Distribution of regional lung aeration and perfusion during conventional and noisy pressure support ventilation in experimental lung injury

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Carvalho AR, Spieth PM, Güldner A, Cuevas M, Carvalho NC, Beda A, Spieth S, Stroczynski C, Wiedemann B, Koch T, Pelosi P, Gama de Abreu M. Distribution of regional lung aeration and perfusion during conventional and noisy pressure support ventilation in experimental lung injury. J Appl Physiol 110: 1083–1092, 2011. First published January 26, 2011; doi:10.1152/japplphysiol.00804.2010.—In acute lung injury (ALI), pressure support ventilation (PSV) may improve oxygenation compared with pressure-controlled ventilation (PCV), and benefit from random variation of pressure support (noisy PSV). We investigated the effects of PCV, PSV, and noisy PSV on gas exchange as well as the distribution of lung aeration and perfusion in 12 pigs with ALI induced by saline lung lavage in supine position. After injury, animals were mechanically ventilated with PCV, PSV, and noisy PSV for 1 h/mode in random sequence. The driving pressure was set to a mean tidal volume of 6 ml/kg and positive end-expiratory pressure to 8 cmH2O in all modes. Functional variables were measured, and the distribution of lung aeration was determined by static and dynamic computed tomography (CT), whereas the distribution of pulmonary blood flow (PBF) was determined by intravenously administered fluorescent microspheres. PSV and noisy PSV improved oxygenation and reduced venous admixture compared with PCV. Mechanical ventilation with PSV and noisy PSV did not decrease nonaerated areas but led to a redistribution of PBF from dorsal to ventral lung regions and reduced tidal reaeration and hyperinflation compared with PCV. Noisy PSV further improved oxygenation and redistributed PBF from caudal to cranial lung regions compared with conventional PSV. We conclude that assisted ventilation with PSV and noisy PSV improves oxygenation compared with PCV through redistribution of PBF from dependent to nondependent areas, thus improving regional ventilation in dependent lung regions. Pressure support ventilation (PSV) is the most frequently used mode of assisted mechanical ventilation (7). Our group (2, 13, 14) and other investigators (17) reported that PSV improves lung function compared with controlled ventilation in experimental acute lung injury (ALI). Recently, Yoshida et al. (43) reported that PSV effectively increases arterial oxygenation in patients with the acute respiratory distress syndrome (ARDS). Furthermore, our group showed that random variation of pressure support (noisy PSV) improves oxygenation and intrapulmonary shunt beyond what is observed with conventional PSV (2, 14).

The improvement in oxygenation during assisted ventilation can be due to either alveolar recruitment and redistribution of ventilation to dependent zones (27, 32, 41) or redistribution of perfusion toward nondependent areas (2). If assisted ventilation recruits the lungs, it may reduce tidal reaeration, which may reflect cyclic closing/reopening of small airways and alveoli. On the contrary, if recruitment does not occur, as suggested by previous findings from our group (2, 14), an increase in tidal reaeration in the dependent and in tidal hyperinflation in the nondependent zones is expected. Both tidal reaeration and hyperinflation have been suggested to promote ventilator-associated lung injury (VALI) (22, 28).

In the present work, we assessed the effects of PSV and noisy PSV compared with protective pressure-controlled ventilation (PCV) on the regional distribution of aeration, tidal reaeration, and hyperinflation as well as distribution of ventilation and pulmonary blood flow (PBF) in a saline lung lavage model of ALI. In all modes investigated, mean tidal volumes (VT) compatible with protective ventilation were used (6 ml/kg). The two major specific goals were to 1) investigate and explain improvements in oxygenation during assisted ventilation with PSV and noisy PSV compared with PCV from the perspective of regional lung ventilation and blood flow and the associations between these and 2) investigate

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CONTROLLED MECHANICAL VENTILATION usually requires sedation and, in the presence of major patient/ventilator asynchrony or severe respiratory failure, even muscle paralysis. As a consequence, a cranial displacement of the diaphragm will occur, contributing to the development of lung collapse in the dependent regions (10, 11, 33). During assisted mechanical ventilation, spontaneous breathing activity may restore the physiological displacement pattern of the diaphragm, recruiting dorsal, and usually better perfused regions, thus improving regional ventilation in dependent lung regions (11, 30, 42).

Pressure support ventilation (PSV) is the most frequently used mode of assisted mechanical ventilation (7). Our group (2, 13, 14) and other investigators (17) reported that PSV improves lung function compared with controlled ventilation in experimental acute lung injury (ALI). Recently, Yoshida et al. (43) reported that PSV effectively increases arterial oxygenation in patients with the acute respiratory distress syndrome (ARDS). Furthermore, our group showed that random variation of pressure support (noisy PSV) improves oxygenation and intrapulmonary shunt beyond what is observed with conventional PSV (2, 14).

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In the present work, we assessed the effects of PSV and noisy PSV compared with protective pressure-controlled ventilation (PCV) on the regional distribution of aeration, tidal reaeration, and hyperinflation as well as distribution of ventilation and pulmonary blood flow (PBF) in a saline lung lavage model of ALI. In all modes investigated, mean tidal volumes (VT) compatible with protective ventilation were used (6 ml/kg). The two major specific goals were to 1) investigate and explain improvements in oxygenation during assisted ventilation with PSV and noisy PSV compared with PCV from the perspective of regional lung ventilation and blood flow and the associations between these and 2) investigate
whether the effects of assisted ventilation with PSV and noisy PSV on regional lung aeration suggest a decreased risk of VALI.

**METHODS**

The protocol of the present study complied with German laws for studies on animals and was approved by the Institutional Animal Care Committee and the Government of the State of Saxony, Germany.

**Anesthesia and Mechanical Ventilation**

Twelve female pigs (33.1–46.6 kg) were premedicated with intramuscular injection of ketamine 10 mg/kg (Ratiopharm, Ulm, Germany) and 1 mg/kg midazolam (Ratiopharm). After endotracheal intubation (8.0 ID; Malinckrodt, Athlone, Ireland), intravenous anesthesia was maintained with midazolam (1–2 mg·kg⁻¹·h⁻¹) and ketamine (15–20 mg·kg⁻¹·h⁻¹). Muscle paralysis was achieved with atracurium (Ratiopharm, 0.5–2.5 mg·kg⁻¹·h⁻¹). Animals were initially ventilated in volume-controlled ventilation using the mechanical ventilator EVITA XL 4 Lab (Dräger Medical, Lübeck, Germany) with VT = 10 ml/kg, fraction of inspired oxygen (FiO₂) = 1.0, inspiratory/expiratory ratio (I:E) = 1:1, positive end-expiratory pressure (PEEP) = 5 cmH₂O, and respiratory rate (RR) to achieve arterial partial pressure of carbon dioxide (PaCO₂) in the range of 35–45 mmHg. Volume status was maintained with E153 (Serumwerk Bernburg) at 5–10 ml·kg⁻¹·h⁻¹ to keep pulmonary capillary wedge pressure (PCWP) between 8 and 12 mmHg.

**Animal Preparation and Induction of Acute Lung Injury**

An indwelling catheter was inserted in the carotid artery, and a pulmonary artery catheter (Opticath; Abbott Laboratories, Abbott Park, IL) was advanced through the external jugular vein. Following baseline measurements, lung injury was induced by repetitive lung lavages with 0.9% saline solution (37–39°C) in the supine position, as described by Lachmann et al. (24). Injury was considered stable if PaCO₂/FiO₂ < 200 mmHg for ≥30 min.

**Respiratory and Hemodynamics Measurements**

A heated pneumotachograph (Fleisch No. 2; Fleisch, Lausanne, Switzerland) connected to a pressure transducer (PXL12X5DN; Sensortech, Troy, NY) was used to assess airflow way. Airway pressure (Paw) was monitored with a second pressure transducer (SCX01DNC; SenSym, Milpitas, CA) whose tip was placed next to the tracheal tube. An esophageal catheter (Erich Jaeger, Höchberg, Germany) was used to measure esophageal pressure (Pes). The position of the esophageal catheter was adjusted to obtain a correlation coefficient of −1.0 between Paw and Pes recordings during end-expiratory breath-hold maneuvers. Paw and Pes swings were caused by respiratory muscle activity in PSV and noisy PSV and external thoracoabdominal compression in PCV. Respiratory signals were digitized at 150 Hz and acquired by a LabView (National Instruments, Austin, TX) routine, as described elsewhere (6).

Respiratory parameters were calculated from recordings of flow, Paw, and Pes lasting 2 min during controlled and 5 min during assisted ventilation. Mean (Paw,mean) and peak (Paw,peak) were determined, whereas mean transpulmonary pressure (Paw,transp) was calculated as mean Paw – Pes. Intrinsic PEEP (PEEPdyn) was computed as the difference between Pes at beginning of inspiratory effort and Pes at the onset of inspiration. The pressure time product (PTP) was calculated as the product of Pes over time during inspiration, taking the Pes value at end of expiration as offset. Respiratory parameters were averaged.

Respiratory gases and pH were analyzed using an ABL 505 (Radiometer, Copenhagen, Denmark), whereas oxygen saturation and hemoglobin concentration were measured with an OSM 3 Hemoximeter (Radiometer).

Mean arterial pressure, pulmonary artery pressure, central venous pressure, and PCWP were measured by a hemodynamic monitor system (CMS; Agilent, Böblingen, Germany). Cardiac output (CO) was measured by conventional thermodilution. CO values were averaged from three measurements distributed along the respiratory cycle.

**Computed Tomography**

Static and dynamic computed tomography (CT) measurements were obtained with a Somatom Sensation 16 (Siemens, Erlangen, Germany).

**Static CT.** Helical CT (CT stat) scans of the whole lung were obtained during controlled mechanical ventilation, before and after the induction of ALI, as well as during PSV and noisy PSV. Scans were obtained during breath-hold maneuvers at the end of expiration, with simultaneous clamping the endotracheal tube to minimize possible artifacts due to respiratory muscle activity. The CT scanner was set as follows: collimation, 16 × 0.75 mm; pitch, 1.35; bed speed, 38.6 mm/s; voltage, 120 kV; and tube current-time product, 120 mAs. Images were reconstructed with slices of 5-mm thickness, without gaps between them, yielding images with 512 × 512 pixels with a surface of 0.443 × 0.443 mm².

**Dynamic CT.** Dynamic CT (CT dyn) measurements were performed at apex (~3 cm cranial to the carina), hilum (at carina level), and base levels (~2–3 cm caudal to the carina). Each level was further divided into four zones of equal heights from ventral to dorsal. CT device settings were similar to CT stat, except that the bed speed was zero. Scans were obtained every 120 ms during a period of 30 s, resulting in ~250 images/level.

**Segmentation and calculations.** Lung boundary contours were semiautomatically demarcated. Images were analyzed for calculation of hyperaerated and normally, poorly, and nonaerated lung compartments, as described elsewhere (39). From CT stat, we computed aeration compartments, total lung volume, total lung gas volume, and tissue mass for whole lungs at the end of expiration, as shown by others (15). From CT dyn, we calculated aeration compartments at the end of expiration and the end of inspiration, as well as tidal reaeration and hyperaeration, as described elsewhere (25). Throughout this work, aeration, tidal reaeration, and hyperaeration are used as synonyms for

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**Fig. 1.** Time course of interventions. Modes 1, 2, and 3 correspond to pressure-controlled ventilation (PCV), pressure support ventilation (PSV), and noisy pressure support ventilation (noisy PSV) in random sequence.

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Table 1. Respiratory variables

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1</th>
<th>Injury</th>
<th>Baseline 2</th>
<th>PCV</th>
<th>PSV</th>
<th>Noisy PSV</th>
<th>Mode Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paw,p, cmH2O</td>
<td>21.4 ± 2.1</td>
<td>36.7 ± 5.3</td>
<td>26.4 ± 2.0</td>
<td>26.6 ± 2.5</td>
<td>27.1 ± 2.9</td>
<td>25.4 ± 3.1</td>
<td>§</td>
</tr>
<tr>
<td>CV of Paw,p, %</td>
<td>1.0 ± 0.3</td>
<td>0.7 ± 0.2</td>
<td>1.0 ± 0.3</td>
<td>1.3 ± 0.8</td>
<td>1.4 ± 1.6</td>
<td>1.8 ± 1.0</td>
<td>#</td>
</tr>
<tr>
<td>VT, ml/kg</td>
<td>9.9 ± 0.1</td>
<td>10.1 ± 0.1</td>
<td>6.0 ± 0.1</td>
<td>6.0 ± 0.1</td>
<td>5.9 ± 0.2</td>
<td>6.0 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>CV of VT, %</td>
<td>0.4 ± 0.1</td>
<td>0.6 ± 0.4</td>
<td>1.0 ± 0.3</td>
<td>1.2 ± 0.8</td>
<td>1.2 ± 0.5</td>
<td>21.4 ± 2.5</td>
<td>§#</td>
</tr>
<tr>
<td>RR, min</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
<td>29 ± 2</td>
<td>30 ± 2</td>
<td>35 ± 5</td>
<td>31 ± 5</td>
<td>*</td>
</tr>
<tr>
<td>MV, l/min</td>
<td>5.1 ± 0.6</td>
<td>5.1 ± 0.6</td>
<td>6.8 ± 0.7</td>
<td>7.1 ± 0.8</td>
<td>8.1 ± 1.2</td>
<td>7.3 ± 0.8</td>
<td>*</td>
</tr>
<tr>
<td>Ti/Ttot</td>
<td>0.50 ± 0.01</td>
<td>0.50 ± 0.01</td>
<td>0.51 ± 0.00</td>
<td>0.51 ± 0.00</td>
<td>0.31 ± 0.04</td>
<td>0.31 ± 0.05</td>
<td>*#</td>
</tr>
<tr>
<td>Paw,cmH2O</td>
<td>11.7 ± 0.9</td>
<td>17.6 ± 1.7</td>
<td>16.4 ± 1.0</td>
<td>16.5 ± 1.4</td>
<td>12.7 ± 1.2</td>
<td>12.4 ± 1.2</td>
<td>*#</td>
</tr>
<tr>
<td>Peep,cmH2O</td>
<td>3.0 ± 1.0</td>
<td>9.4 ± 4.4</td>
<td>8.2 ± 0.3</td>
<td>10.4 ± 6.4</td>
<td>6.6 ± 5.0</td>
<td>6.7 ± 5.3</td>
<td>*#</td>
</tr>
<tr>
<td>PTP, cmH2O·s⁻¹·min⁻¹</td>
<td>10.9 ± 5.8</td>
<td>8.6 ± 5.7</td>
<td>6.6 ± 5.4</td>
<td>6.9 ± 4.4</td>
<td>7.0 ± 5.0</td>
<td>7.3 ± 5.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are given as means ± SD. PCV, pressure-controlled ventilation; PSV, pressure support ventilation; Paw, peak inspiratory pressure; CV, coefficient of variation; VT, tidal volume; RR, respiratory rate; MV, minute ventilation; Ti/Ttot, inspiratory time/total respiratory cycle time ratio; Ppaw, mean airway pressure; Peep, intrinsic positive end-expiratory pressure; PTP, inspiratory esophageal pressure time product; NS, not significant. Differences between mechanical ventilation modes (mode effect) were tested with general linear model statistics and adjusted for repeated measurements. *P < 0.05, PCV vs. PSV; #P < 0.05, PCV vs. noisy PSV; §P < 0.05, PSV vs. noisy PSV.

Regional end-expiratory alveolar expansion, tidal recruitment-derecruitment, and hyperinflation, respectively.

Three-dimensional volume meshes were created by masking the lung boundary of each compartment. Color mapping was used to represent lung aeration compartments.

**Distribution of PBF**

Regional PBF was marked with intravenously administered fluorescent, color-labeled, 15-μm-diameter microspheres. A different color was assigned randomly and administered at each time point. Approximately 1.5 × 10⁶ microspheres were administered over 60 s. Postmortem processing was performed as described previously (20, 21). Briefly, lungs were air-dried for 7 days, with continuous pressure of 25 cmH₂O at the trachea. After coating and embedding, the resulting foam-and-ling block was cut into cubes of 1.3 cm³. Each cube was weighed and assigned a three-dimensional coordinate. After the fluorescent dye was retrieved, fluorescence was read in a luminescence spectrophotometer (LS-50B; PerkinElmer, Beaconsfield, UK) and its intensity normalized to the respective cube weight.

The distribution of PBF along the cranio-caudal and ventro-dorsal axes was assessed by linear regression. Color mapping was used to identify the regional distribution of PBF based on Q_{cal}, which was normalized by the maximum Q_{cal}, with 0.0 representing the lowest and 1.0 the highest perfusion.

**Experimental Protocol**

Figure 1 shows the time course of interventions. Following instrumentation, the lungs were recruited by Paw of 30 cmH₂O for 30 s, and animals were stabilized for 15 min. Baseline 1 measurements were then obtained and injury induced by repetitive saline lung lavages (injury). After injury, animals were ventilated in PCV with PEEP = 8 cmH₂O. O₂ flow = 0.5, the RR to maintain the arterial pH >7.30, and driving pressure titrated to a VT of ~6 ml/kg. After 30 min, baseline 2 measurements were obtained and animals assigned to mechanical ventilation with PCV, PSV, and noisy PSV in random sequence (1 h/mode). A mean VT of 6 ml/kg was used during all modes.

Settings of PCV were the same as baseline 2. To avoid possible confounding effects of inadvertent inspiratory muscle activity, for example, animal/ventilator asynchrony, atracurium was administered at 0.5–2.5 mg·kg⁻¹·h⁻¹ during PCV.

The assisted ventilation modes were performed without muscle paralysis as follows: 1) in PSV mode, the pressure support level (PS = peak – PEEP) was set to achieve a mean VT of ~6 ml/kg. The inspiratory V trigger was 2.0 l/min, and the expiratory cycling-off criterion was 25% of peak VT; 2) in the noisy PSV mode, the ventilator was controlled by a laptop to perform noisy PSV. A set of 600 randomly generated, normally distributed values of pressure support with a coefficient of variation 20% was used, which represents the best compromise between oxygenation and respiratory mechanics (14, 35). After completion of a cycle of 600 breaths, the system looped itself. Other settings were identical to those from PSV.

**Statistical Analysis**

Values are given as means ± SD. Differences in functional variables were tested with general linear model statistics and adjusted for repeated measurements according to the Sidak method. Differences in CT_{stat} variables and in gradients of the distribution of PBF were determined with paired t-tests and multiple comparisons adjusted according to the Bonferroni-Holm procedure. Differences in CT_{dyn} variables were assessed with mixed linear models and adjusted according to Bonferroni. Tests were performed with Matlab (MathWorks) and SAS (Procedure Mixed, Version 8; SAS Institute, Cary, NC). Global statistical significance level was defined as P < 0.05.

**Cluster Analysis**

A nonhierarchical cluster analysis (based on the K-means algorithm) was used to identify lung pieces with a common pattern of changes in PBF at each experimental condition. The Euclidean dis-

Table 2. Gas exchange variables

<table>
<thead>
<tr>
<th></th>
<th>Baseline1</th>
<th>Injury</th>
<th>Baseline 2</th>
<th>PCV</th>
<th>PSV</th>
<th>Noisy PSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paco₂/Fio₂, mmHg</td>
<td>515.8 ± 33.9</td>
<td>130.0 ± 43.0</td>
<td>183.5 ± 45.6</td>
<td>213.8 ± 40.1</td>
<td>255.1 ± 52.6</td>
<td>508.7 ± 59.6*#</td>
</tr>
<tr>
<td>Paco₂, mmHg</td>
<td>37.3 ± 3.5</td>
<td>48.0 ± 6.9</td>
<td>48.4 ± 5.1</td>
<td>52.1 ± 8.7</td>
<td>50.8 ± 5.4</td>
<td>50.5 ± 5.7</td>
</tr>
<tr>
<td>Qva/Qc, %</td>
<td>14.8 ± 6.1</td>
<td>24.8 ± 5.5</td>
<td>15.0 ± 8.8</td>
<td>14.1 ± 5.7</td>
<td>9.3 ± 1.9*</td>
<td>7.6 ± 1.7*#</td>
</tr>
</tbody>
</table>

Data are given as means ± SD. Paco₂/Fio₂, arterial partial pressure of oxygen to inspiratory oxygen fraction ratio; Paco₂, arterial partial pressure of carbon dioxide; Qva/Qc, venous admixture. Differences between mechanical ventilation modes were tested with general linear model statistics and adjusted for repeated measurements. *P < 0.05 vs. PCV; #P < 0.05 vs. PSV.
Data are given as means ± SD. HR, heart rate; CO, cardiac output; MAP, mean arterial blood pressure; MPAP, mean pulmonary arterial blood pressure; PCWP, pulmonary artery occlusion pressure; CVP, central venous pressure; DO2, oxygen delivery; VO2, oxygen consumption. Differences between mechanical ventilation modes (mode effect) were tested with general linear model statistics and adjusted for repeated measurements. *P < 0.05 PCV vs. PSV; #P < 0.05 PCV vs. noisy PSV; NS, not significant.

**RESULTS**

**Respiratory Variables, Gas Exchange, and Hemodynamics**

The effects of each ventilation mode on respiratory variables, gas exchange, and hemodynamics are shown in Tables 1, 2, and 3, respectively. Psw,m and PIm were lower with PSV and noisy PSV compared with PCV. In all ventilation modes investigated, mean VT was ~6 ml/kg. Minute ventilation and respiratory rate were higher during PSV than during PCV. Additionally, Psw,m was slightly lower with noisy PSV than with PSV. PTP did not differ between PSV and noisy PSV.

PSV and noisy PSV led to an increase in the PaO2/FiO2 ratio as well as reduction in venous admixture, CO, and heart rate compared with PCV. PaCO2 did not differ among mechanical ventilation modes.

**Lung Aeration**

Table 4 shows the data computed from CTstat at the end of expiration. ALI was associated with a reduction of total lung gas and normally aerated areas as well as an increase in total lung mass and poorly aerated and nonaerated areas. Total lung mass was slightly higher during PSV and noisy PSV than during PCV. Furthermore, PSV and noisy PSV were associated with a slight, but significant, decrease in hyperaerated and normally aerated compartments as well as an increase in poorly aerated compartments at the end of expiration compared with PCV.

CTdyn data showed similar patterns of distribution of aeration as observed with CTstat. At the end of expiration, both assisted ventilation modes were associated with a reduction of hyperaerated and increase of poorly and nonaerated areas compared with PCV (Fig. 2 and Supplemental Figure S1; Supplemental Material for this article can be found online at the Journal of Applied Physiology website). At the end of inspiration, PSV and noisy PSV led to a reduction in hyperaerated and normally aerated areas as well as an increase in poorly aerated and nonaerated areas compared with PCV. Furthermore, noisy PSV slightly reduced hyperaerated areas at both end of expiration and end of inspiration compared with conventional PSV. CTdyn analysis also revealed that noisy PSV and PSV reduced tidal reaeration and hyperinflation compared with PCV (Fig. 3 and Supplemental Fig. S2).

**Distribution of PBF**

The angular coefficients of the distribution of PBF along the dorsal-ventral and caudal-cranial axes are shown in Table 5. After induction of ALI, PBF was redistributed from dorsal to ventral and from caudal to cranial regions. PSV and noisy PSV were associated with a shift of PBF from dorsal to ventral areas compared with PCV. Furthermore, noisy PSV, but not PSV, led to redistribution of PBF from caudal to cranial areas compared with PCV. There was no redistribution of PBF along the central-peripheral axis with any of the interventions.
DISCUSSION

The main findings of the present study were that, in a saline lung lavage model of ALI under protective ventilation with mean VT of 6 ml/kg,

1) assisted ventilation with PSV and noisy PSV improved oxygenation and reduced venous admixture compared with protective PCV,

2) the improvement in oxygenation during PSV and noisy PSV was not associated with increased aeration in dependent lung regions,

3) noisy PSV and PSV reduced tidal reaeration and hyperinflation compared with PCV,

4) PSV and noisy PSV redistributed the pulmonary perfusion from dorsal to ventral lung regions compared with PCV, and

5) noisy PSV redistributed the pulmonary perfusion from caudal to cranial zones compared with PSV.

To our knowledge, this is the first investigation on the comparative effects of protective PCV, PSV, and noisy PSV with mean VT of 6 ml/kg on lung functional variables as well as distribution of regional aeration and perfusion. Previous studies addressing these issues either did not include controlled mechanical ventilation with VT comparable with assisted ventilation (2) or did not consider noisy PSV (14).

General Aspects

In the present study, CTstat scans were obtained during an expiratory breath-hold maneuver at the end of expiration with simultaneous clamping of the endotracheal tube. Muscle activity was possible during such a maneuver, which could have led to artifacts in the calculations of nonaerated and poorly aerated areas. To overcome this possible limitation, CTdyn, i.e., during
assisted breathing without endotracheal tube clamping, was performed. Whereas CTstat delivered spatial information about aeration, CTdyn permitted temporal assessment of aeration.

To exclude possible effects related to the flow waveform in the regional distribution of aeration and perfusion, we used PCV with a descending exponential flow instead of the volume-controlled ventilation with square flow waveform as the controlled ventilation mode.

The choice of the best control group for comparison with noisy PSV is somewhat difficult. Theoretically, the combination of constant pressure support levels with periodic sighs could be suitable. However, respiratory function did not differ between PSV plus sighs and PSV in a previous study from our group (14).

Although the use of muscle-paralyzing agents during controlled mechanical ventilation is controversial, these agents have been shown to improve gas exchange (12) and even reduce lung injury (9) during ALI/ARDS. Furthermore, inadvertent inspiratory muscle activity may result in animal/ventilator asynchrony. For these reasons, we used a muscle-paralyzing agent during the PCV period only.

Gas Exchange

Spontaneous breathing activity has been proposed as an alternative to improve respiratory function and reduce sedation and circulatory drug support during ALI (37). The beneficial effects of assisted ventilation on lung function have been attributed to the capability of spontaneous breathing activity to recruit, stabilize, and improve ventilation of dependent lung zones, which may still be perfused (18). Accordingly, some investigators (31, 42) suggested that only spontaneous breathing without pressure support is able to effectively recruit atelectatic lung tissue, improving gas exchange. Cereda et al. (4) reported that PSV was not able to improve oxygenation in patients with ALI/ARDS compared with PCV. In contrast to those studies, PSV increased PaO2 and reduced the intrapulmonary shunt in an animal model of ARDS, compared with PCV, at the same VT (17). More recently, Yoshida et al. (43) showed that PSV improves PaO2/FIO2 in patients with ARDS, although PSV mode was not associated with alveolar recruitment. Our data supports that PSV improves oxygenation and reduces intrapulmonary venous admixture compared with PCV. Furthermore, our data showing improved oxygenation with noisy PSV compared with PSV is in line with previous works by our group (14).

Lung Aeration and Distribution of PBF

The main mechanism for improvement of oxygenation during PSV and noisy PSV, compared with PCV, was redistribution of perfusion toward better aerated ventral areas. Thus, lung recruitment or redistribution of ventilation toward dependent zones seems not to represent a precondition for improvement of oxygenation during assisted mechanical ventilation.

The lack of recruitment in dependent lung regions during PSV and noisy PSV may be explained by different factors. First, during PSV and noisy PSV the mechanical ventilator typically cycles off at 25% of peak flow (cycling off criterion), resulting in shorter inspiration times and reduced Paw,m compared with controlled ventilation. The lower Paw,m and Pl,m combined with a shorter inspiratory time and a decreased inspiratory effort during assisted ventilation likely contributed to increased poorly aerated areas and the lack of recruitment of dependent lung regions. Theoretically, if we had matched Paw,m among ventilation modes, PaO2 would likely have been lower during PCV. Furthermore, matching of Paw,m would

Table 5. Gradient of the distribution of relative pulmonary blood flow

<table>
<thead>
<tr>
<th>Axis</th>
<th>PCV</th>
<th>PSV</th>
<th>Noisy PSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal-ventral</td>
<td>-0.0514 ± 0.0726</td>
<td>-0.0008 ± 0.0476*</td>
<td>-0.0002 ± 0.0519*</td>
</tr>
<tr>
<td>Caudal-cranial</td>
<td>0.0351 ± 0.0347</td>
<td>0.0458 ± 0.0248</td>
<td>0.0489 ± 0.0273*</td>
</tr>
<tr>
<td>Central-peripheral</td>
<td>0.0124 ± 0.0251</td>
<td>0.0188 ± 0.0271</td>
<td>0.0133 ± 0.0283</td>
</tr>
</tbody>
</table>

Values are given as means ± SD. The angular coefficient is the parameter “a” of the function y = ax + b, fitted to the data, where y is the relative pulmonary blood flow and x can be the gradient from dorsal (dependent) to ventral (nondependent), caudal to cranial, or central to peripheral lung regions. Negative values of the angular coefficient correspond to a decrease and positive values to an increase of relative pulmonary blood along each gradient. Comparisons were performed with paired t-tests; multiple comparisons were adjusted according the Bonferroni-Holm procedure. *P < 0.05 vs. PCV.
require the use of I:E ratios of 1:3 to 1:4 during PCV, which do not correspond to common practice. Alternatively, PEEP could have been increased during both PSV and noisy PSV or decreased during PCV. Such approaches, however, would have likely favored PSV and noisy PSV over PCV. Second, during PSV and noisy PSV the transpulmonary pressures in juxtadaphragmatic regions may have not been high enough to promote lung recruitment.

The redistribution of PBF to the nondependent regions is likely explained by different patterns of distribution of intrapleural pressures. Controlled mechanical ventilation increases the pleural pressure gradient from nondependent to the dependent zones in experimental lung injury models (16). Theoretically, spontaneous breathing activity during assisted ventilation may generate lower intrapleural pressures also in nondependent zones, which in the presence of lower $P_{aw}$, may lead to reduced regional transpulmonary pressure. The local decrease in transpulmonary pressure may in turn reduce the impedance of the lung capillaries, likely facilitating the redistribution of perfusion from less aerated dependent areas to better aerated nondependent lung zones, which is driven mainly by hypoxic pulmonary vasoconstriction.

There are several possible reasons to explain the different oxygenation response in PSV compared with controlled mechanical ventilation between our study and the findings reported by Cereda et al. (4) and Putensen and colleagues (29, 32). First, our study was performed with an ALI induced by saline lavage, and it is possible that patients in those studies...
suffered from more severe lung injuries. Second, those patients may have had a blunted hypoxic pulmonary vasoconstriction because of circulating proinflammatory mediators or endotoxin (23), which may have impaired redistribution of perfusion toward better-aerated lung zones.

Compared with PSV, noisy PSV further improved oxygenation despite comparable minute ventilation and PaCO₂ levels. Such improvement could be explained partly by a slightly but significantly higher redistribution of perfusion from caudal to cranial zones with noisy PSV, compared with PCV. An enhanced redistribution of PBF from dorsal to ventral during noisy PSV was also evidenced by the metacluster analysis. *Metaclusters* A, C, and F, which represented as much as 30% of the total amount of lung pieces from all used animals.
and showed an increase in PBF, were located at ventral and cranial lung regions.

Active and passive factors may explain the redistribution of PBF from dependent to nondependent regions during spontaneous ventilation with PSV and noisy PSV compared with PCV. Hypoxic pulmonary vasoconstriction, an active endothelial mediated mechanism (34), likely followed redistribution of aeration, playing an important role in the decrease of perfusion in dependent areas. On the other hand, lower regional pleural pressures in nondependent areas may have reduced the impedance of capillaries in nondependent regions passively, facilitating the increase of relative perfusion in those regions.

Theoretically, other mechanisms not investigated in the present work could explain the improvement in gas exchange with noisy PSV, namely enhanced respiratory sinus arrhythmia (26) and the phenomenon of stochastic resonance (38), even if such a phenomenon was not associated with lung recruitment.

Tidal Reaeration and Hyperinflation

Cyclic opening and closing of lung units as well as overdistension may be major determinants of VALI (28, 40). In animal models of ALI, such phenomena seem to be closely related to tidal reaeration and hyperinflation, respectively (1, 3). PSV and noisy PSV led to less tidal reaeration and hyperinflation in dependent and nondependent regions, respectively. The present data suggest that PSV and noisy PSV may improve lung protection compared with PCV with low VT.

Limitations

This study has several limitations. First, the present saline lung lavage model does not reproduce all complex clinical features of ALI, precluding direct extrapolation of our results to the clinical scenario. Second, the observational period was limited to 1 h, and we cannot exclude different effects in the long term. However, we reported previously that the major changes in lung function are observed in the first 60 min of noisy ventilation (36). Third, although we addressed the most frequently used form of assisted ventilation, namely PSV, mechanical ventilation strategies that allow unassisted spontaneous breathing, for example, biphasic intermittent positive airway pressure and airway pressure release ventilation, could lead to different results. Furthermore, other levels of pressure support during PSV and noisy PSV could lead to different levels of inspiratory effort and, consequently, affect the regional distributions of aeration and perfusion. Fourth, changes in the distribution of PBF may have influenced regional CT densities. Since we did not observe recruitment with noisy PSV and PSV, compensation for the effect of redistribution of perfusion would have resulted in even less aeration in dependent lung zones. Fifth, since during CTstat scans a few seconds have elapsed under breath-hold maneuver, poorly aerated and nonaerated areas may have been overestimated in juxtadiaphragmatic regions due to the progressive derecruitment. How- ever, Cdyn analysis, which was performed without endotracheal tube clamping, revealed comparable results in terms of the main findings of distribution of aeration. Sixth, we did not address the impact of PCV, PSV, and noisy PSV on lung damage and inflammation. Seventh, we cannot completely rule out that the use of atracurium did not interfere with the lack of redistribution of PBF during PCV. Laudanosine, a metabolite of atracurium with no effect on muscle paralysis, has been shown to promote vasodilation (5), which could theoretically blunt the redistribution of PBF. However, the dosage of atracurium that causes vasodilation is ~20 times higher than the dosage used for muscle paralysis (8). Thus, it is unlikely that the use of muscle paralysis during PCV influenced our results. Eight, although our study design allowed functional comparisons of modes within single animals (crossover design), it precluded the analysis of the biological impact of those modes. Certainly, this issue deserves further investigation.

Conclusions

In a saline lavage model of ALI, assisted ventilation with PSV and noisy PSV improves oxygenation and intrapulmonary shunt compared with PCV. Such effects are explained not by recruitment of lung units in dependent areas but redistribution of perfusion to better-aerated, nondependent areas. Compared with PSV, noisy PSV redistributes perfusion from caudal to cranial zones, further improving oxygenation. PSV and noisy PSV reduce tidal reaeration and hyperinflation, which could contribute to minimize VALI, compared with protective PCV.

GRANTS

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DISCLOSURES

M. G. de Abreu, P. M. Spieth, and T. Koch have been granted a patent on the noisy pressure support ventilation mode in Germany and have other patents pending.

REFERENCES

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