

# The New England Journal of Medicine

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VOLUME 338

FEBRUARY 5, 1998

NUMBER 6



## THE RELATION OF PNEUMOTHORAX AND OTHER AIR LEAKS TO MORTALITY IN THE ACUTE RESPIRATORY DISTRESS SYNDROME

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### ABSTRACT

**Background** In patients with the acute respiratory distress syndrome, pneumothorax and other air leaks — any extrusion of air outside the tracheobronchial tree — have been attributed to high ventilatory pressures or volumes and linked to increased mortality.

**Methods** We analyzed data from a prospective trial of aerosolized synthetic surfactant in 725 patients with the acute respiratory distress syndrome induced by sepsis. We compared the ventilatory pressures and volumes in the patients without any air leaks (the highest values during the five-day study) with the pressures and volumes in those with pneumothorax or with any air leaks (the highest values during the 16- and 24-hour periods before the complication developed).

**Results** Fifty patients (6.9 percent) had pneumothorax, and 77 (10.6 percent) had pneumothorax or other air leaks. There were no significant differences between patients with air leaks and those without air leaks in any pressure or volume examined. Overall mortality at 30 days was 40.0 percent (95 percent confidence interval, 36.4 to 43.6); among the patients with pneumothorax, it was 46.0 percent (95 percent confidence interval, 32.2 to 59.8), and among those without pneumothorax, it was 39.3 percent (95 percent confidence interval, 35.6 to 43.0;  $P=0.35$ ). The mortality rate was 45.5 percent (95 percent confidence interval, 34.4 to 56.6) in the group with any air leaks and 39.0 percent (95 percent confidence interval, 35.3 to 42.8) in the group without air leaks ( $P=0.28$ ).

**Conclusions** In patients with sepsis-induced acute respiratory distress syndrome who were receiving mechanical ventilation with conventional pressures and volumes, there were no significant correlations between high ventilatory pressures or volumes and the development of pneumothorax or other air leaks. Pneumothorax or other air leaks were not associated with a significantly increased mortality rate. (*N Engl J Med* 1998;338:341-6.)

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OVER the past 20 years, laboratory investigations have led to the belief that high ventilatory pressures result in barotrauma, or more appropriately, air leaks. Air leaks are defined as any extrusion of air outside the tracheobronchial tree, including pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial edema, and subcutaneous emphysema. Air leaks have been associated with acute lung injury and increased mortality in animal models of the acute respiratory distress syndrome.<sup>1-6</sup> These findings have been linked with computed tomographic (CT) evidence that the acute respiratory distress syndrome has a nonuniform distribution throughout the lungs.<sup>7,8</sup> The CT findings and concomitant physiologic studies have led to the postulate that in patients with the acute respiratory distress syndrome, there is a diseased area of the lung that does not take part in ventilation and a normal area that does. The normal area, estimated to be about one third of the normal lung and dubbed the “baby lung,” is thought to be severely damaged by high pressures.<sup>7,8</sup> More recently, air leaks and acute lung injury have been attributed to high ventilatory volumes, or “volutrauma.”<sup>9,10</sup>

In uncontrolled clinical trials of extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal, and new ventilatory modes that limit pressures in patients with the acute respiratory distress syndrome, there have been remarkable reduc-

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tions in the mortality rate — down to about 40 percent, as compared with 90 percent among historical controls.<sup>11-14</sup> Extracorporeal membrane oxygenation did not improve survival in two controlled trials: one with a 90 percent mortality rate and the other with a 38 percent mortality rate.<sup>11,15</sup> The “open lung” ventilatory approach, which uses very low tidal volumes (<6 ml per kilogram of body weight), permissive hypercapnia (usually requiring sodium bicarbonate to moderate pH), and positive end-expiratory pressure to prevent alveolar collapse, has become very popular because of the reportedly low associated mortality rate. One study reported a mortality rate of 33 percent (5 deaths among 15 patients); however, the rate among patients receiving conventional mechanical ventilation was similar (54 percent [7 deaths among 13 patients],  $P = 0.45$ ).<sup>16</sup>

To determine whether pneumothorax or other air leaks are caused by high ventilatory pressures or volumes or are associated with an increased mortality rate at 30 days, we analyzed the data from a prospective, multinational trial of aerosolized synthetic surfactant in 725 patients with sepsis-induced acute respiratory distress syndrome.<sup>17</sup>

## METHODS

Patients with the acute respiratory distress syndrome for 48 hours or less and sepsis or the sepsis syndrome for 96 hours or less were randomly assigned to receive aerosolized surfactant or placebo (0.45 percent saline) continuously for up to five days. The acute respiratory distress syndrome was defined as evidence of diffuse infiltrates on chest radiographs, a ratio of arterial oxygen tension to the fraction of inspired oxygen ( $\text{PaO}_2:\text{FiO}_2$ ) of less than 250 (indicating hypoxemia), and no evidence of left ventricular failure. Patients were enrolled in the study between March 1992 and September 1993. At the time of enrollment, the mean ( $\pm$ SD) age was  $51 \pm 17$  years, the Acute Physiology and Chronic Health Evaluation (APACHE) III score was  $70.5 \pm 25$ , the mean arterial pressure was  $82 \pm 15$  mm Hg, the alveolar-arterial oxygen gradient was  $333.5 \pm 136$  mm Hg, the  $\text{PaO}_2:\text{FiO}_2$  was  $142.5 \pm 73$ , and the fraction of inspired oxygen was  $0.66 \pm 0.19$ .<sup>17</sup> We combined the group of patients receiving synthetic surfactant (Exosurf) and the placebo group, since there were no differences between the groups in mortality at 30 days, demographic characteristics, underlying diseases, number of positive blood cultures, ventilatory mode, positive end-expiratory pressure, arterial oxygen tension, alveolar-arterial oxygen gradient, fraction of inspired oxygen,  $\text{PaO}_2:\text{FiO}_2$ , arterial carbon dioxide tension, pneumothorax or other air leaks, APACHE III score, reason for admission to the intensive care unit, findings on chest radiography, or duration of ventilation.<sup>17</sup>

The mortality rate at 30 days was recorded. Pneumothorax and other air leaks were identified on chest radiographs obtained at least at base line, on days 1 and 3, and within 24 hours of the end of the study but usually daily and for clinical indications. The following measurements were performed every eight hours from the initiation of the study for five days or until discontinuation of aerosolized surfactant or placebo, discontinuation of mechanical ventilation, or death: external positive end-expiratory pressure, peak inspiratory pressure, mean airway pressure, tidal volume, tidal volume per kilogram, minute ventilation, and minute ventilation per kilogram. Plateau pressure was not recorded.

If, as some investigators have postulated, high pressures or volumes cause pneumothorax or other air leaks, then the patients without pneumothorax or other air leaks initially were at risk for

them whenever there were high pressures or volumes during the study period. When pneumothorax or other air leaks develop, the highest pressures or volumes just before their development are most likely to be the cause. Therefore, we compared the highest pressures and volumes at any time during the study in patients without pneumothorax or other air leaks with the highest pressures and volumes in the 16-hour and 24-hour periods before the event in those with pneumothorax or air leaks of any type. Since the data for the two periods did not differ significantly, only the 16-hour data are presented.

Two-tailed Student's *t*-tests were used to compare the mean values for continuous variables in the patients without air leaks, those with any air leaks, and those with pneumothorax.<sup>18</sup> The chi-square test was used to compare distributions of binary variables. Frequency distributions were determined for positive end-expiratory pressure, peak inspiratory pressure, mean airway pressure, tidal volume, tidal volume per kilogram, minute ventilation, and minute ventilation per kilogram in the three groups of patients.<sup>18</sup> Kolmogorov-Smirnov tests for the equality of these distributions were also performed.<sup>19</sup> We developed logistic-regression models and included only patients with complete data for all the measured pressures and volumes to determine whether any of the variables predicted the development of pneumothorax or other air leaks.<sup>20</sup> We used the chi-square statistic to compare the mortality rate at 30 days in the three groups of patients.<sup>18</sup> We determined the statistical power of the analysis of mortality in the three groups. With an alpha error of 5 percent (two-sided), the power was 80 percent.<sup>21</sup> Complete data on individual variables were available for 95.8 percent of the patients, and complete data on variables calculated from two individual values were available for 89.3 percent of the patients. The missing data were unlikely to substantially affect the results.

The initial study was approved by the institutional review board at each participating institution. Written informed consent was obtained from all patients or their legal guardians or next of kin.

## RESULTS

Base-line demographic and clinical characteristics are shown in Table 1. The mean time to the development of pneumothorax was  $53 \pm 37$  hours. Pneumothorax and other air leaks were more common in younger patients, women, patients with lower body weight, and those with lower serum albumin levels. Air leaks other than pneumothorax were more common in patients with higher initial fractions of inspired oxygen. The duration of mechanical ventilation during the study period was  $104.3 \pm 31.2$  hours overall,  $104.0 \pm 31.6$  hours in patients without air leaks,  $106.6 \pm 29$  hours in those with any air leaks, and  $110.2 \pm 21.6$  hours in those with pneumothorax. The overall mean ventilatory values were as follows: positive end-expiratory pressure,  $11.6 \pm 4.9$  cm of water; peak inspiratory pressure,  $45.9 \pm 11.7$  cm of water; mean airway pressure,  $23.8 \pm 0.7$  cm of water; tidal volume, 829.6 ml; tidal volume per kilogram,  $11.4 \pm 3.4$  ml; minute ventilation,  $13.2 \pm 4.9$  liters per minute; and minute ventilation per kilogram,  $0.18 \pm 0.08$  liter per minute.

Pneumothorax developed in 50 patients (6.9 percent; 95 percent confidence interval, 5.1 to 8.7), and air leaks of any type developed in 77 (10.6 percent; 95 percent confidence interval, 8.4 to 12.8). There were no significant differences in any pressures or volumes among the three groups of patients (Table 2).

Analysis of frequency distributions of pressures and volumes showed that there were no values below which pneumothorax or air leaks of any type never occurred or above which they always occurred. In the group of 17 patients with positive end-expiratory pressures of 0 to 4 cm of water, 1 (5.9 percent) had pneumothorax, and in the group of 40 patients with positive end-expiratory pressures of 20 to 50 cm of water, 3 (7.5 percent) had pneumothorax. The incidence of pneumothorax in patients with positive end-expiratory pressures below values used in the "open lung" strategy was 5.0 percent (9 of 180 patients). This finding is similar to that for the most common range of values for conventional positive end-expiratory pressure, 10 to 14 cm of water; pneumothorax developed in 22 of 333 patients (6.6 percent) with values in this range. The results were similar for the other pressures and all the volumes. Kolmogorov-Smirnov tests showed no differences in the distributions of pressures and volumes among the patients without air leaks, those with any air leaks, and those with pneumothorax, except that the patients with pneumothorax had lower values for minute ventilation than the other two groups (P=0.05).

Logistic-regression models of the association between pneumothorax or any air leaks and various combinations of pressures and volumes (Table 2) showed no significant interaction effects. In one model, higher values for positive end-expiratory pressure and respiratory rate were predictive of pneumothorax (P=0.02), but the maximal combination of sensitivity and specificity was only 67.8 percent and 34.7 percent, respectively.

The overall mortality rate at 30 days was 40.0 percent (95 percent confidence interval, 36.4 to 43.6). Thirty-five of the 77 patients with air leaks died (45.5

**TABLE 1.** BASE-LINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE 725 PATIENTS ACCORDING TO THE PRESENCE OR ABSENCE OF AIR LEAKS.\*

CHARACTERISTIC	NO AIR LEAK	AIR LEAK	
		ANY LEAK	PNEUMOTHORAX
Sex — no. (%)			
Male	388 (91.5)	36 (8.5)	20 (4.7)
Female	260 (86.4)	41 (13.6)†	30 (10.0)‡
Race — no. (%)			
Black	100 (90.1)	11 (9.9)	8 (7.2)
White	469 (89.7)	54 (10.3)	35 (6.7)
Other	79 (86.8)	12 (13.2)	7 (7.7)
Age — yr	52.1±17.1	45.1±16.6§	43.2±16.2§
APACHE III score	73.1±25.4	72.2±25.2	68.9±23
Arterial pressure — mm Hg	81.5±14.8	82.8±14.5	83.5±13.6
PaO <sub>2</sub> :FiO <sub>2</sub>	110.6±60.1	98.4±56.7	103.3±57.4
PaO <sub>2</sub> — mm Hg	80.9±48.7	79.3±50.9	80.8±53.6
PaCO <sub>2</sub> — mm Hg	38.6±8	38.6±8.1	38.9±8
pH	7.39±0.1	7.4±0.1	7.41±0.8
FiO <sub>2</sub> — %	77.9±21.6	83.9±19.9	81.3±21.4
Serum albumin — g/dl	2.4±0.4	2.2±0.5¶	2.1±0.4§
Weight — kg	75.8±20.5	71.6±18.7	70.2±18.6
Smoking history — pack-years	32.7±22.8	29.0±22.5	30.1±23.8
Artificial surfactant — no. (%)			
Yes	324 (89.0)	40 (11.0)	27 (7.4)
No	324 (89.8)	37 (10.2)	23 (6.4)

\*Plus-minus values are means ±SD. All P values are for the comparison with the patients without air leaks. APACHE denotes Acute Physiology and Chronic Health Evaluation, PaO<sub>2</sub> arterial oxygen tension, FiO<sub>2</sub> the fraction of inspired oxygen, and PaCO<sub>2</sub> arterial carbon dioxide tension.

†P=0.03 by the chi-square test.

‡P=0.006 by the chi-square test.

§P<0.001 by Student's t-test.

¶P=0.003 by Student's t-test.

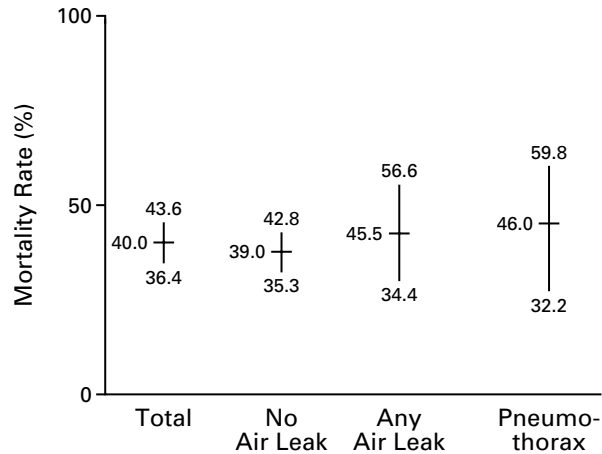
||P=0.05 by Student's t-test.

**TABLE 2.** VENTILATORY PRESSURES AND VOLUMES ACCORDING TO THE PRESENCE OR ABSENCE OF AIR LEAKS.\*

VENTILATORY PRESSURE OR VOLUME	NO AIR LEAK		ANY AIR LEAK		P VALUE†	PNEUMOTHORAX		P VALUE†
	NO. OF PATIENTS	VALUE	NO. OF PATIENTS	VALUE		NO. OF PATIENTS	VALUE	
Pressure (cm of water)								
Positive end-expiratory pressure	644	11.5±4.9	76	12.6±5.3	0.09	49	12.8±5.2	0.09
Peak inspiratory pressure	641	45.8±11.7	75	46.6±12.2	0.58	47	47.3±11.8	0.38
Mean airway pressure	646	23.8±8.7	77	24.0±8.3	0.85	50	24.2±8.7	0.76
Volume								
Tidal volume (ml)	621	832±242	67	783±224	0.10	43	793±256	0.34
Tidal volume/kg (ml)	590	11.4±3	42	11.7±3.3	0.54	42	11.7±3.3	0.54
Minute ventilation (liters/min)	620	13.3±4.9	43	12.2±4.9	0.17	43	12.2±4.9	0.17
Minute ventilation/kg (ml/min)	589	184.2±77	42	184.2±74	1.0	42	184.2±74	1.0

\*Plus-minus values are means ±SD.

†The P value is for the comparison with the patients who had no air leaks.



**Figure 1.** Mortality Rate at 30 Days among 725 Patients with the Acute Respiratory Distress Syndrome, According to the Presence or Absence of Air Leaks.

There were no significant differences among the 648 patients with no air leaks, the 77 patients with any air leaks, and the 50 patients with pneumothorax. The vertical bars denote 95 percent confidence intervals.

percent; 95 percent confidence interval, 34.4 to 56.6), and 253 of the 648 patients without air leaks died (39.0 percent; 95 percent confidence interval, 35.3 to 42.8;  $P=0.28$  by the chi-square test) (Fig. 1). Twenty-three of the 50 patients with pneumothorax died (46.0 percent; 95 percent confidence interval, 32.2 to 59.8), and 265 of the 675 without pneumothorax died (39.3 percent; 95 percent confidence interval, 35.6 to 43.0;  $P=0.35$ ).

## DISCUSSION

In this large series of patients with sepsis-induced acute respiratory distress syndrome, the development of pneumothorax or air leaks of any type was not related to the use of conventional ventilatory pressures and volumes, and pneumothorax or air leaks of any type did not cause an increase in mortality. Our data cast substantial doubt on the view that high ventilatory pressures and volumes are harmful in such patients. This belief has led to a plethora of new ventilatory strategies, the use of increasingly complex and expensive ventilators, iatrogenic acid-base derangements, and widespread use of prolonged muscle paralysis with its attendant increase in morbidity. Such strategies should now be reassessed.

The term "diffuse alveolar damage," which appeared in early descriptions of the pathological findings in patients with the acute respiratory distress syndrome, reflects the gross and microscopical findings in the majority of patients.<sup>22-24</sup> In a patient with the acute respiratory distress syndrome, low lung compliance and increased airway resistance require greater static pressure and greater peak inspiratory pressure to obtain a given lung volume than in a person with nor-

mal lungs.<sup>6,25</sup> The pressure that determines lung volume is the transpulmonary pressure (alveolar pressure minus pleural pressure). In a person with normal lungs, a transpulmonary pressure of 35 to 40 cm of water is sufficient to achieve total lung capacity; this is the arbitrary pressure limit for mechanical ventilation adopted by the American College of Chest Physicians Consensus Conference.<sup>6</sup> Maximal inspiratory pressures in normal men and women between the ages of 20 and 54 years have been reported to be  $124 \pm 44$  and  $87 \pm 32$  cm of water, respectively.<sup>26</sup> These self-generated pressures, which occur with normal activities of daily living, exercise, acute or chronic bronchitis, and pneumonia, are associated with an extremely low risk of pneumothorax or other air leaks. In normal people, these pressures exceed any pressures generated by mechanical ventilation in our study of the acute respiratory distress syndrome and in other such studies that we are aware of.

In 1937, Macklin identified lung overdistention as the cause of air leaks,<sup>27</sup> an observation that was subsequently confirmed.<sup>8,28,29</sup> Kolobow et al. gave normal sheep ventilation at a peak inspiratory pressure of 50 cm of water, which produced tidal volumes that were 500 to 700 percent of the normal value (2500 to 3500 ml, or 36 to 50 ml per kilogram, in a 70-kg man). The results — reduced arterial oxygen tension, reduced compliance, and lung damage described as severe or very severe on gross examination — were attributed to the high peak pressure.<sup>3</sup> The findings were similar with a tidal volume that was about 300 percent of the normal value.<sup>4</sup> In rats pretreated with  $\beta$ -naphthylthiourea and given mechanical ventilation, lung damage occurred at tidal volumes of 25 to 45 ml per kilogram, or approximately 350 to 640 percent of the normal value (1750 to 3350 ml, or 25 to 48 ml per kilogram in a 70-kg man).<sup>30</sup> Capillary damage is also dependent on volume.<sup>30</sup> Thus, high volumes can cause injury in laboratory animals. However, the volumes required to produce these changes far exceed those used in patients with the acute respiratory distress syndrome, even allowing for a decreased volume of ventilating lung. They also exceed the maximal tidal volume of 2500 ml that current ventilators can generate.

In series of patients with the acute respiratory distress syndrome, the reported incidence of air leaks has ranged from 0 to 92 percent; the incidence has been poorly correlated with airway pressure.<sup>31-34</sup> Pelosi and colleagues have shown that although the gradient of hydrostatic pressure is increased from the ventral to the dorsal surface of the lungs in a supine patient with the acute respiratory distress syndrome, the tissue volume is distributed evenly throughout the lungs (i.e., there is no gravitational gradient).<sup>35</sup> This group of investigators found that with increasing levels of positive end-expiratory pressure in the range of 0 to 20 cm of water, the amount of reopen-

ing and collapsing lung tissue decreased, and gas distribution was more homogeneous.<sup>36</sup> These more recent studies<sup>35,36</sup> appear to support the volumes and positive end-expiratory pressure used in the majority of patients undergoing conventional mechanical ventilation.

We found no differences in the frequency of distributions of the measured pressures and volumes among the patients without air leaks, those with any air leaks, and those with pneumothorax. The statistical analyses demonstrated the equality of the distributions, with the exception that a lower value for minute ventilation was associated with a higher incidence of pneumothorax. There were no pressures or volumes below which pneumothorax or air leaks of any type never occurred — which might have suggested a safe ventilatory strategy — or above which they always occurred.

An explanation for the higher frequencies of pneumothorax and air leaks of any type in younger patients, women, and those with lower body weight is not readily apparent. When the data were analyzed separately for men and women, body weight was not significantly associated with the frequency of pneumothorax or air leaks of any type. The correlation of air leaks with lower values for serum albumin and higher values for inspired oxygen tension supports the idea that air leaks occur in patients with more severe lung disease; however, there was no correlation between air leaks and the APACHE III score.

The mortality rate of 40 percent at 30 days is similar to the mortality rates in other studies<sup>37,38</sup> and to the rate reported in both groups in a randomized comparison of pressure-controlled, inverse-ratio ventilation with extracorporeal carbon dioxide removal.<sup>15</sup> Pressure-controlled, inverse-ratio ventilation uses a combination of limited peak pressures, permissive hypercapnia (usually requiring sodium bicarbonate to modulate pH), and inspiration:expiration ratios greater than 1 — thus, the term “inverse ratio.” The inverse-ratio technique provides a variable positive end-expiratory pressure. In a study of 100 patients with acute lung injury, air leaks were correlated with mortality in a multivariate analysis, but less than 2 percent of the deaths were attributable to air leaks.<sup>39</sup> In a study of trauma-induced acute respiratory distress syndrome in which 41 patients were treated with a maximal positive end-expiratory pressure of  $26.7 \pm 9.3$  cm of water and a maximal peak inspiratory pressure of  $62.6 \pm 15.6$  cm of water, only 17 percent of the patients had air leaks of any kind and only 7 percent had pneumothorax possibly attributable to mechanical ventilation.<sup>40</sup> Neither air leaks of any kind nor pneumothorax was associated with increased mortality. These findings are similar to ours, despite the very high ventilatory pressures. If the difference in mortality in our study between the patients with pneumothorax or air leaks of any

type and those without air leaks was unrelated to chance, a considerably larger sample would be required to confirm this difference.

Our study has limitations. Although the data were obtained in a prospective, randomized, placebo-controlled trial, with all patients included in the analyses, the hypotheses we addressed were not the primary end points of the study. In addition, the study period was only five days.

In conclusion, in our large series, the majority of patients underwent mechanical ventilation with conventional mean pressures and volumes: positive end-expiratory pressure,  $11.6 \pm 4.9$  cm of water; peak inspiratory pressure,  $45.9 \pm 11.7$  cm of water; airway pressure,  $23.8 \pm 0.7$  cm of water; tidal volume, 829.6 ml; tidal volume per kilogram,  $11.4 \pm 3.4$  ml; minute ventilation,  $13.2 \pm 4.9$  liters per minute; and minute ventilation per kilogram,  $0.18 \pm 0.08$  liter per minute. Our data confirm the extensive anecdotal evidence that pneumothorax and other air leaks are uncommon in patients undergoing conventional mechanical ventilation for the acute respiratory distress syndrome and suggest that these complications may be related to the severity of the lung injury. Our findings do not provide support for the idea that ventilatory pressures should be limited to predefined values such as a static pressure of 35 to 40 cm of water, since conventional ventilatory pressures and volumes do not appear to affect the lungs adversely.

Supported in part by a grant from Glaxo Wellcome.

*We are indebted to Glaxo Wellcome for transferring the Exosurf data to the University of Michigan Medical Center and School of Public Health and providing support for independent analyses, and to Rebecca Lee for providing secretarial support.*

## REFERENCES

1. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures: protection by positive end-expiratory pressure. *Am Rev Respir Dis* 1974;110:556-65.
2. Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. *Am Rev Respir Dis* 1985;132:880-4.
3. Kolobow T, Moretti MP, Fumagalli R, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation: an experimental study. *Am Rev Respir Dis* 1987;135:312-5.
4. Tsuno K, Prato P, Kolobow T. Acute lung injury from mechanical ventilation at moderately high airway pressures. *J Appl Physiol* 1990;69:956-61.
5. Peevy KJ, Hernandez LA, Moise AA, Parker JC. Barotrauma and microvascular injury in lungs of nonadult rabbits: effect of ventilation pattern. *Crit Care Med* 1990;18:634-7.
6. Slutsky AS. Mechanical ventilation: American College of Chest Physicians' Consensus Conference. *Chest* 1993;104:1833-59. [Erratum, *Chest* 1994;106:656.]
7. Maunder RJ, Shuman WP, McHugh JW, Marglin SI, Butler J. Preservation of normal lung regions in the adult respiratory distress syndrome: analysis by computed tomography. *JAMA* 1986;255:2463-5.
8. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure: computed tomographic scan study. *Am Rev Respir Dis* 1987;136:730-6.
9. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 1988;137:1159-64.

10. Dreyfuss D, Soler P, Saumon G. Mechanical ventilation-induced pulmonary edema: interaction with previous lung alterations. *Am J Respir Crit Care Med* 1995;151:1568-75.
11. Zapol WM, Snider MT, Hill D, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure: a randomized prospective study. *JAMA* 1979;242:2193-6.
12. Prankoff T, Hirschl RB, Steimle CN, Anderson HL III, Bartlett RH. Efficacy of extracorporeal life support in the setting of adult cardiorespiratory failure. *ASAIO J* 1994;40:M339-M343.
13. Gattinoni L, Pesenti A, Mascheroni D, et al. Low-frequency positive-pressure ventilation with extracorporeal CO<sub>2</sub> removal in severe acute respiratory failure. *JAMA* 1986;256:881-6.
14. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med* 1994;22:1568-78.
15. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO<sub>2</sub> removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;149:295-305. [Erratum, *Am J Respir Crit Care Med* 1994;149:838.]
16. Amato MBP, Barbas CSV, Medeiros DM, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: a prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med* 1995;152:1835-46.
17. Anzueto A, Baughman RP, Guntupalli KK, et al. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. *N Engl J Med* 1996;334:1417-21.
18. Remington RD, Schork MA. Statistics with applications to the biological and health sciences. 2nd ed. Englewood Cliffs, N.J.: Prentice-Hall, 1985.
19. Hollander M, Wolfe DA. Nonparametric statistical methods. New York: John Wiley, 1973.
20. Hosmer DW Jr, Lemeshow S. Applied logistic regression. New York: John Wiley, 1989.
21. Meinert CL. Clinical trials: design, conduct, and analysis. Vol. 8 of Monographs in epidemiology and biostatistics. New York: Oxford University Press, 1986.
22. Lamy M, Fallat RJ, Koeniger E, et al. Pathologic features and mechanisms of hypoxemia in adult respiratory distress syndrome. *Am Rev Respir Dis* 1976;114:267-84.
23. Tomaszewski JF Jr. Pulmonary pathology of the adult respiratory distress syndrome. *Clin Chest Med* 1990;11:593-619.
24. Rouby JJ, Lherm T, Martin de Lassale E, et al. Histologic aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure. *Intensive Care Med* 1993;19:383-9.
25. Wright PE, Carmichael LC, Bernard GR. Effect of bronchodilators on lung mechanics in the acute respiratory distress syndrome (ARDS). *Chest* 1994;106:1517-23.
26. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969;99:696-702.
27. Macklin CC. Pneumothorax with massive collapse from experimental local over-inflation of the lung substance. *Can Med Assoc J* 1937;36:414-20.
28. Greenfield LJ, Ebert PA, Benson DW. Effect of positive pressure ventilation on surface tension properties of lung extracts. *Anesthesiology* 1964;25:312-6.
29. Caldwell EJ, Powell RD Jr, Mullooly JP. Interstitial emphysema: a study of physiologic factors involved in experimental induction of the lesion. *Am Rev Respir Dis* 1970;102:516-25.
30. Mathieu-Costello OA, West JB. Are pulmonary capillaries susceptible to mechanical stress? *Chest* 1994;105:Suppl:102S-107S.
31. Tharratt RS, Allen RP, Albertson TE. Pressure controlled inverse ratio ventilation in severe adult respiratory failure. *Chest* 1988;94:755-62.
32. Clevenger FW, Acosta JA, Osler TM, Demarest GB, Fry DE. Barotrauma associated with high-frequency jet ventilation for hypoxic salvage. *Arch Surg* 1990;125:1542-5.
33. Peterson GW, Baier H. Incidence of pulmonary barotrauma in a medical ICU. *Crit Care Med* 1983;11:67-9.
34. Gammon RB, Shin MS, Groves RH Jr, Hardin JM, Hsu C, Buchalter SE. Clinical risk factors for pulmonary barotrauma: a multivariate analysis. *Am J Respir Crit Care Med* 1995;152:1235-40.
35. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;149:8-13.
36. Gattinoni L, Pelosi P, Crotti S, Valenza F. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151:1807-14.
37. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983-1993. *JAMA* 1995;273:306-9.
38. Suchyta MR, Clemmer TP, Orme JF Jr, Morris AH, Elliott CG. Increased survival of ARDS patients with severe hypoxemia (ECMO criteria). *Chest* 1991;99:951-5.
39. Schnapp LM, Chin DP, Szaflarski N, Matthay MA. Frequency and importance of barotrauma in 100 patients with acute lung injury. *Crit Care Med* 1995;23:272-8.
40. DiRusso SM, Nelson LD, Safcsak K, Miller RS. Survival in patients with severe adult respiratory distress syndrome treated with high-level positive end-expiratory pressure. *Crit Care Med* 1995;23:1485-96.