Synthetic surfactant with surfactant protein analogues SP-B and SP-C therapy and experimental acute respiratory distress syndrome

Pavol Mikolka[1,2], Petra Kosutova[2], Michaela Mikolkova[3], Denisa Osinova[3], Anna Rising[1] and Janne Johansson[1]

[1]Division for Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[2]Biomedical Center Martin and Department of Physiology, Jessenius Faculty of Medicine in Martin, Comenius University, Martin, Slovakia
[3]Department of Anaesthesiology and Intensive Care, Martin University Hospital, Martin, Slovakia

pavol.mikolka@uniba.sk

Introduction

Acute respiratory distress syndrome (ARDS) is a life threatening condition characterized by stereotypic response to many different initiating insults (e.g. pneumonia, gastric contents aspiration, sepsis, hemorrhage) [1]. ARDS involves acute diffuse, inflammatory lung injury with pulmonary epithelial and endothelial cellular damage (apoptosis, necrosis) leading to increased pulmonary vascular permeability and development of alveolar oedema, associated with increased physiological dead space and decreased lung compliance and further deteriorates the lung function in the early phase of ARDS [2].

Therapeutic protocol for ARDS patients is almost based on the mechanical ventilation, fluid-restrictive resuscitation strategies and prone positioning, in focus to primarily prevent further iatrogenic lung injury [3]. Patients with ARDS show injury to the alveolar epithelial barrier with consequent surfactant dysfunction. Exogenous pulmonary surfactant has appeared to be an effective adjunctive therapy due to its properties, increasing pulmonary compliance, anti-inflammatory and anti-oedematous function [4]. Several randomized clinical trials of exogenous surfactant therapy in adults with ARDS have been conducted. Surfactant therapy may improve oxygenation but has not been shown to improve mortality, length of intensive care unit stay or duration of mechanical ventilation [5].

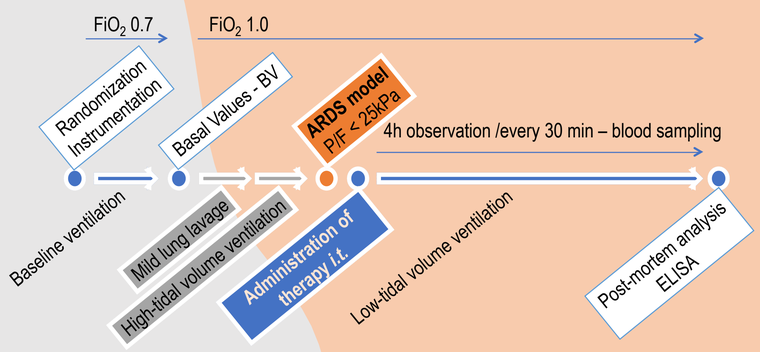
Currently, exogenous surfactant cannot be considered an effective adjunctive therapy in ARDS due to conflicting results may be related to variations in the surfactant composition, biophysical activity, susceptibility to inactivation, and dose. Possible alternative represents synthetic preparations.

CHF5633 is a fully synthetic surfactant preparation consisting of phosphatidylcholine and phosphatidylglycerol, enriched by peptide analogues of both human surfactant proteins SP-B and SP-C. Administration of CHF5633 to preterm rabbit resulted in marked improvement in lung expansion without different from poractant-alfa, improved lung and brain injury scores in experimental respiratory distress syndrome (RDS) and in a first-in-human clinical study showed well toleration by preterm babies with moderate RDS and raised no safety concerns, with a promising clinical efficacy profile. In addition, the structure of the peptide analogues has been modified to be resistant to oxidative injury and may improve resistance to inactivation [6, 7].

Hypothesis

We hypothesized that synthetic surfactant CHF5633 based on synthetic proteins improved lung function and attenuated inflammation compared to the animal derived surfactant poractant alfa in an experimental model of ARDS.

Methods



Baseline ventilation: VT 10mL/kg, PEEP 5cm H2O, RR 30/min, I:E 1:2, FiO2 0.7 for 30 min
Lung lavage: 5 mL/kg; 4 times in total or P/F < 70 kPa
High-tidal volume ventilation: VT 20mL/kg, ZEEP (PEEP 0), RR 20-30/min, I:E 1:2, FiO2 1.0
Low-tidal volume ventilation: VT 8-9mL/kg, PEEP 5cm H2O, RR 30/min, I:E 1:2, FiO2 1.0

Adult New Zealand white rabbits (2.7±0.2 kg)
Two-hit model of ARDS was defined as P/F<25 kPa
- Mild lung lavage
- High volume lung ventilation

The animals were assigned randomly to three groups (n=8 in each): (i) no surfactant treatment, air bolus (Control group); (ii) treatment with the natural modified surfactant poractant alfa; (iii) treatment with CHF5633 surfactant.

Surfactant therapy 2.5 mL/kg, 200 mg phospolipids/kg was given as a bolus intratrachealy:
- ***Modified porcine surfactant Poractant alfa*** (Curosurf®, Chiesi Pharmaceutici, Italy)
- ***Synthetic CHF5633 surfactant*** (Chiesi Pharmaceutici) containing SP-B and SP-C analogs (0.2 and 1.5%, respectively) together with the phospholipids dipalmitoyl-phosphatidylcholine and palmitoyl-oleoyl-phosphoglycerol in the 1:1 ratio (98.3%)

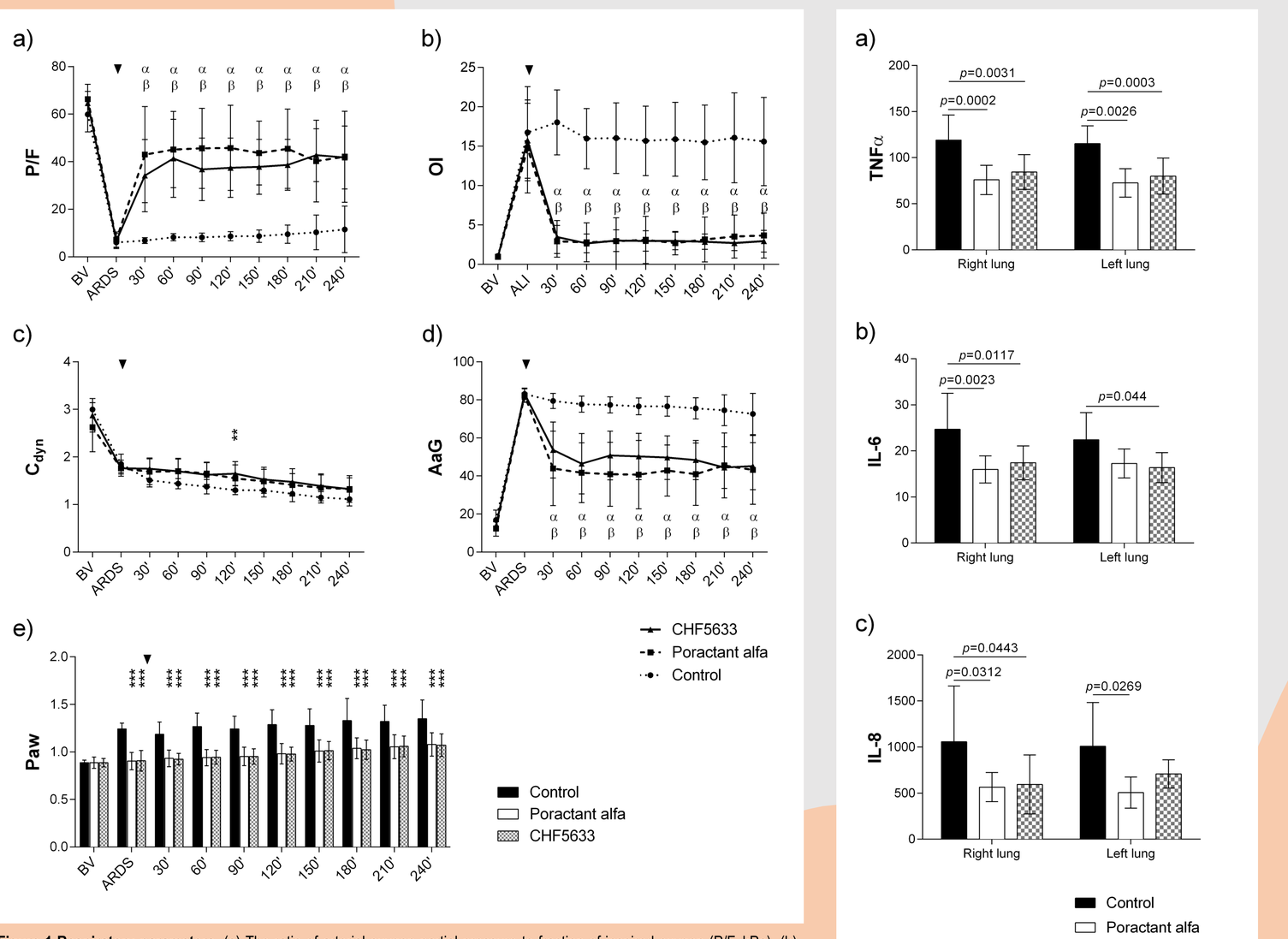


Figure 1 Respiratory parameters. (a) The ratio of arterial oxygen partial pressure to fraction of inspired oxygen (P/F, kPa), (b) oxygenation index (OI), (c) dynamic lung-thorax compliance (C_{dyn}, ml/cmH2O), (d) alveolar-arterial gradient (AaG, kPa), (e) mean airway pressure (Paw, kPa) before (basal value, BV) and ARDS and during 4 hours after administration of surfactant therapy (marked with an arrow). Data are presented as means ± SD. Statistical comparisons: α for poractant alfa and β for CHF5633 *vs.* Control ***p<0.001, for C_{dyn} CHF5633 *vs.* Control **p<0.01.

Figure 2 Inflammatory markers. Levels of cytokines (a) TNFα, (b) IL-6 and (c) IL-8 (all in pg/mL) in the right and left lung tissue homogenate of untreated group (Control), and groups treated with poractant alfa or CHF5633 surfactant. Data are presented as means ± SD. P values from statistical comparisons are shown in absolute values. Horizontal lines represent comparison for poractant alfa or CHF5633 vs. Control.

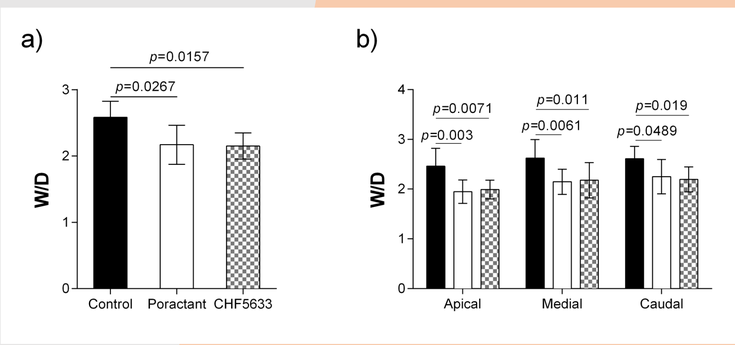


Figure 4 Lung oedema formation. (a) Total lung oedema expressed as wet-dry (W/D) lung weight ratio, (b) W/D of apical, medial and caudal regions of lungs of untreated group (Control), and groups treated with poractant alfa or CHF5633 surfactant. Data are presented as means ± SD. P values from statistical comparisons are shown in absolute values. Horizontal lines represent comparison for poractant alfa or CHF5633 vs. Control.

Conclusion

The pathogenesis of the early phase of ARDS includes not only surfactant dysfunction, but also prominent aspects of inflammation, vascular dysfunction, oxidant injury, cellular injury, and oedema. Herein, we present a two-hit rabbit model of ARDS that recapitulates the prominent features of the disease.

We show that administration of synthetic surfactant CHF5633 in this model results in improved lung functions, decreased oedema formation, and reduced pulmonary inflammation to almost the same degree as poractant alfa.

References

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