PEEP only partly restores disturbed distribution of regional pulmonary blood flow in lung injury

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Kleen, M., B. Zwiessler, and K. Messmer. PEEP only partly restores disturbed distribution of regional pulmonary blood flow in lung injury. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H209–H216, 1998.—The effects of lung injury, positive end-expiratory pressure (PEEP), and norepinephrine on heterogeneity of regional pulmonary blood flow (rPBF) were investigated. We hypothesized that lung injury increases heterogeneity of rPBF and that PEEP ventilation reduces these effects. Heterogeneity of rPBF is scale dependent and was therefore assessed in detail. One may ask the question how perfusion to neighboring lung regions compares. Spatial correlation (\(\rho\)) of perfusion measures local heterogeneity (or, vice versa, local self-similarity) of neighboring organ regions.

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**ACUTE RESPIRATORY DISTRESS syndrome (ARDS)** is a major problem in critical care medicine. The syndrome has been reported to be associated with a wide range of mortality rates of between 26 and 70% (21). Mechanical ventilation with positive end-expiratory pressure (PEEP) has long been a standard part of symptomatic therapy (18). In 1986, decreased gas content in computed tomography images of dependent lung areas of ARDS patients was first demonstrated (6, 23). It was shown recently that PEEP of 5–20 cmH2O significantly reduces this maldistribution of tidal volume (7). Furthermore, high levels of PEEP have been shown to reduce mortality from severe ARDS in a retrospective, uncontrolled study (5).

Infusion of oleic acid (OA) may mimic some vascular aspects of ARDS. The combination of OA-induced pulmonary edema and glass micro-bead embolism has been shown to more closely simulate human ARDS (31). In dogs with OA edema, the administration of PEEP (10 cmH2O) normalized the injury-induced redistribution of perfusion to edematous lung regions (25). Norepinephrine is used as a standard therapy for circulatory support in septic patients who often also suffer from ARDS, since norepinephrine increases peripheral vascular resistance, which is decreased during septicemia (28). The effects of norepinephrine on regional pulmonary blood flow (rPBF) distribution in an ARDS model have not yet been studied.

The purpose of the present study was to determine the effects of various levels of PEEP and the combination of PEEP with norepinephrine infusion on experimental ARDS-induced changes of heterogeneity of pulmonary perfusion using absolute blood flow values. Hitherto, rPBF during ARDS and PEEP therapy has been assessed with either indirect methods or by using only some representative samples from the lung rather than the whole lung.

Heterogeneity of rPBF as measured with relative dispersion (RD; SD/mean) is scale dependent, increasing with higher resolution of measurement. Comparison of data between groups or even between experiments may therefore be inappropriate. The increase of apparent heterogeneity with increasing resolution can be measured with fractal dimension (D). In contrast to RD, D is a resolution-independent measure of heterogeneity of regional perfusion.

Heterogeneity may also be viewed on a small-scale level. One may ask the question how perfusion to neighboring lung regions compares. Spatial correlation (\(\rho\)) of perfusion measures local heterogeneity (or, vice versa, local self-similarity) of neighboring organ regions.

Both D and \(\rho\) have recently been added to the methodological spectrum for assessment of heterogeneity of pulmonary blood flow (9, 10). The effects of experimental lung injury and PEEP ventilation on these parameters have not been studied so far.

The hypotheses were as follows: 1) lung injury increases all measures of heterogeneity of regional pulmonary blood flow; 2) mechanical ventilation with PEEP returns heterogeneity of rPBF to pre-injury values; and 3) norepinephrine further homogenizes blood flow distribution.

**METHODS**

Animal Preparation

Eight foxhounds of either sex weighing 17.7 ± 1.5 kg were studied. The study was approved by the governmental animal care and use committee. All animals received care in compliance with the “Guide for the Care and Use of Laboratory Animals” [Department of Health and Human Services Publication No. (NIH) 85–23, Revised 1985]. The dogs were premedicated with 20 mg/kg propiomazine (Combelen; Bayer, Leverkusen, Germany). Anesthesia was induced by intravenous injection of 20 mg/kg pentobarbital sodium (Nembutal;...
Cevad, Bad Segeberg, Germany), 0.75 mg/kg piritramide (Dipidolor; Janssen, Neuss, Germany), and 0.25 mg/kg alcuronium (Alloferin; Roche, Grenzach-Whylen, Germany) and maintained by continuous infusion of these drugs at a rate of 5, 0.15, and 0.075 mg·kg⁻¹·h⁻¹, respectively. Fluid losses were replaced with Ringer lactate solution at 5 ml·kg⁻¹·h⁻¹. The dogs were endotracheally intubated and mechanically ventilated with 12 breaths/min and a tidal volume of 15–18 ml/kg using 100% oxygen (Servo 900C; Siemens-Elema, Solna, Sweden). Core body temperature was maintained by means of a heating pad.

Surgical Preparation

A catheter for monitoring mean arterial pressure was inserted into the left brachial artery and advanced to the descending aorta. A second catheter was advanced to the superior vena cava via the left brachial vein. A Swan-Ganz catheter (7 Fr; Edwards, Anasco, Puerto Rico) was inserted into the pulmonary artery for measurement of core body temperature and pulmonary artery pressure as well as for injection of microspheres and withdrawal of the reference sample during injection of microspheres. Both injection of microspheres and sampling of blood were performed with the distal port of the catheter in the pulmonary artery. A tip manometer was inserted into the right ventricle via the right external jugular vein for measurement of right ventricular pressures. A side-winder catheter (6 Fr; Cordis, Miami, FL) was introduced under fluoroscopic control via the right common carotid artery into the left atrium for measurement of left atrial pressure. Intrathoracic pressure was estimated using a balloon catheter (National Catheter) inserted into the esophagus and positioned at the level of the atrium. After the catheters were inserted, the dogs were placed in the left lateral decubitus position. In the lateral position, esophageal pressure reliably reflects intrathoracic pressure during PEEP (4). Blood loss due to drawing reference samples was isovolemically replaced with blood. Autologous blood was collected by isovolemic hemodilution with 6% Dextran 60 (Macrodex; Schwa, Glandorf, Germany) to a hematocrit of 28%. The dogs were allowed to stabilize for 30 min after hemodilution. An additional 400–500 ml of blood were obtained from a premedicated, awake donor dog on the day of the experiment. Autologous and homologous blood were mixed, the absence of hemolysis was verified, and the mixture (hematocrit 28 ± 2%) was used for volume substitution and augmentation of intravascular volume during ventilation with PEEP (4).

Experimental Protocol

Thirty minutes after baseline measurements, the lungs were injured with OA and glass beads. After 70 min and measurements, PEEP of 10 cmH₂O was induced, and measurements were taken. Thereafter, the level of PEEP was increased by 5 cmH₂O until 20 cmH₂O was reached. After each increase, measurements were taken. Subsequently, norepinephrine was infused (PEEP at 20 cmH₂O), and a final set of measurements was made. The dose of OA was 0.01 ml/kg. Glass beads with 100-µm mean diameter were obtained, administered until mean pulmonary artery pressure reached 35–40 mmHg. Both OA and glass beads were injected into the right atrium. This technique has been shown to produce a stable ARDS-like syndrome and pulmonary hypertension (31). Norepinephrine was infused at a dose of 0.2–1.0 µg·kg⁻¹·min⁻¹. During PEEP, transmural right ventricular end-diastolic pressure was kept constant by transfusion of blood (3.6 ± 2.1, 4.5 ± 2.4, and 4.5 ± 1.1 ml/kg at 10, 15, and 20 cmH₂O PEEP, respectively). Ten minutes were allowed to elapse after each intravascular volume change. Subsequently, animals were killed by intravenous injection of saturated potassium chloride. The lungs were removed and dried in room air while being kept inflated at a pressure of 20 cmH₂O for 4 days. A time control group was not studied because the course of this experimental ARDS has been studied in detail before (31).

Measurements

Heart rate, right and left ventricular pressures, as well as intrathoracic pressures were monitored continuously on an eight-channel recorder (481, Gould-Brush, Cleveland, OH) and were evaluated at end expiration. To correct for increased absolute intrathoracic pressure during PEEP ventilation, intrathoracic pressure was subtracted from central venous pressure, mean left atrial pressure, and right ventricular pressures to yield transmural pressures. All pressures reported are transmural pressures. Intermittently, thermodilution cardiac output was measured in triplicate (SP 1435, Gould-Statham, Oxnard, CA). Blood gases were measured with an ABL 300 blood-gas analyzer (Radiometer, Copenhagen, Denmark). Stroke volume (SV) was calculated as

\[ SV = \text{cardiac output (ml)/heart rate (ml/min)} \] (1)

Pulmonary vascular resistance (PVR) was calculated as

\[ PVR = (\text{PAP} - \text{PCWP})/\text{CO} \times 80 \text{ (dyn·s·cm}^{-2}) \] (2)

where PAP is pulmonary arterial pressure, PCWP is pulmonary capillary wedge pressure, and CO is cardiac output. The factor 80 in Eq. 2 transforms into the SI unit. Intrapulmonary shunt flow fraction (Qš/Qt) was calculated as

\[ \dot{Q}_s/\dot{Q}_t = (C_{\text{vO}_2} - C_{\text{aO}_2})/(C_{\text{cO}_2} - C_{\text{vO}_2}) \times 100\% \] (3)

where \(C_{\text{cO}_2}\) is pulmonary end-capillary oxygen content calculated as arterial hemoglobin concentration multiplied by the Hufnern number 1.39 plus physically dissolved oxygen (0.0031 times alveolar Po₂). Arterial (Cₐₒ₂) and mixed venous (Cᵥₒ₂) oxygen contents were calculated analogously. Microsphere injections were performed as described below at the time of hemodynamic measurements.

Microsphere Methodology

All lungs were completely dissected into an average of 384 ± 77 specimens. Each tissue block was assigned x-, y-, and z-coordinates. Right and left lungs were each cut into four sagittal slices of equal thickness. The numbered slices (1–8) served as x-coordinates. Each slice was dissected into 15 horizontal blocks reaching from posterior to anterior. The blocks were numbered from bottom to top; these numbers were used as y-coordinates. The blocks were cut into 10 tissue samples (z-coordinates). Tissue specimens were prepared to have approximately equal size with the help of a grid drawn on transparent plastic. Smaller sagittal slices were cut into less blocks and smaller blocks into less final samples. Therefore, only an average of 384 samples was obtained rather than the theoretical number of 1,200 (8 slices × 15 blocks × 10 samples).

Regional perfusion was measured with the reference sample method reported by Heymann et al. (17). For injection, microspheres were transferred into glass vials and suspended in saline to give a total volume of 10 ml. Before injection, the vials were agitated for a minimum of 3 min. Microspheres were then injected over 50 s into the right atrium. During injection, the vial was continuously agitated to prevent settling of the
spheres. For every measurement of rPBF, 528,000–817,000
(mean, 700,000) microspheres labeled with a randomly
selected isotope (\(^{52}\)Sn, \(^{114}\)In, \(^{51}\)Cr, \(^{141}\)Ce, \(^{103}\)Ru, \(^{46}\)Sc, 16.5 ±
0.1-µm diameter; \(^{46}\)Sc, 16.5 ± 0.2-µm diameter; New England
Nuclear-TRAC, Du Pont, Wilmington, DE) were injected. No
cardiorespiratory changes were noted after injection of micro-
spheres. Beginning 10 s before microspheres injection and
lasting for a total of 3 min, reference samples were drawn
from the pulmonary artery at a rate of 3.24 ml/min (pump
model 940A; Harvard Apparatus, South Natick, MA). Refer-
tence and tissue sample radioactivity were counted for 5 min
using a 1,024 channel gamma counter (model 5260; Packard
Instruments, Downers Grove, IL) with a 3-in. sodium iodine
(thallium drifted) detector. Data were half-life corrected, and
accumulated radioactive spectra were separated to obtain activi-
ties from single nuclides using the software package MIC III
(14) (Department of Surgical Research, Heidelberg, Ger-
many). Sample flow (Q˙p; ml/min) was calculated for each
nuclide as
\[
Q˙p = Q˙pr \times \frac{Ip}{Ipr} \times \frac{1}{Ipr^{-1}} (ml/min)
\]
where Q˙pr is withdrawal rate of the pulmonary reference
sample (ml/min), Ip is counts per minute in the pulmonary
reference sample, and Ipr is counts per minute in the tissue
sample. Q˙p was normalized to 100 g dry lung wt.
The number of microspheres in each sample was calculated
using the specific activity per microspheres. This was deter-
mined before the experiments in vitro by assessing the activity
of a specimen with a defined number of microspheres of
each batch. The number of microspheres in each specimen
was counted three times by microscopic examination
different persons, and the results were accepted if the differ-
eence between counts did not exceed 1% and microsphere
counts were between 600 and 1,000. The gamma activity of
a specimen with a defined number of microspheres
was counted three times by microscopic examination
by 10.220.33.4 on June 29, 2017 http://ajpheart.physiology.org/ Downloaded from

Analysis of Heterogeneity of rPBF

Relative dispersion. To determine global heterogeneity of
rPBF, RD (standard deviation/mean) was calculated for each
time point in the protocol. By dividing a measure of dispersion
(SD) by a measure of central tendency (mean), one expresses
the dispersion as a fraction of the mean. Thus it is possible to
compare heterogeneity values from different pulmonary blood
flow states. Because for calculation of RD all regional blood
flow values are averaged, RD represents a global measure of
heterogeneity.

Fractal dimension. Fractal properties of pulmonary blood
flow heterogeneity were demonstrated by Glenny and Robert-
son in 1990 (10). A commonly used approach to analyze the
fractal nature of pulmonary perfusion is to dissect the lung in
small parts and measure the perfusion on this level. Data from
these samples are then recombined to obtain informa-
tion about perfusion of larger samples. If the perfusion is
fractal, the natural logarithm of the decreasing heterogeneity
of perfusion to larger samples is linearly related to the
natural logarithm of the increasing sample size.

Heterogeneity of blood flow to the lung is described with
the RD of regional perfusion. The scale of the applied
measurement is expressed as the relative mass of the recom-
bined tissue samples (m) in relation to a reference tissue
sample mass (m0). Heterogeneity and scale of measurement
of rPBF have been shown to be related according to the
following equation
\[
(RD_m/RD_{m0}) = (m/m0)^{1-D}
\]
where RDm is the relative dispersion of regional perfusion at
some resolution and RDm0 is relative dispersion of regional
perfusion when analyzed with the reference resolution (13).
The variable D in the exponent of Eq. 5 is the fractal
dimension of the perfusion. The slope of the regression line
through multiple data points on a plot of
\[
\ln (R D_m) v s. \ln (m/m0)
\]
is therefore 1 − D. Such plots are therefore used to determine
fractal properties of perfusion of the lung (3, 11, 24).

We calculated D with a computer program developed in
C/C++ (Watcom C/C++ compiler v. 10; Powersoft, Concord,
MA). For calculation of D, individual samples as well as
recombinations to larger tissue units comprising 4, 8, 16, 32,
64, etc., individual samples were used. Recombinations
were achieved by adding the microsphere contents of the samples
comprised in an aggregate sample and dividing the result by
the sum of the weights of samples.

Both the program for calculating spatial correlation and
the program for assessing fractal dimension were validated
with computer-generated data sets with known D and r,
respectively.

Spatial correlation. In 1992, Glenny (9) suggested p of
regional pulmonary perfusion as a new tool for characterizing
distribution of rPBF. Spatial, or three-dimensional, correla-
tion measures the average relationship of blood flow to lung
tissue pieces separated by a certain distance. We chose
the smallest distance for calculation, thus obtaining spatial corre-
lation for neighboring pieces. Spatial correlation as a mea-
sure for averaged, local heterogeneity of pulmonary blood
flow has been shown to change differently upon intervention
than global heterogeneity measured with RD (12). For calcu-
lation of spatial correlation, all blood flow values from tissue
specimens separated by a given distance (multiples of sample
size) are treated as data pairs and are used as variables for a
three-dimensional extension of the standard correlation for-
mula as reported by Glenny (9). We implemented this formula
with a computer program written in C++ (Watcom C/C++
compiler v. 10; Powersoft). For analysis, we used the correla-
tion values of adjacent samples; thus p is a measure of local
gravity-independent heterogeneity of regional pulmonary
perfusion.

Relative gravity-dependent perfusion gradients. Relative
gravity dependent perfusion gradients (RPG) were deter-
mined separately for each lung as
\[
R P G = \frac{P B F_{\text{bottom}} - P B F_{\text{top}}}{P B F_{\text{top}}} \times 100\%
\]
where PBFtop is mean blood flow in the uppermost quarter of
the right and left lungs and PBFbottom is mean blood flow in
the most dependent quarter of the right and left lungs. With
dogs in the left lateral decubitus position, top and bottom
were defined as right and left side of the thorax, respectively.

Histograms. Histograms of pooled rPBF values from all
animals were analyzed using the median as well as the 5th
and 95th percentiles. rPBF was calculated as shown in
Microsphere Methodology.

Statistics

All statistical analyses were performed using the software
package SAS v. 6.10 (SAS Institute, Cary, NC). After a
significant F value was obtained from analysis of variance,
the Student-Newman-Keuls test was applied posteriori to
determine differences between a time point in the protocol
and the respective preceding time point. The type I error level
was set to 5%.
RESULTS

In Table 1, central hemodynamic data and blood gases are summarized. Induction of experimental ARDS resulted in significant tachycardia, a decrease of stroke volume, and increases of mean pulmonary artery pressure (MPAP), pulmonary vascular resistance, mean right ventricular pressure, and right ventricular maximal rate of pressure increase (RV dP/dt max). Cardiac output, arterial pressure, and left atrial pressure were unchanged. Ventilation with 20 cmH2O PEEP caused a significant additional rise of MPAP.

There was a 55% rise of intrapulmonary shunt fraction (Qh/Qt) upon lung injury induction (P < 0.05), a significant acidosis (P < 0.05), a 16% fall of arterial PO2 (PaO2) (P < 0.05), and a 28% rise of arterial PCO2 (PaCO2) (P < 0.05). Mixed venous PO2 (PvO2) was unchanged.

Mechanical ventilation with PEEP elicited significant reduction of Qh/Qt (P < 0.05) and elevation of PaO2 (P < 0.05), whereas arterial pH, PaCO2, and PvO2 remained unchanged.

Figure 1 shows RD of rPBF (global heterogeneity), D of rPBF (scale-independent global heterogeneity), and ρ of the perfusion of adjacent pulmonary tissue samples (local heterogeneity of rPBF). Global heterogeneity of rPBF was altered by lung injury: RD was 0.36 ± 0.06 at baseline and 0.64 ± 0.12 upon induction of lung injury (P < 0.05). Neither administration of PEEP nor therapy with norepinephrine induced any rehomogenization (Fig. 1). D was stable after lung injury (1.25 ± 0.06 vs. 1.34 ± 0.08; P = NS) and was not influenced by PEEP therapy or norepinephrine. Induction of lung injury decreased ρ from 0.44 ± 0.09 at baseline to 0.24 ± 0.09 (P < 0.05). Therapy with 10, 15, and 20 cmH2O PEEP and additional administration of norepinephrine did not change ρ (Fig. 1).

Figure 2 shows the RPG separately for each lung. At baseline, there was a preferential perfusion of the uppermost quarter of both lungs (right, −27 ± 18%; left, −24 ± 18%). Upon embolization, there was a reversal of this distribution. The RPGs changed to 196 ± 115 and 282 ± 184% for the right and left lung, respectively (P < 0.05). PEEP of 10 cmH2O lowered the gradients of both lungs significantly to 116 ± 73 and 143 ± 62%, respectively, for right and left lungs (P < 0.05). PEEP of 15 and 20 cmH2O did not induce further significant decrease of RPG for both lungs (PEEP 15 cmH2O: right, 103 ± 78%; left, 90 ± 52%; PEEP 20 cmH2O: right, 109 ± 105%, left, 124 ± 58%; P = NS). Infusion of norepinephrine, however, lowered the RPG to 50 ± 58% (P < 0.05) in the right lung, which was not significantly different from baseline. In the dependent left lung, the RPG remained at 102 ± 94% with infusion of the vasoconstricting agent. In Fig. 4, the mean

Table 1. Cardiovascular and gas exchange parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Lung Injury</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>20 + NE</th>
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<tr>
<td>HR, min⁻¹</td>
<td>72 ± 19</td>
<td>107 ± 17*</td>
<td>99 ± 16</td>
<td>109 ± 19</td>
<td>124 ± 10</td>
<td>135 ± 31</td>
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<tr>
<td>MAP, Torr</td>
<td>102 ± 9</td>
<td>102 ± 8</td>
<td>108 ± 13</td>
<td>112 ± 17</td>
<td>102 ± 13</td>
<td>110 ± 19</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>3.1 ± 0.7</td>
<td>2.8 ± 0.8</td>
<td>2.5 ± 0.7</td>
<td>2.4 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>SV, ml</td>
<td>44 ± 13</td>
<td>27 ± 8*</td>
<td>25 ± 5</td>
<td>22 ± 5</td>
<td>17 ± 5</td>
<td>20 ± 12</td>
</tr>
<tr>
<td>MLAP, Torr</td>
<td>4.5 ± 3.3</td>
<td>2.6 ± 2.3</td>
<td>2.8 ± 1.9</td>
<td>2.3 ± 1.9</td>
<td>1.8 ± 2.1</td>
<td>2.0 ± 2.6</td>
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<tr>
<td>MPAP, Torr</td>
<td>31 ± 3</td>
<td>32 ± 5*</td>
<td>31 ± 4</td>
<td>32 ± 3</td>
<td>37 ± 3*</td>
<td>38 ± 3</td>
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<tr>
<td>MRVP, Torr</td>
<td>6 ± 2</td>
<td>16 ± 3*</td>
<td>15 ± 3</td>
<td>15 ± 2</td>
<td>17 ± 2</td>
<td>16 ± 2</td>
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<tr>
<td>RVEDP, Torr</td>
<td>1.4 ± 2.5</td>
<td>2.2 ± 2.8</td>
<td>3.0 ± 2.6</td>
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<td>1.0 ± 1.1</td>
<td>−0.5 ± 2.1</td>
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<tr>
<td>RV dP/dt max, Torr/s</td>
<td>370 ± 92</td>
<td>590 ± 174*</td>
<td>505 ± 136</td>
<td>536 ± 136</td>
<td>567 ± 66</td>
<td>1,276 ± 207</td>
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<td>PVR, dyn·s·cm⁻⁵</td>
<td>156 ± 81</td>
<td>907 ± 350*</td>
<td>947 ± 321</td>
<td>1,081 ± 378</td>
<td>1,461 ± 549</td>
<td>1,458 ± 728</td>
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<tr>
<td>Qh/Qt</td>
<td>0.09 ± 0.04</td>
<td>0.14 ± 0.03</td>
<td>0.10 ± 0.04*</td>
<td>0.07 ± 0.03*</td>
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<td>pH₅</td>
<td>7.35 ± 0.04</td>
<td>7.26 ± 0.03</td>
<td>7.27 ± 0.03</td>
<td>7.27 ± 0.04</td>
<td>7.26 ± 0.04</td>
<td>7.23 ± 0.04</td>
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<tr>
<td>PaO₂, Torr</td>
<td>584 ± 39</td>
<td>491 ± 34*</td>
<td>536 ± 34*</td>
<td>579 ± 33*</td>
<td>590 ± 38*</td>
<td>587 ± 35</td>
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<td>PaCO₂, Torr</td>
<td>36 ± 4</td>
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<td>45 ± 6</td>
<td>46 ± 5</td>
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<tr>
<td>PvO₂, Torr</td>
<td>68 ± 15</td>
<td>62 ± 9</td>
<td>60 ± 10</td>
<td>57 ± 10</td>
<td>52 ± 12</td>
<td>54 ± 14</td>
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</table>

Values are means ± SD. HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; SV, stroke volume; MLAP, mean left atrial pressure; MPAP, mean pulmonary artery pressure; RV, right ventricular; MRVP, mean RV pressure; RVEDP, RV end-diastolic pressure; RV dP/dt max, maximal rate of RV pressure increase; PVR, pulmonary vascular resistance; Qh/Qt, intrapulmonary shunt fraction; pH₅, arterial pH; PaO₂, arterial PO2; PaCO₂, arterial PCO2; PVw, mixed venous PO2; PEEP, positive end-expiratory pressure; NE, norepinephrine. To convert Torr to kPa, multiply by 1.33. *P ≤ 0.05 vs. preceding time point.
perfusion values of each slice of both lungs are depicted. The perfusion gradients from dependent to nondependent parts of the lungs, and vice versa, can be deduced from Fig. 4.

The cumulated histograms of rPBF from all animals values are shown in Figure 3. The median blood flow was $3.8 \pm 0.6$ l·min$^{-1}$·100 g$^{-1}$ at baseline and $3.7 \pm 0.9$ l·min$^{-1}$·100 g$^{-1}$ upon lung injury induction ($P = NS$). Ventilation with PEEP of 10 cmH$_2$O elevated median blood flow to $4.2 \pm 2.8$ l·min$^{-1}$·100 g$^{-1}$ ($P < 0.05$).

PEEP of 15 and 20 cmH$_2$O each reduced perfusion $(2.6 \pm 0.4$ and $2.3 \pm 0.3$ l·min$^{-1}$·100 g$^{-1}$, respectively; $P \leq 0.05$). Infusion of norepinephrine did not further change blood flow $(2.1 \pm 0.8$ l·min$^{-1}$·100 g$^{-1}$; $P = NS$). The configuration of the rPBF histograms was distorted with lung injury (Fig. 3). The 5th percentile ($P5$) of rPBF was lowered by lung injury. Application of PEEP did not reverse this, but PEEP of 20 cmH$_2$O further reduced the lower border of the histograms. Additional application of norepinephrine increased $P5$ slightly but consistently. The median lung blood flow was not altered by lung injury. PEEP of 10 cmH$_2$O increased the median blood flow by $0.46$ l·min$^{-1}$·100 g$^{-1}$ as compared with $3.74$ l·min$^{-1}$·100 g$^{-1}$ at baseline. The upper border of the histograms, the 95th percentile, was significantly reduced by 15 cmH$_2$O after an insignificant increase upon lung injury.

DISCUSSION

The main results of the present study are as follows: 1) lung injury caused an increase of both global and local heterogeneity of rPBF, reversal of gravity-dependent blood flow gradients, and alterations of statistical measures of histograms of rPBF. 2) PEEP and, partly, norepinephrine counteracted changes of perfusion gradients and blood flow histograms. However, injury-induced heterogeneity remained high. Neither the global, resolution-dependent RD nor global, resolution-independent fractal D were influenced by PEEP therapy. Local correlation of blood flow was also unchanged.

![Fig. 2. Effects of lung injury, different levels of PEEP, and PEEP plus NE on relative perfusion gradients (RPG) of rPBF. Data are means ± SD. Definitions are as in Fig. 1. *P ≤ 0.05 vs. preceding time point in protocol for left lung. #P ≤ 0.05 vs. preceding time point in protocol for right lung.](image)

![Fig. 3. Effects of lung injury, PEEP, and PEEP plus norepinephrine on histograms of rPBF. Data are cumulated regional blood flow values from 8 dogs. M, median of histogram; P5, 5th percentile of histogram; P95, 95th percentile of histogram. *P ≤ 0.05 vs. preceding time point in protocol.](image)
Data on heterogeneity of regional pulmonary perfusion during respiratory failure are limited. The prone position has been shown to reduce gravitational gradients of regional pulmonary perfusion (30) and reduce venous admixture (1) in dogs with OA edema. High-level PEEP was demonstrated to improve gas exchange in lavage-induced lung injury (2) and to homogenize density distribution in computed tomography images in ARDS patients (7). In 1994, Schuster and Howard (25) showed with indirect perfusion measurements (positron emission tomography) that PEEP reverses OA-induced redistribution of pulmonary perfusion to edematous tissue. Using the multiple inert gas elimination technique, Matamis et al. (22) noted beneficial effects of 17 ± 2 cmH2O PEEP on ventilation-perfusion distribution in patients with acute respiratory failure. Hedenstierna and co-workers (15, 16) reported on the effects of 20 cmH2O PEEP on gravitational gradients in healthy dog lungs by analyzing representative samples rather than whole lungs. In their studies, decreased right ventricular preload was not compensated for, but reduced cardiac output without PEEP did not produce similar patterns of perfusion redistribution (15, 16).

There is one study dealing with distribution of rPBF in OA injury in dogs (27). The authors have calculated peripheral to central perfusion gradients. Early after OA infusion they found a reduction of peripheral perfusion. This seems to be in contrast to our data. We observed an increase in peripheral perfusion in the dependent lung and a decrease of peripheral blood flow in the nondependent lung (Fig. 4). Tarver and colleagues (27) studied only representative samples of one lobe of one lung. We studied the complete lung and observed heterogeneous distribution changes including effects similar to those observed by Tarver et al. We therefore cannot definitely conclude whether our results are in contrast to or in agreement with those of the cited study. Another important difference between our study and that of Tarver et al. is that in the former, animals were placed in the left lateral decubitus posi-
tion and in the latter the prone position was used. The time frame in both studies is very different. We induced OA-glass bead lung injury over a time that was certainly much longer than the time used in Tarver’s study. The latter study was explicitly designed to investigate early effects of OA infusion, whereas we established a more chronic form of lung injury. In conclusion, we think that our results are not necessarily in contrast to those published by Tarver and colleagues.

Spatial Correlation, Relative Dispersion, and Fractal Dimension

Spatial correlation (\( \rho \)) of perfusion of adjacent lung tissue samples is a measure of local similarity of blood flow (9). Lung injury decreased \( \rho \) notably (0.44 ± 0.09 vs. 0.24 ± 0.09) (Fig. 1). This is in contrast to findings of Schuster and Howard (25) who reported a redistribution of perfusion to the most edematous lung regions induced by OA after application of 10 cmH\(_2\)O PEEP. Global heterogeneity of rPBF greatly increased upon lung injury (RD = 0.36 ± 0.06 vs. 0.64 ± 0.12) (Fig. 1) and was influenced neither by PEEP nor by infusion of norepinephrine. The lack of effect of the treatment on these three parameters of heterogeneity is an important finding. From previous data on OA edema, a positive effect of PEEP on distribution of rPBF should have been expected (25). When assessed with more specific methods, however, heterogeneity proved uninfluenced. Therefore, RD and \( \rho \) are valuable parameters of rPBF distribution in this model of lung injury. For testing other therapeutic strategies, it may be useful to use them to show superiority of new concepts.

Relative Perfusion Gradients

At baseline, we found preferential perfusion of the nondependent parts of the lung, which is in agreement with recent findings by Hlastala et al. in horses (19). Relative perfusion gradients were calculated separately for each lung. The dependent part of the left lung was the part adjacent to the lateral thoracic wall, and the nondependent parts were mediastinal regions. For the right lung (superior to the left lung because of the left lateral decubitus position), the dependent part was the mediastinal part and the nondependent part corresponded to those regions next to right lateral thoracic wall. Induction of lung injury reversed RPGs and greatly enhanced the extent of gravity-dependent perfusion inhomogeneity in both lungs (Fig. 2). The difference of the bottom and top parts (left lateral decubitus position of the dogs) of the lungs amounted to two to three times the blood flow in the uppermost parts of the lungs. PEEP of 10 cmH\(_2\)O counteracted these gradients significantly. This is in contrast to the reported effects of PEEP on the noninjured lung in dogs in which 20 cmH\(_2\)O PEEP resulted in marked reduction of perfusion of the uppermost regions of the lung (15, 16). Similarly, PEEP (10 cmH\(_2\)O) redirected perfusion to dependent regions of the lung in a model of OA-induced single-lung injury (20).

In the right (nondependent) lung, norepinephrine further redistributed perfusion to nondependent areas of the lung, thus rendering the resulting RPG not significantly different from baseline values despite the presence of lung injury and 20 cmH\(_2\)O PEEP. The catecholamine was infused in a central vein. The lung is known to clear 30% of this drug during a single passage (8, 26); however, this may or may not be the case in the injured lung. As can be concluded from unchanged values for pulmonary vascular resistance (Table 1), norepinephrine did not vasoconstrict pulmonary vessels. There was, however, a trend toward increased right ventricular contractility (RV dP/dt\(_{\text{max}}\); see Table 1) and increased cardiac output. The effects of norepinephrine infusion on RPGs may therefore probably be explained by a recruitment of pulmonary vessels. Norepinephrine might be of benefit when combined with PEEP in attempts to normalize disturbed gradients of pulmonary blood flow in ARDS. However, norepinephrine failed to further improve Q\(_s\)/Q\(_t\) or PaO\(_2\), in our study and may also cause increased cardiovascular stress, which may be undesirable in critically ill patients.

Histograms of rPBF Values

At baseline, the histogram of rPBF values (Fig. 3) was close to a Gaussian distribution as judged by inspection. Such a normal distribution was also found by Walther et al. (29) in awake sheep. Upon lung injury, the number of values close to zero and the number of extremely high values were increased, which resulted in a left-shifted and skewed histogram. The most prominent change upon ventilation with PEEP (15 cmH\(_2\)O) was the reduced frequency of extremely high values. Thus the rPBF histogram approached prelung injury configuration upon therapy with PEEP. It appears that PEEP therapy removed the tail from the rPBF distribution and added to the frequency of values close to the mean. The median value was reduced by higher levels of PEEP, but the fifth percentile was not greatly reduced; thus the lower median seems due to less high values. Considering improved gas exchange and reduced shunt fraction, we interpret these changes upon PEEP as improvement of distribution of rPBF in this model of lung injury.

Conclusion

In the present study, we provide the first data on spatial correlation and fractal dimension of regional pulmonary blood flow in a model of acute lung injury and PEEP therapy. Our data show that most parameters of heterogeneity are greatly changed by lung injury. PEEP therapy normalizes only the perturbations of perfusion gradients and some of the statistical measures of rPBF histograms. However, neither of the new parameters of blood flow distribution (fractal dimension, spatial correlation) that were changed by lung injury were normalized by PEEP therapy. In addition to restoring ventilation to collapsed or fluid-filled alveoli that are still perfused, PEEP may contribute to improved oxygenation in patients with ARDS by improving disturbed perfusion gradients.
The valuable technical assistance of R. Schwarz, C. Schwikert, and P. Spengler in performing these experiments is gratefully acknowledged. We are indebted to Dr. R. Schosser for the expert support in microsphere measurements.

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Received 16 April 1997; accepted in final form 9 September 1997.

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