# Reversibility of Lung Collapse and Hypoxemia in Early Acute Respiratory Distress Syndrome

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*Rationale:* **The hypothesis that lung collapse is detrimental during the acute respiratory distress syndrome is still debatable. One of the difficulties is the lack of an efficient maneuver to minimize it.**
*Objectives:* **To test if a bedside recruitment strategy, capable of reversing hypoxemia and collapse in > 95% of lung units, is clinically applicable in early acute respiratory distress syndrome.**
*Methods:* **Prospective assessment of a stepwise maximum-recruitment strategy using multislice computed tomography and continuous blood-gas hemodynamic monitoring.**
*Measurements and Main Results:* **Twenty-six patients received sequential increments in inspiratory airway pressures, in 5 cm $H_2O$ steps, until the detection of $Pa_{O_2} + Pa_{CO_2} \geqslant 400$ mm Hg. Whenever this primary target was not met, despite inspiratory pressures reaching 60 cm $H_2O$, the maneuver was considered incomplete. If there was hemodynamic deterioration or barotrauma, the maneuver was to be interrupted. Late assessment of recruitment efficacy was performed by computed tomography (9 patients) or by online continuous monitoring in the intensive care unit (15 patients) up to 6 h. It was possible to open the lung and to keep the lung open in the majority (24/26) of patients, at the expense of transient hemodynamic effects and hypercapnia but without major clinical consequences. No barotrauma directly associated with the maneuver was detected. There was a strong and inverse relationship between arterial oxygenation and percentage of collapsed lung mass ($R = -0.91$; $p < 0.0001$).**
*Conclusions:* **It is often possible to reverse hypoxemia and fully recruit the lung in early acute respiratory distress syndrome. Due to transient side effects, the required maneuver still awaits further evaluation before routine clinical application.**

**Keywords:** acute lung injury; mechanical ventilation; positive end-expiratory pressure; pulmonary shunt; recruitment strategy

Lung collapse is still a concern during the critical care of patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Experimental evidence identifies the presence of airspace collapse and cyclic recruitment as pivotal elements in the development of ventilator-induced lung injury (1–7). When compared with injury caused by overdistension, cyclic alveolar recruitment and collapse due to insufficient recruitment and positive end-expiratory pressure (PEEP) seem to have similar—or even greater—impact on lung injury (1, 3–5).

In contrast with the solid experimental evidence, clinical data confirming this hypothesis are lacking. A *post hoc* analysis of randomized trials conducted on patients with ARDS indicates an association between high PEEP and low mortality (8–10), suggesting the benefits of the open-lung approach (OLA). However, in a recent multicenter randomized trial (11), the Acute Respiratory Distress Syndrome Network (ARDSnet) showed that a 4–5 cm $H_2O$ differential in PEEP had negligible effect on clinical outcome. This latter result was intriguing, suggesting that the former benefits associated with the OLA might essentially be ascribed to lower driving pressures used in that protective protocol (12) and not to the high PEEP simultaneously applied. The OLA controversy persists nowadays (13) because the randomization of this ARDSnet study was found to be unbalanced, with sicker patients selected to the high PEEP group. In addition, lung recruitment strategies were not applied to this high PEEP group.

An additional difficulty in testing the detrimental collapse hypothesis is related to the efficacy of recruitment maneuvers as conventionally proposed. Recent studies have suggested that the success rate of such maneuvers is just modest and dependent on baseline disease. In addition, the oxygenation/mechanical benefits have hardly been sustained over time (14–22). Without a significant reduction of alveolar collapse, and without sustained effects, it is always possible to allege that the negative results were related to suboptimal strategy.

Therefore, the current study proposes a new maximum-recruitment strategy (23, 24) as a preliminary step in a broader project to test the detrimental collapse hypothesis. The clinical efficacy and safety of this strategy will be compared with the previous OLA (10, 25). In addition, by evaluating the correlations between quantitative computed tomography (CT) analysis and gas exchange, we also assessed the use of the index $Pa_{O_2} + Pa_{CO_2} \geqslant 400$ mm Hg as an indicator of maximum lung recruitment in early ALI/ARDS (23). For the rationale for clinical use of such an index, *see* the online supplement. Partial results of this investigation have been previously reported in abstract form (23, 26, 27).

## METHODS

### Patients and Monitoring

The hospital's ethical committee granted approval for this study, and written, informed consent was obtained from patients' relatives. Consecutive intubated patients fulfilling criteria for early ALI/ARDS (28) were recruited. For definitive selection, blood gases had to be collected after 30 min application of 10 cm $H_2O$ PEEP and $V_T$ = 6–8 ml/kg,

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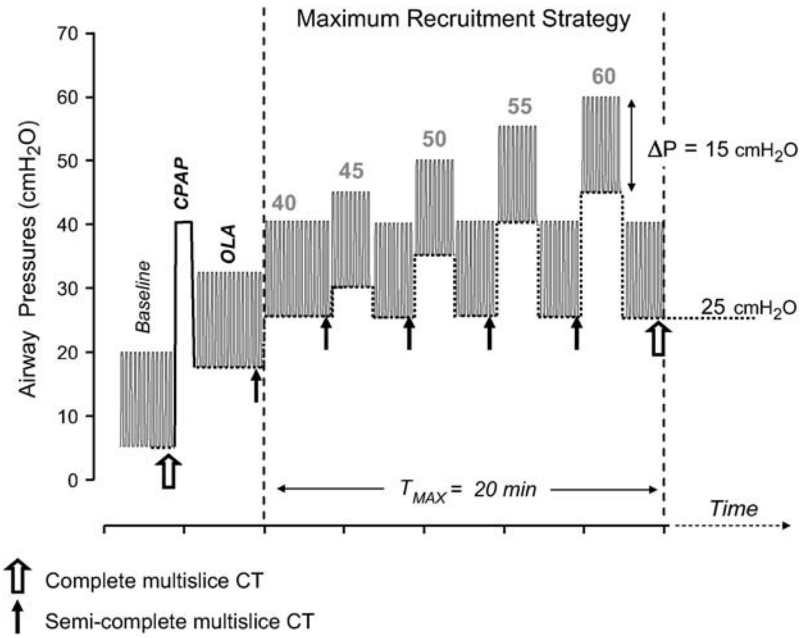


***Figure 1.*** Sketch of pressure–time tracings illustrating the ventilation protocol performed in the computed tomography (CT) room. The maximum-recruitment strategy was performed under pressure-controlled ventilation with frequency = 10/min. Stressing periods of 2 min were alternated with resting periods. *Arrows* indicate physiologic measurements plus CT scanning. CPAP = continuous positive airway pressure; OLA = open-lung approach (median positive end-expiratory pressure = 19 cm $H_2O$).

when the $Pa_{O_2}/FI_{O_2}$ had to be < 300 mm Hg. Patients had to be receiving stable doses of vasopressors, with mean arterial blood pressure > 65 mm Hg and a stable arterial lactate level over the preceding 6 h. Intraarterial blood-gas sensors (radial or femoral artery) (29) and a pulmonary artery catheter were inserted for continuous monitoring of arterial blood gases, cardiac output, and venous saturation (30, 31). Respiratory-system mechanics (32, 33), including plethysmography, were continuously recorded.

### Experimental Protocol

All patients were in the supine position, sedated, and paralyzed, and received 100% oxygen throughout the study. Fluid status was previously

**TABLE 1. ADMISSION AND BASELINE CHARACTERISTICS OF THE STUDY PATIENTS**

| Patient | Age (*yr*) | Sex | $P_{FLEX}$ (*cm $H_2O$*) | $C_{STAT}$ (*ml/cm $H_2O$*) | Predisposing Factor | $Pa_{O_2}/FI_{O_2}$ (*mm Hg*) | APACHE II | Organ Failures* (*n*) | Mech. Vent. (*d*) |
|---|---|---|---|---|---|---|---|---|---|
| 1a | 37 | F | 14.3 | 24 | Pancreatitis | 111 | 15 | 2 | 3 |
| 2a | 40 | M | 17.3 | 22 | Sepsis (peritonitis) | 167 | 15 | 3 | 1 |
| 3a | 29 | F | 17.0 | 9 | PCP, AIDS | 52 | 32 | 2 | 3 |
| 4a | 33 | M | 18.5 | 37 | Leptospirosis, pneumonitis | 269 | 12 | 0 | 3 |
| 5a | 15 | F | 22.0 | 13 | PCP, SLE | 45 | 30 | 2 | 7 |
| 6a | 20 | F | 24.0 | 11 | Bacterial pneumonia, SLE | 66 | 23 | 1 | 2 |
| 7a | 56 | M | 15.0 | 29 | Sepsis, lung strongyloidiasis | 55 | 31 | 4 | 3 |
| 8a | 83 | M | 16.0 | 29 | Sepsis, disseminated lymphoma | 59 | 24 | 3 | 4 |
| 9a | 52 | M | 17.0 | 23 | PCP, AIDS | 48 | 29 | 2 | 3 |
| 10a | 43 | F | 16.0 | 23 | PCP, AIDS | 83 | 22 | 2 | 1 |
| 11a | 46 | M | 10.0 | 35 | Aspiration pneumonia | 61 | 20 | 4 | 4 |
| 1b | 73 | F | — | 31.2 | Sepsis (infected hip prosthesis) | 184 | 24 | 2 | 2 |
| 2b | 50 | M | — | 26.7 | Bacterial pneumonia | 78 | 20 | 2 | 2 |
| 3b | 46 | M | — | 22.7 | PCP, AIDS | 69 | 19 | 1 | 1 |
| 4b | 73 | F | — | 17.0 | Sepsis (subfrenic abscess) | 208 | 21 | 2 | 4 |
| 5b | 20 | F | — | 37.5 | Sepsis (unknown source) | 294 | 12 | 2 | 1 |
| 6b | 62 | F | — | 20.3 | Bacterial pneumonia | 130 | 18 | 1 | 1 |
| 7b | 26 | M | — | 37.2 | Sepsis (vertebral arthritis) | 105 | 18 | 2 | 4 |
| 8b | 40 | F | — | 32.5 | Aspiration pneumonia | 191 | 15 | 0 | 2 |
| 9b | 46 | M | — | 31.6 | Alveolar hemorrhage | 61 | 22 | 2 | 2 |
| 10b | 61 | M | — | 66.7 | Sepsis (colangitis) | 206 | 21 | 3 | 3 |
| 11b | 50 | F | — | 27.3 | Bacterial pneumonia | 81 | 17 | 1 | 2 |
| 12b | 36 | M | — | 23.2 | Bacterial pneumonia | 69 | 15 | 1 | 2 |
| 13b | 54 | M | — | 38.2 | PCP, AIDS | 263 | 17 | 1 | 2 |
| 14b | 22 | F | — | 33.6 | Sepsis (unknown source) | 212 | 17 | 3 | 2 |
| 15b | 31 | M | — | 35.1 | Bacterial pneumonia | 161 | 20 | 1 | 1 |
| Median | 44 | | 17 | 28.2 | | 94 | 20 | 2 | 2 |

*Definition of abbreviations*: APACHE II = Acute Physiology and Chronic Health Evaluation II score; $C_{STAT}$ and $Pa_{O_2}/FI_{O_2}$ = static compliance and $Pa_{O_2}/FI_{O_2}$ ratio measured at positive end-expiratory pressure = 10 cm $H_2O$; Mech. Vent. (*d*) = days on mechanical ventilation before protocol entry; PCP = *Pneumocystis carinii* pneumonia; $P_{FLEX}$ = lower inflection point of the static P-V curve; SLE = systemic lupus erythematosus.

* Extrapulmonary organ failures detected at entry.

optimized according to a predefined protocol based on pulse-pressure variation (34–37). After baseline mechanical ventilation with PEEP = 5–10 cm $H_2O$ and VT = 6 ml/kg (predicted body weight), maintained for 8 min, all patients underwent the stepwise maximum-recruitment strategy specified in Figure 1. Exclusively for the first 11 patients, an additional protocol step was interposed before the maximum-recruitment strategy, corresponding to the OLA (25).

### OLA

After baseline mechanical ventilation, a continuous positive airway pressure of 40 cm $H_2O$ was applied for 40 s. On completion of this recruitment maneuver, PEEP was set at the lower inflexion point (identified from the inspiratory pressure–volume curve) + 2 cm $H_2O$, with driving pressures adjusted to achieve a VT of about 6 ml/kg (25, 38). OLA ventilation at this level was continued for 4 min.

### Maximum-Recruitment Strategy

After baseline or OLA, the maximum-recruitment strategy was applied. PEEP was set to 25 cm $H_2O$ and pressure-control ventilation with 15 cm $H_2O$ driving pressure was applied, producing peak airway pressures of 40 cm $H_2O$ (Figure 1). These settings were maintained for 4 min. After this, PEEP was increased to 30 cm $H_2O$ with pressure-control settings remaining unchanged, resulting in peak airway pressures of 45 cm $H_2O$. This pattern was sustained for 2 min, followed by resetting PEEP to 25 cm $H_2O$ for 2 min. Afterwards, PEEP was increased to 35 cm $H_2O$ for 2 min, followed by a return to 25 cm $H_2O$ PEEP for another 2 min. In a similar manner, this sequence of PEEP increments (5-cm $H_2O$ steps), followed by return to 25 cm $H_2O$ PEEP (resting phase), was continued until peak airway pressures of 60 cm $H_2O$ were reached, whenever necessary. Driving pressures (15 cm $H_2O$) were kept constant throughout the maneuver. All measurements were taken during the resting phase, with PEEP set at 25 cm $H_2O$.

The first step, with peak pressures at 40 cm $H_2O$, was applied to all patients. However, all next steps were conditional on measurements collected at the end of previous resting phase. The protocol was interrupted whenever our blood-gas target was identified ($Pa_{O_2} + Pa_{CO_2} \geq$ 400 mm Hg) or any of our stopping criteria was met: mixed venous oxygen saturation < 80%, mean arterial pressure < 60 mm Hg, or the development of barotrauma (on CT images). If our blood-gas target was not met despite the application of inspiratory pressures of 60 cm $H_2O$, the maneuver was terminated and the recruitment was considered incomplete.

All 26 patients received the maximum-recruitment strategy. The first 11 patients underwent this complete protocol at the CT scanner. The remaining 15 patients underwent the protocol in the intensive care unit (ICU).

### PEEP Titration

Immediately after the maximum-recruitment maneuver, all patients underwent a decremental PEEP titration. Starting from 25 cm $H_2O$, PEEP was decreased in 2 cm $H_2O$ steps and maintained at that level for 4 min, before being again reduced by 2 cm $H_2O$. This continued until we were assured that $Pa_{O_2} + Pa_{CO_2}$ was < 380 mm Hg. Throughout the PEEP trial, VT was kept at 4–5 ml/kg. After detecting the lowest PEEP maintaining the sum of blood gases $\geq$ 400 mm Hg (called optimum PEEP), patients underwent another recruitment maneuver, using the same recruiting pressures used in the last step of the maximum-recruitment maneuver. Afterwards, patients were ventilated at the optimum PEEP level.

For our check of the maintenance of recruitment efficacy, the first 11 patients had an additional CT examination after 30 min at optimum PEEP, and 15 patients (those not receiving a CT scan) had a late evaluation (blood gases, hemodynamics, and a chest X-ray) after 6 h at optimum PEEP with VT $\leq$ 6 ml/kg.

**TABLE 2. CLINICAL OUTCOMES**

| Patient | Recruitment | ICU Death | Hospital Death | Day of Death | Barotrauma* | Chest Wall Tube |
|---|---|---|---|---|---|---|
| 1a | Full | 0 | 0 | — | No | No |
| 2a | Full | 0 | 0 | — | No | No |
| 3a | Full | 1 | 1 | 1 | Subcutaneous emphysema† | No |
| 4a | Full | 0 | 0 | — | No | No |
| 5a | Incomplete | 1 | 1 | 4 | No | No |
| 6a | Incomplete | 1 | 1 | 5 | No | No |
| 7a | Full | 1 | 1 | 5 | No | No |
| 8a | Full | 0 | 1 | 30 | No | No |
| 9a | Full | 1 | 1 | 4 | Yes‡ | Yes |
| 10a | Full | 0 | 1 | 8 | No | No |
| 11a | Full | 1 | 1 | 2 | No | No |
| 1b | Full | 0 | 1 | 46 | No | No |
| 2b | Full | 0 | 0 | — | No | No |
| 3b | Full | 1 | 1 | 2 | No | No |
| 4b | Full | 0 | 1 | 32 | No | No |
| 5b | Full | 1 | 1 | 8 | No | No |
| 6b | Full | 0 | 0 | — | No | No |
| 7b | Full | 0 | 0 | — | No | No |
| 8b | Full | 0 | 0 | — | No | No |
| 9b | Full | 1 | 1 | 15 | No | No |
| 10b | Full | 0 | 0 | — | No | No |
| 11b | Full | 0 | 0 | — | No | No |
| 12b | Full | 1 | 1 | 13 | No | No |
| 13b | Full | 0 | 0 | — | No | No |
| 14b | Full | 1 | 1 | 7 | No | No |
| 15b | Full | 0 | 0 | — | No | No |
| Percentage | 92.3 | 42.3 | 57.7 | | 7.7 | 3.8 |

*Definition of abbreviation*: ICU = intensive care unit.

* Checked for new occurrences of barotrauma until discharge from the ICU.

† Observed 12 h after finishing the protocol, but not present during late (30 min) computed tomography (CT) scanning.

‡ Observed 48 h after finishing the protocol, but not present during late (30 min) CT scanning.

For mortality results: "1" represents death and "0" represents survival. Day of death means time interval (d) between protocol completion and patient death.

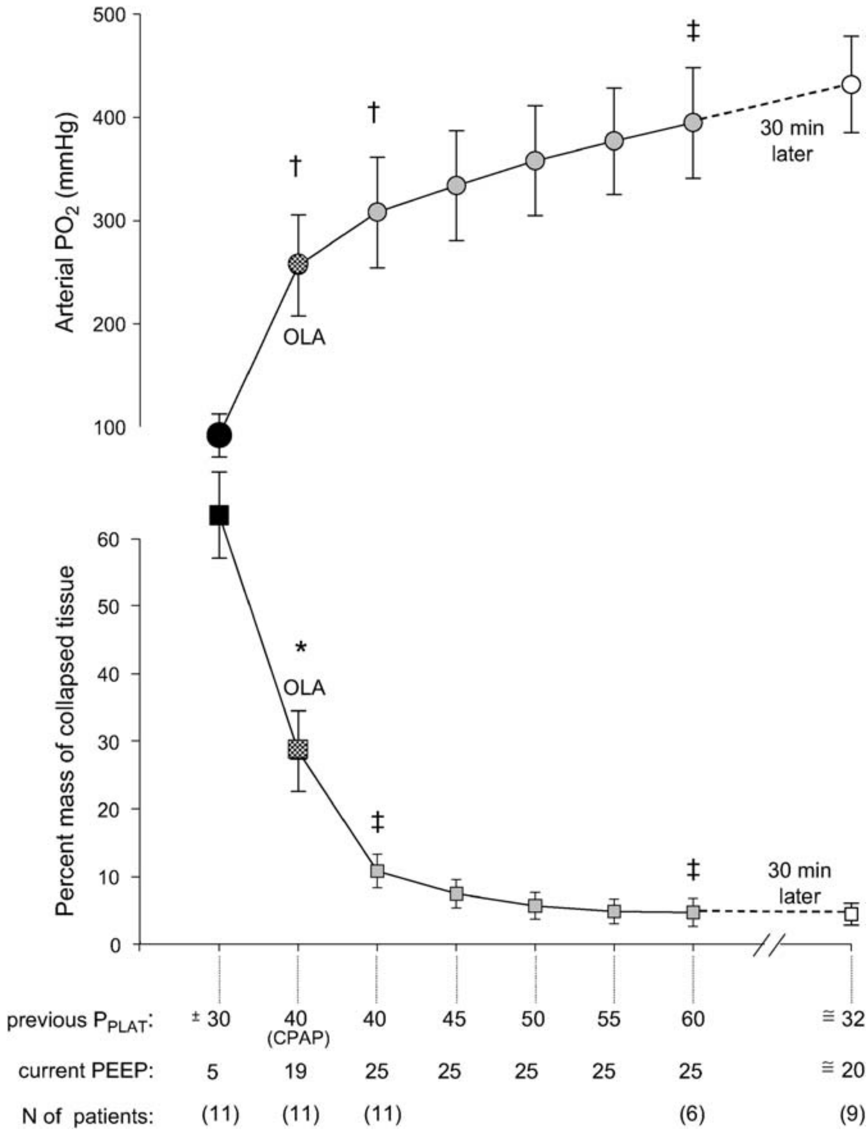


***Figure 2.*** Online oxygenation and corresponding estimate of collapsed lung mass in multislice CT scan. Oxygenation and simultaneous measurements of nonaerated lung mass detected in the first 11 patients during multislice CT. *Symbols* represent significant differences between OLA versus baseline, between first step and OLA, or between the fifth versus first step. *$p < 0.001$; †$p < 0.005$; ‡$p < 0.03$. *Error bars* represent SEM. PEEP = positive end-expiratory pressure; $P_{PLAT}$ = plateau inspiratory pressure.

### Quantitative CT Image Analysis

Complete or semicomplete (from carina to diaphragm) multislice lung CT scanning was performed at each step indicated in Figure 1, during expiratory pause.

For each slice, the inner contour of each hemithorax was manually drawn, excluding the chest wall, mediastinum, pleural effusions, and regions presenting partial volume effects (39). For each region of interest, we computed the number of voxels within each compartment: hyperinflated (−1,000 to −850 Hounsfield units [HU]), normally aerated (−850 to −500 HU), poorly aerated (−500 to −100 HU), and nonaerated (−100 to +100 HU) (40–45). A higher-than-usual threshold between normally aerated and hyperinflated compartments was intentionally chosen to increase sensitivity for detection of hyperinflated areas (44, 45). The corresponding volume (milliliters) and mass (grams) of each compartment, as well as of the whole lung, were calculated (45).

We quantified lung collapse in two ways: (*1*) nonaerated lung mass/total lung mass estimated by multislice CT at $F_{I_{O_2}} = 1$ (i.e., percent mass of collapsed tissue, our proposed definition) and (*2*) nonaerated lung volume/total lung volume under same conditions (i.e., percent volume of collapsed tissue, as proposed by previous investigators) (41, 46–49).

### Statistical Analysis

We used repeated-measures analysis of variance for the comparison of any variable collected multiple times during the protocol. The Bonferroni's adjustment for multiplicity of tests was applied for *post hoc* comparisons between critical steps in the protocol. We used multiple linear regression to assess the relationship between $Pa_{O_2}$ (dependent variable) versus CT-derived, respiratory, or hemodynamic variables (independent variables) (50–53). Because we were expecting a direct correlation between CT variables and pulmonary shunt, we used a logarithmic transformation of blood gases to linearize the relationship between $Pa_{O_2}$ and shunt levels (54). Significance was defined as a p level (bicaudal) $< 0.05$.

## RESULTS

### Characteristics of the Patients

Twenty-six patients were studied between January 1999 and April 2003. Their baseline characteristics are shown in Table 1. Clinical outcomes are listed in Table 2. In the same period, approximately 30 other patients with early ARDS/ALI were screened but not included because of hemodynamic instability or an inability to obtain informed consent.

### Efficacy of Stepwise Maximum-Recruitment Strategy

At the last step of the maximum-recruitment strategy (i.e., the fifth step or any previous step during which our target was achieved), there was a significant improvement in oxygenation

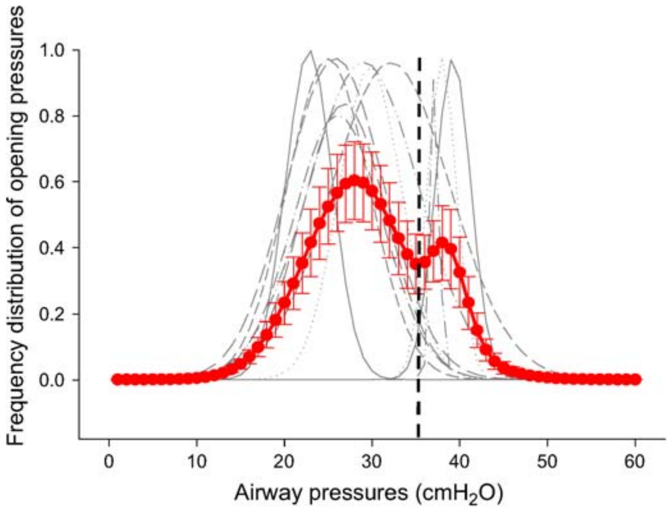


*Figure 3.* Frequency distribution of threshold opening pressures as a function of airway pressures. The distribution of opening pressures for individual patients is displayed in *gray* and the average distribution across patients in *red*. Calculations were performed according to Reference 55.

($p \leqslant 0.001$ when compared with OLA or baseline) and there was a significant reduction in the percent mass of collapsed tissue on CT analysis ($p < 0.01$ when compared with OLA or baseline; Figure 2 shows details of this evolution). The use of airway pressures above 35–40 cm $H_2O$ was crucial to achieve this additional recruitment in selected patients, as evidenced by the frequency distribution of estimated threshold opening pressures—calculated according to Crotti and colleagues (55)—on CT analysis (Figure 3).

To meet the oxygenation criteria 54% of all patients required plateau pressures more than 40 cm $H_2O$ to achieve full recruitment (Figure 4). After plateau pressure = 60 was applied, cm $H_2O$, 2 of 26 patients did not meet our blood-gas target and lung recruitment was considered incomplete (Table 2).

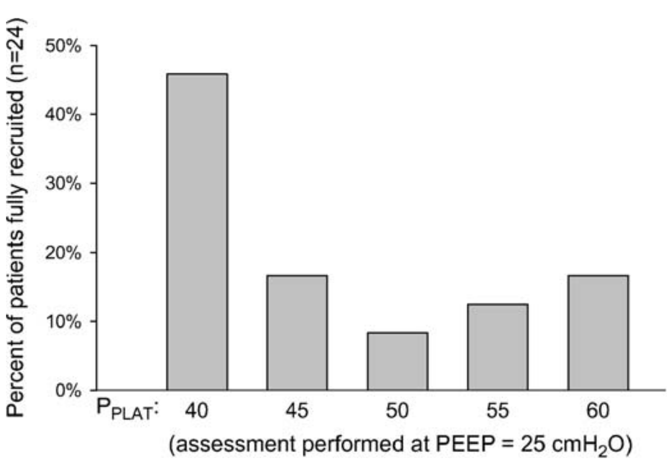


*Figure 4.* Histogram of maximum airway pressures required for full recruitment according to oxygenation criteria. Full recruitment was obtained in 24 of 26 patients (defined as $Pa_{O_2} + Pa_{CO_2} \geqslant 400$ mm Hg).

### Maintaining the Benefits of Recruitment

After the stepwise maximum-recruitment strategy plus PEEP titration procedure, nine patients were kept at optimum PEEP for 30 min (inside the CT room) and the remaining 15 patients were kept at optimum PEEP for 6 h in the ICU. As Figure 5 shows, oxygenation was maintained or increased during the period of recruitment maintenance.

### Side Effects of Stepwise Maximum-Recruitment Strategy

Table 3 exhibits hemodynamic and blood-gas measures taken during the protocol. It was never necessary to interrupt the maximum-recruitment maneuver because the stopping criteria were met.

We compared the fraction of lung volume presenting CT numbers less than −850 HU (corresponding to the hyperinflated compartment) during the first step versus last step of maximum-recruitment strategy. Even when considering the nondependent lung regions only, where hyperinflation was more likely, we could not detect any increase in this hyperinflated compartment. In fact, we observed a decrease in hyperinflation in the nondependent regions (Figure 6).

### Correlation between Oxygenation and Quantitative CT Analysis

Table 4 shows that, among all respiratory, hemodynamic, or CT-derived variables, the percent mass of collapsed tissue showed the best correlation with changes in $Pa_{O_2}$, and was responsible for 72% of the $Pa_{O_2}$ variance in the final multivariate analysis (partial correlation, $R = -0.91$; $p < 0.0001$; Table 4). The inclusion of percent mass of poorly aerated tissue slightly improved the model, explaining an additional 2% of the residual variance ($p = 0.008$).

In addition, the inclusion of dummy variables to account for between-patient effects further improved the linear regression model. The percent mass of collapsed tissue kept its strong correlation with $Pa_{O_2}$ (partial correlation, $R = -0.91$), demonstrating substantial within-patient effects. This demonstrates that the percent mass of collapsed tissue could explain a major part of the $Pa_{O_2}$ changes in the same individual during the protocol steps.

As also shown in Table 4, the percent mass of collapsed tissue was a significantly better explanatory variable for $Pa_{O2}$ variance compared with the traditional estimate of lung collapse (i.e., percent volume of collapsed tissue) (46–49). Figure 7 illustrates an important relationship: the percent-volume calculations systematically underestimated the percent-mass calculations (*see also* Figures E1 and E2 in the online supplement).

As expected from the alveolar gas equation (56), there was an inverse correlation between $Pa_{O_2}$ and $Pa_{CO_2}$ ($p < 0.001$). On average, increments of $Pa_{CO_2}$ (from 80 to 120 mm Hg) were associated with equivalent decrements (44 mm Hg) in $Pa_{O_2}$.

A sensitivity/specificity analysis confirmed the tight correlation between CT analysis and blood gases: a sum of $Pa_{O_2}$ plus $Pa_{CO_2}$ below 400 mm Hg indicated a lung condition with more than 5% of collapse with 85% sensitivity and 82% specificity (receiver operating characteristic [ROC] area = 0.943; *see* Figure E6).

## DISCUSSION

The major findings in this study can be summarized as follows: (*1*) it was possible to reverse lung collapse and to stabilize lung recruitment in the majority (24/26) of patients with early ALI/ARDS, regardless of etiology (primary or secondary); (*2*) the proposed maximum-recruitment strategy recruited the lung

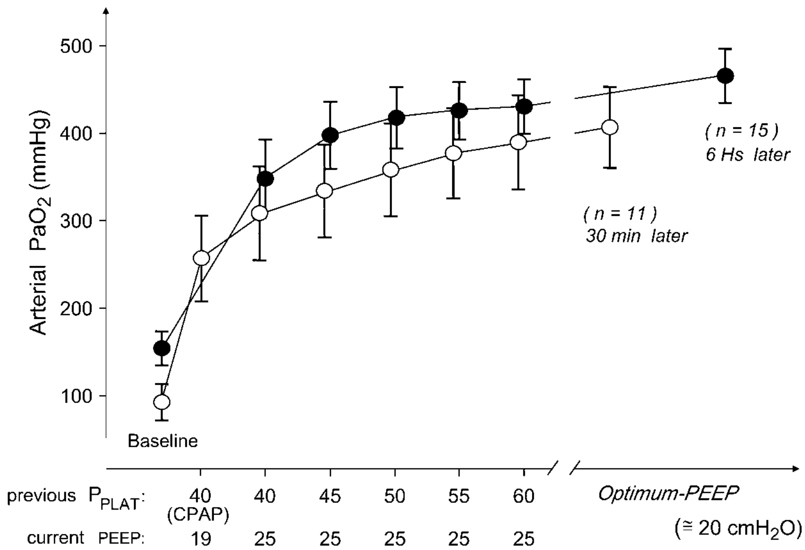


*Figure 5.* Evolution of online oxygenation during the maximum-recruitment strategy and during recruitment maintenance. Patients submitted to the recruitment protocol inside the CT room are represented by *white circles*. *Black circles* represent patients submitted to the maximum-recruitment strategy at the intensive care unit. *Errors bars* represent SEM.

significantly better than the OLA (10); (*3*) there was a strong and inverse correlation between arterial oxygenation and the amount of collapsed lung mass in multislice CT ($R = -0.91$); and (*4*) the index $Pa_{O_2} + Pa_{CO_2} \geqslant 400$ (at 100% oxygen) was a reliable indicator of maximum lung recruitment (< 5% of collapsed lung units; ROC area = 0.943).

The success rate and magnitude of lung recruitment in this study were unusual when compared with previous investigations (14–22), especially considering the high proportion of patients with primary ARDS, including patients with *Pneumocystis* pneumonia (Table 1) (19, 55, 57–62). Among the reasons explaining this efficacy, we must consider our antiderecruitment strategy (26, 63) with PEEP levels kept at 25 cm $H_2O$ during the whole recruiting phase. Such high PEEP levels were intended to work as a recruitment keeper while the patient-specific closing pressures were undetermined. After recruitment, a careful decremental PEEP titration detected the optimum PEEP level, resulting in an average PEEP of 20 cm $H_2O$. This level was still above the average lower inflection point found in our previous studies (10), and also far exceeded PEEP levels used in previous studies of lung recruitment (16–21). Of note, despite the prolonged use of hypercapnia and low tidal volumes, we could maintain a stable open lung confirmed by CT analysis (i.e., collapsed lung mass < 5%) at 30 min after recruitment, or confirmed by maintenance of oxygenation 6 h after recruitment ($Pa_{O_2} + Pa_{CO_2} \geqslant 400$ mm Hg; Figure 5).

In addition to proper PEEP levels, the estimated distribution of threshold-opening pressures illustrated in Figure 3 provides insight into the reasons for previous negative recruitment studies (55). The bimodal shape of the curve suggests that there are two main populations of alveoli in terms of opening pressures. As observed visually during CT scanning (Figure 7), zones of sticky and completely degassed atelectasis, at the most dependent lung (64), frequently require airway opening pressures above 35–40 cm $H_2O$ to recruit (65, 66). Had we not challenged the lung to airway pressures ≅ 60 cm $H_2O$, we might have

**TABLE 3. HEMODYNAMIC AND GAS EXCHANGE MEASURES**

| Situation | Baseline (*n* = 26) | OLA (*n* = 11) | Step 1 (*n* = 26) | Step 2 (*n* = 17) | Step 3 (*n* = 13) | Step 4 (*n* = 11) | Step 5 (*n* = 8) | Titrated PEEP (*n* = 24) |
|---|---|---|---|---|---|---|---|---|
| Cardiac index, ml/min/m², mean (SD) | 5.8 (± 1.9) | 4.7 (± 1.4) | 5.7 (± 1.7) | 5.3 (± 1.8) | 4.8 (± 1.8) | 4.7 (± 1.7) | 4.7§ (± 1.9) | 5.1 (± 1.4) |
| Mean arterial pressure,* mm Hg, mean (SD) | 84 (± 16) | NA | 88 (± 13) | 87 (± 11) | 90 (± 14) | 91 (± 14) | 93† (± 14) | 97 (± 20) |
| Mixed venous saturation, %, mean (SD) | 77 (± 16) | 85† (± 7) | 86‡ (± 8) | 85 (± 8) | 87 (± 7) | 87 (± 7) | 88‡ (± 7) | 86† (± 10) |
| Arterial pH, mean (SD) | 7.15 (± 0.12) | 7.11† (± 0.11) | 7.13 (± 0.13) | 7.10 (± 0.14) | 7.08 (± 0.15) | 6.99 (± 0.11) | 6.94‖ (± 0.11) | 7.15 (± 0.14) |
| Arterial $P_{CO_2}$, mm Hg, mean (SD) | 64 (± 18) | 75† (± 19) | 70 (± 25) | 75 (± 27) | 81 (± 30) | 89 (± 31) | 95‡ (± 34) | 64 (± 18) |
| Ventilator settings during measurements | | | | | | | | |
| PEEP, cm $H_2O$, mean | 5 | 19 | 25 | 25 | 25 | 25 | 25 | 20 (± 5) |
| $P_{PLAT}$, cm $H_2O$, mean | 30 | 31 | 40 | 40 | 40 | 40 | 40 | 32 (± 6) |
| Previous recruiting pressure, cm $H_2O$ | — | 40 | 40 | 45 | 50 | 55 | 60 | — |

*Definition of abbreviations*: NA = not applicable; PEEP = positive end-expiratory pressure; $P_{PLAT}$ = plateau inspiratory pressure.
* For logistical reasons, arterial blood pressure was continuously monitored only for the last 15 patients.
† $p < 0.05$ when compared with baseline (repeated-measures analysis of variance [ANOVA]).
‡ $p < 0.01$ when compared with baseline (repeated-measures ANOVA).
§ $p < 0.01$ when compared with Step 1 (repeated-measures ANOVA).
‖ $p < 0.001$ when compared with baseline (repeated measures ANOVA).

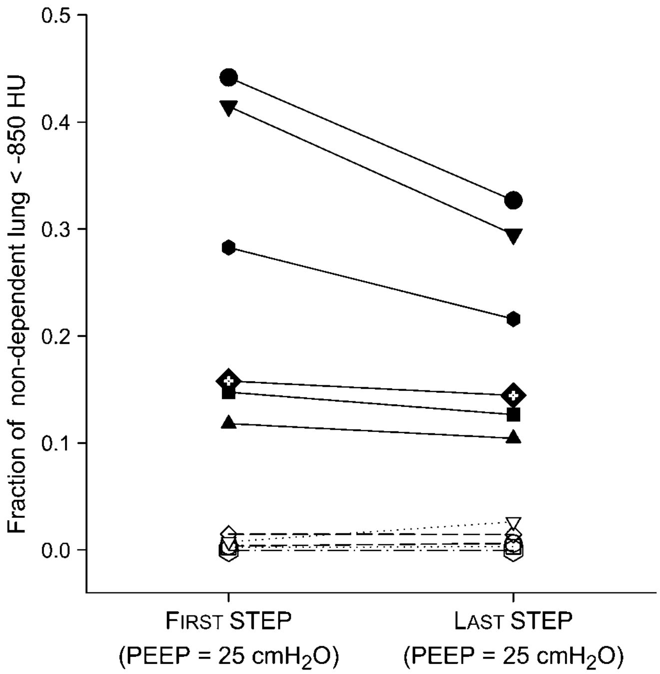


***Figure 6.*** Evolution of nondependent lung hyperinflation. Measurements after the first and last steps of the recruiting maneuver. The decrease of hyperinflated areas was marginally significant ($p = 0.06$) and more prominent in patients with marked hyperinflation before the maneuver ($p = 0.03$, $n = 6$, *black symbols*). Each *symbol* represents an individual patient.

concluded, as previous investigators did (55), that less than 50% of early ARDS can be recruited (Figure 4). The only previous investigation suggesting a similar efficacy of recruitment was the study of Schreiter and colleagues (67), although restricted to a population of patients with chest trauma. Not surprisingly, the protocol was the only one including similarly high inspiratory opening pressures (≅ 65 cm $H_2O$).

When compared with the maximum-recruitment strategy, the OLA (25) was clearly suboptimal. Likely, the combination of insufficient opening pressures and time of application, associated with suboptimal PEEP levels, resulted in significant collapse on CT (≅ 28% of the parenchymal mass) and $Pa_{O_2}$ levels only around 250 mm Hg. This result is in agreement with our previous trial, where we measured shunt levels around 25% in the OLA arm (10). Considering the blood-gas data reported in the recent ARDSnet trial (11), the present investigation also suggests that a recruitment protocol could have further enhanced their oxygenation results.

### Side Effects

Major side effects anticipated for this intense recruitment strategy were barotrauma, hemodynamic impairment, and hyperinflation.

As shown in Table 3, there was transient decrease in cardiac index during the maneuver (Figure E10), not accompanied by deterioration in mixed-venous saturation, or by decrease in systemic arterial blood pressure. We did not observe any direct clinical consequence of such perturbation, but a definitive conclusion about risks deserves further investigation.

The two cases of barotrauma reported in Table 2 occurred after protocol completion and probably reflect the usual

**TABLE 4. VARIABLES EXPLAINING ARTERIAL $P_{O_2}$ CHANGES DURING THE PROTOCOL USING MULTIPLE LINEAR REGRESSION**

| | | | Multivariate Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate Analysis | | Best Model | | Adjusted for "between-patients effect" | | Forcing Inclusion of "% vol of collapsed tissue" | |
| Independent Variables | p Value | Partial Correlation | p Value | Attributable Variance* | p Value | Attributable variance * | p Value | Attributable Variance * |
| Total gas volume | < 0.0001 | 0.55 | 0.04 | — | | | | |
| Percent mass of | | | | | | | | |
| *Collapsed tissue* | ***< 0.0001*** | ***−0.83*** | ***< 0.0001*** | ***71.6%*** | ***< 0.0001*** | ***33.0%*** | ***< 0.0001*** | ***9.3%*** |
| *Poorly aerated tissue* | ***0.482*** | ***−0.08*** | ***0.008*** | ***1.8%*** | ***0.001*** | ***1.3%*** | ***0.001*** | ***1.4%*** |
| Normally aerated tissue | < 0.0001 | 0.76 | 0.93 | — | | | | |
| Hyperinflated tissue | 0.003 | 0.32 | 0.93 | — | | | | |
| Percent volume of | | | | | | | | |
| Collapsed tissue | < 0.0001 | −0.77 | — | — | | | ***0.15*** | ***0.5%*** |
| Poorly aerated tissue | 0.025 | −0.25 | 0.58 | — | | | | |
| Normally aerated tissue | < 0.0001 | 0.74 | 0.08 | — | | | | |
| Hyperinflated tissue | 0.043 | 0.23 | 0.96 | — | | | | |
| PEEP | < 0.0001 | 0.57 | 0.02 | — | | | | |
| Previous plateau pressure | < 0.0001 | 0.48 | 0.03 | — | | | | |
| Compliance | 0.001 | 0.37 | 0.28 | — | | | | |
| Tidal volume | < 0.0001 | 0.50 | 0.41 | — | | | | |
| *Arterial $P_{CO_2}$* | ***0.003*** | ***−0.32*** | ***0.001*** | ***3.0%*** | 0.91 | — | ***0.0003*** | ***3.5%*** |
| Cardiac index | 0.51 | −0.08 | 0.44 | — | | | | |
| Mixed venous saturation | < 0.0001 | 0.63 | 0.09 | — | | | | |
| Best multivariate model | | | < 0.0001 | 80.7% | < 0.0001 | 92.0% | < 0.0001 | 82.1% |

*Definition of abbreviation*: PEEP = positive end-expiratory pressure.

* Attributable variance: percent of variance in the dependent variable explained by the indicated independent variable. It corresponds to the $R^2$ change in the preadjusted model after inclusion of indicated variable.

Variables included in the multivariate models are in bold italics. The remaining variables, in roman type, represent those left out of final model. As shown in the table, the consistency of the best multivariate model, which included the percent mass of collapsed tissue (as opposed to the percent-volume-of-collapse-tissue variable), is further supported by two important findings: (*1*) its higher univariate correlation with $Pa_{O_2}$ and (*2*) the forced inclusion of the "percent volume" variable in the final/best multivariate model resulted in no gain of information ($p = 0.15$). On the contrary, the forced inclusion of "percent mass" in an alternative model (previously adjusted for the "percent volume" variable) produced a reduction of 9.3% in the residual variance of $Pa_{O_2}$ ($p < 0.0001$).

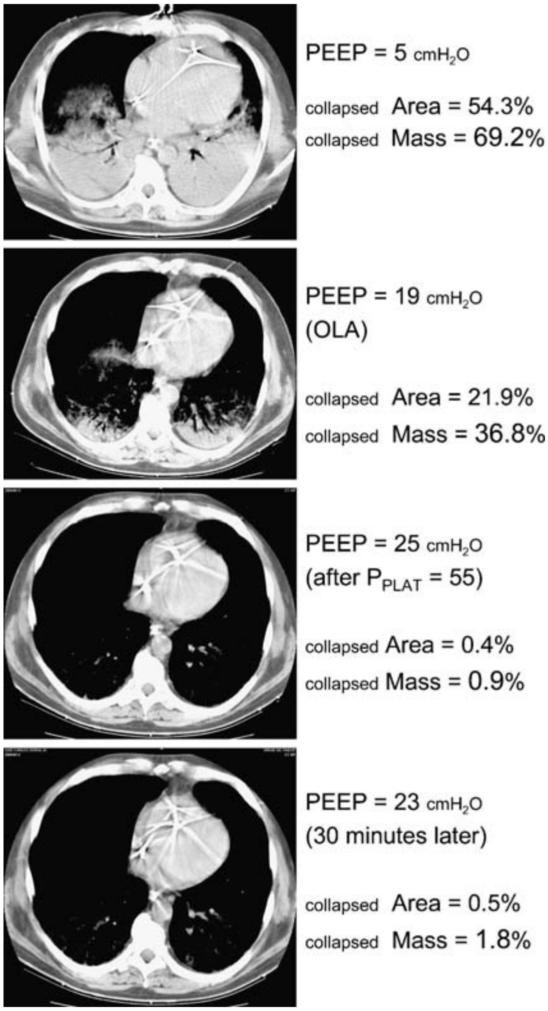


***Figure 7.*** Sequential CT scans obtained in a representative patient during meaningful protocol steps. CT images obtained at baseline, OLA, maximum recruitment, and 30 min later in Patient 9a. The amount of collapsed lung is expressed in two ways: (*1*) as percentage of lung mass, and (*2*) as percentage of lung volume. Both were calculated from multiple slices.

incidence of barotrauma in recent ARDS series (≅ 10%) (12). In line with this observation, none of our patients demonstrated increased hyperinflation on CT. In fact, Figure 6 suggested the opposite: during the protocol, there was a slight decrease of hyperinflation in nondependent lung zones. Massive recruitment with an overall increase in pleural pressure, consequently decreasing transpulmonary pressures at nondependent zones (68), may explain such findings.

We believe that three major precautions minimized potential side effects in this study: (*1*) all patients were previously optimized in terms of vascular volume (34–37, 69) and vasopressor infusion; (*2*) we used pressure-controlled cyclic ventilation instead of vital capacity maneuvers (sustained pressures) during the high stress phases, theoretically minimizing hemodynamic impairment (70–73); and (*3*) the stepwise protocol individualized the opening pressures applied, using the minimum necessary for that individual.

### Correlation between CT and Blood Gases

In contrast with previous investigations, we could demonstrate a high correlation ($R \leqslant -0.91$; Figure 8) between arterial oxygenation and CT estimates for lung collapse (74). According to our multivariate analysis, more than 70% of the acute changes in $Pa_{O_2}$ could be explained by reversible changes in the amount of airspace collapse.

We believe that important methodologic aspects in our study explain such findings. First, each blood-gas/CT-scan pair was obtained at 100% oxygen, during hypoventilation, and after waiting a few minutes under a monotonous ventilation pattern before the next protocol step. Under such conditions, the physiology of gas exchange probably became simplified, exclusively determined by the relative proportion of two major compartments: the aerated and the fully collapsed one. That is, the partially collapsed zones could no longer disturb gas exchange because of the following: (*1*) the few regions with very low ventilation/perfusion ratios rapidly disappeared, being converted to fully collapsed units (generating true shunt) before the moment of our measurement (75, 76); and (*2*) the remaining not-so-low ventilation/perfusion areas, also receiving poor ventilation through intermittently connected airways (but generating enough refreshment to keep the unit patent), could no longer disturb arterial oxygenation due to the absence of nitrogen; inside those alveolar units, any air pocket would necessarily contain a high partial pressure of oxygen, probably producing normal postcapillary $Po_2$ (77, 78). Thus, under such particular circumstances, any impairment in gas exchange should be related to the magnitude of pulmonary shunt, rather than to ventilation/perfusion imbalances. Our regression analysis corroborated this hypothesis: the presence of poorly aerated areas (probably low ventilation/perfusion areas [39]) was responsible for $\leqslant 2\%$ of the residual variance in $Pa_{O_2}$, whatever the regression model (Table 4).

When defining lung collapse during CT analysis, we innovated by calculating the ratio between the mass of atelectatic tissue versus the total lung mass (instead of the traditional volume ratio [46–49]), anticipating that such an estimate would be a reasonable surrogate of pulmonary shunt. In fact, we simply assumed that lung mass should correspond to septal tissue, homogenously filled by capillaries, and that the perfusion per gram of tissue was the same in open or closed areas (i.e., there was negligible hypoxic pulmonary vasoconstriction). These assumptions imply that (*1*) the proportion of nonrecruited/(recruited + nonrecruited) lung mass should correspond to the proportion of capillaries in collapsed areas versus capillaries in the whole lung and (*2*) assuming that capillaries were homogeneously perfused, this proportion should correspond to pulmonary shunt (i.e., the percentage of blood passing through capillaries not participating in gas exchange). The results shown in Table 4 support the rationale of such definition, demonstrating that this new estimate outperformed ($p < 0.0001$) the explanatory power of previous definitions (42, 46–49, 74, 79).

Based on preliminary experience with CT (23, 24), we assumed a methodologic hypothesis for this study—that is, that the detection of $Pa_{O_2} + Pa_{CO_2} \geqslant 400$, while the patient was receiving 100% oxygen, would be a reliable index of complete lung recruitment. Our results validate our hypothesis (Figure 8). Also, the agreement analysis suggests that this formula matches a convenient threshold in quantitative CT analysis, indicating the presence of < 5% collapsed lung mass, with good sensitivity/specificity (*see* Figure E6).

The reason for including $Pa_{CO_2}$ in the formula came from the theoretical consideration that increments of $Pco_2$ in the alveolar space decrease the alveolar $Po_2$ in approximately a 1:1 ratio (*see* Figure E5), especially under low shunt conditions (< 10%) (80). Our regression analysis confirmed this rationale (Table 4), showing an inverse and significant relationship between arterial $Po_2$ and $Pa_{CO_2}$, with an approximate 1:1 ratio.

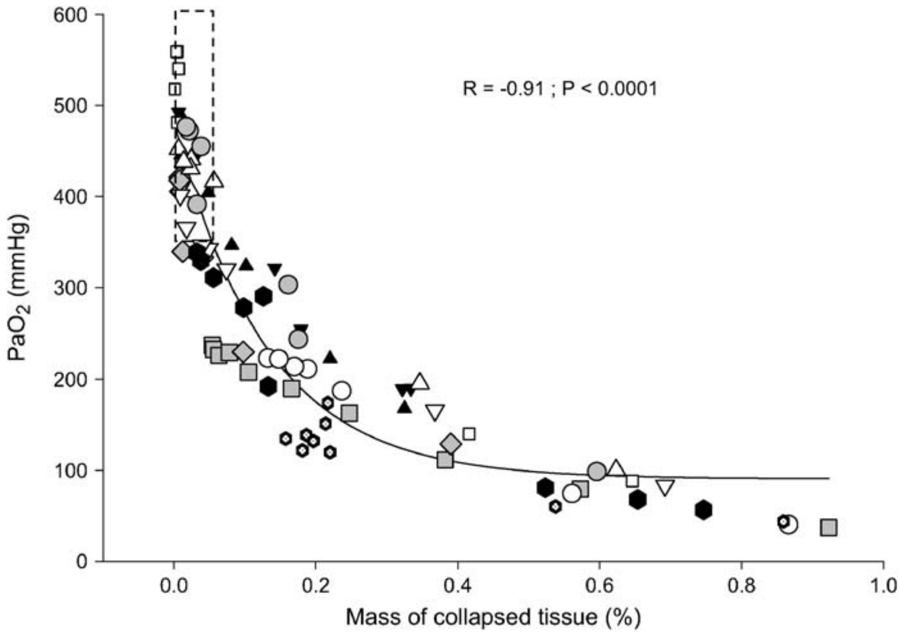


***Figure 8.*** Partial correlation between online $Pa_{O_2}$ and collapsed lung mass (expressed as percent of total lung mass in multislice CT). Samples in the same individual are represented by the same *symbol*. The percentage of collapsed lung mass explained 72% of $Pa_{O_2}$ variance. Note that, at $Pa_{O_2}$ levels above 320 mm Hg (equivalent to $Pa_{O_2} + Pa_{CO_2} \geqslant 400$ mm Hg), most CT scans presented $< 5\%$ of collapse (*marked area*). The arterial $Po_2$ values were corrected according to the predicted effects of other independent variables, drawn from the coefficients of multivariate regression. We used the equation of the best model shown in Table 4. Data points were adjusted to a $Pa_{CO_2} = 80$ mm Hg, which was the average value for all samples. Each *symbol* represents an individual patient.

### Limitations

Although many patients were receiving vasopressors, the proposed maximum-recruitment strategy was only applied after intensive fluid resuscitation and after excluding patients who were rapidly deteriorating. Therefore, one should be cautious about its application to patients not intensively monitored and resuscitated.

Furthermore, the results reported here concern approximately half of patients with ARDS screened and some selection bias must be considered. However, because all exclusions were related to nonfulfillment of predefined criteria for hemodynamic stability or failure to obtain informed consent, the bias, if any, could affect results related to hemodynamic tolerance, but hardly the reported rate of collapse reversal.

### Clinical Implications

Our data suggest that it is possible to reverse the hypoxemia present in the majority of patients with early primary or secondary ARDS because its major cause is reversible airspace collapse with pulmonary shunt. Our strategy results in a sustained recruitment of more than 95% of airspace on CT analysis, at the expense of transient fall in cardiac output, but without directly associated barotrauma. However, whether this strategy will improve outcome or reduce ventilator associated lung injury are matters for future studies.

*Conflict of Interest Statement*: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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