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Prospective Randomized Trial Comparing Pressure-Controlled Ventilation and Volume-Controlled Ventilation in ARDS*

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Study objectives: **To compare in-hospital mortality of patients with ARDS ventilated with either pressure-controlled ventilation (PCV) or volume-controlled ventilation (VCV) with a square-wave inspiratory flow.**
Design: **Multicenter and randomized trial.**
Setting: **Twelve medical-surgical ICUs located in tertiary-care hospitals.**
Patients: **Seventy-nine patients having ARDS, as defined by the American-European Consensus Conference.**
Interventions: **Patients were randomly assigned to be ventilated with either PCV (n = 37) or VCV (n = 42). In both instances, inspiratory plateau pressure was limited to ≤ 35 cm H_2O.**
Measurements and results: **There were no significant differences among the studied groups at the moment of randomization, although there was a trend toward greater renal failure in patients assigned to VCV. Ventilatory settings and blood gases did not significantly differ over time between the two groups. Patients in the VCV group had both a significantly higher in-hospital mortality rate than those in the PCV group (78% vs 51%, respectively) and a higher number of extrapulmonary organ failures (median, 4 vs 2, respectively). The development of renal failure during the study period was also significantly more frequent among VCV patients (64% vs 32%, respectively). Multivariate analysis showed that factors independently associated with an increased mortality rate were the presence of two or more extrapulmonary organ failures (odds ratio [OR], 4.61; 95% confidence interval [CI], 1.38 to 15.40) and acute renal failure (OR, 3.96; 95% CI, 1.10 to 14.28) but not the ventilatory mode used.**
Conclusions: **The increased number of extrapulmonary organ failures developed in patients of the VCV group was strongly associated with a higher mortality rate. The development of organ failures was probably not related to the ventilatory mode.** ***(CHEST 2000; 117:1690–1696)***

Key words: ARDS; mortality; pressure-controlled ventilation; volume-controlled ventilation

Abbreviations: CI = confidence interval; F_{IO_2} = fraction of inspired oxygen; I/E = ratio of inspiration to expiration; OR = odds ratio; PCV = pressure-controlled ventilation; PEEP = positive end-expiratory pressure; VCV = volume-controlled ventilation; V_T = tidal volume

ARDS is associated with mortality rates ranging from 40 to 70%.[1] Clinical management of respiratory failure in ARDS typically requires ventilatory assistance that is aimed at maintaining pulmonary function while the lung injury resolves. Mechanical ventilation, although life-sustaining, can be harmful to the diseased lung, especially when high ventilatory volumes and pressures that cause lung overdistension are used.[2,3] This observation led us to think that ventilatory strategies designed to avoid exposing the lung to high pressures or volumes might improve outcome. Consequently, it has been recommended

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that, under conditions in which lung overdistension is likely to occur, tidal volumes (VTs) and airway pressures should be limited, accepting the attendant increase in arterial carbon dioxide levels.[4] Theoretically, pressure-limited ventilation can be equally provided by either pressure-targeted modes that limit airway pressure to preset levels or by volume-cycled ventilation with tightly set pressure alarms and close monitoring of plateau pressure.

Pressure-controlled ventilation (PCV) is a time-cycled mode in which approximately square waves of pressure are applied and released by means of a decelerating flow.[5] The decelerating waveform results in a more laminar flow at the end of inspiration, resulting in a more even distribution of ventilation in patients who have markedly different resistance values from one region to the lung to another.[6,7] A number of studies have demonstrated an improvement in oxygenation and pulmonary mechanics in patients with ARDS who were switched from volume-controlled ventilation (VCV) to PCV.[8,9] For example, Davis et al[9] prospectively crossed-over 25 patients with acute lung injury from VCV with square flow waveform to PCV and observed that VCV with square flow was associated with significantly lower Pao_2 levels, higher inspiratory peak pressures, and lower mean airway pressures than PCV.

Many years ago in an editorial, Marini and Kelsen[10] emphasized the need for prospective controlled trials comparing PCV to conventional ventilation at fixed transalveolar pressures. Two years later, two prospective and randomized studies comparing PCV and VCV were published.[11,12] Lessard et al[11] compared, in nine patients with ARDS, PCV and VCV while keeping both the level of ventilation and end-expiratory alveolar pressure (*ie*, total positive end-expiratory pressure [PEEP]) constant, and no differences in respiratory mechanics, hemodynamics, or gas exchange parameters were observed. Rappaport et al[12] prospectively compared early application of PCV and VCV in 27 patients with acute hypoxic respiratory failure and found that PCV was associated with a more rapid increase in static compliance and fewer days of mechanical ventilation in patients who survived and were extubated.

No study has evaluated the effect of PCV on the morbidity and in-hospital mortality of ARDS patients. We undertook this study to determine whether hospital mortality of ARDS patients is influenced by the ventilatory mode used (PCV or VCV), when a strategy of mechanical ventilation limiting inspiratory pressure is implemented.

Materials and Methods

Patients

From February 1995 to January 1996, we enrolled patients at 12 ICUs in 12 tertiary-care hospitals. The study was approved by the institutional review board of each medical center, and informed consent was obtained from each patient or the patient's next of kin. The criteria for enrollment were as follows: (1) one or more underlying disease processes that are known to be associated with ARDS (sepsis, shock, pneumonia, multiple transfusions, pulmonary contusion, multiple fractures, gastric aspiration, acute pancreatitis, near-drowning, etc); and (2) diagnostic criteria for ARDS, as defined in the American-European Consensus Conference[13] (acute onset, bilateral chest radiographic infiltrates, pulmonary artery occlusion pressure $\leq$ 18 mm Hg or no evidence of left atrial hypertension, and Pao_2/fraction of inspired oxygen [Fio_2] ratio $\leq$ 200 mm Hg). Exclusion criteria were the following: age $<$ 18 years; pregnancy; head injury; coronary disease; enrollment in another interventional study; immunosuppression; burns; and the presence of any form of barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum, pneumopericardium, or subcutaneous emphysema).

Intervention

Patients were randomly assigned with the use of a random number table to receive either VCV or PCV. Patients were allocated to the two groups in a blinded fashion with the use of opaque, sealed, numbered envelopes, which were opened only when a patient fulfilled all of the inclusion criteria. Randomization was performed by permuted blocks according to the study center.

VCV was always delivered with a square-wave inspiratory flow. For both groups, plateau inspiratory pressure was limited to $\leq$ 35 cm H_2O. PEEP and Fio_2 were titrated to maintain an oxygen saturation of 89 to 92% with the least Fio_2 and a PEEP level never $<$ 5 cm H_2O. Respiratory rate, ratio of inspiration to expiration (I/E), and either VT in the VCV group or inspiratory pressure in the PCV group were adjusted in an attempt to maintain $Paco_2$ at 35 to 45 mm Hg, but hypercapnia was accepted if this target could not be achieved with a plateau pressure $<$ 36 cm H_2O. For both groups, adjustments of the I/E ratio were used at the discretion of the attending physician, with 3:1 being the maximal I/E ratio allowed.

For both groups, IV sodium bicarbonate infusions were permitted if the arterial pH was $<$ 7.20. If the pH remained $<$ 7.20 despite bicarbonate sodium infusion, the VT in the VCV group or the inspiratory pressure in the PCV group was increased until the pH reached $\geq$ 7.20. No study has specifically addressed the use of bicarbonate administration in acute respiratory acidosis. On the one hand, the CO_2 generated from the buffering of protons by exogenous bicarbonate cannot be promptly excreted in the presence of reduced alveolar ventilation, so hypercapnia may be exacerbated. On the other hand, acidosis can blunt the myocardial and vascular responsiveness to catecholamines. It was thought that maintaining arterial pH at $>$ 7.20 theoretically might minimize any adverse circulatory changes associated with respiratory acidosis in the studied patients.

Ventilatory data were recorded daily until successful extubation (defined as a period of $>$ 48 h without mechanical ventilation) or death. The following data were recorded each day: the best Pao_2/Fio_2 ratio, the highest $Paco_2$ level, the lowest arterial pH, the highest plateau pressure, the maximal I/E, the highest VT, the maximal respiratory rate, the appearance of any form of barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum, pneumopericardium, or subcutaneous emphysema), and the dose of sodium bicarbonate administered. Static compliance was measured once a day using a VT of 10 mL/kg body weight and an inspiratory pause of 1.5 s.

The development of multiple organ failure syndrome over the study period also was recorded. Organ failures were defined as follows: (1) renal failure, defined as a serum creatinine level

> 2.0 mg/dL or requirement for artificial renal support; (2) cardiovascular failure, defined as a pulmonary artery occlusion pressure of ≥ 18 mm Hg or a requirement for dopamine, dobutamine, or norepinephrine to maintain a mean arterial BP of > 60 mm Hg or a cardiac index of > 2.5 L/min/m^2; (3) hepatic failure, defined as a total bilirubin level of > 2.5 mg/dL and an elevation of transaminases or alkaline phosphatase to at least twice the upper limit of normal values; (4) coagulation failure, defined as a platelet count of < 60,000/mm^3 and an elevation of the partial thromboplastin time or the prothrombin to > 1.5 times the control value; (5) CNS failure, defined as a score on the Glasgow coma scale of < 10 in the absence of sedation; (6) GI failure, defined as upper digestive tract bleeding or ileus; and (7) metabolic failure, defined as an insulin requirement of > 5 U/h.

Outcome Measures

The primary outcome was the in-hospital mortality rate. Secondary outcomes included the following: (1) in-ICU mortality rate; (2) the length of stay in the ICU and in the hospital; (3) the appearance of any form of barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum, pneumopericardium, or subcutaneous emphysema); and (4) the number of organ failures.

Statistical Analysis

Data are presented as mean and SD. An intention-to-treat analysis was used. A χ^2 test or Fisher's Exact Test was used for comparisons of categorical variables. Continuous variables were compared with a Mann-Whitney *U* test. Kaplan-Meier survival curves were compared using the log-rank test. A p value of < 0.05 was considered to indicate statistical significance.

Results

Seventy-nine patients with ARDS were enrolled in the study, 42 in the VCV group and 37 in the PCV group. There were no significant differences between the studied groups regarding clinical characteristics and risk factors for ARDS at the moment of randomization (Tables 1, 2), although a trend toward a higher rate of acute renal failure was observed in patients of the VCV group (Table 1), and there was also a tendency toward a higher percentage of patients with shock as a risk factor for ARDS in the VCV group than in the PCV group (52% vs 38%, respectively; p = 0.19). The values of ventilatory parameters on days 1, 4, 7, 14, and 21 are presented in Table 3, and those of parameters for arterial blood gases are presented in Table 4. As expected by the study design, ventilatory settings did not differ significantly over time between the two groups. Oxygenation was not different over the study period in patients ventilated with PCV as compared with patients ventilated with VCV.

The main outcomes are summarized in Table 5. Patients in the VCV group had significantly higher in-hospital mortality rates than patients in the PCV group (78% vs 51%, respectively; 95% confidence interval [CI] for the difference between the groups, 4.3 to 50.1%). Survival curves for both groups are shown in Figure 1. Most fatalities resulted from multiple organ failure or shock (PCV group, 68%; VCV group, 71%), but four patients in the PCV group and five patients in the VCV group died from intractable respiratory failure.

There were no significant differences between the two groups for the incidence of barotrauma, the duration of mechanical ventilation, the length of stay in the ICU, or the length of stay in the hospital (Table 5). However, the number of organ failures was significantly higher in patients of the VCV group.

We identified the variables predicting mortality in the univariate analysis, and, thereafter, stepwise

Table 1—*Baseline Demographic and Clinical Characteristics of the Study Groups

Characteristics	VCV (n = 42)	PCV (n = 37)	p Value
Age, yr	59 ± 16	56 ± 17	0.48
Female	12 (29)	13 (35)	0.70
SAPS II score on admission	42 ± 17	39 ± 14	0.71
Duration of mechanical ventilation before entry, d	3 ± 3	4 ± 4	0.30
Lung injury score	2.9 ± 0.5	2.8 ± 0.6	0.46
Pao_2/Fio_2	131 ± 48	126 ± 47	0.63
Static compliance, mL/cm H_2O	30 ± 10	31 ± 14	0.72
Patients without organ failures	6 (14)	7 (19)	0.58
Extrapulmonary organ failures, No.	2.4 ± 1.2	2.1 ± 1.2	0.38
Cardiovascular failure	31 (74)	23 (62)	0.38
Renal failure	12 (28)	5 (13)	0.06
Liver failure	8 (19)	9 (24)	0.77
Coagulation failure	13 (31)	10 (27)	0.89
Digestive failure	11 (26)	10 (27)	0.86
Metabolic failure	3 (7)	2 (5)	0.34
CNS failure	7 (17)	5 (13)	0.23

*Values given as mean ± SD or No. of patients (%), unless otherwise indicated. SAPS = simplified acute physiology score.

Table 2—*Distribution of Risk Factors for ARDS

Risk Factors	VCV (n = 42)	PCV (n = 37)
Sepsis	23	19
Shock	22	14
Pneumonia	18	17
Multiple transfusions	4	3
Pulmonary contusion	—	3
Multiple fractures	3	5
Gastric aspiration	4	4
Acute pancreatitis	4	4
Near-drowning	1	1
Other	2	—

*Values given as No. of patients.

Table 3—*Ventilatory Parameters During the Study Period

Parameters	Day 1		Day 4		Day 7		Day 14		Day 21	
	VCV	PCV	VCV	PCV	VCV	PCV	VCV	PCV	VCV	PCV
Plateau pressure, cm H_2O	32 (5)	33 (6)	32 (6)	33 (7)	34 (7)	34 (8)	32 (7)	36 (9)	33 (11)	31 (5)
Vt, mL/kg	8.3 (2.5)	8.0 (1.9)	8.3 (2.4)	8.2 (2.6)	8.3 (2.6)	8.1 (2.4)	7.8 (2.3)	7.2 (2.2)	8.1 (2.3)	7.8 (3.1)
Respiratory rate, breaths/min	19 (6)	19 (4)	20 (6)	19 (4)	20 (6)	19 (5)	22 (7)	20 (84)	20 (6)	20 (6)
FIO_2, %	0.79 (0.21)	0.73 (0.21)	.73 (0.21)	0.75 (0.23)	0.70 (0.23)	0.66 (0.22)	0.73 (0.24)	0.70 (0.24)	0.57 (0.20)	0.50 (0.07)
Total PEEP, cm H_2O	12 (4)	11 (4)	11 (4)	11 (4)	12 (5)	10 (4)	11 (4)	12 (6)	8 (3)	7 (3)
Tinsp/Ttot, %	0.68† (0.33)	0.87 (0.45)	0.74 (0.40)	0.81 (0.42)	0.81 (0.55)	.81 (0.50)	0.88 (0.66)	0.78 (0.51)	0.81 (0.73)	0.60 (0.22)

*Values given as mean (SD). Tinsp/Ttot = ratio of inspiratory time to total respiratory time.
†$p < 0.05$.

multiple logistic regression analysis was performed to estimate the independent effect of each variable on mortality after controlling for the other variables. The variables associated with a significantly higher mortality rates in the univariate analysis were the following: age, ≥ 65 years (odds ratio [OR], 1.57; 95% CI, 1.13 to 2.17); simplified acute physiology II score on admission, ≥ 40 (OR, 1.63; 95% CI, 1.15 to 2.32); number of extrapulmonary organ failures, ≥ 2 (OR, 2.31; 95% CI, 1.38 to 3.85); acute renal failure (OR, 2.01; 95% CI, 1.38 to 2.92); cardiovascular failure (OR, 1.76; 95% CI, 0.98 to 3.17); coagulation failure (OR, 1.36; 95% CI, 0.99 to 1.86); and VCV (OR, 1.53; 95% CI, 1.08 to 2.17). Only the following two factors were independently associated with an increased mortality rate: the presence of two or more extrapulmonary organ failures over the study period (OR, 4.61; 95% CI, 1.38 to 15.40); and acute renal failure (OR, 3.96; 95% CI, 1.10 to 14.28).

Discussion

The main finding of this study was that, in patients with ARDS who require mechanical ventilation, the way in which mechanical ventilation is provided to deliberately reduce the inspiratory plateau pressure, by decreasing either Vt on VCV or inspiratory pressure on PCV, does not independently influence mortality. We also have found that the mortality of ARDS patients is strongly associated with the development of multiple organ failure, with especially those patients with acute renal failure having a very poor prognosis.

Although the survival rate of ARDS patients may have improved,[14] it still remains at a level of 50% and mainly depends on the severity of the underlying disease and the accompanying organ dysfunction.[1,15–18] In-hospital mortality rates in our patients of the VCV group seem to be extremely high despite studies that have reported similar rates. For example, the study by Amato et al[19] showed a mortality rate of 71% in the conventional ventilation group, and the study by Brochard et al[20] showed a mortality rate around 70% in patients in the pressure-limitation group who developed secondary multiple organ failure. The increased mortality rate in patients of the VCV group as compared with patients of the PCV group was explained as being the result of both the number of extrapulmonary organ failures and the incidence of acute renal failure, the values for which were significantly higher in those VCV patients.

There are a number of possible explanations for the increased incidence of multiple organ failure

Table 4—*Arterial Blood Gases and Compliance During the Study Period

Characteristics	Day 1		Day 4		Day 7		Day 14		Day 21	
	VCV	PCV	VCV	PCV	VCV	PCV	VCV	PCV	VCV	PCV
PaO_2/FIO_2, mm Hg	128 (45)	147 (59)	141 (65)	137 (53)	150 (67)	163 (93)	183 (79)	146 (53)	202 (100)	217 (65)
$PaCO_2$, mm Hg	51 (15)	52 (16)	52 (14)	49 (10)	54 (13)	51 (16)	50 (16)	58 (23)	56 (16)	53 (18)
Arterial pH	7.31 (0.10)	7.31 (0.11)	7.34 (0.10)	7.36 (0.09)	7.35 (0.10)	7.36 (0.10)	7.36 (0.10)	7.35 (0.06)	7.35 (0.09)	7.41 (0.05)
Compliance, mL/cm H_2O	29 (9)	31 (13)	30 (11)	32 (14)	28 (11)	35 (15)	31 (13)	28 (11)	28 (12)	28 (12)

*Values given as mean (SD).

Table 5—*Main Outcomes

Outcomes	VCV (n = 42)	PCV (n = 37)	p Value
In-ICU mortality	29 (69)	18 (49)	0.11
In-hospital mortality	33 (78)	19 (51)	0.02
Barotrauma	4 (9)	6 (16)	0.18
ICU length of stay, d	25 ± 19	21 ± 15	0.46
Hospital length of stay, d	30 ± 24	27 ± 20	0.84
Extrapulmonary organ failures, No.	3.7 ± 1.8	2.6 ± 1.5	0.005
Cardiovascular failure	33 (78)	25 (67)	0.39
Renal failure	27 (64)	12 (32)	0.009
Liver failure	18 (43)	9 (24)	0.13
Coagulation failure	22 (52)	12 (32)	0.12
Digestive failure	16 (38)	11 (30)	0.59
Metabolic failure	7 (17)	4 (16)	0.20
CNS failure	7 (17)	6 (16)	0.24

*Values given as mean ± SD or No. of patients (%), unless otherwise indicated.

syndrome and acute renal failure in the VCV group. First, it is quite likely that patients at risk for renal dysfunction were mainly distributed in the VCV group. Whenever a randomized study is performed, it is reasonable to assume that the randomization process equally distributes risk factors for morbidity and mortality among patients of the studied groups. However, this did not completely work out in our study since a trend toward a higher percentage of patients with either acute renal failure or with shock as a risk factor for ARDS was observed at enrollment in the VCV group. On the other hand, the increase in the relative risk for acute renal failure among patients in the VCV group as compared with those in the PCV group was similar before and after the exposure to VCV (relative risk at the moment of randomization, 112%; and relative risk after entry into the study, 128%). Second, CO_2 has known vasoactive properties that might impair renal blood flow leading to renal failure,[21] but $PaCO_2$ values did not differ significantly over time between the two study groups. Third, VCV caused the impairment of renal function by initiating a systemic inflammatory response. Mechanical ventilation has been shown to have significant effects on the levels of inflammatory cells and soluble mediators in the lung and might play a pivotal role in the pathogenesis of the systemic inflammatory response that leads to multiple organ failure syndrome.[22,23] The hypothesis that VCV induced a more severe systemic inflammatory response than PCV seems as appealing as it is unlikely since the ventilatory strategy used for patients of the VCV group was equally injurious, in terms of end-inspiratory volume and pressure, as that used for patients of the PCV group. The only difference between the two studied ventilatory modes was the inspiratory flow waveform profile, and, at the moment, we are unaware of any study showing that the inspiratory flow waveform profile is a major determinant of ventilator-induced lung injury. Finally, the fact that prospective studies comparing conventional ventilatory strategies with a less injurious ("protective") strategy have reported similar numbers of organ failures in the study groups,[20,24] leads us to think that there is not a causal effect between the way in which mechanical ventilation is delivered and the development of multiple organ failure syndrome.

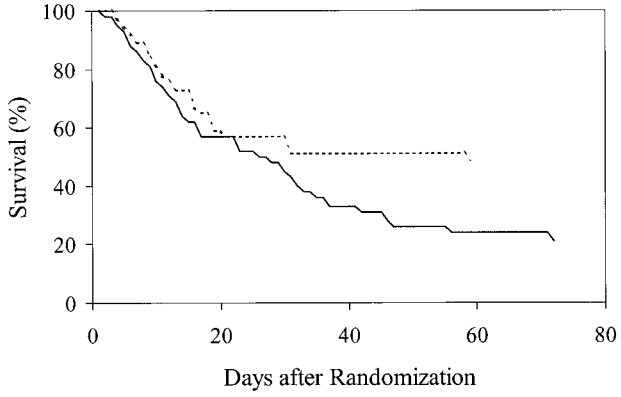

FIGURE 1. The Kaplan-Meier curves of the probability of survival over time between patients in the PCV group (dashed line) and patients in the VCV group (solid line). p = 0.19 for the log-rank test.

Respiratory failure directly accounts for < 20% of deaths in patients with ARDS in several studies.[15,25–27] We have found similar results and have also showed that refractory hypoxemia is as frequent in patients ventilated with PCV as in those ventilated with VCV. Davis et al[9] reported more improved oxygenation with PCV than with VCV when V_T, inspiratory time, and PEEP were held constant and that this finding was thought to be due to an increase in mean airway pressure. However, other authors have demonstrated that oxygenation does not improve, or even deteriorates slightly, when PCV has been compared with VCV, despite a higher mean airway pressure with PCV.[11,28] Our data agree with those of Lessard et al[11] and Mancebo et al[28] that relatively minor differences in gas-exchange efficiency are expected between different patterns of ventilation when peak and mean alveolar pressures are matched at a similar level of minute ventilation and when sufficient end-expiratory alveolar pressures are used.

Since multiple organ failure syndrome remains the primary cause of death in ARDS patients, the pre-

vention of that condition should be a first priority in improving outcome. Randomized studies have demonstrated that ventilatory strategies aimed at avoiding alveolar overdistension by limiting peak alveolar pressure do not have a beneficial effect on the mortality rates of ARDS patients.[20,23] The lack of efficacy of the PCV and VCV strategies on the mortality rates of ARDS patients might be regarded as reasonable by taking into account that a decrease in the number of organ failures could not be achieved in patients of the limited ventilation group as compared with patients of the conventional ventilation group.

Decreasing the mortality rates of ARDS patients will be feasible only by limiting both the inflammatory response and the development of multiple organ failure syndrome. Therefore, further studies are needed to clarify the role of mechanical ventilation in the initiation and propagation of the systemic inflammatory response before new ventilatory strategies aimed at reduce ventilator-induced lung injury are tested in clinical trials.

Appendix

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References

1 Kraft P, Fridrich P, Pernerstorfer T, et al. The acute respiratory distress syndrome: definitions, severity and clinical investigations. Intensive Care Med 1996; 22:519–529
2 Dreyfuss D, Saumon G. Ventilator-induced lung injury. In: Tobin MJ, ed. Principles and practice of mechanical ventilation. New York, NY: McGraw Hill, 1994; 793–811
3 Parker JC, Hernandez LA, Peevy KJ. Mechanisms of ventilator-induced lung injury. Crit Care Med 1993; 21:131–143
4 Slutsky AS. Mechanical ventilation: American College of Chest Physicians' Consensus Conference. Chest 1993; 104: 1833–1859
5 Marini JJ. Pressure-controlled ventilation. In: Tobin MJ, ed. Principles and practice of mechanical ventilation. New York, NY: McGraw-Hill, 1994; 305–318
6 Al-Sady N, Bennett ED. Decelerating inspiratory flow waveform improves lung mechanics and gas exchange in patients on intermittent positive-pressure ventilation. Intensive Care Med 1985; 11:68–75
7 Tharrat RS, Allen RP, Albertson TE. Pressure controlled inverse ratio ventilation in severe adult respiratory failure. Chest 1998; 94:755–762
8 Armstrong BW, MacIntyre NR. Pressure-controlled inverse ratio ventilation that avoids air trapping in the adult respiratory distress syndrome. Crit Care Med 1995; 23:279–285
9 Davis K Jr, Branson RD, Campbell RS, et al. Comparison of volume control and pressure control ventilation: is flow waveform the difference? J Trauma 1996; 41:808–814
10 Marini JJ, Kelsen SG. Re-targeting ventilatory objectives in adult respiratory distress syndrome: new treatment prospects-persistent question. Am Rev Respir Dis 1992; 146:2–3
11 Lessard MR, Guérot E, Lorino H, et al. Effects of pressure-controlled with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. Anesthesiology 1994; 80:972–975
12 Rappaport SH, Shpiner R, Yoshihara G, et al. Randomized, prospective trial of pressure-limited versus volume-controlled ventilation in severe respiratory failure. Crit Care Med 1994; 22:22–32
13 Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149:818–824
14 Milberg JA, Davis DR, Steinberg KP, et al. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. JAMA 1995; 273:306–309
15 Montgomery AB, Stager MA, Carrico CJ, et al. Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985; 132:485–489
16 Sloane PJ, Gee MH, Gottlied JE, et al. A multicenter registry of patients with acute respiratory distress syndrome: physiology and outcome. Am Rev Respir Dis 1992; 146:419–426
17 Bone RC, Balk R, Slotman G, et al. Adult respiratory distress syndrome: sequence and importance of development of multiple organ failure. Chest 1992; 101:320–326
18 Doyle RL, Szaflarski N, Modin GW, et al. Identification of patients with acute lung injury: predictors of mortality. Am J Respir Crit Care Med 1995; 152:1818–1824
19 Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347–354
20 Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. Am J Respir Crit Care Med 1998; 158:1831–1838
21 Bersentes TJ, Simmons DH. Effects of acute acidosis on renal hemodynamics. Am J Physiol 1967; 212:633–640
22 Slutsky AS, Tremblay LN. Multiple system organ failure: is mechanical ventilation a contributory factor? Am J Respir Crit Care Med 1998; 157:1721–1725
23 Ranieri VM, Suetr PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 1999; 282:54–61
24 Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high

risk for acute respiratory distress syndrome. N Engl J Med 1998; 338:355–361
25 Ferring M, Vincent JL. Is outcome from ARDS related to the severity of respiratory failure? Eur Respir J 1997; 10:1297–1300
26 Hudson LD, Milberg JA, Anardi D, et al. Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995; 151:293–301
27 Wang BM, Steinberg KP, Hudson LD. Causes of mortality in patients with the acute respiratory distress syndrome (ARDS): 1981–1994 [abstract]. Am J Respir Crit Care Med 1996; 153(suppl):A593
28 Mancebo J, Vallverdú I, Bak E, et al. Volume-controlled ventilation and pressure-controlled inverse ratio ventilation: a comparison of their effects in ARDS patients. Monaldi Arch Chest Dis 1994; 49:201–207