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Effects of Proportional Assist Ventilation on Inspiratory Muscle Effort in Patients with Chronic Obstructive Pulmonary Disease and Acute Respiratory Failure

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***Background*: Acute respiratory failure may develop in patients with chronic obstructive pulmonary disease because of intrinsic positive end-expiratory pressure (PEEPi) and increased resistive and elastic loads. Proportional assist ventilation is an experimental mode of partial ventilatory support in which the ventilator generates flow to unload the resistive burden (flow assistance: FA) and volume to unload the elastic burden (volume assistance: VA) proportionally to inspiratory muscle effort, and PEEPi can be counterbalanced by application of external PEEP. The authors assessed effects of proportional assist ventilation and optimal ventilatory settings in patients with chronic obstructive pulmonary disease and acute respiratory failure.**

***Methods*: Inspiratory muscles and diaphragmatic efforts were evaluated by measurements of esophageal, gastric, and transdiaphragmatic pressures. Minute ventilation and breathing patterns were evaluated by measuring airway pressure and flow. Measurements were performed during spontaneous breathing, continuous positive airway pressure, FA, FA+PEEP, VA, VA+PEEP, FA+VA, and FA+VA+PEEP.**

***Results*: FA+PEEP provided the greatest improvement in minute ventilation (89 ± 3%) and dyspnea (62 ± 2%). The largest reduction in pressure time product per breath of the respiratory muscles and diaphragm (44 ± 3% and 33 ± 2%, respectively) also was observed during FA+PEEP condition. When VA was added to this setting, a reduction in respiratory rate (50 ± 3%), an increase in inspiratory time (102 ± 6%), and a further reduction in pressure time product per minute (65 ± 2% and 64% for the respiratory muscles and diaphragm, respectively) was observed. However, values of pressure time product per liter of minute ventilation during FA+VA+PEEP did not differ with those observed during FA+PEEP condition. Worsening of patient–ventilator interaction and breathing asynchrony occurred when VA was implemented.**

***Conclusions*: Application of PEEP to counterbalance PEEPi and FA to unload the resistive burden provided the optimal conditions in such patients. Ventilator over-assistance and patient-ventilator asynchrony was observed when VA was added to this setting. The clinical use of proportional assist ventilation should be based on continuous measurements of respiratory mechanics. (Key words: chronic obstructive pulmonary disease, acute respiratory failure, mechanical ventilation, proportional assist ventilation.)**

IN patients with chronic obstructive pulmonary disease (COPD), the respiratory muscle pump functions close to the limit of its capacity to maintain effective ventilation because of the impairment of respiratory mechanics due to: (1) the inspiratory threshold load due to intrinsic positive end-expiratory pressure (PEEPi); (2) the excessive resistive load caused by obstruction of the airways; and (3) the increased elastic load on the muscle pump caused by the hyperinflation of the lungs.[1–4] In such patients, when the load on the respiratory muscle pump becomes excessive, effective ventilation can no longer be maintained, and acute respiratory failure (ARF) will develop, with a perceived sense of breathlessness, hypoxia, hypercapnia, and acidosis.[3] Under these circumstances, mechanical ventilation should restore blood gases to normal levels and relieve dyspnea by unloading the respiratory muscles and increasing alveolar ventilation.[4]

Applying the equation of motion[5] to respiratory mechanics of patients with COPD during ARF and mechanical ventilation, at any instant during the breath, the pressure applied by the ventilator to the respiratory

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system (which during partial ventilatory support includes the pressure generated by the respiratory muscles [Pmus] and the pressure applied across the respiratory system by the ventilator [Pappl]: Pao = Pmus + Pappl) is dissipated against: (1) PEEPi, (2) resistance ($Rtot_{,rs}$), and (3) elastance ($Est_{,rs}$) of the respiratory system[6]; inertial losses are negligible at resting levels of ventilation.[7] In these circumstances, the inspiratory act of breathing in a patient with COPD and ARF and whose lungs are mechanically ventilated can be described at any instant as follows:

$$Pmus + Pappl = PEEPi + Pres + Pel \quad \text{Eq. (1)}$$

where Pres represents the resistive pressure and is a function of flow, as dictated by the pressure-flow relation of the passive respiratory system ($Pres = flow \cdot Rtot_{,rs}$), and Pel represents the elastic recoil pressure and is a function of the volume-pressure relation of the respiratory system with respect to passive functional residual capacity ($Pel = volume \cdot Est_{,rs}$). Assuming that Rtot and Est are linear in the range of tidal ventilation, Eq. 1 becomes:

$$Pmus + Pappl = PEEPi + flow \cdot Rtot_{,rs} + volume \cdot Est_{,rs} \quad \text{Eq. (2)}$$

In recent physiologic studies, it was demonstrated that the application of continuous positive airway pressure (CPAP) during spontaneous breathing (SB),[8,9] or positive end-expiratory pressure (PEEP) during mechanical ventilation,[10] counterbalances PEEPi (*i.e.,* the first term in Eq. 2), decreasing inspiratory muscle effort without causing any adverse effects due to excessive pulmonary hyperinflation. In addition, assisted modes of mechanical ventilation, such as pressure support ventilation (PSV), have been used to minimize both resistive and elastic workload in patients with COPD (*i.e.,* the second and third terms in Eq. 2).[11,12]

Proportional assist ventilation (PAV) was proposed recently as a mode of partial ventilatory support in which the ventilator generates flow and volume to unload the resistive and elastic burden proportional to the inspiratory muscle effort.[13,14] With PAV, pressure applied by the ventilator becomes a function of patient effort: the greater the inspiratory effort, the more airway pressure increases. This relation applies as the level of effort changes from breath to breath. In addition, the pattern of airway pressure within each inspiration reflects the pattern of pressure generated by the patient. With PAV, therefore, what is preset is not a target pressure (as in PSV), but the amount of resistive and elastic unloading and the proportion between ventilator administrated flow and volume and patient inspiratory muscle effort.[13,14] Potential advantages of PAV include a synchronous and harmonious relation between patient and ventilator, the preservation and enhancement of the patient's own control of breathing mechanisms, less peak airway pressure, and less likelihood of overventilation.[13,14] However, despite growing interest in the possible clinical advantages of the use of PAV, there is little information available on the use of PAV in the clinical setting.[14]

The aim of this study was to assess the physiologic consequences of the use of PAV in patients with COPD during ARF and to identify the optimal setting for the use of PAV in such patients.

Methods

Eight patients with COPD admitted to the intensive care unit of the Policlinico Hospital (University of Bari) were studied. The diagnosis of COPD, made on previous pulmonary function tests, was confirmed by their history and physical examination. All patients were nasotracheally intubated (Portex cuffed endotracheal tube with an inner diameter varying from 8 mm to 8.5 mm, Portex, Milan, Italy), and the lungs were mechanically ventilated with a Siemens Servo Ventilator 900C (Siemens Elema AB, Berlin, Germany). The precipitating causes of ARF and pertinent clinical information are shown in table 1. Patients were studied 1-2 days after admission to the intensive care unit. The investigative protocol was approved by the local ethics committee, and written informed consent was obtained from each patient. A physician not involved in the study protocol was always present to provide patient care.

Flow was measured with a heated pneumotachograph (Fleisch No. 2; Fleisch, Lausanne, Switzerland), connected to a differential pressure transducer (Validyne MP 45 ± 2 cmH_2O; Validyne, Northridge, CA), which was inserted between the y piece of the ventilator circuit and the endotracheal tube. The pneumotachograph was linear over the experimental range of flow. Equipment dead space (not including the endotracheal tube) was 70 ml. Airway opening pressure (Pao) was measured proximal to the endotracheal tube with a pressure transducer (Validyne MP 45 ± 100 cmH_2O). Changes in intrathoracic and abdominal pressures were evaluated by assessment of esophageal (Pes) and gastric (Pga)

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Table 1. Patient Characteristics

Patient #	Gender	Age (yr)	Precipitating Causes of ARF	Baseline FEV_1/FVC (l)	$Est_{,rs}$* (cmH_2O/l)	$Rtot_{,rs}$* ($cmH_2O \cdot s/L$)	$PEEPi_{,stat}$* (cmH_2O)	Days of Mechanical Ventilation
1	F	57	Exacerbation COPD	0.33/1.60	28.2	20.5	9.5	1
2	F	62	Pneumonia	0.41/1.19	26.0	22.1	8.4	2
3	M	51	Exacerbation COPD	0.40/1.00	28.2	18.2	10.4	1
4	F	58	Exacerbation COPD	0.65/1.58	22.8	25.1	14.5	1
5	F	51	Exacerbation COPD	0.77/2.11	27.1	24.1	11.1	2
6	M	51	Pneumonia	0.60/2.10	28.6	26.1	7.6	1
7	M	67	Pneumonia	0.91/1.07	26.1	20.1	12.5	2
8	M	49	Exacerbation COPD	0.89/1.77	29.3	22.2	11.5	1

ARF = acute respiratory failure; COPD = Chronic obstructive pulmonary disease; FiO_2 = fraction of inspired oxygen mechanical ventilation; $Est_{,rs}$ = static elastance of the respiratory system; $Rtot_{,rs}$ = total resistance of the respiratory system; $PEEPi_{stat}$ = static intrinsic positive end-expiratory pressure.
* Data obtained during a short trial of respiratory muscle inactivity and controlled mechanical ventilation previous to the experimental procedure.

pressures, which were measured using thin, latex balloon-tipped catheter systems. Both balloons were 10 cm in length and 2.4 cm in circumference and were connected by polyethylene catheters (length 70 cm; internal diameter, 1.7 mm) to separate differential pressure transducers (Validyne MP 45 ± 100 cmH_2O). The esophageal balloon was filled with 0.75 ml air and correctly positioned by means of an occlusion test.[15] The gastric balloon contained 1.0 ml air. All the variables mentioned were displayed on an eight-channel strip-chart recorder (7718A Hewlett-Packard, Cupertino, CA) and collected on a personal computer through a 12-bit analog-to-digital converter at a sample rate of 100 Hz. Subsequent data analysis was performed using the software package ANADAT (RHT-InfoDat, Montreal, Quebec). Tidal volume (V_T) was computed by the digital integration of the flow signal.

Experimental Procedure

Static intrinsic PEEP ($PEEPi_{,stat}$), total resistance ($Rtot_{,rs}$), and static elastance ($Est_{,rs}$) of the respiratory system were obtained using the rapid airway occlusion technique.[16] Measurements of static respiratory mechanics were obtained during respiratory muscles inactivity and controlled mechanical ventilation (CMV). Ventilator parameters were set in such a way as to match the patient breathing pattern recorded during spontaneous breathing.[17] For this purpose, baseline assist mechanical ventilation was discontinued, and the patient was allowed to breathe spontaneously. Twenty to thirty consecutive breaths were collected after 2-3 min of stable breathing pattern and averaged to provide the flow, Pao, Pga, and Pes signals of the "mean representative breath," which were analyzed to obtain the basic pattern of breathing in terms of V_T, respiratory rate, and inspiratory time (Ti)/total breathing cycle time ratio. Respiratory muscle inactivity was then obtained by injecting a short-acting hypnotic agent (0.3 mg/Kg/min propofol for 5 min), and CMV was started. An end-expiratory airway occlusion was performed by pressing the end-expiratory hold knob on the ventilator. Static intrinsic PEEP was measured as the plateau pressure on the Pao signal at 3-5 s after end-expiratory airway occlusion. At the end of the following breath, an end-inspiratory occlusion was performed by pressing the end-inspiratory hold knob on the ventilator. After end-inspiratory occlusion, the Pao signal exhibited an initial drop (maximum pressure [Pmax]-pressure after first drop) followed by a slow decline to an apparent plateau pressure. The corresponding pressure value at 3-5 s after end-inspiratory occlusion was taken as the static end-inspiratory recoil pressure of the respiratory system (Pst).[13] Elastance of the respiratory system was computed by dividing the values of (Pst − $PEEPi_{,stat}$) by V_T. Resistance was calculated by dividing (Pmax − Pst) by the flow immediately preceding the occlusion.[16]

Approximately 20-30 min after static respiratory mechanics measurements, when respiratory muscle activity was regained (judged to have occurred when negative swings in esophageal pressure developed during inspiration) and patients awoke, the Siemens 900C was replaced by a Winnipeg ventilator (University of Manitoba, Winnipeg, Canada), and baseline assist mechanical ventilation was replaced. The Winnipeg ventilator is an experimental prototype designed to provide PAV, which can deliver all conventional modes of ventilation.

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The design and operation of this unit are similar to those previously described.[13,14] The gas delivery system consists of a freely moving piston reciprocating within a chamber. The electronics control a motor that moves a piston from left to right. As the patient inhales, the piston moves freely into the cylinder, providing an initial flow and volume; when the velocity of the piston movement (*i.e.,* inspiratory flow) reaches a preset threshold value, the motor starts to assist the movement of the piston. The flow level required to trigger the motor is variable, and, in the current study, was set at 0.05 l/s.[13,14] When the piston is activated, it creates pressure in the piston chamber, and the forward movement of the piston produces air flow. This air is directed to the patient through a one-way valve, the inspiratory line, and the humidifier, and passive deflation through the exhalation valve is allowed. The piston returns to the starting position, intaking gas from the ventilator input as it moves backwards. An external demand blended gas system is attached to the input opening. When the piston has returned to the starting position, the machine resets and is ready for the next inspiration. CPAP/PEEP can be applied by setting the CPAP/PEEP offset and externally adding a PEEP valve on the exhalation line of the ventilator circuit. The motor applies force to the piston according to different command signals regulated by the operating ventilatory mode.

During PAV, the command signals are instantaneous inspired flow (derived from the rate of forward motion of the piston) and instantaneous inspired volume (derived from piston displacement since the onset of inspiration). Once flow begins, pressure in the chamber rises in proportion to ongoing flow and volume, thereby augmenting the pressure gradient for chest expansion. The amount of assistance for both flow and volume can be set as varying percentage values of the total patient resistance and elastance through external controls. When this percentage is set below patient resistance and elastance, chamber pressure increases only if the patient effort increases. When inspiratory effort decreases at end-inspiration, inspiratory flow decreases and then stops, causing the integrator to reset and the assistance to terminate.

Figure 1 illustrates a schematic diagram of the PAV delivery and control systems used in the current investigation. The piston is coupled to a motor that generates force (*i.e.,* pressure) in proportion to the current applied to it. Instantaneous flow from the piston to the patient is continuously measured by a flowmeter inserted in the inspiratory line and integrated to provide instantaneous volume. Both flow and volume signals are amplified through user controlled gains determining the amount of current flowing to the motor. The flow gain for resistive unloading determines how much pressure will be applied by the ventilator per unit of flow produced by the patient. The scale on the user-controlled gain for resistive unloading is in centimeter of water per liter per second. This component, therefore, has the same unit as resistance. The gain on the volume signal determines how much pressure will result per unit of volume inspired by the patient. The scale on the user-controlled gain for elastic unloading is in centimeter of water per liter. This component, therefore, has the same unit as elastance.

Assuming the user decides to unload the patient's elastic and resistive loads of the 50%, and knowing that patient's resistance and elastance amount to 30 $cmH_2O \cdot s/l$ and 12 cmH_2O/l, respectively, the user will set on the flow gain for resistive unloading the value of 15 $cmH_2O \cdot s/l$ (*i.e.,* the 50% of the measured resistance value) and on the volume gain for elastic unloading the value of 6 cmH_2O/l (*i.e.,* the 50% of the measured elastance value). The ventilator will provide half of the total applied pressure to the respiratory system (the other half results from the contraction of the respiratory muscles) regardless of the distribution of this pressure between flow and volume. Conversely, if the user sets the flow gain for resistive unloading to zero, only the signal of variation of inspired volume will be amplified, and the ventilator will apply pressure exclusively in proportion to changes in inspired volume. If the user sets the volume gain for elastic unloading to zero, only the signal of variation of inspiratory flow will be amplified, and the ventilator will apply pressure exclusively in proportion to changes in inspiratory flow. If the flow and volume gains for resistive and elastic unloading are set higher than the patient's resistance and elastance, the pressure provided by the ventilator at the end of the patient's inspiratory effort will exceed the opposing resistive and elastic pressure. With these conditions, flow and volume delivery will not stop at the end of the patient's inspiratory effort and will continue during expiration. The patient can thereby initiate expiration only by expiratory recruitment of the abdominal muscles. This situation, referred as "runaway," causes patient–ventilator asynchrony, increase of patient's discomfort, and risk of barotrauma. It can be identified when the ventilator extends inspiratory flow beyond the time of contraction of the respiratory muscles and when the expiratory recruitment of abdominal muscles deforms the shape of flow and airway opening pressure signals.[13,14]

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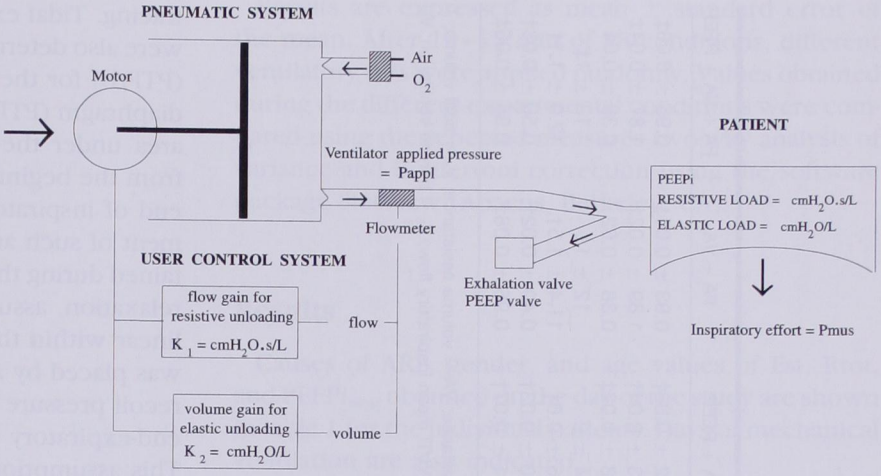

Fig. 1. Schematic diagram of the proportional assist ventilation delivery and control systems. PEEP = positive end-expiratory pressure; PEEPi = intrinsic PEEP. See text for further explanation.

Measurements were performed with the following conditions: (1) during spontaneous breathing (SB); (2) after application of a CPAP level amounting to 80% of $PEEPi_{,stat}$ measured during CMV[18]; (3) during flow assistance (FA) set to a percentage value that restored patients' $Rtot_{,rs}$ to normal levels. This was obtained by setting, on the flow gain for resistive unloading, the difference between measured $Rtot_{,rs}$ minus normal $Rtot_{,rs}$ value (normal values: 4 $cmH_2O \cdot s/l$)[16,19]; (4) during FA and application of a PEEP level amounting to 80% of $PEEPi_{,stat}$[18] (FA+PEEP); (5) during VA set to a percentage that restored patients' $Est_{,rs}$ levels to normal. This was obtained by setting, on the volume gain for elastic unloading, the difference between measured $Est_{,rs}$ minus normal $Est_{,rs}$ value (normal values: ≈15 cmH_2O/l)[16,19]; (6) during VA and application of a PEEP level amounting to 80% of $PEEPi_{,stat}$[18] (VA+PEEP); (7) during FA+VA; and (8) during FA+VA+PEEP.

Measurements were obtained from 20-25 breaths in each experimental condition, after 10-15 min, and establishment of breathing pattern was observed. The fractional inspired oxygen concentration remained constant throughout the study period (0.5 ± 0.1; mean ± standard error of the mean).

Data Analysis

Inspiratory time, expiratory time (Te), and total breathing cycle time were determined from the flow

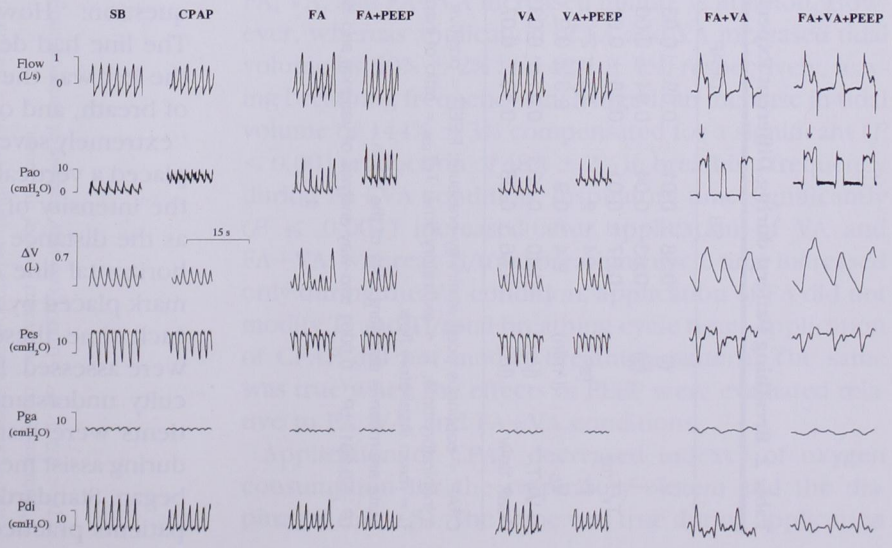

Fig. 2. Experimental records that help illustrate the effects of the different ventilatory settings in a representative patient. From top to bottom: flow, airway opening pressure (Pao), volume (ΔV), esophageal, gastric, and transdiaphragmatic (Pdi) pressures. CPAP = continuous positive airway pressure; FA = flow assistance; PEEP = positive end-expiratory pressure; SB = spontaneous breathing; VA = volume assistance. Arrows indicate "runaway" breaths. See text for explanation.

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Table 2. Breathing Pattern during Different Experimental Conditions*

		SB	CPAP	FA	FA + PEEP	VA	VA + PEEP	FA + VA	FA + VA + PEEP
V_T	(l)	0.38 ± 0.01	0.39 ± 0.03	0.77 ± 0.05†	0.78 ± 0.07†	0.54 ± 0.04†	0.52 ± 0.06†	0.93 ± 0.04‡	0.95 ± 0.06‡
T_I	(s)	0.93 ± 0.04	0.94 ± 0.06	0.96 ± 0.05	0.95 ± 0.04	1.75 ± 0.03†	1.73 ± 0.04†	1.89 ± 0.02‡	1.87 ± 0.04‡
T_I/T_{TOT}		0.37 ± 0.01	0.36 ± 0.01	0.35 ± 0.01	0.35 ± 0.02	0.66 ± 0.01‡	0.68 ± 0.02‡	0.38 ± 0.02	0.39 ± 0.01
Fr	(s^{-1})	24 ± 2	23 ± 2	22 ± 1	22 ± 1	23 ± 1	24 ± 2	12 ± 1‡	13 ± 1‡
V_D	(l/min)	9.4 ± 0.9	9.3 ± 0.9	17.2 ± 0.9†	17.7 ± 0.8‡	12.3 ± 0.6†	12.5 ± 0.6†	11.4 ± 1.5†	12.0 ± 1.1†
V_T/T_I	(l/s)	0.40 ± 0.03	0.41 ± 0.03	0.71 ± 0.02‡	0.69 ± 0.03‡	0.51 ± 0.02†	0.50 ± 0.03†	0.49 ± 0.02†	0.50 ± 0.03†
Peak flow	(l/s)	0.56 ± 0.08	0.53 ± 0.07	0.95 ± 0.07‡	0.96 ± 0.05‡	0.70 ± 0.06†	0.71 ± 0.07†	0.95 ± 0.08‡	0.95 ± 0.06‡

CPAP = continous positive airway pressure; PEEP = positive end-expiratory pressure; SB = spontaneous breathing; FA = flow assistance; VA = volume assistance; V_T = tidal volume; T_I = inspiratory time; T_E = expiratory time; T_I/T_{TOT} = ratio of inspiratory time to total breath cycle duration; Fr = respiratory frequency; Vt/Ti mean inspiratory flow; V_E = minute ventilation; V_T/T_I = mean inspiratory flow.

*Data are mean ± standard error of the mean.

†$P < 0.001$; ‡$P < 0.0001$ two-way analysis of variance and Bonferroni's test *versus* SB.

tracing. Tidal excursions of Pes (ΔPes) and Pdi (ΔPdi) were also determined. Pressure time product per breath (PTP/b) for the inspiratory muscle ($PTP/b_{,Pes}$) and the diaphragm ($PTP/b_{,Pdi}$) were obtained by measuring the area under the Pes and the Pdi signals, respectively, from the beginning of the inspiratory deflection to the end of inspiratory flow.[20] For the Pes signal, measurement of such areas was referred to the Pes tracing obtained during the period of CMV and respiratory muscle relaxation, assuming elastance of the chest wall to be linear within the V_T range.[20] The static chest wall line was placed by assuming that the end-expiratory elastic recoil pressure of the chest wall was equivalent to the end-expiratory position of Pes during tidal breathing.[21] This assumption was verified by occluding the airway at end-expiration (manually operated valve Model 2100; Hans Rudolph, Kansas City, MO) during the different experimental conditions and demonstrating that the end-expiratory position of Pes under occluded breaths was essentially identical to that during unoccluded breaths. Pressure time product per minute ($PTP/min_{,Pes}$ and $PTP/min_{,Pdi}$) was calculated as $PTP/b_{,Pes}$ and $PTP/b_{,Pdi}$ multiplied by respiratory rate. Pressure time product per liter of minute ventilation ($PTP/L_{,Pes}$ and $PTP/L_{,Pdi}$) was calculated as $PTP/min_{,Pes}$ and $PTP/min_{,Pdi}$ divided by minute ventilation.

The intensity of generalized discomfort was rated with a dyspnea visual analogue scale (VAS) 10–15 min after the beginning of each experimental trial.[22,23] The VAS was shown to represent a sensitive tool in the assessment of breathlessness during mechanical ventilation.[22] Patients were asked to place a vertical mark on a printed, 100-mm horizontal scale in response to the question: "How short of breath are you right now?" The line had descriptors below the extreme ends. On the left was the word "none," indicating no shortness of breath, and on the right was the opposite response, "extremely severe." For each ventilatory mode, patients placed a vertical mark on the line that best represented the intensity of their dyspnea. Intensity was measured as the distance in millimeters from the left side of the horizontal line (corresponding to no dyspnea) to the mark placed by the patient. A fresh scale was presented each time these measurements of breathing comfort were assessed. Because patients occasionally have difficulty understanding how to mark the VAS,[24] our patients were instructed carefully in its appropriate use during assist mechanical ventilation before the protocol began. Standardized directions were read aloud, and all patients practiced marking the scale.

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Table 3. Inspiratory Muscle Effort during Different Experimental Conditions*

	SB	CPAP	FA	FA + PEEP	VA	VA + PEEP	FA + VA	FA + VA + PEEP
PTP/b_{Pes} ($cmH_2O \cdot s$)	12.6 ± 0.9	11.0 ± 1.0†	9.8 ± 0.9†	7.2 ± 1.0‡	11.1 ± 0.9†	9.9 ± 0.9†	10.3 ± 1.1†	8.8 ± 0.7†
PTP/b_{Pdi} ($cmH_2O \cdot s$)	11.6 ± 1.0	9.4 ± 1.0†	10.1 ± 0.7†	7.7 ± 0.9‡	11.1 ± 0.9†	8.6 ± 0.8†	9.8 ± 0.8†	9.1 ± 0.9†
PTP/min_{Pes} ($cmH_2O \cdot s/min$)	300.9 ± 5.5	259.7 ± 4.1†	223.1 ± 3.5†	159.3 ± 3.0†	253.9 ± 5.0†	233.6 ± 4.0†	127.3 ± 3.3†	116.5 ± 4.4‡
PTP/min_{Pdi} ($cmH_2O \cdot s/min$)	276.5 ± 4.52	221.8 ± 4.7†	230.4 ± 3.4†	165.0 ± 3.2†	244.6 ± 4.0†	204.1 ± 5.0†	120.8 ± 5.0†	114.1 ± 3.4‡
PTP/L_{Pes} ($cmH_2O \cdot s/l$)	32.1 ± 1.5	27.9 ± 1.0†	13.5 ± 1.1†	9.0 ± 1.2‡	20.8 ± 1.1†	17.6 ± 1.1†	11.1 ± 1.1†	9.9 ± 1.6‡
PTP/L_{Pdi} ($cmH_2O \cdot s/l$)	30.0 ± 1.2	23.1 ± 1.5†	13.0 ± 1.2†	9.7 ± 1.6‡	19.7 ± 1.8†	16.3 ± 1.3†	10.6 ± 1.1†	9.5 ± 1.5‡

CPAP = continous positive airway pressure; PEEP = positive end-expiratory pressure; FA = flow assistance; SB = spontaneous breathing; PTP/b = pressure time product per breath; PTP/min = pressure time product per minute; PTP/L = pressure time product per liter of minute ventilation. VA = volume assistance.

*Data are mean ± standard error of the mean.

†$P < 0.001$; ‡$P < 0.0001$ two-way analysis of variance and Bonferroni's test *versus* SB.

Results are expressed as mean ± standard error of the mean. After 10-15 min of SB conditions, different ventilatory sets were applied randomly. Values obtained during the different experimental conditions were compared using the repeated measures two-way analysis of variance and Bonferroni correction using the software package StatView (Abacus, Berkeley, CA).

Results

Causes of ARF, gender, and age values of Est, Rtot, and $PEEPi_{,stat}$ obtained on the day of the study are shown in table 1 for the individual patients. Days of mechanical ventilation are also indicated.

Experimental records of a representative patient during the different experimental conditions are shown in figure 2. As can be seen, CPAP as well as FA, VA, and VA+FA induced a reduction in the tidal excursion of Pes and Pdi. Application of PEEP induced a further reduction in inspiratory swings of Pes and Pdi. Application of CPAP did not change tidal volume or breathing frequency, whereas application of FA and VA increased tidal volume, leaving breathing frequency unchanged. Conversely, a more relevant increase in tidal volume and a reduction in breathing frequency were observed during FA+VA. Tidal volume and breathing frequency did not change as a result of application of PEEP during FA, VA, and FA+VA conditions. The occurrence of the "runaway" phenomenon was observed only during FA+VA and FA+VA+PEEP conditions.

Effects of the different experimental conditions on breathing pattern are shown in table 2. Application of FA, VA, and FA+VA increased minute ventilation. However, whereas application of FA and VA increased tidal volume by 50% ± 2% and 42% ± 1%, respectively, leaving breathing frequency unchanged, an increase in tidal volume of 144% ± 3% compensated for a significant ($P < 0.001$) reduction of 48% ± 2% in breathing frequency during FA+VA condition. Inspiratory time significantly ($P < 0.001$) increased after application of VA and FA+VA, whereas Ti/total breathing cycle time increased only during the VA condition; application of FA did not modify Ti and Ti/total breathing cycle time. Application of CPAP did not modify breathing pattern. The same was true when the effects of PEEP were evaluated relative to FA, VA, and FA+VA conditions.

Application of CPAP decreased indexes of oxygen consumption for the respiratory system and the diaphragm (table 3). The same was true during application

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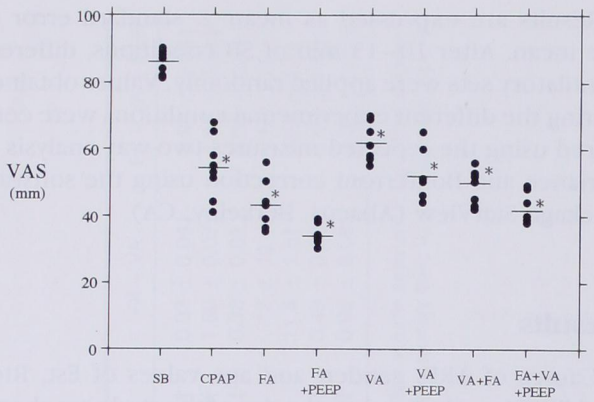

Fig. 3. Visual analog scale (VAS) of patient-perceived sense of breathlessness during the different experimental conditions. CPAP = continuous positive airway pressure; FA = flow assistance; PEEP = positive end-expiratory pressure; SB = spontaneous breathing; VA = volume assistance. *P < 0.001, two-way analysis of variance *versus* SB.

of FA and VA. When FA and VA were applied jointly, the reduction in indexes of oxygen cost of breathing per breath and per liter of minute ventilation did not differ with those observed during FA. Application of PEEP induced a reduction of oxygen cost of breathing during all ventilatory settings (table 3).

During SB, the score for dyspnea amounted to 86.0 ± 1.2 mm. When asked to indicate changes in the degree of breathlessness during the different ventilatory modes with respect to the preceding SB condition, all patients reported a reduction in dyspnea (fig. 3).

To assess the relative contribution of the abdominal muscles during expiration, tidal changes in Pga and volume were plotted in all patients during the eight experimental conditions (fig. 4).[25,26] In all patients, we observed that, during SB, Pga increased during expiration but decreased during inspiration. Application of CPAP, VA, and VA+PEEP, FA+VA, and FA+VA+PEEP did not affect this behavior. However, Pga decreased during inspiration, suggesting that expiratory recruitment of the abdominal muscles was reversed by application of FA and FA+PEEP.

When results were expressed as percentage variations relative to SB condition, and effects of the different ventilator settings were evaluated by Bonferroni's correction, we observed that the most enhanced increase in minute ventilation was found during FA+PEEP condition (fig. 5). The largest reduction in indexes of oxygen cost of breathing per breath also was observed during FA+PEEP condition (44% ± 3% and 33% ± 2% for the respiratory muscles and diaphragm, respectively). When VA was added to this setting, a further reduction in oxygen cost of breathing per minute (65% ± 2% and 64% for the respiratory muscles and diaphragm, respectively) was observed. However, reduction of oxygen cost of breathing per liter of minute ventilation during FA+VA+PEEP (70% ± 5% and 66% ± 4% for the respiratory muscles and diaphragm, respectively) did not differ with those observed during FA+PEEP condition (72% ± 4% and 68% ± 5% for the respiratory muscles and diaphragm, respectively; fig. 5).

Discussion

Proportional assist ventilation is a recently proposed form of partial ventilatory support, in which the ventilator generates flow and volume in proportion to patient effort.[13,14] With PAV, Pappl is a function of flow and volume, both of which are determined by patient effort.

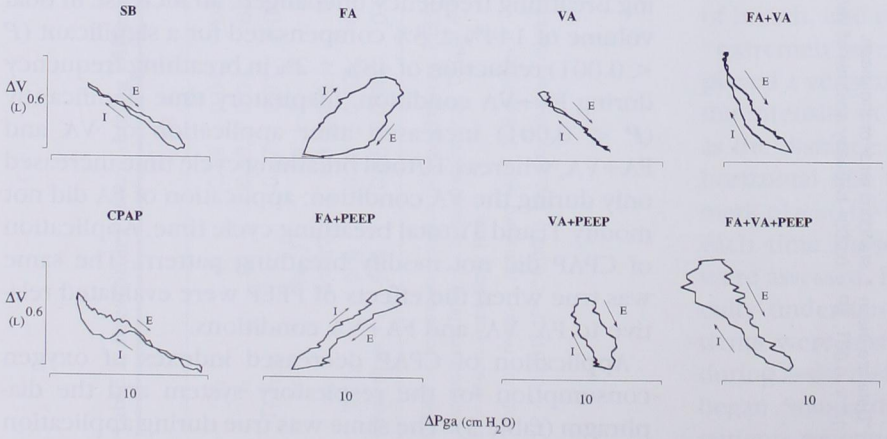

Fig. 4. Tidal abdominal pressure (ΔPga) volume (ΔV) loops in a representative patient during the different experimental conditions. Arrows show the direction of the loop. CPAP = continuous positive airway pressure; E = expiration; FA = flow assistance; I = inspiration; PEEP = positive end-expiratory pressure; SB = spontaneous breathing; VA = volume assistance.

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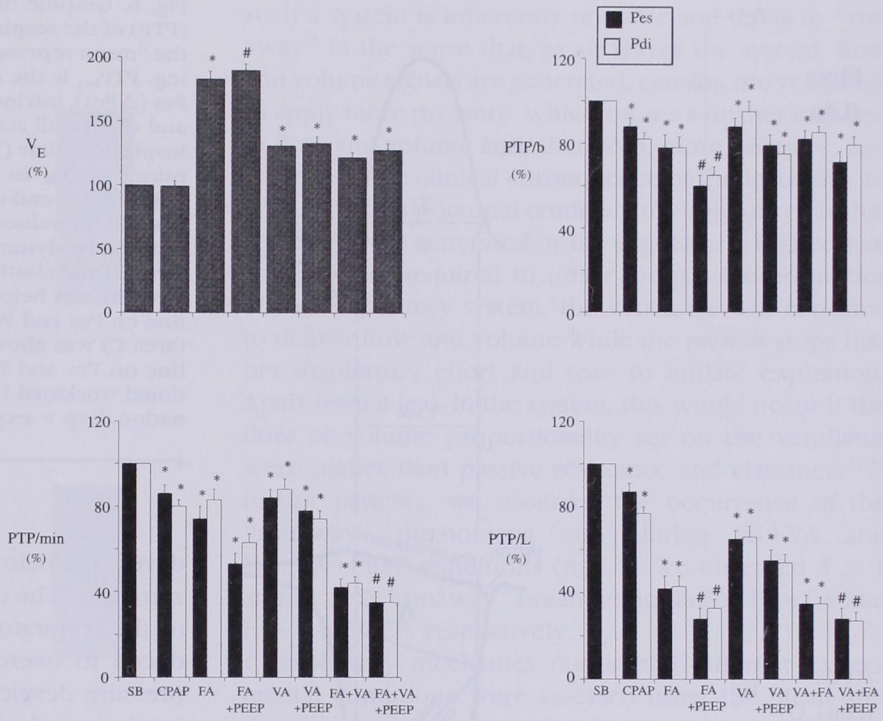

Fig. 5. Variations in minute ventilation (VE), pressure time product (PTP) per breath (PTP/b), per minute (PTP/min), and per liter of minute ventilation (PTP/l) of the respiratory muscles (Pes) and diaphragm (Pdi) expressed as percentage relative to spontaneous breathing condition. CPAP = continuous positive airway pressure; FA = flow assistance. PEEP = positive end-expiratory pressure; SB = spontaneous breathing; VA = volume assistance. *$P < 0.001$, #$P < 0.0001$ two-way analysis of variance and Bonferroni's correction for multiple comparisons.

During PAV, Pappl = ($f_1 \cdot$ flow) + ($f_2 \cdot$ volume); in the case of linearity of f_1 and f_2 functions, and according to Eq. 2, the use of PAV in patients with COPD can be described by the following equation:

$$\text{Pmus} + (k_1 \cdot \text{flow} + k_2 \cdot \text{volume})$$
$$= \text{PEEPi} + \text{Flow} \cdot \text{Rtot}_{,rs} + \text{Volume} \cdot \text{Est}_{,rs} \quad \text{Eq. (3)}$$

where k_1 is the proportionality between Pappl and inspiratory flow rate (in resistance units, $cmH_2O \cdot s/l$) and k_2 is the proportionality between Pappl and inspiratory volume (in elastance units, cmH_2O/l).[13,14] With PAV, what is preset is not a target flow, volume, or Pappl level, but the proportion between inspiratory muscle effort and flow (by regulating coefficient k_1) and volume (by regulating coefficient k_2) (*i.e.,* how much flow and volume will rise for a given increase in Pmus during inspiration).[13,14] Therefore, PAV can independently unload resistive (by applying FA) and elastic (by applying VA) loads. Intrinsic positive end-expiratory pressure can be counterbalanced by applying PEEP. In our patients, PEEPi amounted to 10.70 ± 1.21 cmH_2O. Externally applied CPAP/PEEP level amounted to 8.5 ± 1.1 cmH_2O. This value, which represented 80% of $PEEPi_{stat}$, minimized inspiratory threshold load without causing any further increase in lung volume and intrathoracic pressure.[18] $Rtot_{,rs}$ and $Est_{,rs}$ amounted to 22.23 ± 2.01 $cmH_2O \cdot s/l$ and 27.06 ± 1.89 cmH_2O/l, respectively. Factors k_1 and k_2 in Eq. 3 were respectively set at 18 ± 1 $cmH_2O \cdot s/l$ and 12 ± 1 cmH_2O/l, respectively. This setting allowed us to "normalize" the resistive (normal values of $Rtot_{,rs} \approx 4$ $cmH_2O \cdot s/l$)[16,19] and elastic (normal values of $Est_{,rs} \approx 15$ cmH_2O/l)[16,19] workloads, respectively (fig. 1).

Our results confirm that PAV can unload the respiratory muscles, increase minute ventilation, and reduce patients' perceived sense of breathlessness in patients with COPD during ARF. These data do not demonstrate that PAV is superior to other modes of partial ventilatory support assistance, but they show that PAV works and that flow assistance and PEEP are the essential elements for the optimal PAV setting in patients with COPD.

To interpret these findings, we quantified the relative amount of pressure developed to overcome PEEPi, resistive, and elastic loads from the total inspiratory pressure developed by the respiratory muscles and the diaphragm (Pmus in Eq. 3). Application of the Campbell *et al.* diagram[27] to the inspiratory Pes and Pdi-time profile of the "mean representative breath" obtained during spontaneous breathing allowed the identification of three components on the inspiratory efforts of our

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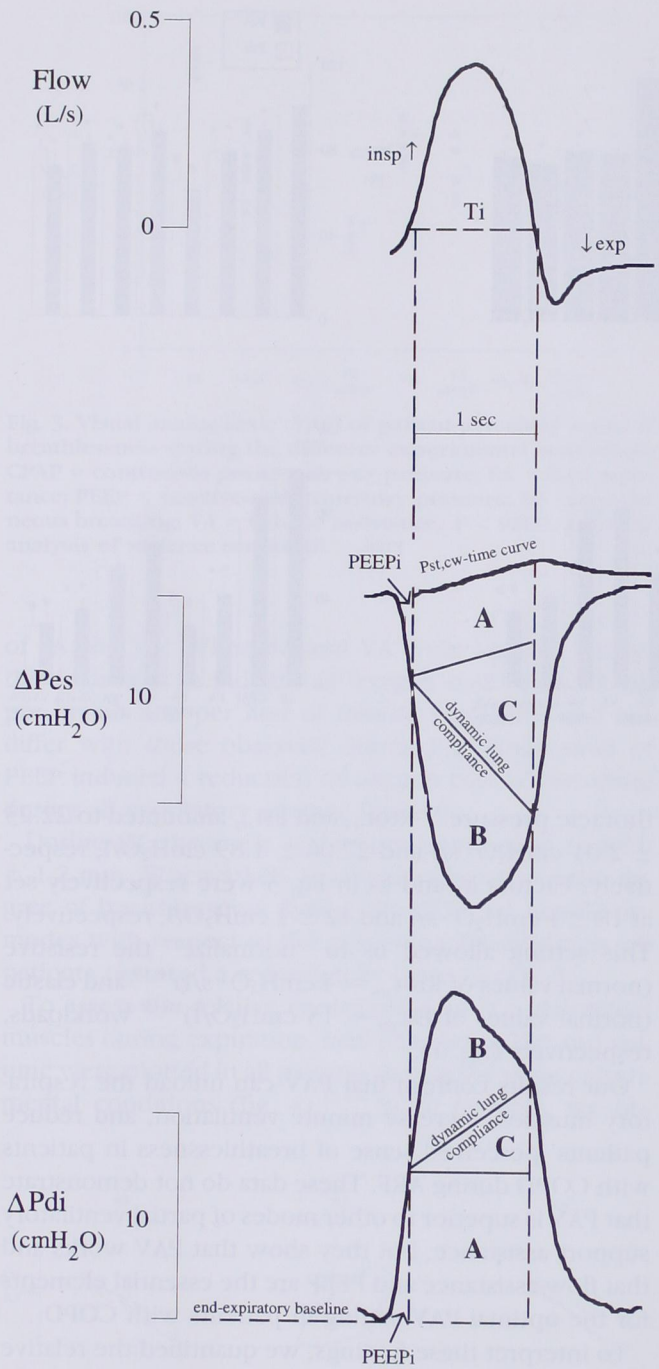

Fig. 6. Graphic measurements of the pressure time product (PTP) of the respiratory muscles (Pes) and diaphragm (Pdi) of the "mean representative breath" during spontaneous breathing. PTP_{Pes} is the area subtended by the inspiratory swing in Pes (ΔPes), intrinsic positive end-expiratory pressure (PEEPi), and chest wall static recoil pressure (Pst,cw)-time curve over inspiratory time (Ti). PTP_{Pdi} is the area subtended by the inspiratory swing in transdiaphragmatic pressure (ΔPdi) and PEEPi above end-expiratory baseline over Ti. The line encompassing the values of Pes at point of zero flow, its slope representing the dynamic lung compliance, identifies the resistive (area B) and elastic (area C) workloads. The resistive workload (area B) was below and above the dynamic lung compliance line on Pes and Pdi traces, respectively. The elastic workload (area C) was above and below the dynamic lung compliance line on Pes and Pdi signals, respectively. Area A is the additional workload induced by PEEPi. See text for further explanation. Exp = expiration; Insp = inspiration.

patients (fig. 6).[20,27,28] First, the inspiratory pressure developed before the onset of inspiratory flow was identified as the inspiratory threshold load resulting from PEEPi. The corresponding area represented the PTP of the respiratory muscles and of the diaphragm produced to overcome PEEPi. Second, the inspiratory pressure developed below the line that connected the points of zero flow. The corresponding area represented the PTP of the respiratory muscles and of the diaphragm produced to overcome resistance. Third, any additional pressure developed during inspiration was defined as inspiratory elastic load, which was assumed to increase at a constant rate from the onset to the end of inspiratory flow, as predicted from constant elastance and inspiratory flow. The corresponding area represented the PTP of the respiratory muscle and of the diaphragm produced to overcome elastance (see figures 1 in references 20 and 28). Our data show that 48% ± 3% of the total inspiratory pressure developed by the respiratory muscles and the diaphragm either per breath (fig. 7, *top*), per minute (fig. 7, *center*), or per liter of minute ventilation (fig. 7, *bottom*) was dissipated to overcome PEEPi, whereas 36% ± 3% and 16% ± 2% of the total inspiratory pressure was developed by the respiratory muscles and the diaphragm to overcome resistance and elastance of the respiratory system. These findings suggest that, in patients with COPD, both the pressure developed by the respiratory muscles and diaphragm to overcome the internal threshold load due to PEEPi and the resistive component represent the major part of the total pressure that arises during the early phase of inspiration; this fraction declines progressively thereafter, whereas the elastic component is negligible in early inspiration and increases progressively later.[29] Therefore, the pattern of decrease in Pes and increase in Pdi is such that, once PEEPi has been overcome, the pressure available to produce flow (and hence flow itself) increases gradually early in inspiration, reaching a peak near mid inspiration and subsequently declining

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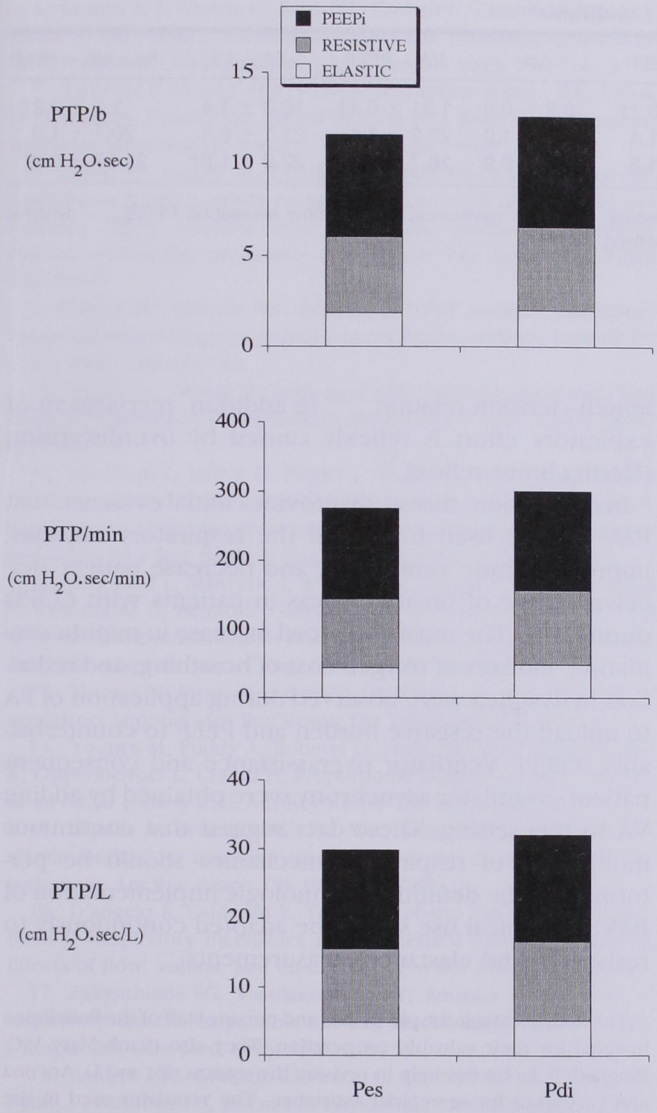

Fig. 7. Averaged values of pressure–time product (PTP) of the respiratory muscles (Pes) and diaphragm (Pdi) per minute (PTP/min) and per liter of minute ventilation (PTP/L) developed to overcome intrinsic positive end-expiratory pressure (PEEPi) and resistive and elastic loads.

(fig. 6). Toward the end of inspiration, Pes and Pdi begin to rise and decline, respectively; once they reach a value less than Pel, the pressure available for flow assumes an opposite direction, and expiration begins.[29,30]

A characteristic feature of PAV is that only an increase in patient inspiratory effort will cause the ventilator to apply more flow and volume (and, therefore, pressure). Proportional assist ventilation can, therefore, be described as a "positive feedback" system.[13,14] On its own, such a system is inherently unstable and tends to "run away" in the sense that, as air leaves the system, flow and volume signals are generated, causing the ventilator to apply more pressure, which causes a further increase in flow and volume and, therefore, more pressure, and so on.[13,14] The clinical consequence of the instability of PAV and of its potential tendency to "run away" is that if the pressure generated by the ventilator is higher than the pressure required to offset the passive properties of the respiratory system, the ventilator will continue to deliver flow and volume while the patient stops his/her inspiratory effort and tries to initiate expiration. Apart from a leak in the system, this would occur if the flow or volume proportionality set on the ventilator were higher than passive resistance and elastance.[13,14] In our patients, we observed the occurrence of the "runaway" phenomena only during FA+VA and FA+VA+PEEP conditions (fig. 2). We observed 5 ± 1 and 11 ± 2 "runaway" breaths/min during FA+VA and FA+VA+PEEP, respectively.

Respiratory mechanics during the different experimental conditions were assessed using the Mead and Wittenberger technique.[5] Briefly, inspiratory pulmonary resistance (R_L) and elastance (E_L) were calculated by fitting the equation of motion of a single compartment model using multilinear regression, as follows:

$$\Delta P_L = R_L \cdot \dot{v} + E_L \cdot \Delta V \qquad \text{Eq. (4)}$$

where ΔP_L are inspiratory changes in transpulmonary pressure (calculated by subtracting Pes from Pao), ΔV are inspiratory changes in lung volume between end-expiratory lung volume and V_T, and $\dot{v}$ is peak inspiratory flow.[31] The level of PEEPi during the different experimental conditions ($PEEPi_{,dyn}$) was measured as the negative deflection in Pes from the onset of inspiratory effort to the point of zero flow.[32] In the case of active recruitment of the abdominal muscles, this value was corrected by subtracting the decrease in Pga, when present, from the decrease in Pes during the interval when $PEEPi_{,dyn}$ was measured (table 4).[32] Our data show that, relative to SB, application of CPAP and PEEP significantly ($P < 0.001$) decreased $PEEPi_{,dyn}$. A significant ($P < 0.001$) reduction in E_L was observed only during application of FA+VA and FA+VA+PEEP. In these circumstances, the occurrence of the "runaway" phenomena may be explained by the fact that the proportionality factor used to unload the elastic burden (k_2 factor in Eq. 3: 12 ± 1 cmH_2O/l), chosen to "normalize" the $Est_{,rs}$ values measured before the study and during CMV, becomes higher than warranted by the elastic proper-

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Table 4. Dynamic Lung Mechanics during Different Experimental Conditions*

	SB	CPAP	FA	FA + PEEP	VA	VA + PEEP	FA + VA	FA + VA + PEEP
$PEEPi_{dyn}$ (cmH_2O)	9.1 ± 1.1	1.11 ± 0.2†	8.4 ± 0.8	0.98 ± 0.1†	9.2 ± 0.9	1.21 ± 0.4†	10.3 ± 1.4	1.2 ± 0.2†
R_L ($cmH_2O \cdot s/l$)	21.1 ± 1.0	21.0 ± 1.0	20.1 ± 1.1	20.7 ± 1.4	21.7 ± 1.0	20.2 ± 1.4	21.1 ± 0.8	20.1 ± 1.0
E_L (cmH_2O/l)	26.3 ± 1.1	26.1 ± 1.1	26.1 ± 1	26.3 ± 1.3	26.0 ± 0.9	26.7 ± 1.1	22.0 ± 1.0†	21.97 ± 0.9†

CPAP = continous positive airway pressure; PEEP = positive end-expiratory pressure; FA = flow assistance; VA = volume assistance; $PEEPi_{dyn}$ = dynamic intrinsic PEEP; E_L = lung elastance; R_L = lung resistance. SB = spontaneous breathing.

*Data are mean ± standard error of the mean.

$P < 0.001$ two-way analysis of variance and Bonferroni's test *versus* SB.

ties of the respiratory system, as a result of the reduction in E_L. These data confirm how, during partial ventilatory support, breathing pattern and respiratory mechanics may change with the level of mechanical support.[33]

Expiration is normally considered a passive phenomenon that relies mostly on the elastic recoil properties of the respiratory system. However, active expiratory muscle recruitment during spontaneous breathing has recently received considerable attention in patients with COPD.[32-35] Our data show that, during SB, Pga increased during expiration but decreased during inspiration. Only application of FA and FA+PEEP conditions reversed expiratory recruitment of the abdominal muscles (fig. 4). A decrease in Pga at the beginning of the inspiratory effort could be determined either by relaxation of the abdominal muscles, if there was active contraction during expiration,[25] or by the action of the rib cage inspiratory muscles on the abdominal pressure.[26] The expiratory pattern of Pga observed in our patients during SB, CPAP, VA, VA+PEEP, and FA+VA, and FA+VA+PEEP conditions (fig. 4) suggests that the abdominal muscles were active during expiration and that the decrease in Pga levels during inspiration was due to muscle relaxation.[32]

The muscles used during active expiration are believed to serve as accessory muscles of inspiration and, during conditions of increased respiratory demand, to share the work, thereby assisting inspiration through several mechanisms. First, the increase in abdominal pressure provides a fulcrum for the diaphragm to help lift the rib cage. Second, an increase in abdominal pressure can reduce the volume of the respiratory system below its equilibrium point, which will then result in an outward recoil of the chest wall (inspiratory action) after relaxation of the respiratory muscles. Third, contraction of the abdominal musculature can cause cephalad displacement of the diaphragm during hyperinflation, resulting in a more favorable diaphragmatic length-tension relation.[25,26] In addition, recruitment of expiratory effort is reflexly caused by overdistension (Hering-Breur reflex).[36]

In conclusion, this study provides initial evidence that PAV can be used to unload the respiratory muscles, improve minute ventilation, and decrease patient perceived sense of breathlessness in patients with COPD during ARF. The most enhanced increase in minute ventilation, indexes of oxygen cost of breathing, and reduction in dyspnea were observed during application of FA to unload the resistive burden and PEEP to counterbalance PEEPi. Ventilator overassistance and consequent patient-ventilator asynchrony were obtained by adding VA to this setting. These data suggest that continuous monitoring of respiratory mechanics should be performed by the definitive technologic implementation of PAV; its clinical use should be adapted continuously to resistance and elastance measurements.

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