Effects of combined high-dose partial liquid ventilation and almitrine on pulmonary gas exchange and hemodynamics in an animal model of acute lung injury

Abstract Objectives: To determine possible additive effects of combined high-dose partial liquid ventilation (PLV) and almitrine bismesylate (ALM) on pulmonary gas exchange and hemodynamics in an animal model of acute lung injury (ALI).

Design and setting: Prospective, controlled animal study in an animal research facility of a university hospital.

Interventions: ALI was induced in 12 anesthetized and mechanically ventilated pigs by repeated wash-out of surfactant. After initiation of PLV with 30 ml/kg perfluorocarbon the animals were randomly assigned to receive either accumulating doses of ALM (0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 μg/kg per minute) for 30 min each (n = 6) or the solvent malic acid (n = 6).

Measurement and results: Pulmonary gas exchange and hemodynamics were measured at the end of each infusion period. Compared to ALI, PLV alone significantly increased arterial oxygen partial pressure (PaO₂) and decreased venous admixture (QVA/QP) and mean pulmonary artery pressure (MPAP). Administration of ALM did not result in a further improvement in PaO₂, QVA/QP or MPAP compared to PLV alone but decreased PaO₂ and increased QVA/QP and MPAP when 16 μg/kg per min ALM was compared to PLV alone.

Conclusions: In an animal model of surfactant depletion induced ALI the combined treatment of PLV and ALM induced no significant improvement in pulmonary gas exchange or hemodynamics when compared to PLV alone. Moreover, high-dose ALM significantly impaired gas exchange and pulmonary hemodynamics.

Key words Liquid ventilation · Perfluorocarbons · Hypoxic pulmonary vasoconstriction

Introduction Partial liquid ventilation (PLV) with perfluorocarbons (PFC) is an experimental therapeutic strategy in the treatment of acute lung injury (ALI). This technique of combined liquid-gas ventilation is performed by intratracheal instillation of PFC in volumes up to the functional residual capacity of the lung (high-dose PLV) during conventional mechanical ventilation. Numerous studies have revealed the efficacy of PLV in improving pulmonary gas exchange in several animal models of ALI and in clinical studies [1, 2, 3, 4, 5, 6, 7, 8]. Possible mechanisms responsible for this beneficial effect of PLV are associated with the physical properties of PFC, i.e., the high solubility for respiratory gases, the positive spreading coefficient, and the high density. The mechanisms suggested for improving pulmonary gas exchange are recruitment of atelectatic lung regions, prevention of alveolar collapse, improvement in lung mechanics, and redistribution of pulmonary blood flow from depen-
dent, poor-ventilated lung regions towards better ventilated ones. Additionally, PLV has been successfully combined with other therapeutic strategies such as inhaled nitric oxide, exogenous surfactant, high-frequency ventilation, and prone position [9, 10, 11, 12, 13, 14].

Another experimental therapeutic strategy in the treatment of ALI is the administration of almitrine bismesylate (ALM), a pulmonary vasoconstrictor. Intravenous ALM seems to produce a dose-dependent pulmonary vasoconstriction preferentially in nonventilated lung areas. Therefore ALM may also improve pulmonary gas exchange by reducing intrapulmonary right-to-left shunt, as indicated by previous studies [15, 16, 17, 18, 19]. In surfactant-depleted pigs our own group have demonstrated a dose-dependent improvement in pulmonary gas exchange due to intravenous ALM alone [20, 21].

As the distribution of PFC in the lung is not homogeneous, PLV may not always provide beneficial effects in all lung units, and blood flow to nonventilated areas may still disturb pulmonary gas exchange. Therefore the aim of this study was to determine possible additive effects of combined high-dose PLV and sequential doses of ALM on pulmonary gas exchange and hemodynamics due to a potential vasoconstriction in hypoxic lung units.

Data acquisition
All hemodynamic measurements were taken in the supine position with zero reference level at the midsternum. Central venous pressure, mean arterial pressure, mean pulmonary artery pressure (MPAP), and pulmonary capillary wedge pressure were transduced (Baxter) and recorded (Hewlett-Packard, Model 665 S, Böblingen, Germany). Cardiac output was measured using standard thermodilution techniques and expressed as the mean of three measurements at end-expiration of different respiratory cycles. Heart rate was traced by the blood pressure curve.

Blood samples were collected simultaneously, and analysis of arterial and mixed venous blood gases (PO2, PCO2), hemoglobin, and oxygen saturation was performed immediately. Blood gases were determined using standard blood gas electrodes (ABL 520, Radiometer, Copenhagen, Denmark). The parameters hemoglobin, arterial oxygen saturation, and mixed venous oxygen saturation were measured via species specific spectroscopy (OSM 3, Radiometer).

Arterial oxygen delivery (DO2), arteriovenous oxygen content difference (avDO2) and venous admixture (QVO2/QT) were calculated using the cardiac output (CO) and the secondary parameters arterial (CaO2), mixed venous (CvO2), and arterial capillary oxygen content (CcO2):

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DO2 = CO \times CaO2 \\
adDO2 = CaO2 - CvO2 \\
QVO2/QT = (CcO2 - CaO2)/(CcO2 - CvO2)
\]

Material and methods

**Animal preparation**

The experimental protocol was approved by the appropriate governmental institution. The study was performed according to the Helsinki convention on the use and care of animals.

After premedication with azaperone (5 mg kg⁻¹ intramuscularly) and atropine (0.05 mg kg⁻¹ intramuscularly) in 12 female pigs weighing 29 ± 3 kg, anesthesia was induced with thiopental (5 mg kg⁻¹) and maintained with continuous infusion of methohexital (50 μg kg⁻¹ min⁻¹) and fentanyl (3 μg kg⁻¹ min⁻¹). Continuous muscle relaxation was achieved with pancuronium (2.5 μg kg⁻¹ min⁻¹). Animals were positioned supine, tracheotomized, and intubated with a 7.0- to 8.0-mm ID endotracheal tube and subjected to volume controlled mechanical ventilation (Servo 900 D Ventilator, Siemens Elema, Lund, Sweden) with an inspiratory oxygen fraction of 1.0, a respiratory rate of 20/min, a tidal volume of 10 ml kg⁻¹, an inspiratory/expiratory time ratio of 1:2 and a positive end-expiratory pressure of 5 cmH2O. The supine position and the ventilator setting remained unchanged throughout the entire study protocol.

A 18-G arterial line (Vygon, Ecouen, France) and a 8.5-Fr venous sheath (Baxter, Irvine, Calif., USA) were inserted percutaneously into femoral vessels. A right heart catheter (model 93A-431.75F, Baxter) was positioned in a pulmonary artery under transduced pressure guidance.

The blood temperature, determined by means of the pulmonary artery catheter, was maintained at 36.7 ± 0.9 °C during the experiment using an infrared warming lamp and a warming pad. A continuous infusion of 4-5 ml kg⁻¹ h⁻¹ of a balanced electrolyte solution was administered for adequate hydration.

**Experimental protocol**

Following animal preparation, a measurement was performed to ensure similar baseline conditions in all animals regarding hemodynamic and pulmonary gas exchange parameters. ALI was induced by surfactant depletion due to repeated lung lavage with saline as previously described and evaluated by Lachmann et al. [22]. Each lavage was performed with 40 ml kg⁻¹ saline prewarmed to a temperature of 37.0 °C. Values for ALI were collected after the PaO2 remained persistently below 100 mmHg for 1 h without any additional lavage. Subsequently PLV was initiated by administering 30 ml kg⁻¹ FC 3280 (3M Chemical Products, Neuss, Germany) via a swivel-connector (Portex, Kent, United Kingdom) into the endotracheal tube without disconnecting the animals from the respirator or interrupting ventilation. As previously evaluated, a volume of 4 ml kg⁻¹ h⁻¹ of FC 3280 was continuously administered to substitute losses due to evaporation [23]. To avoid possible side effects of a disconnection from the respirator animals were not suctioned during the entire study period.

After initiation of PLV the animals were randomized to receive PLV alone (n = 6) or combined PLV and ALM (n = 6) for 180 min until the end of the experiment. Continuous intravenous application of either ALM ( Vectocan injectable, Euthera, Neulilly-sur-Seine, France) or the solvent malic acid was started. Infusion of ALM was started at 0.5 μg kg⁻¹ min⁻¹ for 30 min. Thereafter the applied dose was doubled every 30 min until a dose of 16 μg kg⁻¹ min⁻¹. ALM was achieved (0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 μg kg⁻¹ min⁻¹). At the end of each infusion-period hemodynamics, gas exchange, and ventilator data were measured. The solvent malic acid was applied at equal volumes. At the end of the study all animals were killed by the intravenous administration of potassium chloride.