

Mechanism by Which a Sustained Inflation Can Worsen Oxygenation in Acute Lung Injury

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Background: Sustained lung inflations (recruitment maneuvers [RMs]) are occasionally used during mechanical ventilation of patients with acute lung injury to restore aeration to atelectatic alveoli. However, RMs do not improve, and may even worsen, gas exchange in a fraction of these patients. In this study, the authors sought to determine the mechanism by which an RM can impair gas exchange in acute lung injury.

Methods: The authors selected a model of acute lung injury that was unlikely to exhibit sustained recruitment in response to a lung inflation. In five sheep, lung injury was induced by lavage with 0.2% polysorbate 80 in saline. Positron emission tomography and [¹³N]nitrogen were used to assess regional lung function in dependent, middle, and nondependent lung regions. Physiologic data and positron emission scans were collected before and 5 min after a sustained inflation (continuous positive airway pressure of 50 cm H₂O for 30 s).

Results: All animals showed greater loss of aeration and higher perfusion and shunting blood flow in the dependent region. After the RM, Pao₂ decreased in all animals by 35 ± 22 mmHg (P < 0.05). This decrease in Pao₂ was associated with redistribution of pulmonary blood flow from the middle, more aerated region to the dependent, less aerated region (P < 0.05) and with an increase in the fraction of pulmonary blood flow that was shunted in the dependent region (P < 0.05). Neither respiratory compliance nor aeration of the dependent region improved after the RM.

Conclusions: When a sustained inflation does not restore aeration to atelectatic regions, it can worsen oxygenation by increasing the fraction of pulmonary blood flow that is shunted in nonaerated regions.

THE use of sustained lung inflations to reverse alveolar derecruitment dates back to the 1960s, when they were first used to preserve oxygenation and lung compliance in patients undergoing general anesthesia.¹ Their efficacy in reexpanding atelectatic lung regions during general anesthesia was later confirmed by computed tomography imaging studies.² In recent years, sustained lung inflations (often referred to as *recruitment maneuvers* [RMs]) have been increasingly used to reverse the alveolar derecruitment associated with "low" tidal volume ventilation in patients with acute lung injury (ALI) and

acute respiratory distress syndrome.³⁻⁶ The rationale behind this use of RMs is that intermittent lung inflations can recruit nonaerated alveoli, thus decreasing shunt and favoring a more even distribution of tidal volume among alveolar units, without exposing the lung to the trauma associated with persistent large-volume ventilation.

However, RMs have unexpectedly been reported to worsen oxygenation in a fraction of patients with acute respiratory distress syndrome.⁷ Although physiologic determinants of the response to RMs have been proposed,⁸ the mechanism by which an RM can worsen gas exchange in ALI has not been elucidated. Intuitively, an RM would be expected to improve gas exchange, by recruiting atelectatic alveoli and decreasing shunt. However, if the predominant effect of a sustained lung inflation were to redistribute pulmonary blood flow toward nonaerated regions rather than to recruit atelectatic alveoli, it might worsen gas exchange. This mechanism might explain the worsening of oxygenation observed in some patients with acute respiratory distress syndrome after an RM⁷ as well as the lack of correlation between changes in lung volume and changes in oxygenation reported in some clinical⁷ and experimental⁹ studies of ALI.

In this study, we tested the mechanistic hypothesis that, in ALI, when a sustained lung inflation fails to restore substantial aeration to atelectatic regions, it can worsen gas exchange by diverting pulmonary blood flow to nonaerated regions. To test this hypothesis, we used [¹³N]nitrogen (¹³N₂) and positron emission tomography (PET) to assess the effect of an RM on regional pulmonary perfusion, regional shunting, and regional gas content in an experimental model of ALI. We specifically selected a model that was unlikely to exhibit sustained and substantial recruitment in response to lung inflation.

Materials and Methods

Protocol

The study was approved by our institution's Subcommittee on Research Animal Care (Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts). Five sheep, weighing 21 ± 2 kg (mean ± SD), were anesthetized with thiopental sodium (25-mg/kg intravenous bolus followed by 20 mg · kg⁻¹ · h⁻¹), tracheostomized, paralyzed with pancuronium (0.1 mg · kg⁻¹ · h⁻¹), and mechanically ventilated. An arterial line and a Swan-Ganz catheter (model 93A-131H-7F; Edwards Laboratory, Santa Ana, CA) were inserted through the femoral vessels and used for measurements of systemic

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and pulmonary hemodynamics. An additional catheter was inserted through the right internal jugular vein into the superior vena cava for administration of $^{13}\text{N}_2$ -saline solution.

Lung injury was induced by lavage with 500 ml polysorbate 80, 0.2% (Tween 80; Uniqema, Wilmington, DE), in warm normal saline.¹⁰ After the saline was instilled in the trachea, the animal was turned 360° to make the injury more homogeneous. The saline was drained from the bronchial tree after 1 min of apnea. After the injury, animals were ventilated with an inspired oxygen fraction (FIO_2) of 1, a positive end-expiratory pressure (PEEP) of 0 cm H_2O (zero end-expiratory pressure [ZEEP]), a respiratory rate of 18 breaths/min, and a tidal volume of 11–13 ml/kg. If PaO_2 was greater than 300 mmHg at 30 min after the injury, a second lavage was performed. If PaO_2 was less than 60 mmHg, a PEEP trial of 5, 10, and 15 cm H_2O was performed, and PEEP was set at the value that maximized oxygenation and was kept constant thereafter. After this algorithm, animals 1, 2, and 3 were studied at ZEEP and animals 4 and 5 were studied at, respectively, PEEPs of 15 and 10 cm H_2O . After the target level of hypoxemia was achieved (*i.e.*, $\text{PaO}_2 < 300$ mmHg), the animals were transported from the surgical preparation suite to the PET suite. During transport (approximately 2 min), the animals were ventilated with an Ambu bag at an FIO_2 of 1, and animals 4 and 5 were maintained on the previously set level of end-expiratory pressure by means of a PEEP valve. In the PET suite, the animals were reconnected to the mechanical ventilator, and the previously set ventilatory parameters were resumed. At least 90 min of stabilization⁹ was allowed after transport to the PET suite before the baseline measurements and at least 2 h passed between the last lavage and the baseline measurements.

The study protocol consisted of a baseline (*i.e.*, pre-RM) set of physiologic measurements and PET scans. A volume–pressure (VP) curve of the respiratory system, starting at ZEEP, was then performed, followed by continuous positive airway pressure of 50 cm H_2O for 30 s, release of airway pressure to ZEEP, and a second VP curve. Airway pressure was continuously monitored during the sustained inflation to ensure that it remained at 50 cm H_2O . After the second VP curve, airway pressure was released to the original level of end-expiratory pressure. The VP curves were created by stepwise inflation of the lungs from ZEEP to an airway pressure of 55 cm H_2O and were curve fitted as previously described.^{11,12} Each VP curve took approximately 45 s. Therefore, the total duration of the sequence VP curve–sustained inflation–VP curve was approximately 2 min. In a sense, this entire sequence can be regarded as an RM with repeated inflations. Static inflation compliance of the respiratory system was computed as the volume change above functional residual capacity, measured at 20 cm H_2O of airway pressure from the VP curve, divided by 20 cm H_2O .

In the two animals that were on PEEP, end-expiratory pressure was briefly (approximately 1–2 s) released to ZEEP only at the beginning of each VP curve; otherwise, it was maintained at the initially set PEEP level throughout the measurements.

A post-RM set of physiologic measurements was taken between 3.5 and 4 min after the last VP curve. PET scans were started at 4 min after the last VP curve.

Physiologic Measurements

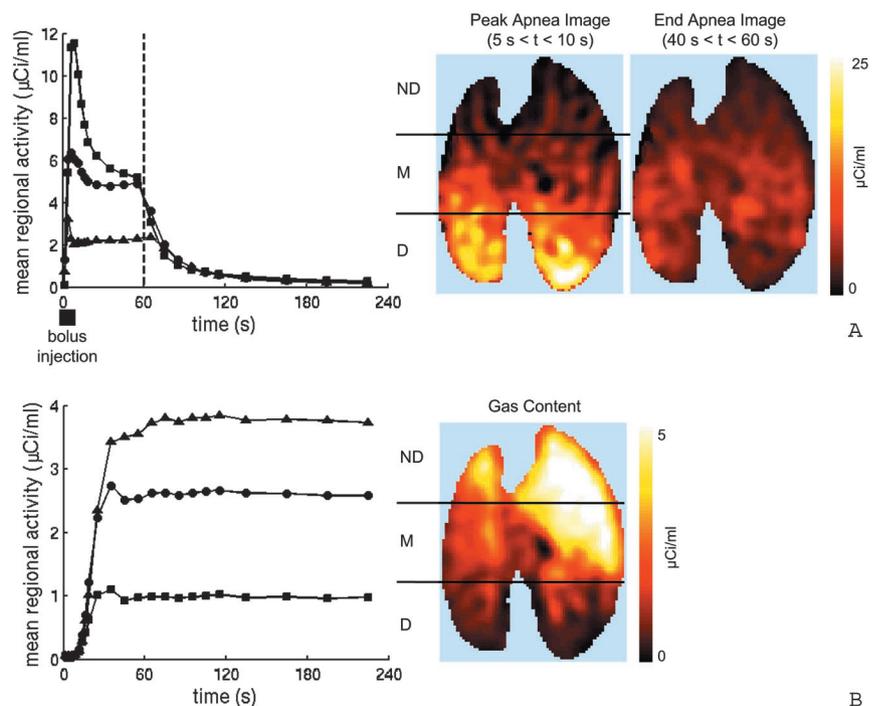
Airway, arterial, and pulmonary arterial pressures were monitored using a strip chart recorder (Hewlett Packard Inc., Palo Alto, CA). Cardiac output was measured by thermodilution (model COM-1; Edwards Laboratory). Blood gases were measured using a rapid blood gas analyzer (model ABL5/BPH5; Radiometer Medical, Copenhagen, Denmark).

PET Measurements

We used a PC-4096 PET scanner (Scanditronix AB, Uppsala, Sweden) that imaged 15 contiguous, 6-mm-thick slices of thorax. Therefore, the imaged lung field did not encompass the entire lung. The spatial resolution of the scanner was 6 mm full-width half-maximum. The imaging protocol and image processing were as described previously.^{13–16} Briefly, with the animal positioned supine in the PET scanner, a single, 10-min transmission scan was performed by using a uniform rotating-pin source of ^{68}Ge . The transmission scan was used to correct $^{13}\text{N}_2$ emission scans for absorption of annihilation photons by body tissues and supporting structures and to identify the lung fields. $^{13}\text{N}_2$ emission scans were then performed in each experimental condition (*i.e.*, before and after RM) to assess regional lung function.

In the PET suite, a previously described custom-made ventilator system was used.¹⁴ This system had two features that made it suited for $^{13}\text{N}_2$ PET scanning. First, it could be switched between an open and a closed configuration while maintaining a constant ventilatory pattern. Therefore, it allowed alveolar equilibration with inhaled $^{13}\text{N}_2$ without disruption of the ventilatory mode and pattern (see $^{13}\text{N}_2$ Inhalation [Regional Gas Fraction] Scan). Second, the end-expiratory pressure could be instantaneously switched between two pressure levels by activating, through a solenoid valve, one of two expiratory lines positioned in parallel. A first level corresponded to the end-expiratory pressure set for mechanical ventilation of each animal (ZEEP or PEEP, depending on the animal). A second level could be set at any desired value of pressure by means of a mechanical valve, and this pressure was maintained by a bias flow even when this second expiratory line was not “active.” By stopping the ventilator and simultaneously activating the solenoid valve, the animal could thus be switched to any preset level of continuous positive airway pressure.

Fig. 1. [^{13}N]nitrogen ($^{13}\text{N}_2$) tracer kinetics and positron emission tomography (PET) images for one animal. Tracer kinetics are shown separately for nondependent (ND; triangles), middle (M; circles), and dependent (D; squares) regions of lung of equal height. In each PET image, the left lung is on the left and the right lung is on the right. (A) After intravenous injection of a bolus of $^{13}\text{N}_2$ -saline over 3 s, PET images were acquired during 60 s of apnea and 3 min of ensuing ventilation. During apnea (left of dashed vertical line), the D region had both a higher peak concentration of $^{13}\text{N}_2$, indicative of higher perfusion per voxel, and a greater clearance of $^{13}\text{N}_2$, indicative of higher shunt, than the M and ND regions. This topographical information is readily visualized from one PET slice of lung, which shows that the D region had greater activity than the M and ND regions during the early (5 s < t < 10 s) phase of apnea (left PET image). The activity in the D region decreased substantially by the end of apnea, whereas this decrease was much less pronounced in the M and ND regions (right PET image). (B) After inhalation of $^{13}\text{N}_2$ through a closed-circuit ventilator system, sequential PET images were acquired during wash-in and equilibration of tracer. Because $^{13}\text{N}_2$ remains confined to the alveolar airspace, its concentration after equilibration is proportional to regional gas content. As both the tracer kinetics and the equilibration PET image show, there was a vertical gradient in gas content, which was lowest in the D region.



$^{13}\text{N}_2$ -Saline Infusion (Regional Perfusion) Scan.

The principle of the $^{13}\text{N}_2$ -saline bolus infusion technique is based on the low solubility of nitrogen in water and tissue (partition coefficient $\lambda_{\text{water/air}} = 0.015$ at 37°C). When $^{13}\text{N}_2$, dissolved in saline (approximately 30 ml), is injected intravenously as a bolus during apnea, the concentration of $^{13}\text{N}_2$ in lung regions that are perfused and aerated increases rapidly until it reaches a plateau that is proportional to regional perfusion.^{13,16,17} Because of its low solubility in blood, on arrival into the pulmonary capillaries, virtually all $^{13}\text{N}_2$ evolves into the alveolar air space at first pass, where it is retained until ventilation is resumed. In contrast, regions of the lung that are perfused but not aerated (*i.e.*, “shunting” regions) do not retain $^{13}\text{N}_2$ during apnea, and the bolus of tracer, after equilibrating with lung tissue and water, is rapidly reabsorbed into the pulmonary venous blood.^{16,18} We used the model of Galletti and Venegas¹⁶ to estimate regional lung function from the kinetics of intravenously injected $^{13}\text{N}_2$, which was measured by taking a series of consecutive PET images during 60 s of apnea at mean airway pressure (fig. 1A). Apnea at mean airway pressure was achieved by stopping the ventilator at the beginning of exhalation and simultaneously switching the active expiratory line to the second level of end-expiratory pressure, which had been previously set at mean airway pressure (see previous explanation of ventilator system). Briefly, the model lumps the alveolar units of each region of interest into two independent

parallel compartments. One compartment represents perfused and aerated units, and the other represents units that are perfused but not aerated (*i.e.*, fluid filled, consolidated, or collapsed) and therefore shunting. By curve fitting the tracer kinetics, the following parameters can be derived from the model for each region: its perfusion and its shunt fraction. We divided the imaged lung field in nondependent, middle, and dependent regions of equal heights. For each region, we calculated its perfusion fraction (F_Q , the fraction of imaged pulmonary blood flow that is going to a region), its shunt fraction (F_S , the fraction of perfusion to a region that is shunted in that region), and its fractional shunted blood flow ($F_{QS} = F_Q \times F_S$, the fraction of imaged pulmonary blood flow that is shunted in a region). As an example, $F_{QS} = 20\%$ in the dependent region means that 20% of the perfusion to the imaged lung is shunted as it traverses the dependent region. Therefore, F_{QS} is additive between regions, and the sum of F_{QS} across all regions represents the PET estimate of the shunt fraction of the imaged lung.

The $^{13}\text{N}_2$ -saline injection was started after the physiologic measurements were completed, at 4 min after the last VP curve. The $^{13}\text{N}_2$ -saline PET scan lasted 4 min (fig. 1A). However, the parameters calculated from the model were derived by curve fitting the tracer kinetics only during the 60-s apnea. Thus, effectively, the regional perfusion measurements derived from the $^{13}\text{N}_2$ -saline scan were completed by 5 min after the last VP curve.

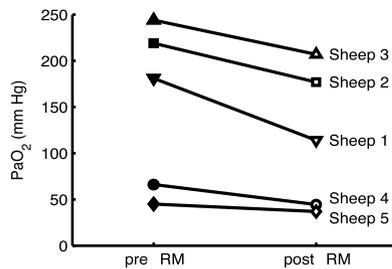


Fig. 2. P_{aO_2} before (filled symbols) and 4 min after (open symbols) the recruitment maneuver (RM). In all animals, P_{aO_2} decreased after the RM.

¹³N₂ Inhalation (Regional Gas Fraction) Scan. After clearance of the injected ¹³N₂ from the lungs, the animals were switched to the closed configuration of the breathing circuit and allowed to equilibrate with inhaled ¹³N₂.¹⁴ Because of its low solubility in water and tissues, inhaled ¹³N₂ remains confined to the alveolar air space, and regional tracer concentration, measured by a PET scan (fig. 1B), is proportional to regional gas content per unit of volume, *i.e.*, gas fraction. For each of the three regions, we calculated its mean-normalized gas fraction (F_G) by dividing the mean concentration of ¹³N₂ within the region by the mean concentration of ¹³N₂ in the imaged lung field.

Statistical Analysis

Statistical analysis was performed with both parametric and nonparametric methods. To test differences between the three lung regions, analysis of variance for repeated measures (parametric) and the Friedman test (nonparametric) were used. A two-tailed Student *t* test for paired data (parametric) and the Sign test (nonparametric) were used to assess differences between pre- and post-RM conditions.¹⁹ Least-squares regression was used to estimate regression relations. Both the Pearson product-moment correlation coefficient (parametric), *R*, and the Spearman rank correlation coefficient (nonparametric), *R_s*, were used to assess correlation between variables.²⁰ Significance was set at $P < 0.05$. Results reported as significant are only those for which both parametric and nonparametric tests revealed significant differences, and the least significant *P* value is presented. Data are mean \pm SD.

Results

Effect of the Injury

There was large interanimal variability in the degree of hypoxemia obtained after lavage, as judged by the pre-RM P_{aO_2} , which ranged from 45 to 244 mmHg (fig. 2). Two animals required PEEP of 10 (animal 5) and 15 (animal 4) cm H₂O, whereas the other three animals were studied at ZEEP. Accordingly, peak and mean airway pressures differed between animals (table 1).

Table 1. Airway Pressures at Baseline for the Five Animals

	Animal				
	1	2	3	4	5
PEEP, cm H ₂ O	0	0	0	15	10
M_{aw} , cm H ₂ O	8	9	7	26	22
P_{aw} , cm H ₂ O	31	33	25	47	52

M_{aw} = mean airway pressure; P_{aw} = peak airway pressure; PEEP = positive end-expiratory pressure.

Analysis of regional lung function showed that mean-normalized gas fraction, F_G , was lowest (fig. 3A) and fractional shunted blood flow, F_{QS} , was highest (fig. 3B) in the dependent region. This indicates that most of the blood flow that was being shunted within the imaged lung was being shunted in the dependent region, which had the largest loss of aeration (fig. 3A) and the highest perfusion (fig. 3C). This implies that the dependent region was contributing the most to the impairment in gas exchange, as shown by the significant, negative correlation between P_{aO_2} and F_{QS} in the dependent region ($R_s = -0.88$, $R = -0.89$, $P < 0.01$). As expected from the nonlinear dissociation curve of blood for oxygen, the relation between P_{aO_2} and F_{QS} (fig. 4) was better described by a power law ($P_{aO_2} = 9.3 \times (F_{QS})^{-1.8}$, $R^2 = 0.85$) than by a linear equation ($P_{aO_2} = -658 \times F_{QS} + 312$, $R^2 = 0.80$) with the same number of parameters.

The tracer kinetics and PET images obtained after intravenous injection (fig. 1A) and inhalation (fig. 1B) of ¹³N₂ show the predominant involvement of the dependent region. During the apnea that followed the intravenous injection of tracer (fig. 1A), the dependent region had both a higher peak concentration of ¹³N₂, indicative of higher perfusion, and a greater clearance of ¹³N₂, indicative of higher shunting, than the other regions. After inhalation and equilibration of the tracer (fig. 1B), the dependent region had a lower concentration of ¹³N₂, indicative of lower gas content, than the other regions.

Effect of the Recruitment Maneuver

After the RM, P_{aO_2} decreased by 35 ± 22 mmHg (table 2). Despite the wide range of baseline levels of hypoxemia, P_{aO_2} worsened in all animals (fig. 2). The relative decrease of P_{aO_2} was between 15% (animal 3) and 37% (animal 1) of the baseline value. P_{aCO_2} increased slightly and, accordingly, pH decreased (table 2). Mean arterial pressure, pulmonary arterial pressure, and cardiac output did not differ from pre-RM values (table 2). Respiratory system compliance did not show a systematic or significant change (table 2).

The changes in regional lung function were consistent with the gas exchange results. After the RM, redistribution of pulmonary blood flow from the middle to the dependent, least aerated region was significant (fig. 3C) and consistent across animals. In this region, F_{QS} increased significantly (fig. 3B) and in all animals (fig. 4)

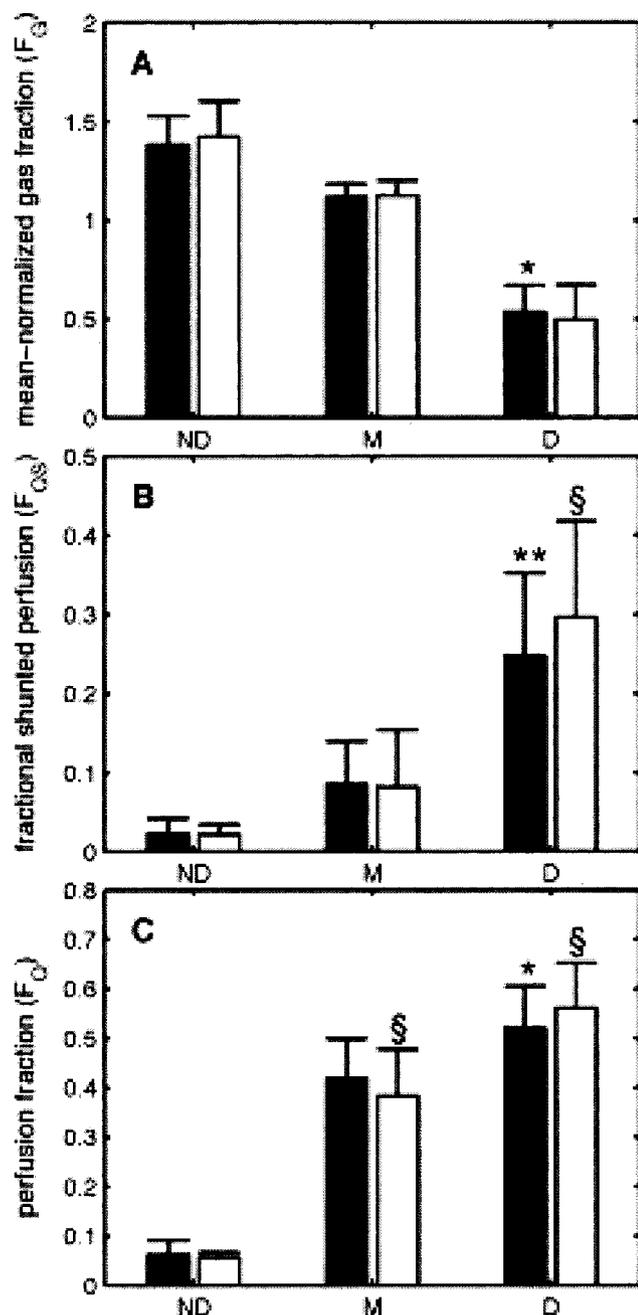


Fig. 3. Regional lung function before (filled bars) and after (open bars) the recruitment maneuver (RM) in nondependent (ND), middle (M), and dependent (D) regions. (A) Mean-normalized gas fraction (F_G) decreased from the ND to the D region. (B) The fraction of imaged pulmonary blood flow that was shunted in each region (F_{QS}) increased from the ND to the D region. The RM further increased F_{QS} in the D region. (C) The fraction of imaged pulmonary blood flow going to each region (F_Q) increased from the ND to the D region. The RM decreased perfusion to the M region and shifted it to the D region. Data are mean \pm SD. * $P < 0.05$, ** $P < 0.01$ between ND, M, and D regions before the RM. § $P < 0.05$ before versus after the RM.

after the RM, whereas it was unchanged in the nondependent and middle regions (fig. 3B). Remarkably, within each animal, the relation between the decrease in P_{aO_2} and the increase in F_{QS} in the dependent region

tended to follow the general relation between P_{aO_2} and F_{QS} obtained for all animals in both conditions (fig. 4; the lines connecting the points corresponding to each animal have a slope similar to the slope of the global regression curve). This suggests that the effect of the RM on shunting pulmonary blood flow in the dependent region was the main determinant of the effect of the RM on P_{aO_2} .

Discussion

The main result of this study is that when a sustained lung inflation is applied to a substrate with low potential for alveolar recruitment, it can worsen gas exchange. Our PET measurements show that the mechanism of this worsening is diversion of pulmonary blood flow toward less aerated regions, with the consequence that a larger fraction of the total pulmonary blood flow is shunted as it traverses these regions. To derive appropriate inferences from the results of this study, its limitations and their implications must be addressed.

Critique of the Experiment

There was large interanimal variability in the baseline (i.e., pre-RM) impairment in gas exchange. Part of this variability was because of the loose, clinical-like definition of lung injury that we adopted ($P_{aO_2}/F_{iO_2} < 300$ mmHg). Previous studies that have aimed for a narrower range of hypoxemia have reported variable lavage volume requirements between animals.^{9,21} These studies, as well as our findings, suggest that there is substantial interanimal variability in the response to lung lavage. Part of this variability may be due to the uneven distribution of the lavage fluid and of the consequent injury. In this respect, it is worth noting that, in spite of our attempt to induce a homogeneous injury to the lung, the resultant injury was heterogeneously distributed, as suggested by the significant vertical gradient of gas fraction (fig. 3A). In particular, the two animals with the most severe hypoxemia had the largest loss of aeration in the dependent region (F_G values of the dependent region were 0.45 and 0.40 in animals 4 and 5, respectively). When the loss of aeration is concentrated in regions that also receive the highest perfusion, as do the dependent regions, then substantial, "true" shunting may occur in these regions. The hypoxemia that originates from these regions may thus be poorly responsive to high F_{iO_2} or even to low and moderate levels of PEEP, as used in this study. Importantly, however, the wide range of hypoxemia did not confound the main result of this study because P_{aO_2} decreased and F_{QS} and F_Q in the dependent region increased in all animals after the RM, irrespective of their baseline P_{aO_2} . The interanimal variability in the degree of hypoxemia actually allowed us to show that regional lung function in the dependent, least aerated

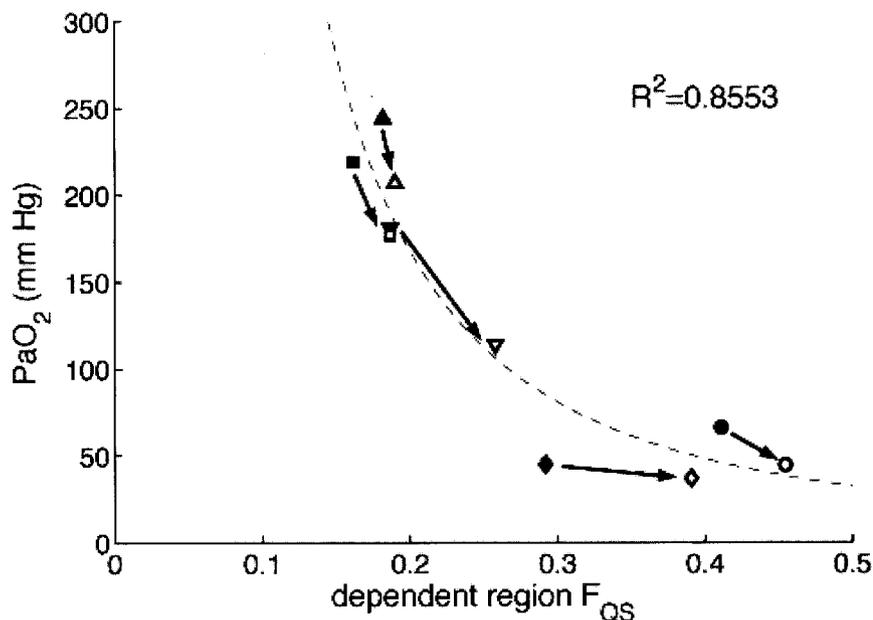


Fig. 4. Correlation between PaO_2 and fractional shunted blood flow (F_{QS}) in the dependent (D) region. The dashed curve represents the regression relation for all 10 data points ($\text{PaO}_2 = 9.3 \times (F_{\text{QS}})^{-1.8}$). Symbols for each animal are as in figure 2. As shown by the arrows, in each animal, PaO_2 decreased and F_{QS} in the D region increased from before (filled symbols) to after (open symbols) the recruitment maneuver (RM). The lines connecting the individual data points corresponding to each animal have approximately the same slope as the dashed curve. This suggests that the effect of the RM on PaO_2 could be largely explained by its effect on F_{QS} in the D region.

region was a strong determinant of global gas exchange over a wide range of PaO_2 values (fig. 4).

In this study, we did not measure absolute lung volumes. In the absence of such volumes, global alveolar recruitment cannot be quantified, and only surrogate measures can be obtained. We used the change in inflation chord compliance, measured between ZEEP and a set level of airway pressure (*i.e.*, 20 cm H_2O), to assess the effect of the sustained inflation on respiratory mechanics. Other authors have used the change in the pressure-weighted sum of inflation chord compliance, measured between PEEP and a set airway pressure, and deflation chord compliance, measured between PEEP and ZEEP, to estimate recruitment.^{8,22,23} We preferred to use the inflation chord compliance only, also in the animals studied at PEEP, to obtain a measurement of respiratory mechanics that was consistent among all animals, despite differences in end-expiratory pressures. The fact that we did not observe any systematic or significant change in compliance, measured at low airway pressure, suggests that it is highly unlikely that our model responded with substantial *and* sustained alveolar recruitment to the lung inflation. This conclusion is further corroborated by the regional gas fraction measurements, which did not show an increase of the gas fraction of the dependent region, relative to the other regions, after the RM (fig. 3A).

Effect of the Recruitment Maneuver

Although RMs seemed to offer little additional benefit during conventional positive-pressure ventilation with "large" tidal volumes,^{24,25} the advent of "low" volume ventilation has revitalized the interest in RMs, and recent reports show that RMs may be of some value in this setting.^{3-5,8,24,26} In some studies, however, an RM did

not improve^{7,8} or even worsened⁷ gas exchange in a fraction of subjects. This resembles what we observed in the current study.

In contrast to a pure saline lavage model of lung injury, in which recruitment has been demonstrated,^{9,27} the polysorbate 80 model has been shown not to respond to a sustained inflation with an improvement in respiratory mechanical impedance.¹⁰ This is most likely because of the permanent and profound inactivation of surfactant by the detergent, which either prevents reopening of collapsed alveolar units or makes them so unstable that, if reopened, virtually immediate collapse occurs when the sustained airway pressure is released. Fast derecruitment has been demonstrated in an oleic acid model of ALI, when PEEP was set at or below 15 cm H_2O , and was virtually complete within a few seconds.²⁸ The fact that we added polysorbate 80 to the lavage and that we did

Table 2. Gas Exchange, Hemodynamics, Respiratory Mechanics, and Ventilatory Parameters

	Before RM	After RM
PaO_2 , mmHg	151 ± 90	116 ± 76*
PaCO_2 , mmHg	37 ± 9	42 ± 11*
pH	7.43 ± 0.09	7.39 ± 0.1*
MAP, mmHg	90 ± 18	85 ± 16
MPAP, mmHg	16 ± 9	17 ± 10
CO, l/min	3.1 ± 0.8	3.1 ± 0.7
C_{rs} , ml/cm H_2O	13.8 ± 4.4	13.7 ± 4.3
V_{T} , ml	254 ± 33	260 ± 29

Data are presented as mean ± SD.

* $P < 0.05$ vs. before recruitment maneuver (RM).

C_{rs} = respiratory system compliance (measured immediately before and after a sustained inflation to 50 cm H_2O airway pressure for 30 s, whereas all other variables were measured before and 4 min after the RM); CO = cardiac output; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PaCO_2 = arterial carbon dioxide tension; PaO_2 = arterial oxygen tension; V_{T} = tidal volume.

not increase the end-expiratory pressure after the RM but left it at the pre-RM value may have contributed to the lack of recruitment. In addition, we intentionally performed the RM at an FiO_2 of 1, which likely favored the redevelopment of reabsorption atelectasis.²⁹ Finally, we applied 50 cm H_2O of continuous airway pressure for 30 s, which, although in line with the settings used in other studies,^{8,22} is probably less effective than repeated inflations.^{7,9,21,27} All these factors were selected by experimental design to minimize the chances of the lung inflation resulting in sustained alveolar recruitment, so that the effect of the lung inflation on the intrapulmonary distribution of regional perfusion and its consequences on global gas exchange could be isolated.

In this study, the worsening of oxygenation after the RM was associated with an increase in the fraction of pulmonary blood flow being shunted in the least aerated, dependent region (figs. 3B and 4) and with diversion of pulmonary blood flow from the middle, more aerated region to the dependent, less aerated one (fig. 3C). Thomas *et al.*³⁰ showed that pulmonary vascular resistance increased when lung volume was increased above 50% of total lung capacity. If a lung inflation resulted predominantly in overexpansion of aerated regions rather than in alveolar recruitment, the increase in pulmonary vascular resistance in aerated regions could divert perfusion toward nonaerated regions. Indeed, surface tension forces that develop at the gas-fluid interface within the airways that feed to nonaerated regions are expected to prevent transmission of the increased airway pressure to the capillaries inside nonaerated regions. This shift of perfusion from aerated to nonaerated regions may recruit pulmonary vasculature in regions of hypoxic pulmonary vasoconstriction and thus effectively decrease pulmonary vascular resistance within nonaerated regions. The change in the regional distribution of pulmonary vascular resistance may persist even after the sustained airway pressure is released because the newly recruited vasculature may require some time to derecruit. This might explain why changes in regional pulmonary perfusion could still be detected by 4–5 min after the RM, despite the fact that, by then, pulmonary arterial pressure had returned to baseline levels.

A focal distribution of the loss of aeration and the associated heterogeneity in regional compliance may thus be the determinants of the effect that a sustained change in airway pressure has on the intrapulmonary distribution of regional blood flow and regional shunting, in addition to possibly determining its effect on recruitment^{31–33} and hyperinflation.^{33,34} Indeed, for a given applied pressure, regional lung expansion depends on regional compliance.

It is important to note that our results differ from those obtained in other models of diffuse³⁵ or localized^{36,37} lung injury in which redistribution of perfusion after application of PEEP was associated with a decrease in

the amount of edema³⁵ or shunting^{36,37} in the regions toward which perfusion redistributed. This suggests that, in those models, restored aeration, with relief from the mechanical effects of alveolar edema and release of hypoxic pulmonary vasoconstriction, was the cause of the redistribution of perfusion. Consequently, global gas exchange tended to improve, not worsen, as it did in our study. In addition, in contrast to the mechanisms that have been invoked to explain PEEP-induced redistribution of pulmonary perfusion toward dependent regions in healthy, anesthetized animals,^{38,39} which are based on the “zonal” model,^{40,41} the mechanism that we hypothesized is not necessarily gravitational in nature. In principle, this mechanism would act to redistribute pulmonary blood flow toward nonaerated areas irrespective of their location along the vertical axis (*i.e.*, dependent *vs.* nondependent). This mechanism has been previously invoked to explain PEEP-induced redistribution of pulmonary blood flow toward affected lobes in lobar pneumonia,^{42,43} which represents the extreme case of focal injury and heterogeneity in regional compliance. Our results suggest that the loss of aeration does not need to be confined to large, anatomically bounded regions for this mechanism to act but that it can have any topographical distribution, provided it remains heterogeneous. Furthermore, by combining measurements of regional perfusion, shunting, and aeration, we have shown that redistribution of pulmonary perfusion to atelectatic or consolidated regions can occur in the absence of restored aeration and thus represent a mechanism of impairment, rather than improvement,^{36,37,43} of global gas exchange.

In summary, in a model of ALI that did not respond to a sustained lung inflation with stable and substantial alveolar recruitment, we have shown that an RM can worsen oxygenation by increasing the fraction of pulmonary blood flow that is shunted in less aerated lung regions. The broader implication of this study is that, in the presence of nonreversible or partially reversible loss of lung aeration, the effect of a sustained increase in airway pressure on gas exchange depends strongly on the redistribution of pulmonary blood flow toward regions that remain nonaerated. This may be a particularly important factor in ALI patients with a focal distribution of lung hyperdensities, in whom heterogeneity of regional compliance may become substantial. We emphasize that this study has no implication on whether RMs should or should not be used in the ventilatory management of patients with ALI because RMs may have beneficial effects that are unrelated to gas exchange,⁴⁴ and RMs have been shown to improve gas exchange in other experimental models of lung injury^{9,21} and in several patients with ALI.^{3–5,7,8,26} However, our results show a mechanism of worsening of gas exchange that can explain unexpected observations that may puzzle curious

anesthesiologists and intensivists in their daily clinical practice.

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