Small dose of exogenous surfactant combined with partial liquid ventilation in experimental acute lung injury: effects on gas exchange, haemodynamics, lung mechanics, and lung pathology

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A combination of exogenous surfactant and partial liquid ventilation (PLV) with perfluorocarbons should enhance gas exchange, improve respiratory mechanics and reduce tissue damage of the lung in acute lung injury (ALI). We used a small dose of exogenous surfactant with and without PLV in an experimental model of ALI and studied the effects on gas exchange, haemodynamics, lung mechanics, and lung pathology. ALI was induced by repeated lavages (PaO₂/FIO₂ less than 13 kPa) in 24 anaesthetized, tracheotomized and mechanically ventilated (FIO₂ 1.0) juvenile pigs. They were treated randomly with either a single intratracheal dose of surfactant (50 mg kg⁻¹, Curosurf®, Serono AG, München, Germany) (SURF-group, n=8), a single intratracheal dose of surfactant (50 mg kg⁻¹, Curosurf®) followed by PLV with 30 ml kg⁻¹ of perfluorocarbon (PF 5080, 3M, Germany) (SURF-PLV-group, n=8) or no further intervention (controls, n=8). Pulmonary gas exchange, respiratory mechanics, and haemodynamics were measured hourly for a 6 h period. In the SURF-group, the intrapulmonary right-to-left shunt (Qs/Qt) decreased significantly from mean 51 (SEM 5)% after lavage to 12 (2)%, and PaO₂ increased significantly from 8.1 (0.7) to 61.2 (4.7) kPa compared with controls and compared with the SURF-PLV-group (P<0.05). In the SURF-PLV-group, Qs/Qt decreased significantly from 54 (3)% after induction of ALI to 26 (3)% and PaO₂ increased significantly from 7.2 (0.5) to 30.8 (5.0) kPa compared with controls (P<0.05). Static compliance of the respiratory system (Crs), significantly improved in the SURF-PLV-group compared with controls (P<0.05). Upon histological examination, the SURF-group revealed the lowest total injury score compared with controls and the SURF-PLV-group (P<0.05). We conclude that in this experimental model of ALI, treatment with a small dose of exogenous surfactant improves pulmonary gas exchange and reduces the lung injury more effectively than the combined treatment of a small dose of exogenous surfactant and PLV.

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Deficiency of alveolar surfactant, pulmonary hypertension, intrapulmonary right-to-left shunting, and poor arterial oxygenation are features of both experimental acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS).¹ Loss of surfactant increases surface tension, end-expiratory alveolar collapse, and atelectasis.

Mechanical ventilation can further damage the alveolo-capillary unit by overdistension, and cyclic collapse and reopening of terminal airways.²–⁵ Mechanical ventilation with
tidal volumes of 6 ml kg\(^{-1}\), a positive end-expiratory pressure (PEEP) level above the lower inflection point, and a peak inspiratory pressure below the upper inflection point may protect against this effect.\(^6\) Other treatments to reduce the mechanical shear stress of the lung include surfactant replacement,\(^7\)–\(^11\) partial liquid ventilation (PLV),\(^12\)–\(^17\) and extracorporeal membrane oxygenation (ECMO).\(^18\) Giving surfactant may reduce surface tension, improve gas exchange and lung mechanics.\(^7\)–\(^11\) In PLV the lung is partially filled with a perfluorocarbon and conventional mechanical ventilation is resumed. PLV can improve gas exchange and lung mechanics without significantly affecting systemic circulation.\(^12\)–\(^17\)

Exogenous surfactant and PLV have been investigated using different doses and different experimental models of ALI.\(^19\)–\(^29\) The effects on gas exchange, haemodynamics, lung mechanics, and lung damage were variable.

A combination of 100 mg kg\(^{-1}\) of surfactant with PLV, restored pulmonary gas exchange more efficiently in an experimental model of neonatal ALI than surfactant therapy alone. However, a combination of PLV with only 5 mg kg\(^{-1}\) of surfactant failed to give additional benefit compared with PLV alone.\(^27\)\(^29\)

We compared a single dose of 50 mg kg\(^{-1}\) surfactant alone vs 50 mg kg\(^{-1}\) surfactant combined with PLV in a pig model of ALI, with measurements of gas exchange, haemodynamics, respiratory mechanics, and progression of lung injury.

Methods
This study was approved by the Berlin Animal Protection Committee in accordance with German Animal Protection Law, and conforms with the Guide for the Care and Use of Laboratory Animals (DHHS, PHS, NIH Publication No. 85-23).

General experimental procedures
We studied 24 piglets (weight 23–27 kg), aged between 6 and 8 weeks. Anaesthesia was induced with thiopental (10 mg kg\(^{-1}\) i.v.) and fentanyl (10 \(\mu\)g kg\(^{-1}\) i.v. followed by an infusion of 0.05–0.08 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)). Muscle relaxation was obtained with pancuronium bromide (0.15 mg kg\(^{-1}\) i.v. bolus, followed by a continuous infusion of 2.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)). Immediately after induction, the pigs were tracheotomized and intubated with a 9.0 mm outer diameter tracheal tube, fitted with a heat and moisture exchanger.

The animals were placed supine and ventilated in a volume controlled mode (tidal volume 10–12 ml kg\(^{-1}\), respiratory rate 16 min\(^{-1}\), \(F_\text{O}_2\) 1.0, I:E ratio 1:1, PEEP 5 cm H\(_\text{O}\)) with an EVITA 2 model 76 ventilator (Dräger, Lübeck, Germany). Core temperature was maintained within \(\pm 0.5^\circ\)C of the pre-study value using a heating pad. No drugs were used to support the circulation.

We placed a pulmonary artery catheter (model 93A-431-7.5 Fr, Baxter Healthcare Corporation, Irvine, CA, USA) percutaneously via the femoral vein, and an arterial cannula (18 G; Vygon, Ecouen, France) into the femoral artery, for blood sampling and haemodynamic measurements. Heart rate (HR), central venous pressure (CVP), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), and pulmonary artery wedge pressure (PCWP) were recorded using a Hewlett-Packard monitoring system (Model 66 S, Böblingen, Germany). Measurements were taken with pigs in the supine position with zero at the level of the midaxilla. Vascular pressures were the average taken at end-expiration of three successive respiratory cycles. Cardiac output (CO) was determined by thermodilution using the mean of four measurements (10 ml saline at 1–5\(^\circ\)C) arbitrarily performed during different phases of the respiratory cycle. Intrapulmonary shunt (\(Q_\text{Si}/Q_\text{T}\)), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated using standard formulae.

All blood samples (arterial and mixed venous) were collected anaerobically, and analysed within 5 min (ABL 520, Radiometer, Copenhagen, Denmark). Arterial oxygen saturation (\(S_\text{aO}_2\)) and mixed venous oxygen saturation (\(S_\text{vO}_2\)) were measured by spectrophotometry with the analyser calibrated with pig blood (OSM 3 Hemoximeter, Radiometer). Static compliance of the respiratory system (C\(_{RS}\)) was determined using automated inspiratory, repetitive occlusions (1 s) at single volume steps (SCASS).\(^30\)

Measurements started with 10 ml \(V_t\) up to a maximum \(V_t\) of 10–12 ml kg\(^{-1}\), using volume steps of 10 ml each. C\(_{RS}\) was calculated as mean of all generated pressure–volume curves from the inspiratory limb.

Lung tissue from all animals was examined histologically. After killing the animals, the tracheal tube was clamped at end-expiration (PEEP 5 cm H\(_\text{O}\)) and the lungs were removed. Perfluorocarbon was left in situ in animals treated with PLV. Tissues were fixed in 5% formalin. Specimens from the cranial ventral (non-dependent) and caudal dorsal (dependent) lobes were stained with haematoxylin and eosin and then scored using a semiquantitative scoring system by an experienced veterinary pathologist (A. S-K.), blinded to treatment, for interstitial infiltration, interstitial oedema, emphysema, and atelectasis. Each variable was scored using a 0–4-point scale, with no injury scored 0, injury in 25% of the field scored 1, injury in 50% of the field scored 2, injury in 75% of the field scored 3, and injury throughout the field scored 4. The total score maximum was 16.

Induction of ALI
Repeated lavage with warmed isotonic saline (37\(^\circ\)C) was done to produce lung surfactant depletion as reported by Lachmann and co-workers, and described in detail elsewhere.\(^31\)\(^32\) Induction of ALI was assumed when the \(P_{\text{aO}_2}/F_\text{O}_2\) ratio was persistently less than 13 kPa for 1 h.
Experimental procedure

After induction of ALI, the animals were randomly assigned to receive a single intratracheal dose of surfactant alone (50 mg kg$^{-1}$, Curosurf\textsuperscript{®}) (SURF-group, $n=8$), or a single intratracheal dose of surfactant (50 mg kg$^{-1}$), followed after 30 min by 30 ml kg$^{-1}$ of perfluorocarbon (PF 5080, 3M, Germany) (SURF-PLV-group, $n=8$), or no further intervention (controls, $n=8$). Evaporative losses of PF 5080 were replaced at a dose of 4 (3) ml kg$^{-1}$ every hour as previously found by our group.\textsuperscript{33}

PF 5080 (C$_8$F$_{18}$) is a non-ozone-depleting PFC with boiling point 102°C, density (at 25°C) 1.76 g ml$^{-1}$, viscosity (at 25°C) 1.4 cp, vapour pressure (at 37°C) 6.8 kPa, solubility of oxygen (at 37°C) 49 ml 100 ml$^{-1}$, solubility of carbon dioxide (at 37°C) 176 ml 100 ml$^{-1}$, and surface tension (at 25°C) of 15 dyn s cm$^{-1}$ (information taken from 3M data sheet). Curosurf\textsuperscript{®} is isolated from minced pig lungs and contains 99% lipids, mainly phospholipids, and 1% low molecular weight hydrophobic apoproteins SP-B and SP-C.\textsuperscript{16}

Statistical analysis

Results are expressed as mean (SEM). The data were obtained at baseline (pre-lavage), immediately after the induction of ALI (post-lavage), and at hourly intervals thereafter, for 6 h thereafter. Statistical analysis was performed using SPSS for Windows 8.0 and Sigmastat (SPSS Inc., Chicago, IL, USA). Differences between groups were evaluated using Kruskal–Wallis ANOVA followed by post hoc comparisons with Dunn’s test (intergroup comparison). The Friedman test was used to compare the data after induction of ALI with the data measured during the subsequent 6 h (intragroup comparison). For post hoc testing, Dunn’s test also was applied. Statistical significance was assumed at $P<0.05$.

Results

All animals were comparable with regard to body weight and pre-study conditions. Pre-lavage data of pulmonary gas exchange, lung compliance, and haemodynamics did not differ significantly between groups (Tables 1 and 2).

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (beats min$^{-1}$) Mean (SEM)</th>
<th>MABP (mm Hg) Mean (SEM)</th>
<th>MPAP (mm Hg) Mean (SEM)</th>
<th>CO (litre min$^{-1}$) Mean (SEM)</th>
<th>SVR (dyn s cm$^{-1}$) Mean (SEM)</th>
<th>PVR (dyn s cm$^{-1}$) Mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>SURF 77 (4)</td>
<td>102 (5)</td>
<td>20 (1)</td>
<td>3.6 (0.2)</td>
<td>2081 (119)</td>
<td>149 (30)</td>
</tr>
<tr>
<td>Controls</td>
<td>95 (9)</td>
<td>88 (5)</td>
<td>20 (1)</td>
<td>3.8 (0.5)</td>
<td>2026 (285)</td>
<td>241 (52)</td>
</tr>
<tr>
<td>ALI</td>
<td>SURF 102 (11)</td>
<td>94 (4)</td>
<td>25 (1)</td>
<td>4.4 (0.6)</td>
<td>1650 (210)</td>
<td>266 (49)</td>
</tr>
<tr>
<td>Controls</td>
<td>102 (6)</td>
<td>89 (4)</td>
<td>28 (2)</td>
<td>4.4 (0.4)</td>
<td>1593 (191)</td>
<td>268 (28)</td>
</tr>
<tr>
<td>1 h</td>
<td>SURF 92 (10)</td>
<td>91 (4)</td>
<td>27 (2)</td>
<td>3.7 (0.3)</td>
<td>1718 (227)</td>
<td>301 (53)</td>
</tr>
<tr>
<td>Controls</td>
<td>93 (6)</td>
<td>89 (6)</td>
<td>28 (2)</td>
<td>3.8 (0.2)</td>
<td>1769 (150)</td>
<td>335 (63)</td>
</tr>
<tr>
<td>SURF-PLV</td>
<td>100 (6)</td>
<td>92 (6)</td>
<td>32 (2)</td>
<td>4.0 (0.3)</td>
<td>1614 (160)</td>
<td>366 (38)</td>
</tr>
<tr>
<td>Controls</td>
<td>93 (5)</td>
<td>87 (7)</td>
<td>30 (2)</td>
<td>3.9 (0.4)</td>
<td>1688 (243)</td>
<td>329 (49)</td>
</tr>
<tr>
<td>2 h</td>
<td>SURF 88 (9)</td>
<td>92 (6)</td>
<td>28 (2)</td>
<td>3.4 (0.3)</td>
<td>1930 (163)</td>
<td>392 (60)</td>
</tr>
<tr>
<td>Controls</td>
<td>89 (5)</td>
<td>94 (5)</td>
<td>34 (2)</td>
<td>3.5 (0.3)</td>
<td>1944 (229)</td>
<td>466 (76)</td>
</tr>
<tr>
<td>SURF-PLV</td>
<td>93 (7)</td>
<td>83 (7)</td>
<td>35 (2)</td>
<td>3.4 (0.2)</td>
<td>1697 (194)</td>
<td>466 (33)</td>
</tr>
<tr>
<td>3 h</td>
<td>SURF 86 (9)</td>
<td>98 (6)</td>
<td>30 (2)</td>
<td>2.8 (0.2)</td>
<td>2573 (186)</td>
<td>525 (73)</td>
</tr>
<tr>
<td>Controls</td>
<td>88 (6)</td>
<td>93 (2)</td>
<td>36 (2)</td>
<td>3.1 (0.3)</td>
<td>2145 (192)</td>
<td>578 (79)</td>
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<tr>
<td>SURF-PLV</td>
<td>100 (10)</td>
<td>87 (8)</td>
<td>36 (2)</td>
<td>3.8 (0.4)</td>
<td>1767 (279)</td>
<td>486 (50)</td>
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<tr>
<td>Controls</td>
<td>97 (10)</td>
<td>89 (9)</td>
<td>39 (2)</td>
<td>3.7 (0.3)</td>
<td>1845 (326)</td>
<td>563 (70)</td>
</tr>
<tr>
<td>4 h</td>
<td>SURF 77 (5)</td>
<td>99 (5)</td>
<td>30 (2)</td>
<td>2.6 (0.2)</td>
<td>2723 (176)</td>
<td>592 (79)</td>
</tr>
<tr>
<td>Controls</td>
<td>90 (5)</td>
<td>91 (4)</td>
<td>38 (2)</td>
<td>2.9 (0.3)</td>
<td>2278 (258)</td>
<td>667 (69)</td>
</tr>
<tr>
<td>SURF-PLV</td>
<td>97 (10)</td>
<td>89 (9)</td>
<td>39 (2)</td>
<td>3.7 (0.3)</td>
<td>1845 (326)</td>
<td>563 (70)</td>
</tr>
<tr>
<td>5 h</td>
<td>SURF 79 (8)</td>
<td>99 (5)</td>
<td>29 (2)</td>
<td>2.6 (0.2)</td>
<td>2831 (207)</td>
<td>581 (98)</td>
</tr>
<tr>
<td>Controls</td>
<td>93 (11)</td>
<td>88 (6)</td>
<td>39 (2)</td>
<td>3.2 (0.4)</td>
<td>2009 (290)</td>
<td>663 (104)</td>
</tr>
<tr>
<td>SURF-PLV</td>
<td>102 (9)</td>
<td>81 (9)</td>
<td>41 (2)</td>
<td>3.5 (0.4)</td>
<td>1742 (323)</td>
<td>596 (100)</td>
</tr>
<tr>
<td>6 h</td>
<td>SURF 80 (8)</td>
<td>97 (5)</td>
<td>30 (3)</td>
<td>2.6 (0.2)</td>
<td>2662 (188)</td>
<td>560 (83)</td>
</tr>
<tr>
<td>Controls</td>
<td>95 (8)</td>
<td>82 (7)</td>
<td>40 (1)</td>
<td>3.1 (0.3)</td>
<td>1857 (337)</td>
<td>659 (82)</td>
</tr>
</tbody>
</table>

Exogenous surfactant and PLV

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (beats min$^{-1}$) Mean (SEM)</th>
<th>MABP (mm Hg) Mean (SEM)</th>
<th>MPAP (mm Hg) Mean (SEM)</th>
<th>CO (litre min$^{-1}$) Mean (SEM)</th>
<th>SVR (dyn s cm$^{-1}$) Mean (SEM)</th>
<th>PVR (dyn s cm$^{-1}$) Mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>109 (7)</td>
<td>74 (11)</td>
<td>41 (3)</td>
<td>3.5 (0.5)</td>
<td>1601 (427)</td>
<td>627 (110)</td>
</tr>
</tbody>
</table>
Gas exchange
Surfactant alone improved $P_{A_O_2}$ from 8.1 (0.7) kPa after onset of ALI to 61.2 (4.7) kPa after 6 h of treatment ($P<0.05$ vs controls; Fig. 1, Table 2). The increase of $P_{A_O_2}$ in the SURF-group was greater than the increase in the SURF-PLV-group after 6 h of treatment ($P<0.05$ vs SURF-PLV; Fig. 1, Table 2). In the PLV-SURF-group the increase of $P_{A_O_2}$ from 7.2 (0.5) kPa after onset of ALI to 30.8 (5.0) kPa after 6 h of treatment was greater than in controls ($P<0.05$ vs controls; Fig. 1, Table 2).

In the SURF group $\dot{Q}_O_2/\dot{V}_O_2$ decreased significantly compared with controls (51 (5)% at onset of ALI to 12 (2)% 6 h after treatment, $P<0.05$ vs controls; Fig. 2, Table 2). In the SURF-PLV-group $\dot{Q}_O_2/\dot{V}_O_2$ was significantly decreased compared with controls (54 (4)% at onset of ALI to 26 (3)% after 6 h of treatment, $P<0.05$ vs controls; Fig. 2, Table 2).

Haemodynamics
There were no significant changes between groups in HR, MABP, and SVR. In the SURF-group the MPAP increased from 25 (1) mm Hg at onset of ALI to 30 (3) mm Hg after 6 h of treatment, and was significantly less than in controls and in the SURF-PLV-group ($P<0.05$ vs controls and vs SURF-PLV; Fig. 3, Table 1). In the SURF-group, PVR increased significantly from 266 (49) dyn s cm$^{-5}$ at onset of ALI to 560 (83) dyn s cm$^{-5}$ at 6 h of treatment ($P<0.05$ vs ALI-values; Table 1). In the SURF-PLV-group, PVR increased significantly from 268 (28) to 659 (82) dyn s cm$^{-5}$ ($P<0.05$ vs ALI-values, Table 1). In the SURF-group and in the SURF-PLV-group, CO decreased significantly during the treatment period compared with ALI-values ($P<0.05$ vs ALI-values; Table 1). In controls there were no significant changes in PVR and CO.

Lung mechanics
After induction of ALI, static compliance of the respiratory system decreased from 22 (2) ml cm H$_2$O$^{-1}$ in all groups to 9 (1) ml cm H$_2$O$^{-1}$. No further changes of $C_{RS}$ occurred in the SURF-group. In the SURF-PLV-group, $C_{RS}$ improved significantly compared with controls from 9 (1) to 15 (0.4) ml cm H$_2$O$^{-1}$ at 6 h of treatment ($P<0.05$ vs controls; Fig. 4, Table 2).

Lung injury
The non-dependent lobes in the SURF-group had a significantly smaller injury score for interstitial oedema and emphysema compared with controls and the SURF-PLV-
group (P<0.05, Table 3). In the SURF-PLV-group, scores for interstitial oedema were significantly greater compared with controls in the non-dependent lobes (P<0.05, Table 3). Comparing tissue damage in dependent lobes, the SURF-group had significantly less atelectasis and emphysema than controls (P<0.05) and less interstitial oedema and emphysema than the SURF-PLV-group (P<0.05, Table 3). In the SURF-PLV-group, interstitial infiltration and atelectasis of the dependent lobes was less than in controls and the SURF-group (P<0.05 vs controls and vs SURF), while interstitial oedema and emphysema in the dependent lobes in the SURF-PLV-group was greater than in controls and the SURF-group (P<0.05, Table 3).

The overall lung injury score of the SURF-group was less in the non-dependent lobes, compared with the SURF-PLV-group and controls (P<0.05, Table 3).

**Survival**

All animals in both treatment groups survived to the end of the study. In the control-group, four animals died of irreversible hypoxaemia during the study, one after 3 h, two after 4 h, and one 5 h after induction of ALI (Table 2).

**Discussion**

In this study, we compared the effects of a single, small dose of surfactant alone and combined with a full dose of PLV on oxygenation, haemodynamics, respiratory mechanics, and lung injury in an animal model of ALI. A small dose of surfactant was better than a combined treatment with a small dose of surfactant and PLV to restore gas exchange. Respiratory mechanics were only improved in the group treated with the combination of surfactant and PLV. Atelectasis, interstitial oedema, and emphysema were significantly less in the surfactant group than in controls. Compared with the group receiving surfactant and PLV, the surfactant group had a significant smaller total lung injury score.

Surfactant therapy combined with PLV has been studied in different types of ALI. Studies have been done in surfactant deficient pre-term animals, isolated lungs of pre-term animals, newborn animals with ALI induced by surfactant wash-out, and experimental ALI in adult animals. Criteria for onset of ALI after surfactant wash-out was a PaO2/FiO2 ratio below 8 kPa (60 mm Hg), with the exception of the studies by Hartog and co-workers and Kelly and co-workers, who used a value below 13 kPa (100 mm Hg) to indicate ALI. The duration of PaO2/FiO2 less than 8 kPa of 30 min to indicate the induction of ALI was specified only in one study. Our lavage procedure caused a stable PaO2/FiO2 ratio of 7.6 (0.6) kPa (57 (5) mm Hg) for at least 1 h after the last lavage. The severity of the lung injury in our animals resembles surfactant deficient pre-term animals, shown by the high shunt fraction, which was 54 (4)% after lung injury.

Mrozek and co-workers compared four different treatments in newborn piglets, after induction of ALI. One group received 100 mg kg⁻¹ surfactant, one group received PFC in a dose equivalent to the functional residual capacity, one group received PFC 30 min after surfactant replacement, and one group received surfactant 30 min after instillation of
In contrast to our finding that a single dose of surfactant caused the greatest improvement in $P_{A\text{O}_2}$, Mrozek and colleagues found that a combination of surfactant and PLV was better than the effect of surfactant alone on gas exchange, lung mechanics, and lung pathology. They made no comment on the decrease in $P_{A\text{O}_2}$ after instillation of PFC in the group treated with PLV after surfactant replacement.

These differences could be attributed to the following: (1) different timepoints of measurement, (2) the use of a bovine surfactant (Survanta), (3) a higher dose of surfactant (100 mg kg$^{-1}$), (4) newborn piglets as study subjects, and (5) the use of pre-oxygenated perflubron (LiquiVent). Another difference was positioning the animals while filling the lungs with PFC, which might have allowed greater perfluorocarbon dose and a more homogenous distribution of PFC throughout the lungs, although this technique appears to be impractical under clinical circumstances. In a study of ALI induced in premature lambs, Leach and co-workers compared either surfactant replacement, a combination of surfactant and PLV, or PLV alone. In this study, a very small dose (5 mg kg$^{-1}$) of an artificial surfactant (Exosurf) did not improve oxygenation and respiratory mechanics when compared with conventional ventilation. The combination of surfactant and PLV was not better than PLV alone. Leach and co-workers attributed the lack of surfactant efficacy to the small dose used and to the modest physiologic activity of synthetic surfactant, which gives a greater surface tension than natural surfactant.

In our study, improvements in oxygenation and intrapulmonary right-to-left shunt were delayed in the SURF-PLV-group. This could have been because: (1) PLV was started 30 min after surfactant was instilled, to avoid wash-out of exogenous surfactant; (2) inhomogeneous surfactant distribution could have caused PFC to only enter some regions and, thereby, limit alveolar recruitment. Leach and co-workers describe a transient increase in the expiratory resistance of their surfactant-PLV group and suggested that the distal movement of perfluorocarbons could have been delayed, as surfactant will remain in small airways and alveolar ducts.

In a study from Göthberg and co-workers using a model of premature ALI, the treatment of PLV combined with conventional ventilation or combined with high-frequency oscillatory ventilation (HFOV) 2 h after giving 100 mg kg$^{-1}$ of surfactant (Infasurf) improved oxygenation compared with treatment with surfactant and conventional ventilation alone. HFOV after surfactant replacement improved $P_{A\text{O}_2}$ to a similar extent than HFOV combined with PLV and was significantly more effective than PLV and conventional ventilation. The different results of a treatment with PLV and conventional ventilation after surfactant replacement, compared with our data, might be because of different models, a different PFC, a later application of PFC, and different doses of surfactant. Improvement in oxygenation with HFOV, with and without PLV, could be explained by changes in airway pressures and the development of a high intrinsic PEEP from the ventilatory pattern. Previous studies showed that combining PFC and high levels of PEEP enhances the effects of PLV on pulmonary gas exchange.

The improvement in $C_{RS}$ in our piglets treated with the combination of surfactant and PLV supports the findings of other investigators, and appears to be dose dependent. We measured the static compliance of the respiratory system, with an inspiratory shutter technique, to exclude...
effects of PFC vapour-pressure on expiratory volumes. We used 30 ml kg\(^{-1}\) of perfluorocarbon, approximately the functional residual capacity of healthy lungs and added further liquid according to our past observations.\(^{32}\) Tütüncü and co-workers compared the effects of PLV with 18 ml kg\(^{-1}\) PFC with PLV using 18 ml kg\(^{-1}\) saline, in a similar model of ALI in rabbits, and found that compliance of the respiratory system increased in the PFC group.\(^{13}\) Studying adult rabbits with induced ALI, Kelly and colleagues compared the effects of different treatments.\(^{20}\) The treatments were PLV with 20 ml kg\(^{-1}\) PFC, nebulized PFC, 100 mg kg\(^{-1}\) artificial surfactant (ALEC), 100 mg kg\(^{-1}\) porcine surfactant (Curosurf\(^{30}\)), the combination of PLV and ALEC, the combination of PLV and Curosurf\(^{30}\), and a control group. Our observations support their findings for arterial oxygenation. Regarding lung mechanics, 100 mg kg\(^{-1}\) of Curosurf\(^{30}\) improved compliance as effectively as the combination of PLV and Curosurf.\(^{30}\) In our study, the smaller dose of exogenous surfactant, was not sufficient to improve lung mechanics. Kelly and co-workers point out that surfactant from animals contains surfactant apoproteins, which prevent inhibition of surfactant by protein-rich fluid in lungs after induction of ALI, and that this effect is dose-dependent.\(^{20}\) In studies in humans, lung compliance decreases after surfactant treatment, despite increases in functional residual capacity and improvements in oxygenation. This could be because of slow recruitment of atelectatic lung areas, with stabilization of the initially opened lung units.\(^{34,35}\) Lack of improvement in lung compliance after surfactant administration in experimental ALI was also found by Mrozek and co-workers.\(^{27}\) We consider that the small dose of surfactant used in our study did not entirely overcome surfactant inhibition, and that the amount of lung tissue opened up in the SURF-group, although sufficient to improve gas exchange, was not sufficient to produce effects on \(C_{RS}\).

<table>
<thead>
<tr>
<th></th>
<th>Non-dependent lobes</th>
<th>Dependent lobes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SURF</td>
<td>PFC-SURF</td>
</tr>
<tr>
<td></td>
<td>Mean SEM</td>
<td>Mean SEM</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>0.68(^*$) 0.09</td>
<td>0.94(^*$) 0.1</td>
</tr>
<tr>
<td>Interstitial infiltration</td>
<td>1.38 0.1</td>
<td>0.31(^*$) 0.08</td>
</tr>
<tr>
<td>Interstitial oedema</td>
<td>0.1(^*$) 0.04</td>
<td>1.52(^*$) 0.09</td>
</tr>
<tr>
<td>Emphysema</td>
<td>0.11(^*$) 0.03</td>
<td>1.76(^*$) 0.15</td>
</tr>
<tr>
<td>Total injury score</td>
<td>2.27(^*$) 0.8</td>
<td>4.33(^*$) 3.86</td>
</tr>
</tbody>
</table>

Treatment with surfactant alone caused less histological injury, for interstitial oedema, atelectasis, and emphysema compared with controls and compared with the SURF-PLV-group. Comparing the overall lung injury scores between groups, treatment with surfactant alone caused less damage in non-dependent lobes compared with controls and the SURF-PLV-group. A small dose of surfactant reduces the inflammatory response in ALI, prevents further atelectasis, and improves gas exchange. The effects on inflammation could be attributed to the apoproteins of natural surfactant, which might prevent inflammation. The greater lung injury scores in the SURF-PLV-group contrasts with previous results of Mrozek and co-workers, who found least injury with the combined treatment.\(^{27}\) They suggest that the lower inspiratory pressures needed for effective alveolar ventilation could be the reason for less lung injury in this group. The different PFC used for PLV and a higher dose of surfactant could account for these differences. In rats with lavage-induced ALI, Hartog and colleagues compared lung injury after treatment with surfactant, PLV, and high values of PEEP vs healthy controls and injured controls.\(^{22}\) Surfactant prevented progression of lung injury, when compared with healthy controls, and PLV increased lung tissue injury compared with healthy controls.

In our study, we found that cardiac output decreased significantly during the study in both treatment groups, which has not been reported previously in short term studies of lavage-induced lung injury.\(^{36,37}\) However, \(D_{O_2}\) and \(V_{O_2}\) remained unchanged in both groups, indicating maintenance of a sufficient oxygen delivery. A possible explanation for the lower values of CO might be reduced sympathetic activity in both treatment groups because of better oxygenation. This view is supported by poorer survival in control animals. As suggested by Dantzker and co-workers, a reduction in CO could reduce the intrapulmonary right-to-left shunt.\(^{38}\) The magnitude of this mechanism of shunt


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38 Dantzker DR, Lynch JP, Weg JG. Depression of cardiac output is a mechanism of shunt reduction in the therapy of acute respiratory failure. Chest 1980; 77: 636–42