Reabsorption atelectasis in a porcine model of ARDS: regional and temporal effects of airway closure, oxygen, and distending pressure

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Reabsorption atelectasis in a porcine model of ARDS: regional and temporal effects of airway closure, oxygen, and distending pressure. J Appl Physiol 115: 1464–1473, 2013. First published September 5, 2013; doi:10.1152/japplphysiol.00763.2013.—Little is known about the small airways dysfunction in acute respiratory distress syndrome (ARDS). By computed tomography (CT) imaging in a porcine experimental model of early ARDS, we aimed at studying the location and magnitude of peripheral airway closure and alveolar collapse under high and low distending pressures and high and low inspiratory oxygen fraction (FIO2). Six piglets were mechanically ventilated under anesthesia and muscle relaxation. Four animals underwent saline-washout lung injury, and two served as healthy controls. Beyond the site of assumed airway closure, gas was expected to be trapped in the injured lungs, promoting alveolar collapse. This was tested by ventilation with an FIO2 of 0.25 and 1 in sequence during low and high distending pressures. In the most dependent regions, the gas/tissue ratio of end-expiratory CT, after previous ventilation with FIO2 0.25 low-driving pressure, was significantly higher than after ventilation with FIO2 1; with high-driving pressure, this difference disappeared. Also, significant reduction in poorly aerated tissue and a correlated increase in nonaerated tissue in end-expiratory CT with FIO2 1 low-driving pressure were seen. When high-driving pressure was applied or after previous ventilation with FIO2 0.25 and low-driving pressure, this pattern disappeared. The findings suggest that low distending pressures produce widespread dependent airway closure and with high FIO2, subsequent absorption atelectasis. Low FIO2 prevented alveolar collapse during the study period because of slow absorption of gas behind closed airways.

Small airways dysfunction; absorption atelectasis; acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a frequent and important cause of morbidity and mortality in critically ill patients (46, 50). It is well known that mechanical ventilation in itself can harm the lung and cause ventilator-induced lung injury (VILI) (17, 21), which can induce or aggravate ARDS. Much debate remains, however, over pivotal concepts regarding the pathophysiology and regional distribution of VILI (2, 9, 16, 18).

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One of the hypothesized mechanisms of VILI is the low-volume injury that predominates in more dependent regions of the lungs and in previously damaged lungs prone to collapse (16, 17, 43, 44, 57). Ventilation, at low lung volumes and pressures, may cause airway and alveolar fluid-structure instabilities that can lead to cyclic opening and closing (recruitment and derecruitment) of small airways and alveoli (2, 9, 16–18, 26, 43, 61). The pulmonary epithelium is particularly at risk of being damaged by mechanical stresses associated with cyclic opening and closing (4, 5, 10–12, 52, 60). Mechanical stresses induced epithelial cell damage in a model of airway reopening (5, 35), and the pressure gradient was the primary determinant of mechanical damage.

Clinical studies indicate that gas absorption plays a key role in the genesis of anesthesia-related atelectasis (27, 49). Absorption atelectasis can occur by either complete airway occlusion or by reduction of the inspired ventilation-perfusion ratio (VA/Q) to below a critical level (15). Beyond the site of airway closure, gas is trapped with a predisposition to absorption atelectasis. Nonetheless, there is little information (1, 28) on how much of this conceptual framework is applicable in ARDS.

With the use of static and dynamic computed tomography (CT) imaging in a porcine experimental model of early ARDS, we aimed at studying the location and magnitude of peripheral airway closure under high and low distending pressures and high and low inspiratory oxygen fraction (FIO2). Our hypothesis was that by using low distending pressures and high FIO2, stable and dependent airway closure, without tidal recruitment and with subsequent absorption atelectasis, can be demonstrated, suggesting that airway closure is an important mechanism in causing lung collapse in ARDS. Furthermore, we also devised the hypothesis that the combination of low distending pressures and low FIO2 can, for some time, prevent alveolar collapse by means of producing air trapping behind closed airways, and with high distending pressures, the differences mediated by the high and low FIO2 decrease due to the opening—continuously or cyclically—of the small airways.

Materials and Methods

Investigational protocol. The study was approved by the Animal Ethics Committee of Uppsala University (Sweden), and the care and handling of the animals were in accord with National Institutes of Health guidelines for ethical animal treatment. We studied six piglets (2–3 mo old, weighing 28.4 ± 2.8 kg) of mixed Hampshire, Yorkshire, and Swedish country breeds, obtained from a local breeder. All
animals underwent the same routine instrumentation; intravenous anesthesia using a combination of fentanyl, ketamine, and midazolam; muscle relaxation using pancuronium after adequate anesthesia was established; and monitoring as described previously (7, 8, 54). Animals were tracheotomized and mechanically ventilated via a cuffed, 7-mm internal diameter endotracheal tube (Mallinckrodt Pharmaceuticals, Athlone, Ireland), using a Servo-i ventilator (Maquet Critical Care, Solna, Sweden). All protocol steps were performed with the animals lying in the supine position.

After preparation and baseline measurements of arterial blood gases and hemodynamic and respiratory parameters, we established a one-hit lung-injury model in four animals (ARDS group) (39), which comprised repeated lung lavages with 30 ml/kg warmed isotonic saline, applied until a stable ratio of partial pressure of arterial oxygen (PaO2)/FIO2 <150 mmHg was reached with the following ventilatory settings: positive end-expiratory pressure (PEEP) 7 cmH2O, plateau pressure (Pplat) 30 cmH2O, FIO2 1, respiratory rate (RR) 20 breaths/min, and the ratio of the duration of inspiration to the duration of expiration (I:E) 1:1. A recruitment maneuver was then performed with PEEP 35 cmH2O, Pplat 50 cmH2O, RR 20 breaths/min, and FIO2 1, during 1 min.

Two animals (Control group) did not undergo the lung-injury phase and served as healthy control animals. They were ventilated with a minimal Pplat, enough to achieve 8 ml/kg tidal volume, RR to keep partial pressure of arterial carbon dioxide between 35 and 45 mmHg, PEEP 5 cmH2O, I:E 1:1, and FIO2 0.4.

Then, all animals were submitted to a driving pressure (Pplat – total PEEP) titration procedure, consisting of decremental driving pressures to identify the lowest pressure capable to keep arterial saturation by pulse oximetry at 88% during 4 min (10 min for the Control group). During the driving pressure titration procedure, PEEP level was 5 cmH2O, FIO2 1, and RR 20 breaths/min. A recruitment maneuver was then performed as described above (PEEP 35 cmH2O, Pplat 50 cmH2O, RR 20 breaths/min, 1 min), followed by ventilation in pressure-controlled mode with PEEP 15 cmH2O, FIO2 0.25, RR 20 breaths/min, and tidal volume 8 ml/kg.

Fluid therapy was maintained constant throughout the study period at a rate of 7.5 ml/kg and 7.5 ml/h.

CT protocol. The CT protocol is described in detail here, since it forms the basis for the study (see also Figs. 1 and 2). In the CT facility, the piglet was positioned supine, and a scanogram of the whole lung was acquired using a high-resolution, 64-slice CT Somatom Definition (Siemens AG, Erlangen, Germany). After 10 min, PEEP was reduced to 5 cmH2O, and driving pressure was set to the low value titrated previously. FIO2 was then turned to 1. A 60-s dynamic CT acquisition of a fixed slice, located between the heart and diaphragm, was performed just after this closing maneuver (time 0) and repeated after 4 min (10 min for the Control group). At the end of the second dynamic acquisition, an end-expiratory hold maneuver and an end-inspiratory hold maneuver were performed, and a corresponding scan of the whole lung in both conditions was acquired. Two different sets of images were thus generated: end-expiratory CT after previous ventilation with FIO2 0.25 and low-driving pressure (EE_25%_LOW) and end-inspiratory CT after previous ventilation with FIO2 0.25 and low-driving pressure (EI_25%_LOW). Driving pressure was then set to 40 cmH2O (25 cmH2O in the Control group), keeping PEEP 5 cmH2O and FIO2 1. After 10 min with the new settings, another end-expiratory hold maneuver and an end-inspiratory hold maneuver were performed again, and the corresponding scan of the whole lung in both conditions was acquired, generating an end-expiratory CT after previous ventilation with FIO2 0.25 and high-driving pressure (EE_25%_HIGH) and end-inspiratory CT after previous ventilation with FIO2 0.25 and high-driving pressure (EI_25%_HIGH).

To homogenize gas composition in the whole lung, the lung-recruitment maneuver described previously was applied again, and each piglet was ventilated with PEEP 15 cmH2O, driving pressure enough to achieve 8 ml/kg tidal volume, RR 20 breaths/min, and FIO2 1 for 10 min. After this period, PEEP was set to 5 cmH2O and driving pressure to the low value titrated previously. FIO2 was kept at 1. A 60-s dynamic acquisition of the same transverse plane scanned previously at time 0 and after 4 min was acquired (10 min for the Control group). The end-expiratory and end-inspiratory hold maneuvers were again performed as before, generating the corresponding end-expiratory CT after ventilation with FIO2 1 and low-driving pressure.

\[ P_{aw} \text{ (cm H}_2\text{O)} \]

\[ \text{LOW DP 25%} \quad \text{HIGH DP 25%} \quad \text{LOW DP 100%} \quad \text{HIGH DP 100%} \]

\[ \text{EEHM} \quad \text{EIHM} \quad \text{EEHM} \quad \text{EIHM} \]

\[ \text{DYNAMIC CT} \quad \text{DYNAMIC CT} \]

\[ \text{LAVAGE} \quad \text{FIO}_2 \text{ 0.25} \quad \text{FIO}_2 \text{ 1} \]

Fig. 1. Computed tomography (CT) protocol. Sketch of the CT protocol: time sequence of all steps performed in the CT facility with the correspondent mechanical ventilation settings. P_{aw} = airway pressure; EEHM = end-expiratory hold maneuver; EIHM = end-inspiratory hold maneuver; FIO2 = inspiratory oxygen fraction; DP = driving pressure.
Medicine standard image files, produced by the CT scanner, were authors (G. Perchiazzi). The Digital Imaging and Communications in R2008a (MathWorks, Natick, MA), purposely written by one of the formed by using scripts for the Image Processing Toolbox for MatLab temporal interval between images in the dynamic series was 50 ms. Voxel dimensions of each image were 5 mm central venous blood gas samples were collected. pressure, and central venous pressure were measured, and arterial and apperance. At the end of each experimental step, cardiac output, wedge pressure (EI_100%_HIGH) were acquired.

Dynamic and static CT images were acquired as 5 mm-thick slices. Voxel dimensions of each image were 5 mm × 0.5 mm × 0.5 mm. The temporal interval between images in the dynamic series was 50 ms.

Image processing and calculations. All calculations were performed by using scripts for the Image Processing Toolbox for MatLab R2008a (MathWorks, Natick, MA), purposely written by one of the authors (G. Perchiazzi). The Digital Imaging and Communications in Medicine standard image files, produced by the CT scanner, were directly transferred to the MatLab software. Each image was processed as a matrix of voxels, as done in Perchiazzi et al. (45). Lung parenchyma in each image was outlined manually and selected. The set of images referring to the entire lung acquired in static conditions was studied according to a gravitational vector. Knowing voxel dimensions (Vvox) and their CT density expressed in Hounsfield units (HU), gas volume (Vgas), and tissue volume (Vtiss) of each voxel were calculated according to the following formulas (see also Fig. 2)

\[ V_{\text{gas}} = V_{\text{vox}} \times (-\text{HU}/1,000) \]  
\[ V_{\text{tiss}} = V_{\text{vox}} \times [1 - (-\text{HU}/1,000)] \]

From Eqs. 1 and 2, several variables have been derived: gas content/level (Vgas,level), which is the sum of Vgas of the n voxels included in that level, and tissue content/level (Vtiss,level), which is the sum of Vtiss of the n voxels included in that level; gas/tissue ratio (g/t) was also calculated for each lung level, as described previously (19)

\[ g/t = V_{\text{gas,level}} / V_{\text{tiss,level}} \]

In the CT images, nonaerated lung (atelectasis) was calculated as the voxel population, with HU values ranging from +100 to −100; poorly aerated lung between −100 and −500; normally aerated between −500 and −900; and overaerated between −900 HU and −1,000 HU.

We also quantified the percent mass of normally, poorly, and nonaerated tissue (collapsed lung parenchyma) (6) in each gravitational level, expressed as a percentage of the tissue content in the entire gravitational level.

**Statistical analysis.** Variables were tested for normality with the Shapiro-Wilk test. We expressed values as means and SDs for normally distributed variables and median and interquartile ranges (25–75%) otherwise. For normally distributed variables, we used repeated-measures ANOVA for the comparison of any variable collected multiple times during the protocol. The Bonferroni adjustment for multiple tests was applied for post hoc comparisons. When the assumption of normality was violated, we used the Friedman test as the nonparametric alternative to the repeated-measures ANOVA test. Pairwise, planned contrasts were performed with a Bonferroni correction for multiple comparisons.

g/t Ratios were compared directly by the Kolmogorov-Smirnov two-sample test, treating each paired measurement as an independent observation (i.e., without accounting for intra- vs. interindividual differences).

Spearman rank correlation (r<sub>S</sub>) was run to assess the relationship between the amount of poorly aerated tissue in the expiratory CT, acquired after previous ventilation with FIO2 0.25 and low-driving pressure, and the amount of nonaerated tissue in the expiratory CT, acquired after ventilation with FIO2 1 and high-driving pressure. We chose r<sub>S</sub> because not all variables were normally distributed, as assessed by the Shapiro-Wilk test (P < 0.05). Preliminary analysis showed the relationship to be monotonic.

All statistical tests were two-tailed, and the significance was set at P < 0.05.

**RESULTS**

The main physiological data are shown in Table 1. The Control group, as expected, presented normal values throughout the experiment (37).

The low-driving pressure titrated for the ARDS group was 16 ± 3.6 cmH<sub>2</sub>O and for the Control group, 4 cmH<sub>2</sub>O, with PEEP set at 5 cmH<sub>2</sub>O.

**g/t Ratio in the Control group.** When low-driving pressure was applied, no differences in g/t ratio were found between FIO2 0.25 and FIO2 1 and between inspiratory and expiratory CT along all gravitational levels (Fig. 3, A and B). When high-driving pressure was applied, clear differences in g/t ratio were detected between inspiratory and expiratory CT along most of all gravitational levels and FIO2 tested. In addition,
Table 1. Physiological variables

<table>
<thead>
<tr>
<th>Ventilation</th>
<th>Baseline</th>
<th>Low-Driving Pressure</th>
<th>Low-Driving Pressure</th>
<th>High-Driving Pressure</th>
<th>High-Driving Pressure</th>
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<tr>
<td>FIO2, 0.25</td>
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<tr>
<td>Cdyn, ml/cmH2O</td>
<td>22 ± 6</td>
<td>14 ± 6</td>
<td>13 ± 6</td>
<td>25 ± 11</td>
<td>22 ± 8</td>
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<tr>
<td>Driving pressure, cmH2O</td>
<td>10 ± 2</td>
<td>16 ± 3</td>
<td>16 ± 3</td>
<td>40 ± 0</td>
<td>40 ± 0</td>
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<td>PEEP, cmH2O</td>
<td>15.0 ± 0</td>
<td>5.4 ± 1</td>
<td>5.4 ± 1</td>
<td>5.5 ± 1</td>
<td>5.5 ± 1</td>
</tr>
<tr>
<td>Vt, ml</td>
<td>236 ± 22</td>
<td>189 ± 53</td>
<td>205 ± 90</td>
<td>909 ± 211</td>
<td>836 ± 246</td>
</tr>
<tr>
<td>R, cmH2O·1⁻¹·s⁻¹</td>
<td>15 ± 2</td>
<td>23 ± 5</td>
<td>23 ± 6</td>
<td>30 ± 7</td>
<td>32 ± 4*</td>
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<td>Gas exchange</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>PaO2/FIO2, mmHg</td>
<td>532 ± 24</td>
<td>185 ± 167</td>
<td>154 ± 174*</td>
<td>396 ± 157</td>
<td>362 ± 131</td>
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<tr>
<td>PaCO2, mmHg</td>
<td>38 ± 4</td>
<td>51 ± 14</td>
<td>52 ± 15</td>
<td>24 ± 8</td>
<td>28 ± 16</td>
</tr>
<tr>
<td>pH</td>
<td>7.47 ± 0.03</td>
<td>7.30 ± 0.07</td>
<td>7.30 ± 0.10</td>
<td>7.60 ± 0.12</td>
<td>7.55 ± 0.15</td>
</tr>
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<td>SpO2, %</td>
<td>100 ± 0</td>
<td>91 ± 10</td>
<td>79 ± 20</td>
<td>96 ± 4</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>SvO2, %</td>
<td>46 ± 10</td>
<td>60 ± 22</td>
<td>48 ± 14</td>
<td>62 ± 16</td>
<td>66 ± 14</td>
</tr>
<tr>
<td>Venous admixture, %</td>
<td>1 ± 0</td>
<td>21 ± 8*</td>
<td>29 ± 11*</td>
<td>5 ± 3</td>
<td>18 ± 6</td>
</tr>
</tbody>
</table>

**Hemodynamic**

| MAP, mmHg                   | 64 ± 8   | 75 ± 16             | 76 ± 19              | 58 ± 14              | 61 ± 14               |
| CVP, mmHg                   | 24 ± 1   | 34 ± 6              | 36 ± 8              | 37 ± 6              | 35 ± 4                |
| PAWP, mmHg                  | 12 ± 2   | 10 ± 1              | 11 ± 1              | 12 ± 1              | 11 ± 2               |
| CO, l/min                   | 2.2 ± 0.5 | 3.2 ± 0.8            | 3.5 ± 1.3            | 2.7 ± 0.4            | 2.6 ± 1.1             |
| HR                          | 96 ± 8   | 99 ± 15             | 100 ± 12            | 114 ± 15            | 106 ± 8               |

FIO2 = fraction of inspired oxygen; Cdyn = dynamic compliance; driving pressure = [plateau pressure – total positive end-expiratory pressure (PEEP); Vt = tidal volume; Raw = airway resistance; PaO2 = partial pressure of arterial oxygen; PaCO2 = partial pressure of arterial carbon dioxide; pH = arterial pH; SpO2 = pulse oximeter oxygen saturation; SvO2 = mixed venous oxygen saturation; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = central venous pressure; PAWP = pulmonary artery wedge pressure; CO = cardiac output; HR = heart rate. Values are means ± SD. *Significant differences (P < 0.05) when compared with baseline.

when high-driving pressure was used, neither inspiratory nor expiratory CT showed any differences in g/t ratio between ventilation with FIO2 0.25 and 1.

**g/t Ratio in the ARDS group.** For low-driving pressure in the most dependent part of the lung, the g/t ratio of the expiratory CT, acquired after previous ventilation with FIO2 0.25 and with low-driving pressure, was significantly higher than the corresponding one after previous ventilation with FIO2 1 (Fig. 4A). However, when high-driving pressure was applied, the significant difference in the expiratory CT, found previously between FIO2 0.25 and FIO2 1 in the most dependent part of the lung, disappeared (Fig. 4B).

When comparing low- and high-driving pressure after previous ventilation with FIO2 1, a significant difference in g/t ratio was demonstrated in the expiratory CT in the most dependent lung level (P < 0.01).

The end-inspiratory and end-expiratory g/t ratios at the different vertical levels of the lung are shown in Fig. 4. It can be seen that with low-driving pressures, the tidal aeration is small, as indicated by the small differences between the inspiratory and expiratory points (Fig. 4A). It can also be seen that in the most dependent part of the lung, there is no inspiratory increase in aeration, suggesting no ventilation, whether there is certain constant aeration (trapped gas behind closed airways) or no gas at all (alveolar collapse). This extends up to one-third of the distance from the bottom of the lung. Normal aeration, corresponding to a g/t ratio of 0.5 or higher (−900 < HU < −500), occurs half-way up the lung.

With high-driving pressure, the differences between the inspiratory and expiratory g/t ratios are increased as a consequence of larger tidal aeration. Ventilation is primarily delivered to the middle half of the lung along the gravitational axis (Fig. 4B).

Figure 5A shows a significant reduction in the amount of poorly aerated tissue along the gravitational vector, and Fig. 5B, a significant and correlated increase in the amount of nonaerated tissue at end-expiration after previous ventilation with FIO2 1 and low-driving pressure. But when high-driving pressure was applied, this pattern disappeared (Fig. 5, C and D). After previous ventilation with FIO2 0.25 and low-driving pressure, the end-expiratory CT displayed a stable amount of poorly aerated and nonaerated tissue in the most dependent regions of the lung (Fig. 5, E and F).

There was a strong, positive correlation between the amount of poorly aerated tissue in the expiratory CT acquired after previous ventilation with FIO2 0.25 and low-driving pressure and the amount of nonaerated tissue in the expiratory CT acquired after ventilation with FIO2 1 and low-driving pressure: rs(35) = 0.747; P < 0.0005 (Fig. 6).

**DISCUSSION**

The present study was an attempt to evaluate, by means of static and dynamic CT imaging, the location and magnitude of peripheral airway closure under high and low distending pressures and high and low FIO2 in an animal model of ARDS. We found that low distending pressures and high FIO2 produced dependent airway closure with subsequent absorption atelectasis. However, the combination of the same low distending pressures but with low FIO2 substantially prevented alveolar collapse, likely by means of producing air trapping behind continuously closed airways. Coherently, when high-driving pressures were tested, this difference, mediated by the high and low FIO2, vanished, strongly arguing that the high-driving pressure leads to continuous or cyclical opening of the small airways, enabling ventilation of these distal lung units.

In our protocol, we allowed 4 min for absorption atelectasis to appear (see Movies files, available as Supplemental material). The rate of absorption of gas from an unventilated region
Fig. 3. g/t ratio vs. lung height in the Control group. Individual data from the 2 healthy pigs are shown. A: control animal 1; B: control animal 2. Data are presented as mean. EE_25%_LOW/HIGH = end-expiratory CT after previous ventilation with FIO\textsubscript{2} 0.25 and low-/high-driving pressure; EI_25%_LOW/HIGH = end-inspiratory CT after previous ventilation with FIO\textsubscript{2} 0.25 and low-/high-driving pressure; EE_100%_LOW/HIGH = end-expiratory CT after ventilation with FIO\textsubscript{2} 1 and low-/high-driving pressure; EI_100%_LOW/HIGH = end-inspiratory CT after ventilation with FIO\textsubscript{2} 1 and low-/high-driving pressure.
of the lung depends on the composition of the gas in that area when ventilation to it ceases and the composition of the inspired gas (13, 14). When the inspired gas is 100% oxygen, the rate of collapse is faster than when air is breathed (13, 14). It has been demonstrated that if 100% oxygen is used, a few minutes are enough for lung collapse (14, 27, 33, 34, 48, 49). With cyclic airway closure, no alveolar collapse would occur during these 4 min unless the inspired V_A/Q is extremely low (≤ 0.01), in practice, indistinguishable from continuous closure.

The corresponding respiratory system compliances (Table 1), after the 4-min ventilation with low-driving pressure of the two entrapped gas compositions (25% and 100% oxygen), fit with stable airway closure and gas trapping during the low-driving pressure steps. The strong, positive correlation between the amount of poorly aerated tissue in the expiratory CT, acquired after previous ventilation with FIO2 0.25 and low-driving pressure, and the amount of nonaerated tissue in the expiratory CT, acquired after ventilation with FIO2 1 and low-driving pressure, substantiates that absorption atelectasis was an important mechanism in causing lung collapse in our ARDS model. Moreover, we found no significant differences in venous admixture and PaO2/FIO2 between the two following conditions: when gas was trapped behind closed airways (low-driving pressure + low FIO2) and when alveoli had collapsed (low-driving pressure + high FIO2). Thus perfusion is similar, whether a region is collapsed or is aerated but nonventilated. These findings fit with observations by Benumof (3)—that hypoxic pulmonary vasoconstriction is the main mechanism of reduced blood flow in atelectatic regions, not mechanical obstruction.

With the use of a similar technique of measuring reabsorption atelectasis, Lundblad et al. (41) showed that airway hyperresponsiveness in allergic mice could be largely explained by airway closure. Coherent with our findings, they showed that the airway closure during bronchoconstriction was not a random event but occurred at the dorsal, basal region of the lung. Thus gravity determined the location of airway closure in the asthmatic mice, similar to the distribution of airway closure in our study in ARDS pigs.
Rylander and coworkers (51) studied the size and distribution of a “poorly aerated” compartment in ARDS patients and concluded an uneven distribution of ventilation due to the presence of small-airway closure and/or obstruction. Recently, Wellman et al. (60) have shown that patterns of ventilation heterogeneity are compatible with airway narrowing or closure in poorly aerated lung regions. They found that increased ventilation heterogeneity during mechanical ventilation with high tidal volume and zero PEEP occurs primarily at length scales <60 mm, with a significant component derived from subresolution (<12 mm) length scales. Components of specific ventilation heterogeneity at length scales of <12, 12–36, and 36–60 mm were highest in poorly aerated regions. Total ventilation heterogeneity was highly correlated with the computed fraction of lung with slow washout, suggesting a role of airway narrowing or closure in regions of increased specific ventilation heterogeneity. Finally, high levels of PEEP reduced the <60-mm length-scale components of ventilation heterogeneity by increasing lung inflation in all regions to normal levels, with effects on both alveolar inflation and airway patency.

Moreover, calculations on CT scan data and the Supplementary Movies enable us to identify, estimate, and distinguish between regions with a predominance of continuously open small airways and regions with a predominance of tidal opening and closing of their small airways.

Airway dysfunction has been recognized increasingly as an important contributor to pulmonary impairment in patients with ARDS (32, 42, 47). Animal models of ARDS have shown that in addition to damage to the parenchyma, small airway injuries are characterized by bronchiolar epithelial necrosis and sloughing and by rupture of alveolar-bronchiolar attachments (10–12). The loss of mechanical alveolar/airway interdependence, airway epithelial injury, interstitial edema, and alveolar collapse may all contribute to distal airway instability (32). It has been reported recently that in humans who died with ARDS, small airway changes were characterized by wall thickening with inflammation, extracellular matrix remodeling, and epithelial denudation (42). Importantly, the degree of airway epithelial denudation in these patients was associated with disease severity.

It is known that surfactant protects the lung from damage; however, even mild surfactant dysfunction can lead to severe lung injury (55, 56). Bilek et al. (5) investigated the mechanical stresses that induce epithelial cell damage in a model of airway reopening, and their results suggest that the pressure gradient is the primary determinant of mechanical damage. We have found that low distending pressures and high FIO2 produce widespread, dependent airway closure with subsequent absorption atelectasis in an experimental model of early ARDS. We think that it is important to underscore the potential consequent-associated epithelial cell damage if it is applied high-

Fig. 5. A and B: percent mass of poorly and collapsed tissue vs. lung height in the ARDS group during ventilation with low-driving pressure and FIO2 1. Data are presented as mean ± SE. * Significant reduction in the percent mass of poorly aerated tissue (A) along the gravitational vector in end-expiratory CT after ventilation with FIO2 1 and low-driving pressure; † significant increase in the percent mass of collapsed tissue (B) along the gravitational vector in end-expiratory CT after ventilation with FIO2 1 and low-driving pressure. C and D: percent mass of poorly and collapsed tissue vs. lung height in the ARDS group during ventilation with high-driving pressure and FIO2 1. Data are presented as mean ± SE. Note the similar amount of poorly aerated tissue along the whole vertical distance of the lung and the smaller amount of atelectasis in the lower half of the lung compared with the findings during ventilation with low-driving pressure. E and F: percent mass of poorly and collapsed tissue vs. lung height in the ARDS group during ventilation with low-driving pressure and FIO2 0.25. Data are presented as mean ± SE. Note the similar amount of poorly aerated tissue along the whole vertical distance of the lung and the smaller amount of atelectasis in the lower half of the lung compared with the findings during ventilation with low-driving pressure.
driving pressures on top of this condition, promoting tidal airway reopening and closing.

Our data call attention for the conceivable, following vicious cycle with a potential threatening feedback: reduced lung volume and surfactant dysfunction promote small airways closure; this causes alveolar gas trapping; if the trapped gas is mainly oxygen reabsorption atelectasis will happen in a few minutes; if afterward, high-driving pressure ventilation is used, atelectrauma may occur. Atelectrauma is referred to the adverse effects of cyclic opening and closing of alveolar units. Peripheral airway injury may also occur in the small airways that are cyclically opened and closed. This whole pathway can play a primary role in the activation of the inflammatory signaling cascade. This rationale supports a concept that we could call “reabsorption atelectasis,” in which the application of high-driving pressures, after the collapse and persistent closure of lung units and consequent absorption atelectasis, will generate a vicious cycle, in which the smaller the ventilated lung is, the higher VILI-triggering forces will be.

There are potential explanations for the dependent location of the absorption atelectasis that we have found. One of the key phenomena in early ARDS is an inflammation of the lungs originating from local or systemic disease. Consequently, these lungs are characterized by increased lung mass due to inflammatory infiltrate and interstitial edema, resulting from increased capillary permeability (59). In an organ designed to be composed mostly of air, this accounts for a big change in density and lung mechanics. These heavier lungs tend to collapse under their own weight following a gravitational gradient (6, 30). This pressure exerted by the overlying lung tissue was called superimposed pressure (20) and is one of the key factors in promoting lung collapse (22), as well as their surfactant dysfunction (24, 25, 40). Other suggested factors are reduced thoracic wall compliance, the weight of the heart and mediastinal structures (31), as well as the pressure exerted by the diaphragm and pleural effusions. In the early 1960s, a study of regional pressure in the pleural space of dogs led to the conclusion that the lung behaved like a liquid body (38) in such a way that pressure applied on any given point is transmitted throughout the organ in a hydrostatic pattern and that the lung could therefore be looked at in terms of isogravitational levels that would exhibit similar pressure responses. The data of the step when absorption atelectasis occurred suggest a liquid-like behavior of the lung, with lung density distributed homogeneously in isogravitational levels. At this step, we observed a marked and progressive increase in lung density from nondependent to more dependent areas, with virtually no change throughout a given isogravitational level. Neither cranio-caudally nor right-to-left significant gradient of density was found, even though the left lung has larger parenchymal areas under the heart fossa. These data suggest that the influence exerted by the diaphragm, chest wall, and weight of the heart, rather than being localized, is distributed diffusely throughout the lung. In addition, there is experimental evidence of an anatomically fixed vascular plethora on the dorsal portions of the lung (23), leading to the existence of a nongravitational portion of the observed ventrodorsal density gradient (29). Thus some portion of the gravitational density gradient observed may be due to this “anatomically fixed” vascular gradient.

Limitations include first that the surfactant depletion model used in this study, as opposed to other experimental models and human ARDS (36), is characterized by a homogeneous distribution of the lung lesions, in which full lung recruitment is easily obtained. Also, the lung-injury model studied did not represent the complexity of the lung injury in ARDS, and it has yet to be established whether these experimental findings can be detected effectively in patients with ARDS. Second, the effects of chest-wall compliance and abdominal pressure were not taken into account in the measurements and were considered unchanged during the protocol. We are assuming that the driving pressure at the airway opening is a good surrogate for the local transpulmonary driving pressure. This assumption has been discussed extensively in CT studies assessing local lung mechanics (53). It is based on the premise that the lung is a freely deformable body within the chest wall, and thus chest-wall compliance affects the lung as a whole. This assumption also requires that the chest-wall compliance is constant across the different conditions. By these reasonable assumptions, heterogeneities caused by gravity are expected to create a gradient of pleural pressures in proportion to lung weight but not a gradient of driving pressures. Therefore, we consider driving pressure to be constant for all voxels, irrespective of their location along the gravitational vector. As we follow the gravity vector inside of the lung, the increasing offsets in expiratory transpulmonary pressures cause a “right shift” in the local pressure-volume curves, with little effect on its overall shape. Third, the short-term measurement is another limitation. Finally, the number of animals was small, limiting the power of the statistical analysis.

Conclusions. The present findings suggest that low distending pressures and high FIO2 produce widespread dependent airway closure with subsequent absorption atelectasis in an experimental model of early ARDS. Low FIO2 substantially prevented atelectasis by much slower absorption of alveolar gas behind closed airways (air trapping). Recruitment maneuvers should delay, or even prevent, absorption atelectasis in the closed-off regions if the recruitment is performed with low
oxygen concentration. Whether this significant amount of airway closure, reabsorption atelectasis, and potential associated atelectrauma and peripheral airway injury critical elements in ventilator-associated lung injury is a matter for future studies.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

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