

Short-term Cardiorespiratory Effects of Proportional Assist and Pressure-support Ventilation in Patients with Acute Lung Injury/Acute Respiratory Distress Syndrome

Eumorfia Kondili, M.D.,* Nectaria Xirouchaki, M.D.,* Katerina Vaporidi, M.D.,†
 Maria Klimathianaki, M.D.,† Dimitris Georgopoulos, M.D., Ph.D.‡

Background: Recent data indicate that assisted modes of mechanical ventilation improve pulmonary gas exchange in patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). Proportional assist ventilation (PAV) is a new mode of support that amplifies the ventilatory output of the patient effort and improves patient-ventilator synchrony. It is not known whether this mode may be used in patients with ALI/ARDS. The aim of this study was to compare the effects of PAV and pressure-support ventilation on breathing pattern, hemodynamics, and gas exchange in a homogenous group of patients with ALI/ARDS due to sepsis.

Methods: Twelve mechanically ventilated patients with ALI/ARDS (mean ratio of partial pressure of arterial oxygen to fractional concentration of oxygen 190 ± 49 mmHg) were prospectively studied. Patients received pressure-support ventilation and PAV in random order for 30 min while maintaining mean airway pressure constant. With both modes, the level of applied positive end-expiratory pressure (7.1 ± 2.1 cm H₂O) was kept unchanged throughout. At the end of each study period, cardiorespiratory data were obtained, and dead space to tidal volume ratio was measured.

Results: With both modes, none of the patients exhibited clinical signs of distress. With PAV, breathing frequency and cardiac index were slightly but significantly higher than the corresponding values with pressure-support ventilation (24.5 ± 6.9 vs. 21.4 ± 6.9 breaths/min and 4.4 ± 1.6 vs. 4.1 ± 1.3 l · min⁻¹ · m⁻², respectively). None of the other parameters differ significantly between modes.

Conclusions: In patients with ALI/ARDS due to sepsis, PAV and pressure-support ventilation both have clinically comparable short-term effects on gas exchange and hemodynamics.

ACUTE lung injury (ALI) and acute respiratory distress syndrome (ARDS) represent different levels of pulmonary gas exchange disturbance caused by a common clinical disorder characterized by injury to the alveolar epithelial and endothelial barriers of the lung, acute inflammation, and protein-rich pulmonary edema leading to acute respiratory failure and often to mechanical ventilatory support.¹⁻⁵ In the past decade, the early re-institution of spontaneous breathing during the ventilatory support of intubated patients with ALI/ARDS has become an important therapeutic option to avoid the various complications associated with controlled mechanical ventilation.^{6,7} Among the various modes of as-

sisted mechanical ventilation, pressure support (PS) has been applied successfully in patients with ARDS.⁸ It has been shown that in patients with ARDS receiving controlled mechanical ventilation, the early institution of PS is associated with no significant alteration in oxygenation or in hemodynamics.⁸

Proportional assist ventilation (PAV) is a new mode of support that amplifies the patient's effort.⁹⁻¹¹ Contrary to PS—in which pressure assist is constant—with PAV, the ventilator pressure is proportional to instantaneous flow (flow assist, expressed in cm H₂O · l⁻¹ · s⁻¹) and volume (volume assist, expressed in cm H₂O/l) and hence to pressure generated by the respiratory muscles. The proportionality between applied pressure and both flow and volume is preset and dictates the magnitude of the decrease, respectively, in resistive and elastic load faced by the inspiratory muscles.⁹⁻¹¹ Because flow assist and volume assist must be less than the patient's resistance and elastance, respectively, the operation of this mode necessitates the measurement of respiratory system mechanics.

Although PAV has been applied in patients with acute respiratory failure due to a variety of causes,¹²⁻¹⁴ data in patients with ALI/ARDS are scanty. Recently, Varelmann *et al.*¹⁵ reported that in patients with acute hypoxemic respiratory failure, PAV has comparable short-term (approximately 30 min) cardiorespiratory effects to PS. However, several of the patients either did not meet the oxygenation criterion for ALI/ARDS or exhibited near normal respiratory system mechanics, whereas some patients were studied late in the course of their disease (> 4 weeks), where lung fibrosis may prevail.

In patients with ALI/ARDS, PAV might have either detrimental or beneficial effects on gas exchange and hemodynamics.¹⁰ For example, it has been shown that there is a wide variability in desired tidal volume (V_T) among patients ventilated on PAV (range, 3.4–14.1 ml/kg).¹⁶ Low V_T may lead to deterioration of gas exchange due to atelectasis formation and increase in dead space-to-tidal volume ratio (V_D/V_T), whereas high V_T may result in overdistention.¹⁰ On the hand, it is possible that PAV may improve the ventilation/perfusion matching and reduce the shunt-like effect and total ventilatory requirements, mainly due to inspiratory airway pressure-time profile and better patient-ventilator synchrony.¹⁰ In addition, the effects of PAV on gas exchange may be influenced by alteration in cardiac output.

The aim of this study was to investigate, in a homog-

* Consultant, † Resident in Intensive Care, ‡ Professor of Medicine.

Received from the Intensive Care Medicine Department, University Hospital of Heraklion, Medical School, University of Crete, Heraklion, Crete, Greece. Submitted for publication January 30, 2006. Accepted for publication June 19, 2006. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Kondili: Intensive Care Medicine Department, University Hospital of Heraklion 71110, University of Crete, Heraklion, Crete, Greece. kondi@med.uoc.gr. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

enous group of patients with ALI/ARDS due to sepsis during the acute phase of their illness, the short-term effects of PAV on ventilatory and hemodynamic parameters and gas exchange and to compare these to those observed with PS. We hypothesized that in this group of patients characterized by significant disturbances in gas exchange and cardiorespiratory parameters, PAV would be equally effective to PS and might be an alternative mode of assisted mechanical ventilation.

Materials and Methods

Patients

Twelve patients admitted to the intensive care unit for management of acute respiratory failure due to ALI/ARDS secondary to sepsis were prospectively studied. At the time of the study, all patients were hemodynamically stable, with pulmonary arterial catheters in place for fluid management and hemodynamic monitoring. The exclusion criteria were a previous history of chronic obstructive pulmonary disease, hemodynamic instability, and the presence of intrathoracic drainage tube with persistent air leak. All patients were ventilated with PS mode through cuffed endotracheal (10 patients) or tracheostomy tubes (2 patients). The level of PS and the applied positive end-expiratory pressure were set by the primary physician, who was not involved in the study. None of the patients were eligible for a weaning T-piece trial. All patients were sedated with propofol ($1.0\text{--}1.5\text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) to achieve acceptable oxygenation and patient-ventilator synchrony as judged by the primary physician. The level of sedation was such as to achieve a score of 3 on the Ramsay scale (response to commands only).

The protocol was approved by the institutional ethics committee, and informed consent was obtained from the patients or their next of kin.

Measurements

Flow, volume, and airway pressure (P_{aw}) were measured breath by breath. Heart rate and systemic arterial pressure were continuously recorded on patient's monitor. Central venous pressure, mean pulmonary artery pressure, and pulmonary capillary wedge pressure were measured at end-expiration. Cardiac output was measured by the thermodilution technique (Vigilance Monitor; Edwards Lifesciences, Irvine, CA). Cardiac index, stroke volume index, oxygen delivery index, oxygen consumption index, systemic and pulmonary vascular resistance indices, and the shunt-like effect (Q_s/Q_T) were calculated using standard formulas.¹⁷

Protocol

The patients were connected to a ventilator (Evita 4; Dräger, Lubeck, Germany) able to ventilate them with PS

and PAV. Initially, the patients were placed on volume-control constant flow mode and ventilated with a V_T comparable to that during PS. Respiratory inactivity was achieved by injecting a short-term hypnotic agent (propofol, 1–2 mg/kg) and by adjusting the ventilator rate upward. When passive ventilation was obtained, the respiratory system mechanics (resistance and elastance) were measured by the technique of rapid airway occlusion using standard formulas.¹⁸

Thirty minutes after these measurements, when respiratory muscle activity was resumed (*i.e.*, the patient started to trigger the ventilator at his or her usual rate), the patients were ventilated randomly with PAV or PS. With PS, the level of assist was equal to that set by the primary physician before the study. With PAV, the proportionalities for both flow and volume assist were set at the same percentage of the measured resistance and elastance, respectively, and adjusted such as to obtain a mean airway pressure similar to that during PS. Positive end-expiratory pressure was set to values determined by the primary physician when the patients were ventilated with PS. The patients were ventilated in each mode for 30 min, and after that period, hemodynamic data were obtained. Ventilatory parameters were recorded for an additional 10-min period. The patients were withdrawn from the study if they exhibited one of the following: (1) clinical signs of excessive work of breathing (use of accessory muscles, paradoxical motion of the diaphragm or alternans), (2) diaphoresis, (3) heart rate greater than 130 beats/min, or (4) systolic blood pressure greater than 180 mmHg or less than 90 mmHg. New or additional administration of intravenous fluid, vasoactive drug, and sedative agents and a necessity—judged by the primary physician—to change either the level of positive end-expiratory pressure or fractional concentration of oxygen during the study period were also reasons to withdraw the patient from the protocol.

Data Analysis

The V_D/V_T was calculated using the Enghoff modification of the Bohr equation. The V_T and respiratory rate were recorded on a breath-by-breath basis for a period of 10 min after each 30-min period, and the average values were calculated. Inspiratory time and expiratory time were measured as the interval between the beginning and the end of inspiratory and expiratory flow, respectively. Coefficient of variation of V_T was also calculated and served as an index of V_T variability. Inspiratory airway pressure 0.1 s after airway occlusion ($P_{0.1}$) was estimated by an automatic maneuver integrated in the ventilator.

In all patients, flow-time waveform during PAV and PS was carefully examined for signs indicative of patient-ventilator asynchrony. Runaway phenomena due to flow or volume overassist were identified as previously described.^{9,11}

Table 1. Baseline Patient Characteristics and Ventilator Parameters with PS and PAV

Patient	Sex	Age, yr	Pao ₂ /Fio ₂ , mmHg	Ers, cm H ₂ O/l	Rrs, cm H ₂ O · l ⁻¹ · s ⁻¹	PEEP, cm H ₂ O	PS, cm H ₂ O	FA-VA, %	Days on MV
1	M	74	183	25	15	5	17	75	4
2	F	40	166	30	18	9	19	75	5
3	M	25	201	29	12	10	26	70	9
4	F	71	179	30	12	8	23	50	12
5	M	67	155	25	23	9	19	65	3
6	F	67	158	21	15	5	16	75	10
7	M	56	287	30	13	5	11	45	4
8	M	50	127	20	18	7	17	75	6
9	M	78	252	26	20	5	16	50	4
10	F	77	243	20	13	5	15	50	7
11	F	63	132	30	19	10	26	75	6
12	F	71	203	22	15	7	22	50	10
Mean		61.6	191	25.7	16.0	7.1	18.9	62.9	6.6
SD		16.1	49	4.1	3.5	2.1	4.6	12.7	3.0

Ers = respiratory system elastance; FA-VA = flow and volume assist during proportional assist ventilation (% of Rrs and Ers, respectively); MV = mechanical ventilation; Pao₂/Fio₂ = ratio of partial pressure of arterial oxygen to fractional concentration of oxygen; PAV = proportional assist ventilation; PEEP = positive end-expiratory pressure; PS = pressure support; Rrs = respiratory system resistance.

Statistical Analysis

Results are expressed as mean ± SD. Data were tested for normal distribution by the Shapiro-Wilk W test and analyzed by a two-sided paired *t* test. Differences were considered to be statistically significant if *P* was less than 0.05.

Results

Patient characteristics and ventilator settings with both modes of support are shown in table 1. None of the patients were withdrawn from the study. With both modes, none of the patients exhibited clinical signs of distress. Ineffective efforts, double triggering, and run-away phenomena were not observed during the study periods. In 8 of 12 patients, inspection of flow-time and pressure-time waveforms during PS revealed a flow and P_{aw} pattern indicative of delayed opening of expiratory valve. Features compatible with premature opening of expiratory valve were not observed.

By study design, mean airway pressure did not differ during PAV and PS, averaging 9.1 ± 1.9 and 9.1 ± 1.8 cm H₂O, respectively. Ventilatory parameters are shown in table 2. With PAV, peak airway pressure was slightly but significantly lower than that with PS, whereas breathing frequency and inspiratory time-to-total breath duration ratio (T_i/T_{TOT}) were significantly higher than those during PS. The variability of V_T did not differ between modes.

Hemodynamic variables, arterial blood gases, and V_D/V_T are shown in table 3. With PAV, cardiac index was slightly but significantly higher than that with PS, due to significantly higher stroke volume index. None of the other hemodynamic parameters differed significantly between the two modes. PAV and PS had comparable effects on blood gases and V_D/V_T.

Discussion

The main findings of this study in critically ill patients with ALI/ARDS due to sepsis were that (1) PAV and PS had clinically comparable short-term effects on gas exchange, V_D/V_T, and hemodynamics; and (2) the breathing pattern differed significantly between modes, being more rapid and shallow with PAV.

A homogenous group of patients with ALI/ARDS was studied. In all patients, an infectious cause of ALI/ARDS was identified. In the majority of the patients, V_D/V_T was above 0.6, signifying a group of patients with high mortality.^{19,20} In addition, 8 patients were studied between the 3rd and 7th days and 4 were studied between the 9th and 12th days of the mechanical ventilation. Therefore, contrary to other studies,^{15,21} we studied patients with ALI/ARDS relatively early in the course of their illness and having increased risk of death and severe disturbance of gas exchange (low ratio of partial pressure of arterial oxygen to fractional concentration of oxygen) and respiratory system mechanics (increased respiratory system elastance).

In several studies in which PS and PAV were com-

Table 2. Ventilatory Parameters

	PS	PAV
V _T , ml/kg IBW	8.0 ± 1.6	7.7 ± 1.9*
V _E , l/min	10.9 ± 3.5	11.6 ± 3.3
Coefficient variation of V _T , %	7.67 ± 6.5	8.88 ± 4.98
RR, breaths/min	21.4 ± 6.9	24.5 ± 6.9*
T _i , s	0.99 ± 0.4	0.93 ± 0.3
T _i /T _{TOT} , s	0.32 ± 0.1	0.36 ± 0.1*
Ppeak, cm H ₂ O	21.0 ± 6.0	19.2 ± 7.3*
P0.1, cm H ₂ O	3.5 ± 2.1	3.7 ± 2.3

* Significantly different from the value with pressure support (PS).

IBW = ideal body weight; P0.1 = inspiratory airway pressure 0.1 s after airway occlusion; PAV = proportional assist ventilation; Ppeak = peak inspiratory pressure; RR = respiratory rate; T_i = inspiratory time; T_i/T_{TOT} = inspiratory time to total breath duration ratio; V_E = minute ventilation; V_T = tidal volume.

Table 3. Blood Gasses and Hemodynamic Parameters

	PS	PAV
Pao ₂ , mmHg	80.2 ± 11.1	81.0 ± 11.7
Paco ₂ , mmHg	44.8 ± 11.6	45.4 ± 10.0
Pvo ₂ , mmHg	36.4 ± 3.4	37.4 ± 3.5
MAP, mmHg	82.5 ± 7.6	83.4 ± 9.8
Heart rate, beats/min	92.5 ± 13.9	92.9 ± 14.36
CVP, mmHg	7.2 ± 4.2	7.9 ± 4.5
CI, l · min ⁻¹ · m ⁻²	4.1 ± 1.3	4.4 ± 1.6*
Pwedge, mmHg	10.1 ± 2.9	11.3 ± 4.4
PAP, mmHg	24.8 ± 7.5	25.2 ± 7.7
SVI, ml · beat ⁻¹ · m ⁻²	45 ± 9	48 ± 12
SVRI, dyn · s ⁻¹ · cm ⁻⁵ · m ⁻²	1,531 ± 409	1,479 ± 403
PVRI, dyn · s ⁻¹ · cm ⁻⁵ · m ⁻²	288 ± 117	246 ± 107
D' O ₂ l, ml · min ⁻¹ · m ⁻²	550 ± 160	590 ± 191
V' O ₂ l, ml · min ⁻¹ · m ⁻²	165 ± 42	166 ± 45
Q' _S /Q' _T , %	22.5 ± 6.7	23.2 ± 6.3
V _D /V _T	0.67 ± 0.07	0.68 ± 0.07

* Significantly different from the value with pressure support (PS).

CI = cardiac index; CVP = central venous pressure; D' O₂l = oxygen delivery index; MAP = mean arterial pressure; Paco₂ = partial pressure of arterial carbon dioxide; Pao₂ = partial pressure of arterial oxygen; PAP = mean pulmonary arterial pressure; PAV = proportional assist ventilation; Pvo₂ = partial pressure of mixed venous oxygen; PVRI = pulmonary vascular resistance index; Pwedge = pulmonary wedge pressure; Q' _S/Q' _T = shunt-like effect; SVI = stroke volume index; SVRI = systemic vascular resistance index; V_D/V_T = dead space-to-tidal volume ratio; V' O₂l = oxygen consumption index.

pared, the assist level was titrated to obtain a similar mean inspiratory airway pressure between modes.^{15,21} On the contrary, in our study we chose to match mean airway pressure between modes for two reasons. First, in patients with ALI/ARDS, mean airway pressure is an important determinant of oxygenation.²²⁻²⁴ Second, it has been shown that ventilator inspiratory and expiratory time may differ between the two modes.⁹⁻¹¹ Therefore, setting the assist level by targeting mean inspiratory airway pressure may result in different actual ventilator assistance if ventilator inspiratory time and total breath duration differ substantially. On the other hand, calculation of mean airway pressure takes into account ventilator inspiratory time and total breath duration.²⁴ In our study, T_I/T_{TOT} and total breath duration differed significantly between modes, thus justifying the method of titration of the assist level we used.

We observed that the mode of support had a significant effect on breathing frequency, which was significantly higher with PAV than that with PS. In all but three patients, respiratory rate was higher with PAV than that with PS. In some patients, the difference in respiratory rate was substantial, and with PAV, breathing frequency of up to 34 breaths/min was observed. Although it is believed that high breathing frequency may be a sign of excessive work of breathing and inadequate assist level, studies have shown that respiratory rate is not good predictor of work of breathing or pressure-time product during assisted modes of support.²⁵ Particularly during PAV, high respiratory rate may not indicate distress, but it may represent the spontaneously selected pattern of

breathing.^{12,16} In our study, during PAV, although V_T was slightly lower than that with PS, none of the patients exhibited clinical signs of excessive work of breathing. Furthermore, P0.1—a reliable index of respiratory drive and inspiratory work of breathing in mechanically ventilated patients²⁶—was comparable between modes. It follows that the higher breathing frequency with PAV cannot likely be explained by inadequate support. On the other hand, the higher breathing frequency with PAV may due to different patient-ventilator interaction in terms of expiratory asynchrony (delayed or premature opening of exhalation valve) and V_T. With PAV, expiratory asynchrony is not an important issue, because with this mode, inspiratory flow is linked to the patient's inspiratory effort.^{9,11} This is not the case with PS, in which delayed opening or premature closing of exhalation valve is the rule.⁵ Indeed, we observed that in patients with large differences in breathing frequency, inspection of pressure-time and flow-time waveforms during PS revealed a pressure and flow pattern suggesting delayed opening of expiratory valve.⁵ It has been shown that this type of expiratory asynchrony has a powerful influence *via* a reflex pathway, on breath timing; neural expiratory time increases and respiratory rate decreases with increasing the time that mechanical inspiration extends into neural expiration (delayed opening of expiratory valve).²⁷⁻³⁰ This suggests but does not prove that expiratory asynchrony may contribute to some extent to the observed difference in breathing frequency between modes.

In our patients, V_D/V_T was markedly increased in accordance with previous studies showing that in patients with ALI/ARDS, increased dead space is the rule.^{19,20} Furthermore, despite the fact that, with PAV, V_T was slightly lower and breathing frequency was higher than these with PS, we observed that V_D/V_T did not differ between modes. Therefore, at least for short term, the effects of PAV and PS on dead space fraction were comparable.

In variance with our findings, Varelmann *et al.*¹⁵ and Delaere *et al.*²¹ reported in non-chronic obstructive pulmonary disease patients with acute respiratory failure that PAV and PS showed similar effects on breathing frequency and minute ventilation. In these studies, the assist level of PAV was either fixed (50% and 80%)²¹ or titrated to obtain a similar mean inspiratory airway pressure with PS.¹⁵ Notwithstanding the different assist titration criteria, the discrepancy between our study and those of Varelmann *et al.* and Delaere *et al.* may be explained by the population studied. Delaere *et al.* studied patients who were ready to be weaned from the ventilator, whereas in the study of Varelmann *et al.*, in several patients the oxygenation criterion for ALI/ARDS was not met and respiratory system mechanics were normal.^{15,21} Furthermore, some patients in the study of Varelmann *et al.* were examined late in the course of

their disease (> 4 weeks). On the other hand, we studied patients during the acute course of their illness who did not meet criteria for weaning and had severe disturbance of gas exchange and respiratory system mechanics.

In accord with recent studies, our study showed that the effects of PAV and PS on gas exchange and hemodynamics were clinically comparable.^{15,21} The observed difference in cardiac output and oxygen delivery, entirely due to stroke volume variation, was probably too small to be of clinical significance. This small increase did not affect the shunt-like effect, which remained virtually the same. Therefore, at similar mean airway pressure, both modes may equally support gas exchange in patients with ALI/ARDS in whom disturbance of oxygenation is the cardinal sign.

Several studies have shown that compared with PS, the variability of V_T with PAV is considerably higher.^{14,16,31} In the current study, the variability of V_T with both modes of support was approximately 10%, a value that is considerably lower than that reported previously, at least with PAV. We believe that this discrepancy may be explained by the population studied. In our study, a homogenous group of patients with ALI/ARDS due to sepsis was studied. As expected, this group of patients had severe restrictive respiratory system disease as indicated by the high values of respiratory system elastance. Studies have shown that both systemic inflammatory response syndrome—a prerequisite for sepsis definition—and restrictive lung disease are associated with decreased V_T variability.^{32,33}

Limitations of the Study

This investigation was a physiologic study, and caution should be exercised in applying our findings to everyday clinical practice. Only 12 patients were studied, PAV was applied for a limited time (30 min), and it is not known whether similar results would be obtained during an extended period of PAV. For example, in patients in whom PAV is associated with very low V_T (approximately 300 ml), a deterioration of oxygenation over time may be observed due to atelectasis formation.³⁴ Further studies are needed to resolve this issue.

Conclusions

Our study demonstrated that, in our patients with ALI/ARDS due to sepsis, PAV and PS titrated such as to obtain a similar mean airway pressure had comparable short-term effects on gas exchange and hemodynamics. PAV might be an alternative mode of assisted mechanical ventilation in such patients.

References

1. Abraham E, Matthay MA, Dinarello CA, Vincent JL, Cohen J, Opal SM, Glauser M, Parsons P, Fisher CJ Jr, Repine JE: Consensus conference definitions

for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: Time for a reevaluation. *Crit Care Med* 2000; 28:232-5

2. Artigas A, Bernard GR, Carlet J, Dreyfuss D, Gattinoni L, Hudson L, Lamy M, Marini JJ, Matthay MA, Pinsky MR, Spragg R, Suter PM: The American-European Consensus Conference on ARDS: II. Ventilatory, pharmacologic, supportive therapy, study design strategies and issues related to recovery and remodeling. *Intensive Care Med* 1998; 24:378-98

3. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R: The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149:818-24

4. Steinberg KP, Hudson LD: Acute lung injury and acute respiratory distress syndrome: The clinical syndrome. *Clin Chest Med* 2000; 21:401-17

5. Georgopoulos D, Prinianakis G, Kondili E: Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Med* 2006; 32:34-47

6. Putensen C, Hering R, Muders T, Wrigge H: Assisted breathing is better in acute respiratory failure. *Curr Opin Crit Care* 2005; 11:63-8

7. Putensen C, Zech S, Wrigge H, Zinserling J, Stuber F, Von Spiegel T, Mutz N: Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit Care Med* 2001; 164:43-9

8. Cereda M, Foti G, Marcora B, Gili M, Giacomini M, Sparacino ME, Pesenti A: Pressure support ventilation in patients with acute lung injury. *Crit Care Med* 2000; 28:1269-75

9. Younes M: Proportional assist ventilation, a new approach to ventilatory support: Theory. *Am Rev Respir Dis* 1992; 145:114-20

10. Younes M: Proportional Assists Ventilation. New York, McGraw-Hill, 1994, pp 349-67

11. Younes M, Puddy A, Roberts D, Light RB, Quesada A, Taylor K, Oppenheimer L, Cramp H: Proportional assist ventilation: Results of an initial clinical trial. *Am Rev Respir Dis* 1992; 145:121-9

12. Giannouli E, Webster K, Roberts D, Younes M: Response of ventilator-dependent patients to different levels of pressure support and proportional assist. *Am J Respir Crit Care Med* 1999; 159:1716-25

13. Wrigge H, Golisch W, Zinserling J, Sydow M, Almeling G, Burchardi H: Proportional assist *versus* pressure support ventilation: Effects on breathing pattern and respiratory work of patients with chronic obstructive pulmonary disease. *Intensive Care Med* 1999; 25:790-8

14. Wrigge H, Varelmann D, Zinserling J, Hering R, Kuhl R, Putensen C: Proportional assist ventilation combined with automatic tube compensation: A promising concept of augmented spontaneous breathing? [in German]. *Anaesthesist* 2003; 52:341-8

15. Varelmann D, Wrigge H, Zinserling J, Muders T, Hering R, Putensen C: Proportional assist *versus* pressure support ventilation in patients with acute respiratory failure: Cardiorespiratory responses to artificially increased ventilatory demand. *Crit Care Med* 2005; 33:1968-75

16. Marantz S, Patrick W, Webster K, Roberts D, Oppenheimer L, Younes M: Response of ventilator-dependent patients to different levels of proportional assist. *J Appl Physiol* 1996; 80:397-403

17. Koch S: The Critical Care Catalogue, Appendix, Critical Care, 2nd edition. Edited by Civetta JM, Taylor RW, Kirby RR. Philadelphia, Lippincott, 1992, pp 1925-44

18. Tobin M, Vav de Graaff WB: Monitoring of lung mechanics and work of breathing, Principles and Practice of Mechanical Ventilation. Edited by Tobin MJ. New York, McGraw-Hill, 1994, pp 967-1003

19. Kallet RH, Alonso JA, Pittet JF, Matthay MA: Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. *Respir Care* 2004; 49:1008-14

20. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, Matthay MA: Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002; 346:1281-6

21. Delaere S, Roeseler J, D'Hoore W, Matte P, Reynaert M, Joliet P, Sottiaux T, Liistro G: Respiratory muscle workload in intubated, spontaneously breathing patients without COPD: Pressure support *versus* proportional assist ventilation. *Intensive Care Med* 2003; 29:949-54

22. Gattinoni L, Marcolin R, Caspani ML, Fumagalli R, Mascheroni D, Pesenti A: Constant mean airway pressure with different patterns of positive pressure breathing during the adult respiratory distress syndrome. *Bull Eur Physiopathol Respir* 1985; 21:275-9

23. Pesenti A, Marcolin R, Prato P, Borelli M, Riboni A, Gattinoni L: Mean airway pressure *versus* positive end-expiratory pressure during mechanical ventilation. *Crit Care Med* 1985; 13:34-7

24. Marini JJ, Ravenscraft SA: Mean airway pressure: Physiologic determinants and clinical importance: II. Clinical implications. *Crit Care Med* 1992; 20:1604-16

25. Banner MJ, Kirby RR, Kirton OC, DeHaven CB, Blanch PB: Breathing frequency and pattern are poor predictors of work of breathing in patients receiving pressure support ventilation. *Chest* 1995; 108:1338-44

26. Mancebo J, Albaladejo P, Touchard D, Bak E, Subirana M, Lemaire F, Harf A, Brochard L: Airway occlusion pressure to titrate positive end-expiratory pressure in patients with dynamic hyperinflation. *ANESTHESIOLOGY* 2000; 93:81-90

27. Kondili E, Prinianakis G, Anastasaki M, Georgopoulos D: Acute effects of ventilator settings on respiratory motor output in patients with acute lung injury. *Intensive Care Med* 2001; 27:1147-57
28. Kondili E, Prinianakis G, Georgopoulos D: Patient-ventilator interaction. *Br J Anaesth* 2003; 91:106-19
29. Younes M, Kun J, Webster K, Roberts D: Response of ventilator-dependent patients to delayed opening of exhalation valve. *Am J Respir Crit Care Med* 2002; 166:21-30
30. Xirouhaki N, Kondili E, Mitrouska I, Sifakas N, Georgopoulos D: Response of respiratory motor output to varying pressure in mechanically ventilated patients. *Eur Respir J* 1999; 14:508-16
31. Fernandez-Vivas M, Caturla-Such J, Gonzalez de la Rosa J, Acosta-Escribano J, Alvarez-Sanchez B, Canovas-Robles J: Noninvasive pressure support *versus* proportional assist ventilation in acute respiratory failure. *Intensive Care Med* 2003; 29:1126-33
32. Bien MY, Hseu SS, Yien HW, Kuo BI, Lin YT, Wang JH, Kou YR: Breathing pattern variability: A weaning predictor in postoperative patients recovering from systemic inflammatory response syndrome. *Intensive Care Med* 2004; 30:241-7
33. Brack T, Jubran A, Tobin MJ: Dyspnea and decreased variability of breathing in patients with restrictive lung disease. *Am J Respir Crit Care Med* 2002; 165:1260-4
34. Richard JC, Maggiore SM, Jonson B, Mancebo J, Lemaire F, Brochard L: Influence of tidal volume on alveolar recruitment: Respective role of PEEP and a recruitment maneuver. *Am J Respir Crit Care Med* 2001; 163:1609-13