines of the T-tube were separated by a Hans–Rudolph one-way valve to allow selective inspiratory line occlusion by means of a pneumatic shutter during the expiration preceding the $P_{0.1}$ measurement. During mechanical ventilation, $P_{0.1}$ was assessed according to Conti and colleagues (23) during activation of the trigger mechanism of the ventilator by recording the magnitude of the airway pressure decay in the first 100 ms after the onset of inspiratory effort against the closed demand valve. We used this second method during assisted ventilation, as good agreement has been found between this method and the conventional $P_{0.1}$ measurement we adopted during SB (23). Both during SB and assisted mechanical ventilation $P_{0.1}$ was considered as the average of three measurements.

Experimental Procedure and Study Design

Patients were studied in the morning and were free to choose the most comfortable position so as to minimize their breathlessness. After topical anesthesia (xylocaine spray, 10%), two balloon-tipped catheters were inserted consecutively through the nose into the stomach, patients being encouraged to swallow during this procedure. The balloons were then inflated with 1 ml of air, and a positive pressure swing synchronous with manual pressure of the abdominal wall indicated that they were in the stomach. The esophageal balloon was then deflated and withdrawn into the middle third of the esophagus and inflated with 0.5–0.7 ml of air (4). The "occlusion test" (24) was performed to verify the correct positioning of the esophageal balloon and was satisfactory in every instance.

Once the patient appeared to be accustomed to the experimental setting and measuring equipment, the ventilatory mode and setting prescribed by the caring physician was discontinued. Physiologic measurements were then taken, first during unsupported spontaneous breathing and then under three conditions: (*1*) CPAP, (*2*) PAV, and (*3*) CPAP + PAV. During the procedure, ventilatory modes (CPAP, PAV, and CPAP + PAV) were delivered by the Winnipeg ventilator (University of Manitoba/Health Science Centre, Winnipeg, Manitoba, Canada) developed by M. Younes and J. Zarychta. CPAP, delivered by demand flow, was set at a level close to $PEEP_{i,dyn}$ measured during SB in all but two patients. Patient 1 did not tolerate levels of CPAP > 5 cm H_2O. Hence, we did not exceed this level, even though it represented only 60% of $PEEP_{i,dyn}$. Patient 2 tolerated very well a CPAP amounting to 10 cm H_2O, which was greater than the $PEEP_{i,dyn}$ of 6.4 cm H_2O. We used this higher CPAP in Patient 2 to compensate for the impossibility of adequately setting FA as explained below. PAV settings (volume assist, VA, and flow assist, FA) were chosen to "normalize" elastic and resistive patient workload. We reasoned that, as VA and FA can selectively counterbalance abnormal elastance and resistance of the respiratory system (7, 8), it could be of interest to describe the behavior of respiratory centers when the patients' respiratory muscles had to face only a "normal" inspiratory load. As the chest wall mechanics are considered normal in patients with COPD (25), we decided to set FA and VA so as to correct only for R_L and $E_{L_{dyn}}$, respectively. The range of normality adopted in our study was 4.3 to 12.5 cm H_2O/L for dynamic lung elastance, and 1.3 to 4.4 cm H_2O/L/s for lung resistance, in line with Frank and coworkers (26). After having estimated $E_{L_{dyn}}$ and R_L during SB we set VA and FA so as to keep the elastic and resistive workload within the above-mentioned normal ranges, PAV taking care of the abnormal component of elastic and resistive workload. In Patient 2, despite several attempts, it was not possible to raise FA above 5 cm H_2O/L/s owing the patient's discomfort. However, in this patient, as previously mentioned, CPAP exceeded $PEEP_{i,dyn}$ (but not $PEEP_{i,st}$), providing a sort of compensation for the lower FA. The settings of the ventilator as well as the individual values of lung mechanics are shown in Table 3.

In every instance the first set of physiological measurements was taken while the patient was breathing spontaneously through the tracheostomy/nasotracheal tube and measuring equipment in order to compute baseline respiratory mechanics to set CPAP and PAV. After this, CPAP, PAV, and CPAP + PAV ventilatory modes were administered in random order. The control condition, as well as each ventilatory mode, were maintained for about 20 min, the total duration of the procedure not exceeding 2 h.

TABLE 3

RESPIRATORY MECHANICS DURING SPONTANEOUS BREATHING, AND PAV SETTINGS

No.	PEEPi,dyn ($cm\ H_2O$)	PEEPi,st ($cm\ H_2O$)	$E_{L_{dyn}}$ ($cm\ H_2O/L$)	R_L ($cm\ H_2O/L/s$)	CPAP ($cm\ H_2O$)	VA ($cm\ H_2O/L$)	FA ($cm\ H_2O/L/s$)
1	8.5	13.9	17.8	11.8	5	12	10
2	6.4	16.4	23.6	25.1	10	10	5
3	15.1	19.1	25.3	28.0	10	15	25
4	11.2	11.2	26.4	18.7	10	10	15
5	6.2	8.6	14.0	14.4	5	5	10
6	8.2	8.6	15.6	24.3	7	5	20
7	5.4	8.5	19.8	19.0	4	10	15
8	5.0	6.3	9.9	11.0	5	3	7
Mean	8.3	11.6	19.1	19.0	7.0	8.8	13.4
SD	3.4	4.5	5.8	6.4	2.6	4.1	6.7

Definition of abbreviations: CPAP = continuous positive airway pressure; $E_{L_{dyn}}$ = dynamic lung elastance; FA = flow assist; PAV = VA + FA; PEEPi,dyn = dynamic intrinsic positive end-expiratory pressure; PEEPi,st = static intrinsic positive end-expiratory pressure; R_L = inspiratory resistance; VA = volume assist.

Data Analysis

Using a personal computer (Compaq 386 equipped with an 80387 math coprocessor [Compaq, Houston, TX] and a DT2801/A A/D board [Data Translation, Marlboro, MA]), all signals were analog-to-digital converted, displayed online throughout the procedure, and stored on 3.5-in. floppy diskettes at a sampling rate of 100 Hz. Data were collected under each experimental condition, namely SB, CPAP, and CPAP + PAV, once a stable breathing pattern had been established, generally after about 15–20 min. The mean value of each physiologic variable during the last minute of recording was used for subsequent analysis.

Results are expressed as means ± 1 SD. One-way analysis of variance for repeated measures (ANOVA) was performed, and when allowed by the F value, the significance between treatments was computed using Fisher's protected least significant difference test. Probability values less than 0.05 were considered significant.

RESULTS

As shown in Table 4, CPAP did not cause significant changes in the breathing pattern, whereas PAV determined a substantial increase in $\dot{V}_E$ (+38% compared with SB). The combination of CPAP + PAV profoundly modified the breathing pattern compared with the other three conditions. In fact, the increase in $\dot{V}_E$ was similar to that found during PAV alone, but it was determined by a significantly greater V_T associated with a reduced breathing frequency, such suggesting an increase in alveolar ventilation. Both T_I and T_E became longer, with a substantially stable T_I/T_{tot}. As a consequence of ventilatory assistance with PAV, V_T/T_I significantly increased with respect to SB. Lung elastance and resistance did not change with any kind of ventilatory support. By contrast, $PEEP_{i,dyn}$ was markedly reduced by CPAP applied during either spontaneous breathing or PAV (Figure 2). It must be noted that $PEEP_{i,dyn}$ decreased from 8.3 ± 3.4 cm H_2O during SB to 6.8 ± 3.9 cm H_2O during PAV (−18% on average), although this change was not statistically significant.

Figure 3 shows that, on average, $P_{0.1}$ was similarly reduced by CPAP (−45%) or PAV (−50%) if compared with SB values, and that a further reduction was obtained with the CPAP + PAV combination (−43%) if compared with the PAV condition. The decrease in the neuromuscular drive with CPAP or PAV, as well as with the combination of the two, and the increase in V_T/T_I during PAV and CPAP + PAV (Table 4), reduced the effective inspiratory impedance from 18.4 ± 7.8 cm $H_2O/L/s$ during SB to 8.2 ± 3.1 cm $H_2O/L/s$ during CPAP to 6.4 ± 4.4 cm $H_2O/L/s$ during PAV and to 3.8 ± 4.1 cm $H_2O/L/s$ during CPAP + PAV (Figure 3).

The reduction in neuromuscular drive was associated with

TABLE 4

BREATHING PATTERN DURING SPONTANEOUS BREATHING AND DURING DIFFERENT MODES OF VENTILATORY ASSISTANCE*

	SB	CPAP	PAV	CPAP + PAV
$\dot{V}_E$, L/min	6.6 ± 3.1	8.4 ± 2.7	9.1 ± 3.2†	9.7 ± 3.8†
V_T, L	0.33 ± 0.14	0.44 ± 0.11	0.48 ± 0.16	0.69 ± 0.33†‡§
f, breaths/min	21.0 ± 6.5	19.3 ± 4.9	19.0 ± 3.2	14.6 ± 4.6†‡§
T_I, s	0.95 ± 0.37	1.09 ± 0.28	0.96 ± 0.21	1.25 ± 0.32†§
T_E, s	2.27 ± 1.19	2.20 ± 0.70	2.27 ± 0.51	3.17 ± 1.06†‡§
Ttot, s	3.22 ± 1.42	3.30 ± 0.85	3.23 ± 0.48	4.43 ± 1.21†‡§
T_I/Ttot	0.31 ± 0.09	0.34 ± 0.08	0.30 ± 0.08	0.29 ± 0.08†‡
V_T/T_I, L/s	0.36 ± 0.16	0.43 ± 0.16	0.51 ± 0.17†	0.57 ± 0.22†‡

Definition of abbreviations: CPAP = continuous positive airway pressure; f = breathing frequency measured on flow tracing; PAV = proportional assist ventilation; SB = spontaneous breathing; T_E = expiratory time; T_I = inspiratory time; T_I/Tot = duty cycle; Ttot = total breathing cycle time; $\dot{V}_E$ = minute ventilation; V_T = tidal volume; V_T/T_I = mean inspiratory flow.

* Values are means ± SD for all patients.

† $p < 0.05$, treatment versus SB.

‡ $p < 0.05$, treatment versus CPAP.

§ $p < 0.05$, PAV versus CPAP + PAV.

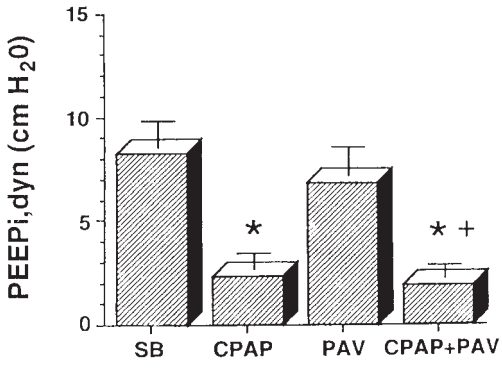

Figure 2. Changes in dynamic intrinsic positive end-expiratory pressure ($PEEP_{i,dyn}$) throughout the procedure. SB = spontaneous breathing; CPAP = continuous positive airway pressure; PAV = proportional assist ventilation. Bars represent means ± 1 SE. Statistics: ANOVA for repeated measurements; *$p < 0.05$, treatment versus SB; $^+p < 0.05$, CPAP + PAV versus PAV. Application of CPAP to both SB and PAV effectively counterbalanced intrinsic PEEP.

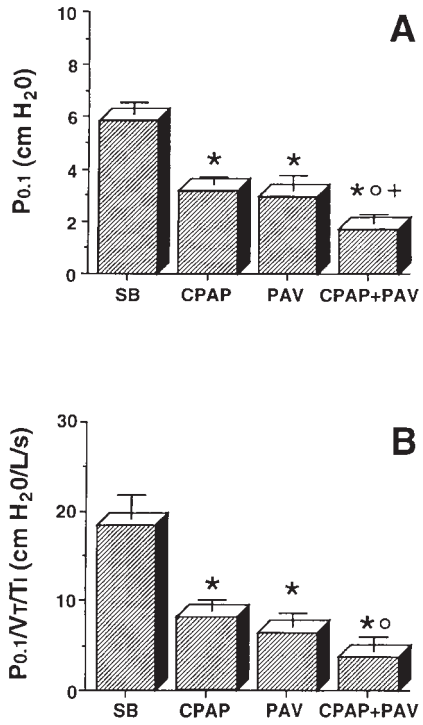

Figure 3. Changes in neuromuscular drive ($P_{0.1}$, *A*) and effective inspiratory impedance ($P_{0.1}/V_T/T_I$, *B*) throughout the procedure. Other symbols as in Figure 2. Bars represent means ± 1 SE. Statistics: ANOVA for repeated measurements; *p < 0.05, treatment versus SB; °p < 0.05, treatment versus CPAP; +p < 0.05, CPAP + PAV versus PAV. *See text* for comments.

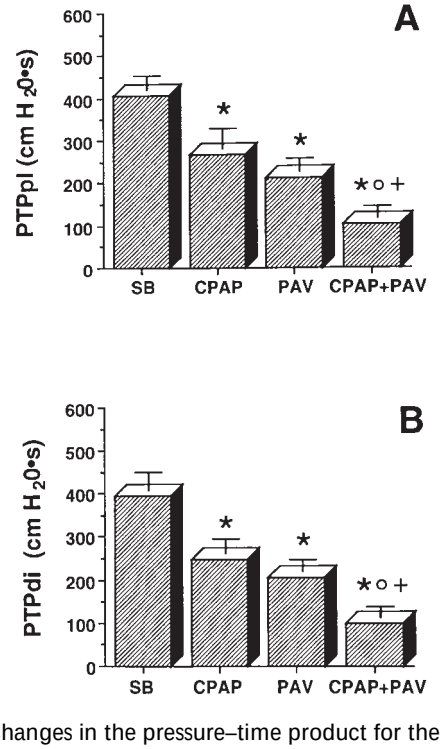

Figure 4. Changes in the pressure–time product for the inspiratory muscles (PTPpl, *A*) and for the diaphragm (PTPdi, *B*) throughout the procedure. Other symbols as in Figure 2. *Bars* represent means ± 1 SE. Statistics: ANOVA for repeated measurements; *p < 0.05, treatment versus SB; °p < 0.05, treatment versus CPAP; +p < 0.05, CPAP + PAV versus PAV. *See text* for comments.

a parallel reduction in the magnitude of the patients' inspiratory effort, as indicated by the changes in both PTPpl and PTPdi (Figure 4). Figure 5 shows mean inspiratory transdiaphragmatic pressure expressed as a function of transdiaphragmatic maximum pressure ($\overline{Pdi}$/Pdi,max ratio) (20, 21). Mean inspiratory Pdi was on average higher than 40% of the Pdi,max value during SB, a level of effort considered impossible to maintain indefinitely (20, 21). Figure 5 also shows that the application of PAV or CPAP decreased mean inspiratory Pdi to 26 and 25% of Pdi,max, respectively, the difference between the two treatments being not significant. The combination of CPAP + PAV further reduced mean inspiratory Pdi to 12% of Pdi,max, this value being significantly lower than that of all the other conditions (SB, CPAP, and PAV).

Figure 6 illustrates the patient–ventilator interaction. As shown in Figure 6A, there was a complete correspondence between the respiratory frequency obtained by the number of patients' efforts measured on the Pdi tracing (fdi) and respiratory frequency measured on the flow tracing throughout the experimental procedure. In other words, neither during spontaneous breathing, nor with any kind of ventilatory support, i.e., CPAP, PAV, CPAP + PAV, were ineffective inspiratory efforts observed. Moreover, Figure 6B shows that the portion of the Pdi swing after the start of inspiratory flow (i.e., Tdi − Tlead) was always longer than T_I, indicating that the patient was always controlling the duration of the mechanically assisted breaths.

DISCUSSION

The results of this study show that, in ventilator-dependent patients with COPD with difficult weaning, PAV improved minute ventilation and unloaded the inspiratory muscles while CPAP, tailored at a value close to $PEEP_{i,dyn}$, reduced the patients' neuromuscular drive and inspiratory effort without significant effects on the breathing pattern. The combination of CPAP and PAV further increased tidal volume and decreased the magnitude of the patients' inspiratory neuromuscular

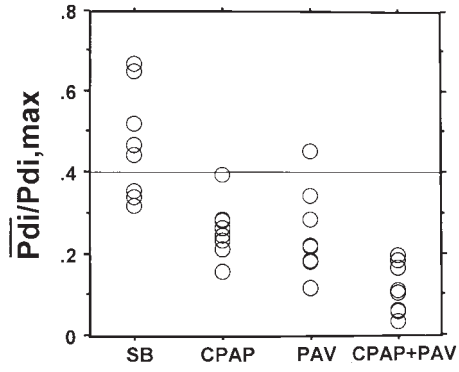

Figure 5. Changes in the mean inspiratory Pdi expressed as fraction of Pdi,max ($\overline{Pdi}$/Pdi,max ratio) throughout the procedure. The *horizontal line* represents the threshold above which the mean inspiratory Pdi is greater than 40% of the Pdi,max. *Open circles* represent data from single patients. Other symbols as in Figure 2. Significant reductions in $\overline{Pdi}$/Pdi,max ratio ($p < 0.05$) were obtained with the application of CPAP and PAV with respect to SB. A further significant decrease of the $\overline{Pdi}$/Pdi,max ratio ($p < 0.05$) was obtained when combining CPAP with PAV.

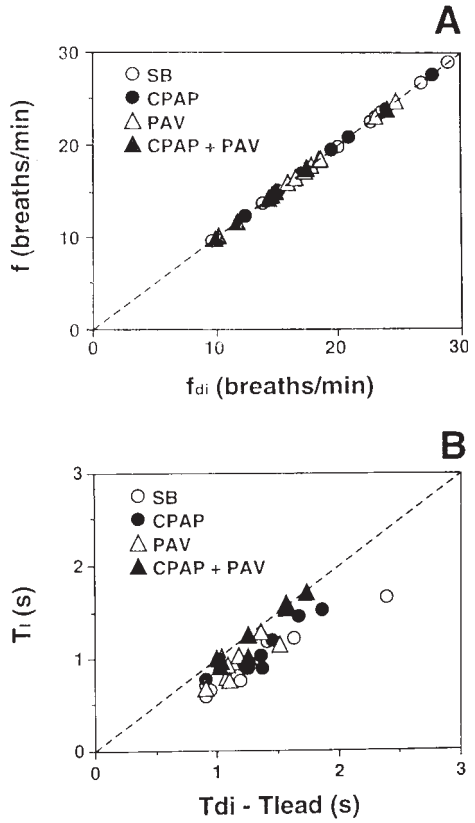

Figure 6. Individual data of patient–ventilator interactions during assisted ventilation. (*A*) Relationship between respiratory frequency (f) computed on flow tracing and respiratory frequency computed on Pdi tracing (fdi). Other symbols as in Figure 2. f and fdi during SB are shown to exclude the presence of ineffective inspiratory efforts in this condition. All points lie on the identity line (*dashed line*). (*B*) Relationship between inspiratory time (T_I) and the portion of Pdi swing that follows the start of the inspiratory flow (Tdi − Tlead). Other symbols as in Figure 2. The relationship between T_I and Tdi − Tlead during SB is shown for comparison with treatments. All points lie below the identity line (*dashed line*), indicating that, during assisted ventilation with CPAP, PAV, and CPAP + PAV, the diaphragm was always contracting, at least throughout the delivery of assisted inspiratory flow.

drive and muscle effort to a level similar to that observed in normal subjects (27, 28).

The beneficial impact of CPAP on the patients in this study is in line with some previous work (4, 15) and with the pathophysiology of ventilator-dependent patients with COPD (29). In these patients the magnitude of the inspiratory muscle contraction must exceed the level of $PEEP_i$, i.e., the end-expiratory elastic recoil pressure, in order to create a subatmospheric pressure in the central airway either to generate inspiratory flow and volume or to trigger the ventilator. Studies have shown that, in patients with severe COPD and respiratory failure, $PEEP_i$ may represent about 40% of the total inspiratory effort when acute or chronic respiratory failure occurs (4, 8, 30). As a result, while mechanical ventilation may support the true inspiration, CPAP is needed to offset $PEEP_i$, i.e., the inspiratory threshold load. A previous study with PSV in ventilator-dependent patients with COPD (4) showed that the combination of CPAP and PSV not only further reduced inspiratory muscle effort compared with either support alone, but also could unload the patient's inspiratory muscles better than PSV alone at the same level of total inspiratory support pressure. Similar data were obtained by Nava and colleagues (10), confirming that $PEEP_i$ is a substantial load in COPD patients with respiratory failure. However, in our previous study (4), patient–ventilator asynchrony was manifested by a patient's ineffective efforts at PSV of 20 and 25 cm H_2O even in the presence of 5 cm H_2O of CPAP. This was not the case in the present study. Whether this different result is due to the difference between PSV and PAV (7) or to patient characteristics cannot be established on the basis of this study, in which no comparison was made between PSV and PAV. However, we may report on the basis of our measurements of the breathing pattern that with PAV the ventilator did not compromise the time available for expiration, as was observed with other ventilatory modes (9), a fact that can be explained by the difference between PSV and PAV in the kind of support provided. First, it should be said that both PSV and PAV, at least for the setting examined in both studies, could unload the inspiratory muscles. In theory, however, PAV ceases whenever the inspiratory effort ends, unless the "run-away" phenomenon occurs (7), whereas PSV, after the patient's trigger, may be completely independent of the duration of the neural inspiration (7). Under such circumstances, the pressure boost continues until the opposing mechanical impedance of the patient's respiratory system exceeds the ability of the set level of PSV to inflate the lungs. As suggested by Nava and colleagues (10) and by Appendini and colleagues (4), in patients with high lung compliance PSV may generate excessive tidal volume, which then requires a long expiratory time to be exhaled, in particular in patients with COPD who have expiratory flow limitation. The long expiration may be poorly compatible with the patient's central frequency (31), so that inspiratory efforts occur during expiration, which are ineffective because of the excessive respiratory elastic recoil to be counterbalanced (5). In line with theoretical predictions, such dyssynchrony between patient and ventilator did not occur during PAV in our study.

As previously mentioned, our study data on difficult-to-wean patients with COPD show that PAV improves ventilation, reduces the neuromuscular drive, and unloads the inspiratory muscles. PAV is a new mode of mechanical ventilation that was introduced by Younes and colleagues (7). The few published short-term physiologic and clinical studies have demonstrated that PAV may be used in the ICU setting to treat patients with acute respiratory failure due to different etiologies (8, 31, 32). In those studies PAV improved arterial blood gases and unloaded the inspiratory muscles. One study by Ranieri and colleagues investigated the effect of different settings of PAV on patients with acute respiratory failure due to exacerbation of COPD on the first or second day after admission to the ICU and institution of mechanical ventilation (8). In the present study, ventilator-dependent patients with COPD had been ventilated for longer than 3 wk and six of them were tracheostomized. Hence, we examined the patients at a different stage of their disease, when discontinuation of mechanical ventilation had become problematic and long-term ventilatory support was under consideration. Ranieri and colleagues (8) set PAV with different combinations of FA, VA, and PEEP, demonstrating that application of PEEP with only FA provided the greatest inspiratory muscle unloading. This result is in line with their (8) measurements of respiratory mechanics in COPD patients with respiratory failure, in whom $PEEP_i$ and flow resistance provide most of the ventilatory workload, i.e., about 80%. However, Ranieri and colleagues (8) concluded that FA and VA should both be set during PAV

to optimize patient comfort. A similar conclusion was suggested by Navalesi and colleagues (32) and by Younes (7). Therefore in our study we used only PAV with the two components. Moreover, in agreement with Ranieri and colleagues (8), we found that application of CPAP during PAV had an additive effect (if compared with PAV alone) in unloading the inspiratory muscles, by counterbalancing $PEEP_i$, and, if tailored close to $PEEP_{i,dyn}$, should not increase the risk of adverse effects for patients. Indeed, previous studies have shown that values of CPAP close to $PEEP_{i,dyn}$, and hence lower than $PEEP_{i,st}$, did not have harmful effects on pulmonary hyperinflation because expiratory flow limitation prevents any significant increase in lung volume until CPAP exceeds $PEEP_i$ (29). Finally, it should be mentioned that PAV itself could have positive effects on dynamic hyperinflation. Indeed, we found a reduction (even if not statistically significant) of $PEEP_{i,dyn}$ close to 18% during PAV if compared with SB. This could represent a "true" reduction of intrinsic PEEP, compared with CPAP, which can effectively counterbalance intrinsic PEEP but cannot reduce the level of dynamic hyperinflation. Thus, it may well be that the effects of the combination of PAV and CPAP on $PEEP_{i,dyn}$ found in our study could be due to a combination of these two aforementioned mechanisms.

In this protocol, we did not examine different levels of PAV, as this has been done in other studies (32). Rather, we set PAV so as to relieve the patient's respiratory muscles by taking care of the abnormal component of elastance and resistance, such that the patient was breathing with a close to normal ventilatory workload. Under these circumstances, application of CPAP close to the level of $PEEP_{i,dyn}$ during PAV brought the values of PTP, both PTPdi and PTPpl, within normal range (28). On average, the reduction in the magnitude of the patient's inspiratory effort was associated with a significant reduction in the neuromuscular drive as assessed by $P_{0.1}$, when support was offered either by CPAP or by PAV, but $P_{0.1}$ came close to normal values only with the CPAP + PAV combination. These findings seem to be relevant, as neither CPAP nor PAV used alone was able to reduce in every instance the inspiratory effort at levels that can be reasonably sustained without developing ventilatory failure. Indeed, during CPAP and PAV used alone, in at least two patients the mean inspiratory Pdi was still above or close to 40% of the Pdi,max value (Figure 5), a level of mean inspiratory effort considered unsustainable and the cause of ventilatory failure (20, 21). This fact can be explained by an analysis of the workload of our difficult-to-wean patients, in whom it was composed of a variable combination of abnormal $PEEP_i$, inspiratory lung resistance, and dynamic lung elastance (Table 3). In other words, application of CPAP in a patient with highly resistive and moderately increased elastic workload, or of PAV in a patient with high levels of $PEEP_i$, can be insufficient in providing effective ventilatory assistance. These and some previous data (8, 32) indicate that PAV could be an attractive tool for ventilating difficult-to-wean patients with COPD, provided that a sufficient level of CPAP is set by the ventilator to counterbalance most of $PEEP_i$ when it represents a major burden for the inspiratory muscles.

Ideally, to set PAV one should know the patient's respiratory mechanics (7). The run-away technique developed by Younes and colleagues (7) has been used to this end (31, 33, 34). Navalesi and colleagues (32) and Ranieri and colleagues (8) measured patient respiratory mechanics by means of the occlusion technique during controlled mechanical ventilation (9). The end-inspiratory occlusion technique, however, requires respiratory muscle relaxation, which can be obtained easily during controlled mechanical ventilation, but not in awake, actively breathing patients. In addition, the use of the end-inspiratory occlusion technique to set PAV is based on some unproved assumptions. First, a measurement obtained under a passive condition is freely extrapolated to actively breathing patients. Second, the measurement obtained at end-inspiration may not reflect the respiratory mechanics during tidal breathing owing to differences in tidal volume and nonlinearity in the volume–pressure curves, which have been observed in both acute (35) and chronic COPD (9). In our study we used the esophageal balloon technique to measure lung mechanics and set PAV. Assuming that the chest wall mechanics were affected little or not at all, as previously suggested (25), we reasoned that PAV should take care of the amount of lung resistance and elastance exceeding normal values, such that patients could ventilate with a close to normal ventilatory workload. Combined with CPAP, set to counterbalance the significant levels of $PEEP_i$ common in these patients (Table 3), PAV brought PTPdi within the normal limits defined in the literature (28). This indirectly suggests that the estimations of the inspiratory lung mechanics made with the esophageal balloon technique were reasonably accurate, and effective in setting PAV in those patients in whom chest wall impairment is questionable. However, the esophageal balloon technique may be poorly suited to routine clinical practice. Hence, we think that guidelines for setting PAV in the clinical setting are still insufficient and remain an open, key question to be solved with further research.

In conclusion, the results of this study show that PAV can unload the inspiratory muscles in ventilator-dependent patients with COPD and that the combination of PAV and CPAP produces the most favorable effects on both ventilatory pattern and patient inspiratory effort. These data are in line with the pathophysiology of ventilator-dependent patients with COPD. In the patients of this study we did not observe any of the patient–ventilator dyssynchrony found in a previous study of similar patients and PSV. However, in our opinion, a major problem for the widespread application of PAV in the clinical setting is the lack of an easy technique to measure patient respiratory mechanics, a prerequisite both for establishing guidelines to set PAV and for tailoring PAV to the individual patient.

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