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ORIGINAL ARTICLE

Surfactant deactivation in a pediatric model induces hypovolemia and fluid shift to the extravascular lung compartment

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Keywords
pulmonary surfactant; preload; hypovolemia; transpulmonary thermodilution; extravascular lung water

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Summary

Background: Surfactant deficiency is the pivotal abnormality in Neonatal and Acute Respiratory Distress Syndrome. Surfactant deactivation can produce hypoxemia, loss of lung compliance, and pulmonary edema, but its circulatory consequences are less understood.
Objective: To describe the sequential hemodynamic changes and pulmonary edema formation after surfactant deactivation in piglets.
Methods: Surfactant deactivation was induced by tracheal instillation of polysorbate 20 in 15 anesthetized and mechanically ventilated Large White piglets. The hemodynamic consequences of surfactant deactivation were assessed at 30, 120, and 240 min by transpulmonary thermodilution and traditional methods.
Results: Surfactant deactivation caused hypoxemia, reduced lung compliance, and progressively increased lung water content ($P < 0.01$). Early hypovolemia was observed, with reductions of the global end-diastolic volume and stroke volume ($P < 0.05$). Reduced cardiac output was observed at the end of the study ($P < 0.05$). Standard monitoring was unable to detect these early preload alterations. Surprisingly, the bronchoalveolar protein content was greatly increased at the end of the study compared with baseline levels ($P < 0.01$). This finding was inconsistent with the notion that the pulmonary edema induced by surfactant deactivation was exclusively caused by high surface tension.
Conclusions: Hypovolemia develops early after surfactant deactivation, in part due to the resulting fluid shift from the intravascular compartment to the lungs.

Introduction

Pulmonary surfactant is a mixture of lipids and proteins that lines the alveolar air–liquid interface. The presence of surfactant lowers the interfacial tension to levels that make ventilation possible with minimal transpulmonary pressure swings. Surfactant deficiency or deactivation is a pivotal abnormality in neonatal respiratory distress syndrome (RDS) and participates in the pathogenesis of Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS) (1,2).

Surfactant depletion and deactivation models have been used extensively to study the pathophysiology of ARDS and the effect of different ventilatory strategies on the injured lung (3). Surfactant deactivation produces alveolar instability and collapse, leading to severe hypoxemia, loss of lung compliance, and high-tension pulmonary edema (4,5). The circulatory consequences of surfactant deactivation have received far less attention than its direct pulmonary effects. Only standard noninvasive monitoring and conventional cardiac filling pressure measurements have been used for hemodynamic

assessment. Single thermal transpulmonary thermodilution (TPTD) allows estimation of the intrathoracic compartmental volumes with advanced analysis of the thermodilution curve. In adults, these volumetric indices serve better than traditional methods for determining preload and volume responsiveness (6,7). Single thermal TPTD can also be used to calculate extravascular lung water (EVLW), which is an estimate of the interstitial water content of the lungs (6,8).

Our objective was to describe the sequential changes in intrathoracic blood compartments and development of lung edema with transpulmonary thermodilution after surfactant deactivation in piglets.

Materials and methods

A total of 15 2-week-old anesthetized Large White piglets (4.9 ± 0.35 kg) were used in this study. The experimental protocol was approved by Facultad de Medicina Clínica Alemana Universidad del Desarrollo Ethics Committee and the National Bioethics Adviser's Committee (CONICYT, Comisión Nacional de Investigación Científica y Tecnológica). All of the experimental procedures were consistent with the Guiding Principles in the Care and Use of Laboratory Animals adopted by the American Physiological Society.

Surgical preparation and anesthesia

Animals were premedicated with intramuscular acepromazine (1.1 $mg \cdot kg^{-1}$) and ketamine (20 $mg \cdot kg^{-1}$). The trachea was cannulated with a 3.5-mm (internal diameter) cuffed tracheostomy tube (Mallinckrodt Shiley, St. Louis, MO, USA), the left jugular vein with a 4F double-lumen catheter (Arrow, Reading, PA, USA), and the right axillary artery with a 4F thermistor-tipped catheter (PiCCO® PV2014L08, Pulsion Medical Systems, Munich, Germany), all via cutdown. Anesthesia and neuromuscular blockade were maintained by continuous infusion of propofol (10 $mg \cdot kg^{-1} \cdot h^{-1}$), fentanyl (4 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and pancuronium (0.2 $mg \cdot kg^{-1} \cdot h^{-1}$) throughout the experiment. Hydration was maintained with a continuous infusion of normal saline (10 $ml \cdot kg^{-1} \cdot h^{-1}$). The temperature was kept at 37.1 ± 0.6°C with conventional convective methods.

Mechanical ventilation

Animals were ventilated with an EVITA XL® (Dräger Medical, Lübeck, Germany) ventilator under the volume-control mode. The initial settings were as follows: tidal volume (V_T), 10 $ml \cdot kg^{-1}$; positive end-expiratory pressure (PEEP), 5 cmH_2O; respiratory rate (f_R), 20 breaths per min; inspiratory time, 0.75 s; and oxygen inspiratory fraction (FIO_2), 0.5. After detergent instillation, the V_T was reduced to 6 $ml \cdot kg^{-1}$, PEEP was increased to 10 cmH_2O, f_R was adjusted to 40 breaths per min, and inspiratory time and FIO_2 were maintained at their initial levels.

Induction of lung injury

Polyoxyethylene [20] sorbitan monolaurate (polysorbate 20) (Sigma-Aldrich, St. Louis, MO, USA), commercially known as Tween® 20, is a nonionic detergent that has been used in experimental models of ALI/ARDS. Experimental data suggest that polysorbate 20 induces strong deactivation of the pulmonary surfactant, sparing the ultrastructure of the alveolar-capillary membrane (9). Therefore, polysorbate 20 is one of the most interesting models available to study pulmonary surfactant system dysfunction (4,5).

After the onset of mechanical ventilation, the animals were placed in the lateral decubitus position. A 10% (v/v) solution of polysorbate 20 in saline was instilled (1 $ml \cdot kg^{-1}$) in the airway of the dependent lung via a 2-mm catheter. The procedure was repeated with the animal rotated to the opposite side. Residual fluid was suctioned from the airway. Lung injury was targeted to achieve $PaO_2 < 100$ mmHg, with $FIO_2 = 0.5$ and PEEP = 10 cmH_2O and with the piglet in the supine position, by 20 min after detergent solution instillation. If this target was not met, then the instillation was repeated as described.

Measurements

Hemodynamic and respiratory measurements were performed in the supine position at baseline and at 30, 120, and 240 min after polysorbate 20 instillation.

Pulmonary measurements

Arterial blood gases were determined with the i-STAT® System and i-STAT® EG6+ Cartridges (Abbott Laboratories, Princeton, NJ, USA) from blood samples drawn from the arterial catheter. Oxygenation was assessed with the PaO_2/FIO_2 ratio and alveolar-arterial oxygen tension, (A-a)PO_2. The (A-a)PO_2 was defined as $(P_{bar} - P_{water}) \times FIO_2 - (PaCO_2/0.8)$, where P_{bar} is barometric pressure, P_{water} is water vapor pressure, and $PaCO_2$ is carbon dioxide partial pressure. The static respiratory system compliance (C_{RS}) was calculated as $V_T/(P_{pl} - PEEP_{TOT})$, P_{pl} is plateau pressure measured after 4-s inspiratory hold and $PEEP_{TOT}$ is the total end-expiratory airway pressure measured after 4-s expiratory hold. These variables were recorded from the ventilator display.

Hemodynamic measurements

The heart rate (HR), mean arterial pressure (MAP), and central venous pressure (CVP) were monitored with an Infinity Delta XL® monitor (Dräger Medical, Lübeck, Germany). Zero pressure was set at the midaxillary line. The central venous hemoglobin oxygen saturation ($ScvO_2$) was assessed from blood samples drawn from the jugular catheter with the i-STAT® analyser. The indexed cardiac output (CO), stroke volume index (SVI), global end-diastolic volume index (GEDV), and EVLW were measured by TPTD with a commercially available device (PiCCO Plus).

According to manufacturer's instructions, single thermal indicator TPTD was performed in triplicate by injection of a cold saline solution bolus (5 ml, <8°C) into the superior cava vein through the jugular catheter. Basically, the thermistor in the tip of the axillary arterial catheter measured the downstream temperature variations. The CO was computed from an analysis of the thermodilution curve with a modified Stewart–Hamilton algorithm. The GEDV and EVLW were calculated with a different algorithm in the same device, which is derived from the mean transit time and the downslope time of the thermal indicator, as described in detail elsewhere (10). Body surface area was calculated as K/weight (in kg)$^{2/3}$, where $K = 0.112$ for pigs (11).

Before hemodynamic data were recorded at baseline and after polysorbate 20 instillation, the intravascular volume status was optimized by providing successive 10-ml·kg^{-1} intravenous colloid boluses (Voluven® 6%, Fresenius Kabi, Germany) until CO did not increase by >10%.

Lung edema assessment

Bronchoalveolar lavage (BAL) was performed before polysorbate 20 instillation and at the end of the experiment, with 10 ml of normal saline. The BAL samples were centrifuged at 1000 RCF. The total protein content of the supernatant was determined with the bicinchoninic acid method (Pierce® Microplate BCA Protein Assay Kit-Reducing Agent Compatible; Thermo Scientific, Rockford, IL, USA), to avoid possible interference with polysorbate 20. The EVLW was measured by TPTD, as described above.

At the end of the study period, anesthetized animals (Status 3-Plane 2) were euthanized by intravascular infusion of 10% potassium chloride until ventricular fibrillation or asystole was detected. Thoracotomy was performed, and the lungs were removed. The pulmonary extravascular water volume (PEWV) of the left lung was measured gravimetrically (12) with the method described by Demling *et al*. (13). For reference gravimetry, six animals (sham group) were handled in a fashion identical to the study group animals, except that polysorbate 20 instillation was not performed. After 60 min of mechanical ventilation, these animals were euthanized, and the left lung was surgically extracted for gravimetry assessment.

Statistical analysis

To detect a 15% reduction in GEDV after lung insult ($\alpha = 0.05$, power 80%), it was calculated that a sample size of 15 piglets was needed (14). Datasets were tested for normal distribution with the Shapiro–Wilk test. To compare hemodynamic and respiratory variables during the experiment, an ANOVA for repeated measurements was performed with Greenhouse-Geisser correction for sphericity when required. A *posthoc* test using Bonferroni's correction was performed for pairwise comparisons. Pearson's correlation and linear regression were also performed. Data were computed as the mean ± SEM. A $P < 0.05$ was considered statistically significant for all test, except for ANOVA *posthoc* comparisons where a P-value < 0.0125 was considered significant.

Results

All of the animals completed the experimental protocol. Two animals required a second polysorbate 20 instillation to achieve the target PaO_2/FIO_2 ratio.

Pulmonary measurements

Surfactant deactivation caused strong pulmonary dysfunction, as evidenced by significant decreases in the PaO_2/FIO_2 ratio and C_{RS}, increases in (A-a)PO_2, and progression of respiratory acidosis. The PaO_2/FIO_2 ratio and (A-a)PO_2 improved steadily from 30 min onward, but did not reach baseline levels by 240 min (Table 1). The intrinsic PEEP was constant during the experiment (1.1 ± 0.3 cmH_2O).

Hemodynamic measurements

The cardiac frequency was increased at 30 min after ALI induction and remained stable thereafter. The MAP and CVP remained stable throughout the experiment. The $S_{cv}O_2$ tended to decrease after ALI induction (Table 1). A significant decrease of 13% in CO with respect to the baseline was observed at 120 min. The SVI gradually decreased from 30 min after surfactant deactivation, reaching a 25.2% of reduction at 240 min. The GEDV decreased at 120 min, and then remained stable in the subsequent measurement. On the other hand, EVLW increased progressively after surfactant deactivation at 30, 120, and 240 min (Figure 1).

Table 1 Respiratory and hemodynamic data at baseline (BL) and at 30, 120, and 240 min after Tween®20 instillation. Data are shown as the mean ± SEM

Parameters	BL	30 min	120 min	240 min	*P*-value
pH	7.22 ± 0.02	7.13 ± 0.02*	7.19 ± 0.03	7.17 ± 0.03	0.06
$PaCO_2$ (mmHg)	51.5 ± 1.9	67.6 ± 3.9*	63.5 ± 3.8*	65.9 ± 2.7*	<0.01
PaO_2/FIO_2	340 ± 16	157 ± 10*	203 ± 19 *	243 ± 23*†	<0.01
C_{RS} (ml·cmH_2O·kg^{-1})	1.70 ± 0.14	1.00 ± 0.08*	1.01 ± 0.07*	1.02 ± 0.09*	<0.01
(A-a)PO_2 (mmHg)	104 ± 7	232 ± 8*	225 ± 23*	203 ± 26*	<0.01
HR (bpm)	132 ± 8	155 ± 7*	156 ± 12*	171 ± 10*	0.04
MAP (mmHg)	70 ± 3	72 ± 5	70 ± 3	64 ± 3*	0.05
CVP (mmHg)	8.0 ± 0.5	7.7 ± 0.6	8.57 ± 0.6	9.2 ± 0.4	0.24
$ScvO_2$ (%)	82 ± 2	78 ± 2	77 ± 2	73 ± 3*	0.04

$PaCO_2$: arterial carbon dioxide; C_{RS}: respiratory system compliance; (A-a)PO_2: alveolar-arterial partial pressure oxygen gradient; HR: heart rate; MAP: mean arterial pressure; CVP: central venous pressure; $ScvO_2$: central venous hemoglobin oxygen saturation.
Listed *P*-value is for repeated measures ANOVA, significance set at $P < 0.05$. *$P < 0.0125$ vs BL values and †$P < 0.0125$ vs values at 30 min after surfactant deactivation for pairwise comparisons with Bonferroni's correction.

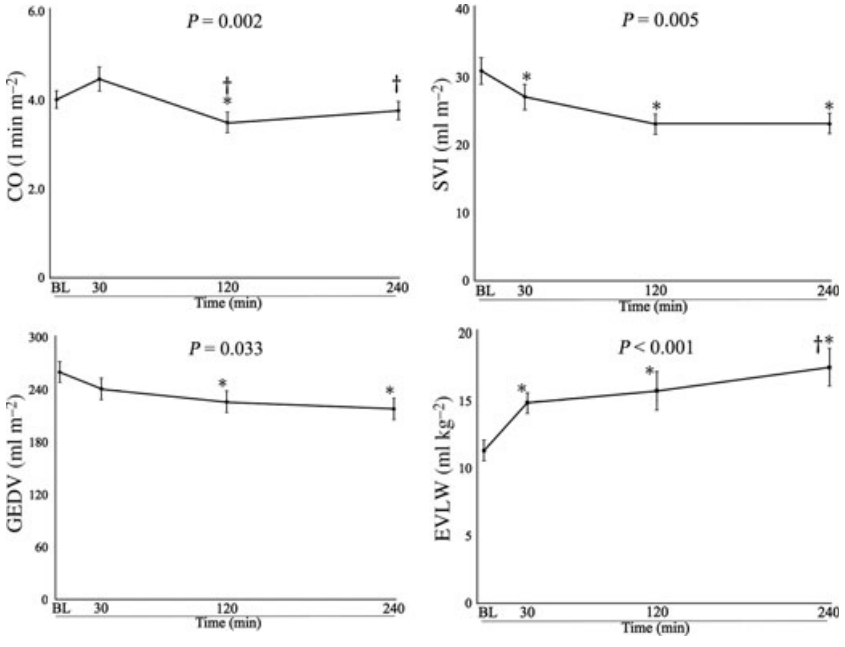

Figure 1 Cardiac output (CO), stroke volume index (SVI), global end-diastolic volume (GEDV), and extravascular lung water index (EVLW) at baseline (BL) and at 30, 120, and 240 min after surfactant deactivation. Data are shown as the mean ± SEM. Listed *P*-value is for repeated measures ANOVA, significance set at $P < 0.05$. *$P < 0.0125$ vs BL values and †$P < 0.0125$ vs values at 30 min after surfactant deactivation for pairwise comparisons with *posthoc* analysis with Bonferroni's correction.

The progressive reduction in SVI was associated with a decrease in GEDV ($r = 0.59$, $P < 0.01$). The percentage change (Δ) in GEDV demonstrated a moderate correlation with ΔSVI ($r = 0.50$, $P < 0.01$). There was a moderate inverse relationship between PEWV and GEDV ($r = -0.529$, $P < 0.01$). Linear regression analysis revealed a poor correlation between PEWV and GEDV (Figure 2).

Lung edema assessment

The EVLW had a close correlation with (A-a)PO_2 ($r = 0.95$, $P < 0.01$), and a moderate inverse correlation with C_{RS} ($r = -0.55$, $P < 0.01$). The BAL protein content showed a very large increase from baseline (0.3 ± 0.2 g·l^{-1}) to the end of the experiment (6.2 ± 2.8 g·l^{-1}) ($P < 0.01$). There was a moderate direct correlation between BAL protein content and EVLW ($r = 0.69$, $P < 0.01$) and (A-a)PO_2 ($r = 0.57$, $P < 0.01$). Also, a low inverse correlation was observed between BAL protein content and C_{RS} ($r = -0.48$, $P < 0.01$).

The gravimetric PEWV values of animals in the injury and sham groups were 10.4 ± 0.4 and 5.1 ± 0.1 ml·kg^{-1}, respectively ($P < 0.01$). There was low to moderate direct correlations between gravimetric PEWV and EVLW ($r = 0.6$, $P < 0.01$), BAL protein content

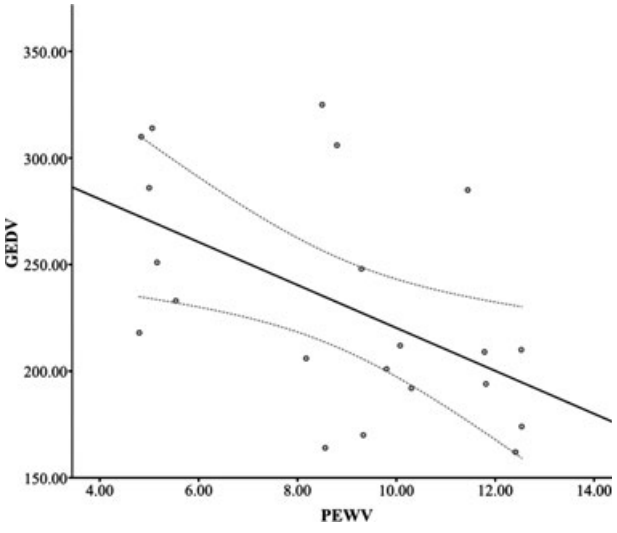

Figure 2 Linear regression analysis between global end-diastolic volume (GEDV, $ml \cdot m^{-2}$) and gravimetric pulmonary extravascular water volume (PEWV, $ml \cdot kg^{-1}$) in the experimental model. PEWV = 16.27 + −0.031 × GEDV ($R^2 = 0.281$, $P = 0.01$). Solid line represents the regression line; dashed lines indicate 95% confidence intervals.

($r = 0.46$, $P = 0.04$), and (A-a)PO_2 ($r = 0.68$, $P < 0.01$). Also, a low inverse correlation between gravimetric PEWV and C_{RS} ($r = -0.51$, $P = 0.02$) was observed.

Discussion

This study describes the evolutive course of the vascular compartments and pulmonary edema after surfactant deactivation in piglets. In addition to the expected lung dysfunction, surfactant deactivation also produced acute hypovolemia and pulmonary edema. Compared to detection by traditional methods, hemodynamic alterations were detected earlier by the volumetric preload markers, SVI, and GEDV.

Hemodynamic alterations, including tachycardia and an early decrease in SVI, were observed after surfactant deactivation. These changes were followed by a reduction in GEDV and CO at 120 min. Nonsignificant decreases in MAP and $ScvO_2$ were observed in the last measurements of the experiment. These findings are consistent with previous studies that described reductions in the systolic arterial blood pressure and CO after surfactant deactivation (15–18). Unfortunately, these previous studies primarily described the effects of surfactant deactivation on lung function and only partially explained the hemodynamic alterations. The magnitude and sequential progression of hypovolemia observed, decreasing GEDV 13%, SVI > 20%, and CO > 10%, suggest that advanced hemodynamic monitoring (i.e. echocardiography, pulse contour analysis, and TPTD) may be needed in the initial stages of ALI. These techniques may help to titrate fluid requirements to correct hypovolemia, limiting the harmful effects of fluid overload.

Our results, which were obtained with standard and TPTD methods, are compatible with the occurrence of acute hypovolemia. Hypovolemia is an early event in the development of acute lung injury (19), but it has not previously been measured with TPTD. In our study, conventional methods of hemodynamic monitoring (e.g. MAP and CVP) were less sensitive than TPTD monitoring in detecting early preload-related alterations. This low sensitivity may have been related to the fluids that subjects received before and immediately after lung injury. Fluid administration was performed for hemodynamic stabilization: specifically, to keep CO in the non-dependent segment of the Frank–Starling curve (volume responsiveness) at the beginning of the observation period (20). Tachycardia was observed at 30 min, but it is a nonspecific sign that may be influenced by many factors in this model, such as gas exchange alterations.

Hypovolemia was detected earlier by SVI and GEDV than by MAP or CVP. This finding is consistent with previous clinical studies, which found that volumetric indices are better indicators of cardiac preload than manometric measurements. Indeed, manometric measurements are influenced by factors other than preload, such as changes in venous tone, intrathoracic pressures, and ventricular compliance and geometry (21). The moderate correlation between SVI and GEDV supports the reduction in cardiac preload during the observation period, because they are measured with different algorithms of the thermodilution curve analysis.

After surfactant deactivation, the piglets displayed moderate lung dysfunction, with reductions in the PaO_2/FIO_2 ratio and C_{RS} and increases in (A-a)PO_2 at 30 min. The progressive increases in EVLW at 120 and 240 min, together with the higher gravimetric PEWV at the end of the study with respect to sham animals, indicate lung edema development.

Previous experimental data showed lung edema formation after surfactant deactivation (5,9,17). The theoretical basis for this so-called high surface tension pulmonary edema was initially described by Pattle and Clements in terms of the negative hydrostatic pressure produced by the high surface tension of the alveolus, which tended to collapse when the functionality of the surfactant system was absent (22,23). This fact was experimentally documented by Bredenberg and Nieman, who reproduced this form of lung edema after surfactant inactivation without causing significant variations in the plasma oncotic pressure or left ventricle end-diastolic pressure (5,17).

In this study, we were able to measure the BAL total protein content using a method that did not interfere with the detergent present in the supernatant fluid. Surprisingly, we found that the BAL protein content increased almost 20 times. This finding might be inconsistent with an exclusively hydrostatic pulmonary edema, and it may suggest that surfactant deactivation has an inadvertent effect on the permeability of the alveolar-capillary membrane to proteins. The moderate correlation between EVLW, BAL protein content, and gravimetric PEWV with multiple parameters of lung dysfunction suggests that increased vascular permeability may be an important feature in surfactant deactivation–mediated lung injury, but not the only. Patients with ARDS frequently display atelectasis, hypoxic pulmonary vasoconstriction, diffuse alveolar hemorrhage, and other conditions that may have an additive effect on pulmonary dysfunction (24).

Despite the significant reduction in the PaO_2/FIO_2 ratio at 30 min, there was a progressive recovery of oxygenation at 120 and 240 min. This finding was also observed in previous reports. It has mainly been attributed to the time-dependent effect of moderate PEEP on unstable alveoli, rather than to a recovery of the function of the surfactant system (25). In support of this hypothesis, EVLW and hemodynamic dysfunction in our model continued to worsen in successive measurements and became uncoupled from oxygenation improvement. These findings suggested the persistence of permeability alteration in lungs.

This study has some limitations. First, TPTD is not the gold standard for measuring CO and SVI. Although this method has been validated in pediatric models and children (26–28), caution is needed in its clinical use, because the normal ranges of derived volumetric data (GEDV and EVLW) in children are different from those in adults (14,29,30). Second, it is unclear whether GEDV and EVLW computed by PiCCO® are accurate indicators of the circulating blood volume and lung water content, respectively. However, clinical data support the usefulness of sequential measurements of these variables over time (31–33). Third, the simultaneous changes in GEDV and EVLW could be attributable to a mathematical coupling; however, the sequential reductions in SVI and CO suggest that this finding is not an artifact of the method. Fourth, it is impossible to isolate the hemodynamic contributions of individual components of the ventilatory support strategy, particularly PEEP, V_T, and gas exchange abnormalities. Our protocol with low V_T, moderate PEEP, and permissive hypercapnia is consistent with the contemporary care of RDS, but use of this protocol may have diminished the impact of V_T on preload and the lung inflammatory response. Moreover, intrinsic PEEP had no significant role in our findings.

Fifth, although the presence of lung edema implies a shift of fluid from the vascular to the extravascular compartments, this process was not the only implicated mechanism of reducing the circulating blood volume. Other potential mechanisms could include systemic capillary leak, organ edema, and third-space formation due to systemic inflammation. Accordingly, the poor correlation between pulmonary edema and the volumetric preload markers suggests that pulmonary edema was not the primary pathogenic mechanism responsible for

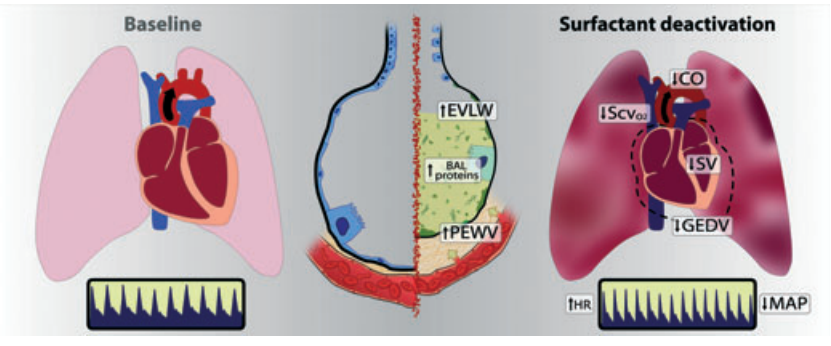

Figure 3 Graphical summary of findings with the surfactant deactivation model. After tracheal instillation of polysorbate 20, the lung mechanics and gas exchange became severely altered. This response was due to the development of pulmonary edema, as demonstrated by increases in the extravascular lung water index (EVLW) and pulmonary extravascular water volume (PEWV) (centre). In terms of hemodynamic alterations, tachycardia, hypotension (bottom), and reductions in stroke volume (SV), cardiac output (CO), global end-diastolic volume (GEDV), and central venous hemoglobin oxygen saturation ($S_{cv}O_2$) were observed (right). Surprisingly, the bronchoalveolar protein (BAL) content at the end of the study was greatly increased compared with baseline levels (centre). This finding is inconsistent with the notion that the pulmonary edema was exclusively caused by high surface tension. These data suggest that hypovolemia developed early after detergent instillation, and that the shifting of fluid from the intravascular compartment to the lungs contributed to its development. (HR, heart rate; MAP, mean arterial pressure)

the acute hypovolemia. This fact is obvious when we consider that both volumetric preload markers showed a reduction of 20–25% (about 15 $ml \cdot kg^{-1}$), whereas the gravimetry pulmonary edema only increased by 5 $ml \cdot kg^{-1}$. Moreover, during the study period, GEDV and EVLW did not seem to reach a plateau, and their changes could have been larger with a longer follow-up period.

Finally, information available to date and the methods used in this study are insufficient to determine the role of the permeability of the alveolar-capillary membrane in this model of high surface tension pulmonary edema. This finding should be corroborated in future studies, especially because none of the previous studies using polysorbate 20 (Tween® 20) instillation showed a disruptive effect on the alveolar-capillary membrane (5,9,34).

Conclusions

The hemodynamic findings obtained with our surfactant deactivation model are consistent with the development of acute hypovolemia, due (in part) to fluid extravasation from the intravascular to the extravascular pulmonary compartments (Figure 3). The early onsets of pulmonary edema and hypoxemia are in line with previous descriptions of high surface tension pulmonary edema secondary to surfactant deactivation. Nevertheless, the lack of a parallelism between hypoxemia and pulmonary edema and the observed increase in BAL protein content may suggest the presence of other mechanisms of pulmonary edema. This possibility should be investigated in future studies.

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Conflict of interest

No conflicts of interest declared.

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