

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 27, 2006

VOL. 354 NO. 17

## Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome

Luciano Gattinoni, M.D., F.R.C.P., Pietro Caironi, M.D., Massimo Cressoni, M.D., Davide Chiumello, M.D., V. Marco Ranieri, M.D., Michael Quintel, M.D., Ph.D., Sebastiano Russo, M.D., Nicolò Patroniti, M.D., Rodrigo Cornejo, M.D., and Guillermo Bagedo, M.D.

### ABSTRACT

#### BACKGROUND

In the acute respiratory distress syndrome (ARDS), positive end-expiratory pressure (PEEP) may decrease ventilator-induced lung injury by keeping lung regions open that otherwise would be collapsed. Since the effects of PEEP probably depend on the recruitability of lung tissue, we conducted a study to examine the relationship between the percentage of potentially recruitable lung, as indicated by computed tomography (CT), and the clinical and physiological effects of PEEP.

#### METHODS

Sixty-eight patients with acute lung injury or ARDS underwent whole-lung CT during breath-holding sessions at airway pressures of 5, 15, and 45 cm of water. The percentage of potentially recruitable lung was defined as the proportion of lung tissue in which aeration was restored at airway pressures between 5 and 45 cm of water.

#### RESULTS

The percentage of potentially recruitable lung varied widely in the population, accounting for a mean ( $\pm$ SD) of  $13\pm 11$  percent of the lung weight, and was highly correlated with the percentage of lung tissue in which aeration was maintained after the application of PEEP ( $r^2=0.72$ ,  $P<0.001$ ). On average, 24 percent of the lung could not be recruited. Patients with a higher percentage of potentially recruitable lung (greater than the median value of 9 percent) had greater total lung weights ( $P<0.001$ ), poorer oxygenation (defined as a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen) ( $P<0.001$ ) and respiratory-system compliance ( $P=0.002$ ), higher levels of dead space ( $P=0.002$ ), and higher rates of death ( $P=0.02$ ) than patients with a lower percentage of potentially recruitable lung. The combined physiological variables predicted, with a sensitivity of 71 percent and a specificity of 59 percent, whether a patient's proportion of potentially recruitable lung was higher or lower than the median.

#### CONCLUSIONS

In ARDS, the percentage of potentially recruitable lung is extremely variable and is strongly associated with the response to PEEP.

From the Istituto di Anestesiologia e Rianimazione, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena di Milano, Università degli Studi di Milano, Milan (L.G., P.C., M.C., D.C.); the Dipartimento di Anestesia, Azienda Ospedaliera San Giovanni Battista-Molinette, Università degli Studi di Torino, Turin, Italy (V.M.R.); Anaesthesiologie II, Operative Intensivmedizin, Universitätsklinikum Göttingen, Göttingen, Germany (M.Q., S.R.); the Dipartimento di Medicina Perioperatoria e Terapia Intensiva, Azienda Ospedaliera San Gerardo di Monza, Università degli Studi Milano-Bicocca, Milan (N.P.); and the Departamentos de Anestesiología y Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile (R.C., G.B.). Address reprint requests to Prof. Gattinoni at the Istituto di Anestesiologia e Rianimazione, Fondazione IRCCS-Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena di Milano, Università degli Studi di Milano, Via F. Sforza 35, Milan 20122, Italy, or at gattinon@policlinico.mi.it.

N Engl J Med 2006;354:1775-86.

Copyright © 2006 Massachusetts Medical Society.

**A**CUTE RESPIRATORY DISTRESS SYNDROME (ARDS) is a clinical syndrome characterized by inflammatory pulmonary edema, severe hypoxemia, stiff lungs, and diffuse endothelial and epithelial injury.<sup>1,2</sup> Mechanical ventilation is often implemented in these patients to restore adequate oxygenation. However, it has become evident over the past two decades that mechanical ventilation itself can augment or cause pulmonary damage that is indistinguishable from that caused by ARDS.<sup>3</sup> As a consequence, the therapeutic target of mechanical ventilation in patients with ARDS has shifted from the maintenance of “normal gas exchange”<sup>4</sup> to the protection of the lung from ventilator-induced lung injury.<sup>5-7</sup>

The lung-protection strategy combines the use of higher levels of positive end-expiratory pressure (PEEP) (greater than 12 to 15 cm of water) and low tidal volumes to prevent regional and global stress and strain on the lung parenchyma.<sup>8-10</sup> Ventilation at low tidal volumes alone has been shown to increase survival among patients with acute lung injury or ARDS,<sup>11</sup> and the addition of higher PEEP to low tidal volumes did not further increase survival.<sup>12</sup> In patients with low levels of recruitable lung (i.e., lung tissue in which aeration can be restored),<sup>13-16</sup> however, the application of higher levels of PEEP may be more harmful than beneficial, since it will serve only to increase inflation of lung regions that are already open, increasing the stress and strain on these regions.<sup>17</sup> It follows that knowledge of the capacity of the lung to become and remain recruited should be a prerequisite for a rational determination of the levels of PEEP to be applied.

Using computed tomography (CT) to analyze the entire lung in patients with ARDS, we measured the percentage of lung that can be recruited, termed “potentially recruitable lung,” by increasing airway pressures.<sup>18,19</sup> We also investigated the relationship between the percentage of lung that can be recruited by this maneuver and the changes in physiological respiratory variables during mechanical ventilation with lower or higher PEEP.

## METHODS

### PATIENTS

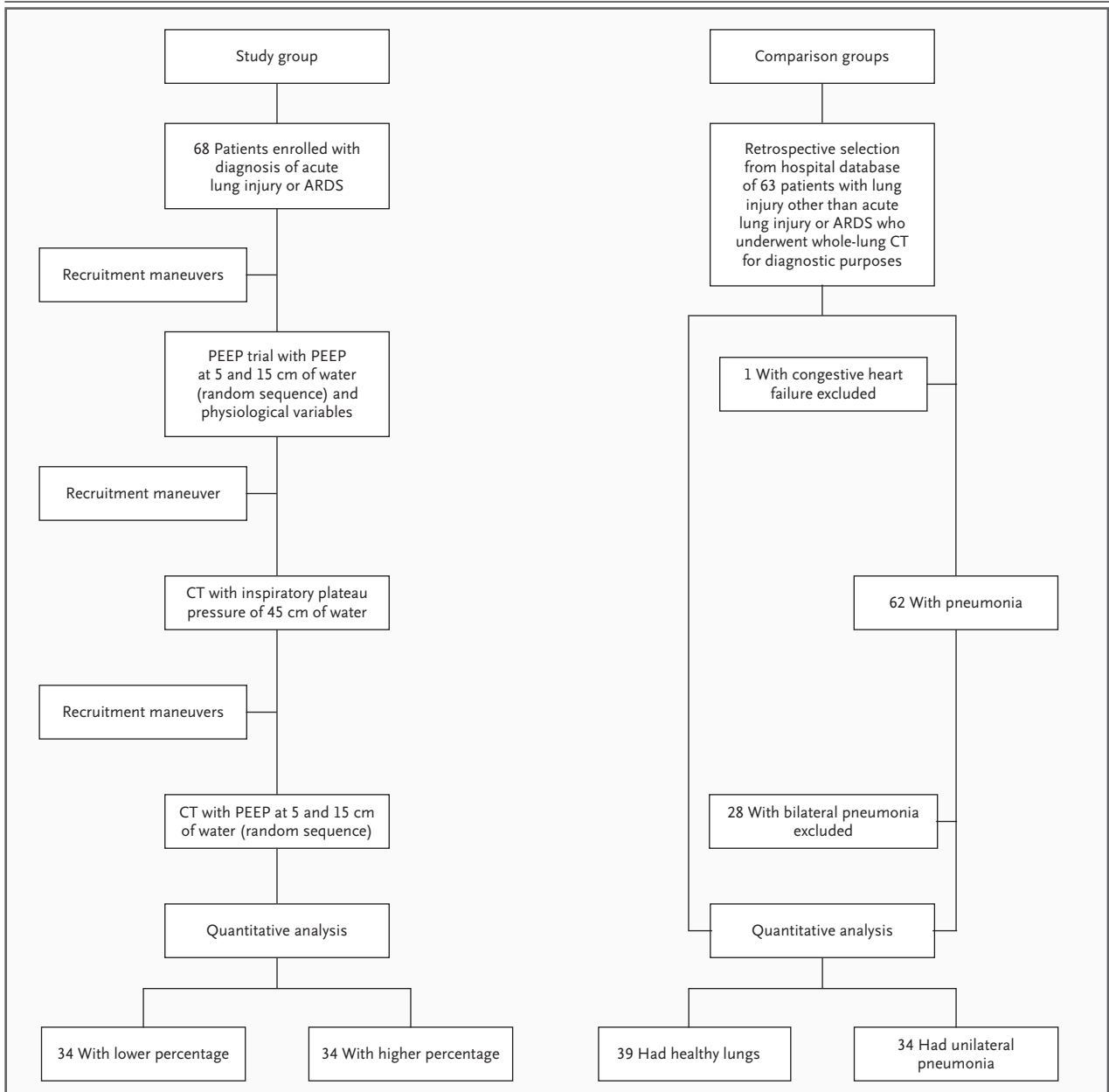
The patients were studied from June 2003 through January 2005 at four university hospitals. The study was approved by the institutional review board of

each hospital, and written informed consent was obtained according to the national regulations of the participating institutions (consent was delayed in Italy until after the patients had recovered from the effects of sedation, obtained from a legal representative in Germany, and obtained from the next of kin in Chile; for details see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

Patients were enrolled if they met the standard criteria for acute lung injury: a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ( $\text{PaO}_2:\text{FiO}_2$ ) of less than 300, the presence of bilateral pulmonary infiltrates on the chest radiograph, and no clinical evidence of left atrial hypertension (defined by a pulmonary-capillary wedge pressure of 18 mm Hg or less, if measured).<sup>20</sup> The exclusion criteria were an age of less than 16 years, pregnancy, and chronic obstructive pulmonary disease, according to the patient’s medical history. The underlying cause of acute lung injury or ARDS was recorded by each institution, but no specific classifications were defined a priori. Patients with healthy lungs and patients with unilateral pneumonia who underwent CT for clinical purposes from April 2001 through June 2005 were retrospectively selected from five hospitals and included in the study for comparison (Fig. 1 and the Supplementary Appendix).

### PEEP TRIAL

The clinical characteristics of the patients, respiratory variables, and ventilator settings were recorded before the study. Immediately before each step of the PEEP trial, as well as before each CT session, a recruitment maneuver — that is, a sustained inflation of the lungs to higher airway pressures and volumes than are obtained during tidal ventilation — was performed in which the patient underwent ventilation for two minutes in the pressure-controlled mode at an inspiratory plateau pressure of 45 cm of water, a PEEP of 5 cm of water, a respiratory rate of 10 breaths per minute, and a 1:1 ratio of inspiration to expiration.<sup>21,22</sup> After the recruitment maneuver, PEEP at a level of 5 or 15 cm of water was randomly applied (Fig. 1). The tidal volume (8 to 10 ml per kilogram of predicted body weight),  $\text{FiO}_2$ , and respiratory rate were identical to the values used in everyday clinical treatment. After 20 minutes, the systemic arterial and central venous pressures and blood gas tensions, min-



**Figure 1. Enrollment and Study Protocol.**

In the study group, a recruitment maneuver was performed immediately before application of each PEEP level. In the comparison groups, patients with bilateral pneumonia were excluded from the analysis to limit the possible confounding factors caused by the partial overlapping between patients with less severe acute lung injury or ARDS and patients with bilateral pneumonia (see the Supplementary Appendix for further details). Therefore, only patients with unilateral pneumonia, who by definition did not meet the inclusion criteria for acute lung injury or ARDS, were included. The group with a lower percentage of potentially recruitable lung includes patients with potentially recruitable lung values at or below the overall median of 9 percent, and the group with a higher percentage of potentially recruitable lung includes patients with values above the median.

ute ventilation, and inspiratory plateau pressure were recorded. The dead-space fraction and the end-tidal partial pressure of carbon dioxide were measured with a CO<sub>2</sub>SMO monitor (Novamatrix).

Standard formulas were used to calculate the right-to-left intrapulmonary shunt fraction, alveolar dead-space fraction, and respiratory-system compliance (see the Supplementary Appendix).

**COMPUTED TOMOGRAPHY**

The CT scanner was set as follows: collimation, 5 mm; interval, 5 mm; bed speed, 15 mm per second; voltage, 140 kV; and current, 240 mA. A whole-lung CT scan was performed at an inspiratory-plateau pressure of 45 cm of water during an end-inspiratory pause (ranging from 15 to 25 seconds) and thereafter at PEEP values of 5 and 15 cm of water applied in a random order during an end-expiratory pause (ranging from 15 to 25 seconds). Immediately before each CT scan was obtained, a recruitment maneuver was performed, as described above (Fig. 1); the ventilator settings were otherwise kept identical to those used during the PEEP trial. The patients included in the comparison groups underwent only one CT of the whole lung, for diagnostic purposes. The cross-sectional lung images were processed and analyzed by a custom-designed software package, as described previously<sup>49</sup> (see the Supplementary Appendix). Briefly, the outline of the lungs was manually drawn in each image, excluding the hilar vessels, by investigators unaware of the airway pressure applied. Specific lung weight was assumed to be equal to 1, and the total lung weight was calculated from the physical density of the lung expressed in Hounsfield units. Similarly, the tissue weights of lung regions with different degrees of aeration were calculated. The regions were classified as nonaerated (density between +100 and -100 Hounsfield units), poorly aerated (density between -101 and -500 Hounsfield units), normally aerated (density between -501 and -900 Hounsfield units), and hyperinflated (density between -901 and -1000 Hounsfield units). The percentage of potentially recruitable lung was defined as the proportion of the total lung weight accounted for by nonaerated lung tissue in which aeration was restored (according to CT) by an airway pressure of 45 cm of water from an airway pressure of 5 cm of water.

**STATISTICAL ANALYSIS**

Comparison of prestudy clinical variables, respiratory physiological variables, and CT results was performed by one-way analysis of variance or Student's *t*-test in the case of variables that were normally distributed; by the Kruskal-Wallis test, the Wilcoxon test, or two-way analysis of variance on a rank-sum test in the case of variables that did not appear normally distributed on graphic inspection; and by the chi-square test or Fisher's exact test in the case of qualitative variables. When

analysis of variance revealed a significant difference, Bonferroni's *t*-test or Dunn's test was used, as appropriate, to correct for multiple comparisons. Mortality rates were analyzed by the chi-square test. Mortality rates were based on the number of deaths occurring in the intensive care unit (ICU) among patients with acute lung injury or ARDS and the number of deaths occurring in the hospital among patients with unilateral pneumonia. Multiple backward logistic-regression analysis was used to investigate the possible association between outcome and the percentage of potentially recruitable lung, as well as other measurements used to estimate the severity of the systemic illness and of the lung injury. The Hosmer-Lemeshow goodness-of-fit test and the C statistic were used to verify the adequacy of the models.

To obtain a bedside estimate of the percentage of potentially recruitable lung using only physiological respiratory measurements, we measured the changes in the PaO<sub>2</sub>:FiO<sub>2</sub>, the partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>), the percentage of alveolar dead space, and respiratory-system compliance associated with increasing the PEEP from 5 to 15 cm of water while minute ventilation and FiO<sub>2</sub> were held constant. An increase in the PaO<sub>2</sub>:FiO<sub>2</sub>, a decrease in the PaCO<sub>2</sub> or alveolar dead space, or an increase in respiratory-system compliance was defined as a positive response, and any change in the opposite direction was defined as a negative response, irrespective of the magnitude of the change. *P* values of less than 0.05 were considered to indicate statistical significance. All reported *P* values are two-sided. Data are expressed as means (±SD) and 95 percent confidence intervals when appropriate.

**RESULTS**

A total of 68 patients were enrolled in the study: 19 had acute lung injury without ARDS, and 49 had ARDS (Fig. 1 and Table 1). The overall mortality rate in the ICU among the study population was 28 percent. The percentage of potentially recruitable lung, as assessed by CT, varied widely within the study population (Fig. 2); the average was 13±11 percent of the total lung weight (95 percent confidence interval, 10 to 16 percent; median, 9 percent), corresponding to an absolute weight of 217±232 g of recruitable lung tissue (95 percent confidence interval, 161 to 273; median, 134).

**Table 1. Baseline Characteristics of the Study Population.\***

Characteristic	Overall Population (N=68)	Patients with Lower Percentage of Potentially Recrutable Lung (N=34)†	Patients with Higher Percentage of Potentially Recrutable Lung (N=34)‡	P Value§
Age — yr	55±17	56±16	53±18	0.48
Female sex — no. (%)	33 (49)	15 (44)	18 (53)	0.47
Body-mass index	25±5	26±5	24±4	0.21
SAPS II score¶	37±11	37±12	36±9	0.91
Tidal volume — ml/kg of predicted body weight	8.8±1.9	8.9±2.0	8.8±1.7	0.78
Minute ventilation — liters/min	9.8±3.0	9.5±2.7	10.1±3.3	0.45
Respiratory rate — breaths/min	18±7	17±6	19±7	0.57
PEEP — cm of water	11.1±3.0	10.8±2.9	11.5±3.1	0.34
Plateau pressure — cm of water	25±4	23±3	26±4	0.005
Respiratory-system compliance — ml/cm of water¶¶	44±17	49±16	40±18	0.02
PaO <sub>2</sub> :FiO <sub>2</sub>	200±77	225±70	176±77	0.008
FiO <sub>2</sub>	0.50±0.15	0.46±0.10	0.54±0.18	0.07
PaCO <sub>2</sub> — mm Hg	42±14	38±8	46±17	0.04
Arterial pH	7.40±0.08	7.41±0.08	7.37±0.07	0.01
Cause of lung injury — no. (%)				
Pneumonia	25 (37)	7 (21)	18 (53)	0.01
Sepsis	24 (35)	17 (50)	7 (21)	0.02
Aspiration	4 (6)	3 (9)	1 (3)	0.61
Trauma	3 (4)	3 (9)	0	0.24
Other	12 (18)	4 (12)	8 (24)	0.34
Fluid balance before study — ml/day**	1413±2027	1427±2016	1398±2071	0.97
Days of ventilation before study††	5±6	5±6	6±6	0.50
Type of lung injury				0.02
Acute lung injury	19	14	5	
ARDS	49	20	29	

\* Plus-minus values are means ±SD. Because of rounding, percentages may not total 100. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Patients in the group with a lower percentage of potentially recruitable lung had values at or below 9 percent, the median value for the study population, and patients in the group with a higher percentage of potentially recruitable lung had values greater than 9 percent.

‡ P values were obtained by Student's t-test, Wilcoxon's test, Fisher's exact test, or the chi-square test, as appropriate.

§ The Simplified Acute Physiology Score (SAPS II)<sup>23</sup> was used to assess the severity of systemic illness at study entry. Scores can range from 0 to 163, with higher scores indicating more severe illness.

¶ Respiratory-system compliance was calculated as the ratio of the tidal volume to the difference between inspiratory plateau pressure and PEEP.

|| Other causes of acute lung injury included anaphylactic shock, recent surgery, and bone marrow transplantation.

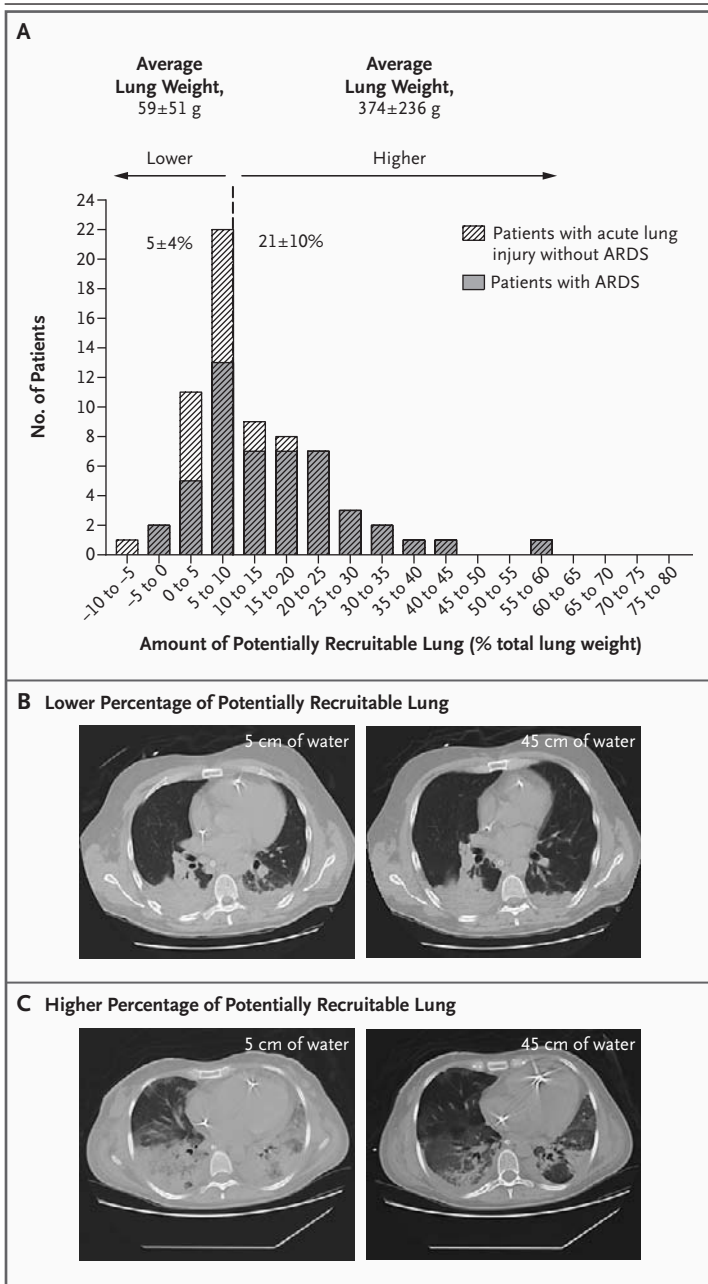
\*\* The fluid balance before the study was the average daily fluid balance for each patient during the last five days before the study.

†† Days of mechanical ventilation before the study were counted from the day of intubation (day 0) to the beginning of the study.

#### FUNCTIONAL ANATOMY ACCORDING TO CT FINDINGS AND RESPONSE TO PEEP

The study population was divided into quartiles according to the percentage of potentially recruit-

able lung (Fig. 3A); the average values were 2±4 percent of total lung weight in quartile 1 (range, -9.2 to 5.7 percent), 7±1 percent in quartile 2 (range, 5.8 to 9.4 percent), 14±3 percent in quartile 3 (range,



**Figure 2.** Frequency Distribution of Patients According to the Percentage of Potentially Recruitable Lung (Panel A) and CT Images at Airway Pressures of 5 and 45 cm of Water from Patients with a Lower Percentage of Potentially Recruitable Lung (Panel B) and Those with a Higher Percentage of Potentially Recruitable Lung (Panel C).

Panel A shows the frequency distribution of the 68 patients in the overall study group according to the percentage of potentially recruitable lung, expressed as the percentage of total lung weight. Acute lung injury without ARDS was defined by a  $\text{PaO}_2:\text{FiO}_2$  of less than 300 but not less than 200, and ARDS was defined by a  $\text{PaO}_2:\text{FiO}_2$  of less than 200. The percentage of potentially recruitable lung was defined as the proportion of lung tissue in which aeration is restored at airway pressures between 5 and 45 cm of water. Panel B shows representative CT slices of the lung obtained 2 cm above the diaphragm dome at airway pressures of 5 cm of water (left) and 45 cm of water (right) from a patient with a lower percentage of potentially recruitable lung (at or below the median value of 9 percent of total lung weight). Lung injury developed in the patient after an episode of severe acute pancreatitis ( $\text{PaO}_2:\text{FiO}_2$ , 296 at an airway pressure of 5 cm of water;  $\text{PaCO}_2$ , 34 mm Hg; and respiratory-system compliance, 44 ml per centimeter of water). The percentage of potentially recruitable lung was 4 percent, and the proportion of consolidated lung tissue was 33 percent of the total lung weight. Panel C shows representative CT slices of the lung obtained 2 cm above the diaphragm dome at airway pressures of 5 cm of water (left) and 45 cm of water (right) from a patient in the group with a higher percentage of potentially recruitable lung. Lung injury developed in the patient after an episode of severe pneumonia ( $\text{PaO}_2:\text{FiO}_2$ , 106 at a PEEP of 5 cm of water;  $\text{PaCO}_2$ , 58 mm Hg; and respiratory-system compliance, 25 ml per cm of water). The percentage of potentially recruitable lung was 37 percent, and the proportion of consolidated lung tissue was 27 percent of the total lung weight.

9.5 to 18.6 percent), and  $28 \pm 10$  percent in quartile 4 (range, 18.7 to 59.3 percent). In each group, the increase in airway pressure from 5 to 15 to 45 cm of water induced a progressive increase in the percentage of hyperinflated and normally aerated lung tissue ( $P < 0.01$  for both variables), paralleled by a decrease in the percentage of nonaerated lung tissue ( $P < 0.01$ ). In contrast, in all four groups, about 24 percent of the lung could not be recruited, even at an airway pressure of 45 cm of water.

The decrease in the percentage of nonaerated lung tissue as PEEP was raised from 5 to 15 cm of water was highly correlated with the percentage of potentially recruitable lung ( $r^2 = 0.72$ ,  $P < 0.001$ ) (Fig. 3B). The near-constant fraction of the percentage of potentially recruitable lung that remained recruited at a PEEP of 15 cm of water was about 50 percent, irrespective of its absolute percentage, as indicated by the slope of the plot in Figure 3B.

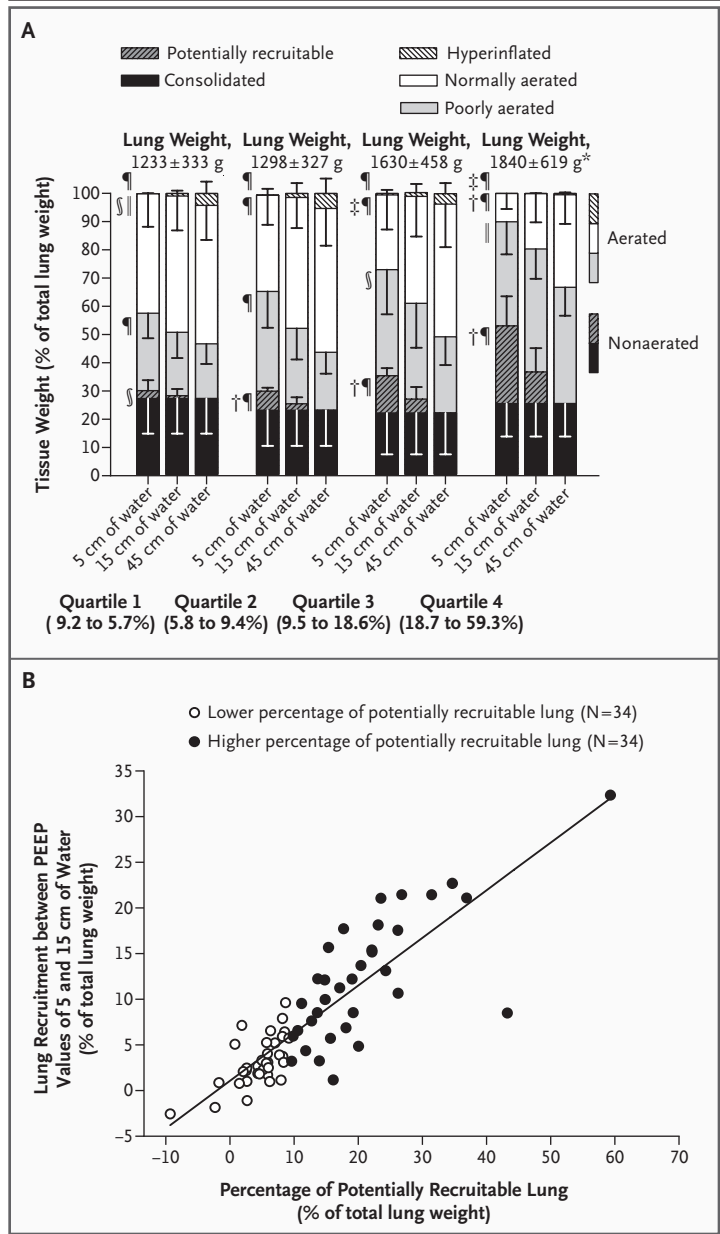
**CLINICAL CHARACTERISTICS AND OVERALL SEVERITY OF LUNG INJURY**

We divided the patients into two groups according to the percentage of potentially recruitable lung: at or below the median value of 9 percent of total lung weight or greater than the median value

**Figure 3. Lung Recruitment in Response to Changes in Airway Pressure in Patients with Acute Lung Injury or ARDS, According to the Percentage of Potentially Recrutable Lung.**

Panel A shows the proportion of total lung tissue classified as nonaerated, poorly aerated, normally aerated, and hyperinflated in response to three values of airway pressure in patients with different percentages of potentially recruitable lung. The study population was divided into quartiles of 17 patients each according to the percentage of potentially recruitable lung. Nonaerated lung tissue was also divided into potentially recruitable tissue (nonaerated tissue in which aeration was restored at airway pressures between 5 and 45 cm of water) and consolidated tissue (tissue remaining nonaerated despite an airway pressure of 45 cm of water). The asterisk denotes  $P < 0.01$  for the comparison with patients with a very low or low percentage of potentially recruitable lung (first and second quartiles), the daggers  $P < 0.01$  for the comparison with patients in the other quartiles, the double dagger  $P < 0.01$  for the comparison with patients with a very low percentage of potentially recruitable lung (first quartile), the section marks  $P < 0.05$  for the comparison with an airway pressure of 45 cm of water in patients within the same quartile, the paragraph mark  $P < 0.01$  for the comparison with airway pressures of 15 and 45 cm of water for patients within the same quartile, and the double slashes  $P < 0.05$  for the comparison with a PEEP value of 15 cm of water for patients within the same quartile. Panel B shows lung recruitment induced by increasing PEEP from 5 to 15 cm of water in the overall study population — that is, the decrease in nonaerated lung tissue between PEEP values of 5 and 15 cm of water, as a function of the percentage of potentially recruitable lung; both values are expressed as proportions of the total lung weight measured at a baseline PEEP of 5 cm of water ( $r^2 = 0.72$ ,  $P < 0.001$ , slope = 0.52 and y intercept = 1.03). A linear function ( $y = ax + y_0$ ) was used.

for the study population. In the prestudy period, the two groups had similar clinical characteristics with regard to age, severity of illness (as assessed by the Simplified Acute Physiology Score [SAPS II]<sup>23</sup>), daily fluid balance, and number of days of mechanical ventilation before the beginning of the study (Table 1). The tidal volume and PEEP level used clinically for mechanical ventilation were similar in the two groups. In contrast, at baseline, patients in the group with a higher percentage of potentially recruitable lung had a lower  $PaO_2:FiO_2$  ( $P = 0.008$ ), a higher  $PaCO_2$  ( $P = 0.04$ ), and lower respiratory-system compliance ( $P = 0.02$ ) than those in the group with a lower percentage of potentially recruitable lung (Table 1). Acute lung injury or ARDS resulting from sepsis was more frequent among patients



in the group with a lower percentage of recruitable lung ( $P = 0.02$ ), whereas acute lung injury or ARDS resulting from pneumonia was more frequent among patients in the group with a higher percentage ( $P = 0.01$ ) (Table 1 and the Supplementary Appendix).

The association between the percentage of potentially recruitable lung and the severity of the overall lung injury was examined at a PEEP of 5 cm of water. The total lung weight was greater ( $P < 0.001$ ), the proportion of nonaerated lung tissue was higher ( $P = 0.001$ ), the  $PaO_2:FiO_2$  was

**Table 2. Baseline Characteristics, Functional Anatomy According to CT Findings, and Mortality Rates in Patients with Healthy Lungs, Patients with Unilateral Pneumonia, and Patients with Acute Lung Injury or ARDS and with Lower or Higher Percentages of Potentially Recrutable Lung.\***

Variable	Patients with Healthy Lungs (N = 39)		Patients with Unilateral Pneumonia (N = 34)		Patients with Acute Lung Injury or ARDS†		P Value‡
	Overall Population (N = 68)	Lower Percentage of Potentially Recrutable Lung (N = 34)	Higher Percentage of Potentially Recrutable Lung (N = 34)	Overall Population (N = 68)	Lower Percentage of Potentially Recrutable Lung (N = 34)	Higher Percentage of Potentially Recrutable Lung (N = 34)	
Age — yr	62±19	65±18	65±18	55±17§	56±16	53±18	0.01
SAPS II score¶	—	35±16	35±16	37±11	37±12	36±9	0.18
Total lung weight — g	850±201	1215±329  **	1215±329  **	1500±506  ††	1266±327**	1735±547‡‡	<0.001
Non-aerated lung tissue — % of total lung weight§§	3±2	28±14  **	28±14  **	37±16  ††	30±12**	44±17‡‡	<0.001
Aerated lung tissue — % of total lung weight§§	97±2	72±14  **	72±14  **	63±16  ††	70±12**	56±17‡‡	<0.001
PaO <sub>2</sub> :FiO <sub>2</sub> ¶¶	—	219±103	219±103	165±69	194±65**	135±60‡‡	0.01
PaCO <sub>2</sub> — mm Hg¶¶	—	40±8	40±8	42±9	39±7	44±10	0.50
Respiratory-system compliance — ml/cm of water***	—	—	—	44±19	51±19	38±15	0.002
Dead space — % of tidal volume†††	—	—	—	57±13	51±12	63±13	0.002
Shunt — % of cardiac output‡‡‡	—	—	—	39±15	34±12	45±17	0.008
Mortality — no. (% of patients)§§§	—	6 (18)	6 (18)	19 (28)	5 (15)	14 (41)¶¶¶	0.25

\* Two statistical analyses are reported: the comparison between patients with healthy lungs, patients with unilateral pneumonia, and the overall population of patients with acute lung injury or ARDS, as well as the comparison between each single group of patients (patients with healthy lungs, patients with unilateral pneumonia, patients with acute lung injury or ARDS with a lower percentage of potentially recruitable lung, and patients with acute lung injury or ARDS with a higher percentage of potentially recruitable lung). Because of rounding, percentages may not total 100. Plus-minus values are means ±SD.

† Patients in the group with a lower percentage of potentially recruitable lung had values at or below 9 percent, the median value for the study population, and patients in the group with a higher percentage of potentially recruitable lung had values greater than 9 percent.

‡ P values were obtained by one-way analysis of variance, the Kruskal-Wallis test, Student's t-test, Wilcoxon's test, and the chi-square test, as appropriate; comparisons were made between patients with healthy lungs, patients with unilateral pneumonia, and the overall population of patients with acute lung injury or ARDS.

§ P<0.05 for the comparison with patients with unilateral pneumonia.

¶ The Simplified Acute Physiology Score (SAPS II)<sup>23</sup> was used to assess the severity of systemic illness at study entry. Scores can range from 0 to 163, with higher scores indicating more severe illness.

|| P<0.01 for the comparison with patients with healthy lungs.

\*\* P<0.05 for the comparison with healthy lungs; comparisons were made between patients with healthy lungs, patients with unilateral pneumonia, patients with acute lung injury or ARDS and a lower percentage of potentially recruitable lung, and patients with acute lung injury or ARDS and a higher percentage of potentially recruitable lung.

†† P<0.01 for the comparison with patients with either healthy lungs or unilateral pneumonia.

‡‡ P<0.001 for the comparison with other groups of patients; comparisons were made between patients with healthy lungs, patients with unilateral pneumonia, patients with acute lung injury or ARDS and a lower percentage of potentially recruitable lung, and patients with acute lung injury or ARDS and a higher percentage of potentially recruitable lung.

§§ Non-aerated lung tissue is the portion of lung parenchyma with a density between +100 and -100 Hounsfield units, and aerated lung tissue is the portion of lung parenchyma with a density between -101 and -1000 Hounsfield units. For simplicity, normally aerated, poorly aerated, and hyperinflated lung tissue were classified as aerated tissue. Thus, the percentage of aerated tissue is the percentage of lung tissue open to aeration, irrespective of the specific degree of aeration.

¶¶ Measurements of PaO<sub>2</sub>:FIO<sub>2</sub> and PaCO<sub>2</sub> were available for 31 patients with unilateral pneumonia.

||| P<0.001 for the comparison with patients with acute lung injury or ARDS and a lower percentage of potentially recruitable lung.

\*\*\* Respiratory-system compliance was calculated as the ratio of the tidal volume to the difference between inspiratory plateau pressure and PEEP.

††† Dead space was calculated by a standard formula (see the Supplementary Appendix). This measurement, obtained at a PEEP value of 5 cm of water, was available for 48 patients with acute lung injury or ARDS (23 in the group with a lower percentage of recruitable lung and 25 in the group with a higher percentage of recruitable lung).

‡‡‡ The intrapulmonary right-to-left shunt was calculated by a standard formula (see the Supplementary Appendix). This measurement, obtained at a PEEP value of 5 cm of water, was available for 60 patients (29 in the group with a lower percentage of recruitable lung and 31 in the group with a higher percentage of recruitable lung).

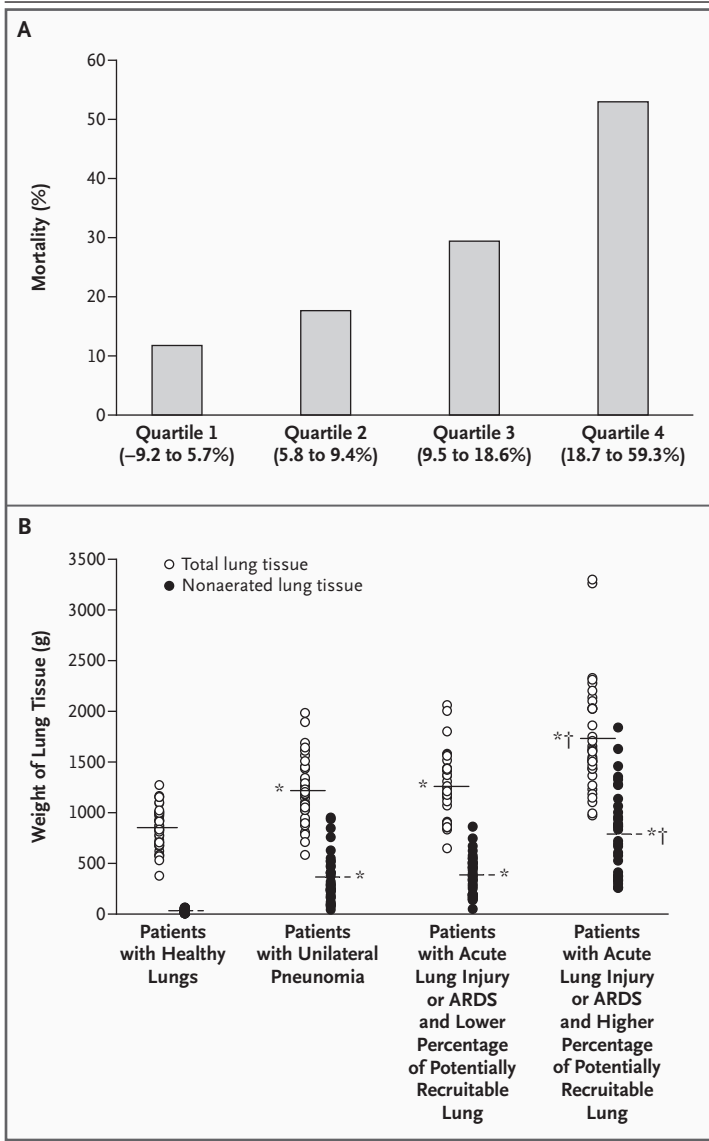
§§§ The number of deaths occurring in the hospital was recorded for patients with unilateral pneumonia and the number of deaths in the ICU for patients with acute lung injury or ARDS. The mean length of stay after admission was 25±21 days for patients in the hospital and 29±27 days for patients in the ICU; length of stay includes both patients who died and those who were discharged.

¶¶¶ P<0.05 for the comparison with patients with acute lung injury or ARDS and a lower percentage of potentially recruitable lung.

lower (P<0.001), the respiratory-system compliance was lower (P=0.002), the PaCO<sub>2</sub> was higher (P=0.02), the percentage of dead space was higher (P=0.002), the shunt fraction was higher (P=0.008), and the mortality rate was higher (P=0.02) in the group with a higher percentage of potentially recruitable lung than in the group with a lower percentage of potentially recruitable lung (Table 2).

An association was observed between the percentage of potentially recruitable lung and the risk of death (Fig. 4A). To investigate whether there was an association between mortality and other measurements of severity of illness, a multivariate analysis for independent predictors of mortality was performed. The SAPS II score was included as a marker of the overall severity of the systemic illness, and the percentage of potentially recruitable lung, the percentage of non-aerated lung tissue, the PaO<sub>2</sub>:FIO<sub>2</sub>, the PaCO<sub>2</sub>, and the respiratory-system compliance at a PEEP of 5 cm of water were included as markers of the severity of lung injury. The SAPS II score and the percentage of potentially recruitable lung appeared to be independently associated with an increased risk of death (P=0.47 by the Hosmer-Lemeshow goodness-of-fit test; C=0.78); the odds ratios for each one-point increase in the SAPS II score and in the percentage of potentially recruitable lung were 1.08 (95 percent confidence interval, 1.02 to 1.15) and 1.08 (95 percent confidence interval, 1.01 to 1.14), respectively.

We further characterized these findings as specific for acute lung injury or ARDS by retrospectively evaluating a group of 39 patients with healthy lungs and a group of 34 patients with unilateral pneumonia (20 patients who were breathing spontaneously and 14 patients who were undergoing mechanical ventilation) (see the Supplementary Appendix) and comparing the findings with those of the study population (Fig. 1). Among patients with either healthy lungs or unilateral pneumonia, the total lung weight and the proportion of non-aerated lung tissue were lower and the proportion of normally aerated lung tissue was higher than among the overall population of patients with acute lung injury or ARDS (P<0.01 for all comparisons). However, the greatest differences between patients with unilateral pneumonia and patients with acute lung injury or ARDS was among the patients in the latter group who had a higher percentage of recruitable lung. The functional anatomy, as determined by CT, appeared to



**Figure 4.** Mortality in Relation to the Percentage of Potentially Recruitable Lung (Panel A) and Pulmonary Anatomy According to CT Findings in Patients with Healthy Lungs, Patients with Unilateral Pneumonia, and Patients with Acute Lung Injury or ARDS (Panel B).

Panel A shows the mortality rate in the ICU (mean length of stay, 29±27 days; range, 2 to 163) among patients with acute lung injury or ARDS (P=0.34 by the Hosmer–Lemeshow goodness-of-fit test; C=0.72). Results are shown for quartiles of 17 patients each according to the percentage of potentially recruitable lung. Panel B shows the weights of total lung tissue and nonaerated lung tissue in 39 patients with healthy lungs, 34 patients with unilateral pneumonia, 34 patients with acute lung injury or ARDS with a lower percentage of potentially recruitable lung (at or below the overall median value of 9 percent), and 34 patients with acute lung injury or ARDS with a higher percentage of potentially recruitable lung. Data from the patients with healthy lungs and unilateral pneumonia were obtained from a whole-lung CT obtained for diagnostic purposes. Data from patients with acute lung injury or ARDS were obtained from a whole-lung CT performed at a PEEP of 5 cm of water. Solid lines represent mean values of total lung weight, and dashed lines mean values of nonaerated lung-tissue weight. Asterisks denote P<0.01 for the comparison with patients with healthy lungs; daggers denote P<0.01 for the comparison between the groups of patients with acute lung injury or ARDS and a higher percentage of potentially recruitable lung and the other three groups.

be very similar in patients with unilateral pneumonia and patients with acute lung injury or ARDS and a lower percentage of recruitable lung (Table 2 and Fig. 4B).

**PREDICTION OF THE PERCENTAGE OF POTENTIALLY RECRUITABLE LUNG**

To provide a bedside estimate of the percentage of potentially recruitable lung, we initially hypothesized that in patients with a higher percentage of potentially recruitable lung, at least two of the following three changes in respiratory variables would occur when PEEP was increased from 5 to

15 cm of water: an increase in the PaO<sub>2</sub>:FiO<sub>2</sub>, a decrease in the PaCO<sub>2</sub>, or an increase in the respiratory-system compliance. However, the power of this test to predict which patients had a higher percentage of potentially recruitable lung had a sensitivity of 71 percent and a specificity of 59 percent. A post hoc analysis was used to evaluate other combinations of different physiological respiratory variables that were tested as predictors of the percentage of potentially recruitable lung. Among these combinations, a PaO<sub>2</sub>:FiO<sub>2</sub> of less than 150 at a PEEP of 5 cm of water had a sensitivity of 74 percent and a specificity of 79 percent. The combination of variables that yielded the best results appeared to be the presence of at least two of the following: a PaO<sub>2</sub>:FiO<sub>2</sub> of less than 150 at a PEEP of 5 cm of water, any decrease in alveolar dead space, and an increase in respiratory-system compliance when PEEP was increased from 5 to 15 cm of water (sensitivity, 79 percent; specificity, 81 percent) (see the Supplementary Appendix).

## DISCUSSION

CT revealed that the percentage of potentially recruitable lung varied widely among patients with acute lung injury or ARDS, from a negligible fraction to more than 50 percent of the total lung weight. Furthermore, we demonstrated that the effect of PEEP on lung recruitment was closely associated with the percentage of potentially recruitable lung and that the percentage of potentially recruitable lung was itself highly correlated with the overall severity of lung injury.

In clinical practice, lung recruitment is usually considered a useful strategy.<sup>8,9,24</sup> For this reason, it has been suggested that the condition of patients with a high percentage of potentially recruitable lung is better than that of patients with a lower percentage of potentially recruitable lung, given the presence of similar degrees of lung injury. Surprisingly, among our patients, a higher percentage of potentially recruitable lung correlated with markedly poorer gas exchange and respiratory mechanics, a greater severity of lung injury, and a higher mortality rate, even though the severity of their systemic illness at study entry, as assessed by the SAPS II score, was similar in patients with higher and those with lower percentages of potentially recruitable lung (see the Supplementary Appendix). An association between the percentage of potentially recruitable lung and the severity of lung injury, although unexpected, appears logical. In healthy lungs, the percentage of potentially recruitable lung is close to 0 percent, because the alveolar units are usually not collapsed. When ARDS affects the lungs, the extent of the inflammatory pulmonary edema is linked to the likelihood of gravity-dependent alveolar collapse<sup>18,25</sup> and thus to the percentage of potentially recruitable lung. It is tempting to speculate that the “core disease” is reflected by the unrecruitable lung tissue at 45 cm of water (about 24 percent of the total lung weight), whereas the extent of the surrounding inflammatory reaction<sup>26</sup> is reflected by the collapsed but openable lung tissue — that is, the potentially recruitable lung.

The use of respiratory physiological variables that can be measured at the bedside to ascertain the percentage of potentially recruitable lung was less specific and sensitive than expected. However, we think that analysis of CT findings can identify the increase in aeration of previously col-

lapsed lung regions (“anatomical” lung recruitment<sup>19</sup>), whereas changes in respiratory physiological variables are specifically related to “functional” recruitment of lung tissue to participation in gas exchange — that is, to an improvement in the overall ventilation–perfusion ratio. The anatomical and the functional lung recruitment can coincide only if the restoration of aeration of pulmonary units, as detected by CT, occurs in association with the absence of a change in perfusion of the same units. Our data support the hypothesis that anatomical and functional lung recruitment are at least partially dissociated.

We believe that knowledge of the percentage of potentially recruitable lung may be important for establishing the therapeutic efficacy of PEEP. Setting levels of PEEP independently of the percentage of potentially recruitable lung, which was the strategy used by Brower et al.,<sup>12</sup> may offset the possible benefits of PEEP. Our data show that the use of higher PEEP levels in patients with a lower percentage of potentially recruitable lung provides little benefit and may actually be harmful. To determine whether different levels of PEEP may affect the outcome among patients with acute lung injury or ARDS, a formal study will be necessary, but it should be limited to patients with a higher percentage of potentially recruitable lung. Although the use of higher PEEP levels seems appropriate in these patients, it should be formally tested. Since about 60 percent of lung parenchyma is already open to aeration in patients with a higher percentage of potentially recruitable lung, this portion of the lung may be unnecessarily exposed to increased stress and strain with the use of higher PEEP levels.<sup>27</sup> While we wait for such a study to be performed, in our daily practice we limit the use of PEEP levels of more than 15 cm of water to patients with a higher percentage of potentially recruitable lung<sup>28</sup> and of PEEP levels below 10 cm of water to those with a lower percentage of potentially recruitable lung.

Dr. Gattinoni reports having received consulting and lecture fees from KCI; Dr. Ranieri reports serving as a consultant to Maquet and having received grant support from Tyco; and Dr. Quintel reports having received consulting fees from Siemens/Maquet, Novalung, Dräger Medical, Abbott Laboratories, and Gambro. No other potential conflict of interest relevant to this article was reported.

We are indebted to Angelo Colombo, M.D., Ph.D., of the Terapia Intensiva Neuroscienze, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS)—Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena di Milano, Milan, for statistical advice; to Pietro Biondetti, M.D., Marco Lazzarini, M.D., Benedetta Finamore, M.D., and Cristian Bonelli of the Dipartimento di

Radiologia, Fondazione IRCCS-Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena di Milano, Milan, for technical assistance with analysis of CT findings; to Milena Racagni, M.D., Laura Landi, M.D., Alice D'Adda, M.D., Serena Azzari, M.D., Sonia Terragni, M.D., Federico Polli, M.D., Paola Cozzi, M.D., Giuliana Motta, M.D., Federica Tallarini, M.D., Cristian Carsenzola, M.D., and Monica Chierichetti, M.D., of the Istituto di Anestesiologia e Rianimazione, Fondazione IRCCS-Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena di Milano, Università degli Studi di Milano, Milan, for help with the data analysis; to Ferdinando Raimondi, M.D., of the I Servizio di Anestesia e Rianimazione,

Ospedale Luigi Sacco di Milano, Milan; Antonio Pesenti, M.D., of the Dipartimento di Medicina Perioperatoria e Terapia Intensiva, Azienda Ospedaliera S. Gerardo di Monza, Università degli Studi Milano-Bicocca, Milan; Roberto Fumagalli, M.D., of the Dipartimento di Anestesia e Rianimazione, Ospedali Riuniti di Bergamo, Università degli Studi Milano-Bicocca, Milan; and Danilo Radrizani, M.D., of the Dipartimento Emergenza Urgenza, Ospedale Civile di Legnano, Legnano, Italy, for their cooperation in retrieving data for control groups; to the study patients for their participation; and to the physicians and nursing staff of the participating units for their valuable cooperation.

## REFERENCES

- Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;2:319-23.
- Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000;342:1334-49.
- Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998;157:294-323.
- Pontoppidan H, Geffin B, Lowenstein E. Acute respiratory failure in the adult. *N Engl J Med* 1972;287:799-806.
- Gattinoni L, Agostoni A, Pesenti A, et al. Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO<sub>2</sub>. *Lancet* 1980;2:292-4.
- Kolobov 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.
- Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 1990;16:372-7.
- Lachmann B. Open up the lung and keep the lung open. *Intensive Care Med* 1992;18:319-21.
- Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338:347-54.
- Ranieri VM, Suter 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.
- Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome: the Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8.
- Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327-36.
- Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med* 2001;164:131-40.
- Villagra A, Ochagavia A, Vataua S, et al. Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002;165:165-70.
- Grasso S, Mascia L, Del Turco M, et al. Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology* 2002;96:795-802.
- Brower RG, Morris A, MacIntyre N, et al. Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. *Crit Care Med* 2003;31:2592-7. [Erratum, *Crit Care Med* 2004;32:907.]
- Levy MM. PEEP in ARDS — how much is enough? *N Engl J Med* 2004;351:389-91.
- Gattinoni L, D'Andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. *JAMA* 1993;269:2122-7. [Erratum, *JAMA* 1993;270:1814.]
- Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med* 2001;164:1701-11.
- 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;149:818-24.
- Piazzini E, Villagra A, Lopez-Aguilar J, Blanch L. Clinical review: the implications of experimental and clinical studies of recruitment maneuvers in acute lung injury. *Crit Care* 2004;8:115-21.
- Lapinsky SE, Mehta S. Bench-to bedside review: recruitment and recruiting maneuvers. *Crit Care* 2005;9:60-5.
- Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270:2957-63. [Erratum, *JAMA* 1994;271:1321.]
- Papadakos PJ, Lachmann B. The open lung concept of alveolar recruitment can improve outcome in respiratory failure and ARDS. *Mt Sinai J Med* 2002;69:73-7.
- 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.
- Terashima T, Matsubara H, Nakamura M, et al. Local Pseudomonas instillation induces contralateral lung injury and plasma cytokines. *Am J Respir Crit Care Med* 1996;153:1600-5.
- Gattinoni L, Carlesso E, Cadringer P, Valenza F, Vagginelli F, Chiumello D. Physical and biological triggers of ventilator-induced lung injury and its prevention. *Eur Respir J Suppl* 2003;47:15s-25s.
- Grasso S, Fanelli V, Cafarelli A, et al. Effects of high versus low positive end-expiratory pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005;171:1002-8.

Copyright © 2006 Massachusetts Medical Society.