

# How (not) to injure the preterm lung

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# Valorization



## RELEVANCE

My research concentrates on how the transition after birth of infants born prematurely (i.e. birth before 37 weeks of gestation) can be improved. Worldwide, the overall rate of preterm birth is rising. Due to advances in neonatal medicine, survival rates increased dramatically in the past 40 years, especially in infants born very prematurely (i.e. birth before 28 weeks of gestation). Nevertheless, preterm birth is still the most important single cause for mortality in the neonatal period, with almost a million deaths related to prematurity worldwide in 2013.

The improvement in survival was achieved mainly by implementing therapeutic interventions supporting the lung function of these very immature children. Adequate pulmonary function is necessary for gas exchange and is a prerequisite for survival of preterm infants. Major milestones in neonatal medicine include antenatal maternal steroid therapy to induce lung maturation in utero, exogenous surfactant administration as replacement therapy for the insufficient endogenous surfactant production in the preterm lung, and the appliance of continuous positive airway pressure (CPAP) helping to keep the premature airways open and to reduce postnatal lung injury.

After birth, the preterm lung is very susceptible to injury. Although postnatal therapeutic interventions are necessary to establish and maintain pulmonary function, these interventions can induce lung injury and interfere with lung development, resulting in structural and functional impairment of the lung. Finally, lung injury can persist and contribute to chronic lung disease of preterm children, bronchopulmonary dysplasia (BPD). BPD is the most common diagnosis in children born extreme prematurely between 22-28 weeks gestational age, with incidences reported from approximately 40% to 70%. Recent data from the U.S. suggests that the incidence of BPD is rising in this group of extremely preterm babies, while mortality decreases. In addition, direct costs for extreme premature infants increase by more than 31,000\$ per child if BPD is present.

The consequences of preterm lung injury can however last the whole life: Survivors of prematurity have per se a higher risk for long-term impairment of lung function pulmonary morbidities like asthma, and this risk is markedly pronounced in preterm infants diagnosed with BPD. Lung function impairment of former very low birth weight infants with BPD can be found until adulthood. In addition, BPD is an important independent risk factor for an impaired neurocognitive outcome in preterm infants. Therefore, long-term impairment of quality of life, but also lifelong health care costs put a high burden on both the individual and society, reaching far beyond the neonatal period.

Despite advances in neonatal therapy, prophylactic and therapeutic means for management of BPD are scarce. Therefore, there is an urgent need to explore new therapeutic options, but also to adjust known therapeutic concepts in order to reduce pulmonary impairment in these vulnerable patients.

## INNOVATION

The results described in this thesis all bear the potential to improve pulmonary function of preterm infants by optimizing delivery room interventions leading to reduced lung injury. We have tested different innovative approaches to achieve this goal by

- testing technology to improve pharmacological therapy,
- applying existing procedures in a new environment to a new patient population,
- combining existing drug therapies to understand synergistic mechanisms, and
- testing an established pharmacological intervention in a new form of administration.

Using a unique translational large-animal model, this research paves the way to bring these approaches to the patient.

The results presented in this thesis are of interest for different groups. Patients and their parents will profit from improved short- and long-term outcome after premature birth. Survivors of preterm birth carry a lifelong health burden. Reducing lung injury can help to avoid pulmonary diseases in later childhood and adulthood associated with BPD, such as asthma or emphysema, and to avoid morbidities associated with BPD such as impaired neurocognitive development. In summary, BPD is associated with impaired quality of life, but also with a high socioeconomic burden. Research helping to improve the preterm lung has therefore positive effects for both the individual patient and for society.

However, a single gold standard strategy does not exist. A combination of pharmacological and technical interventions can be the key to solve this problem. Our results are therefore of interest for doctors and caretakers engaged in neonatal intensive care, by providing important information about how therapeutic strategies interact or can be combined in order to provide best possible care not only with respect to the acute effects, but also in the context of long-term morbidities of survivors of premature birth.

Furthermore, these results are of interest for developers of technical equipment and infrastructure, but also for pharmaceutical research and pharmaceutical companies. We expect that our results regarding different therapeutic strategies help to develop innovative, clinically applicable products already within the next years.

Our results regarding nebulization of surfactant further show that a close collaboration between pharmaceutical researchers and developers of technical equipment is a prerequisite for successful development of an innovative therapeutic strategy. Both surfactant replacement and nebulization per se are techniques established in the past decades. However, merging these two interventions depends on a variety of factors, as we could show in our experiments. Before nebulized surfactant can become a standard clinical application, translational research as performed in our model will help to identify factors interacting with treatment results and lead to optimized treatment protocols. Knowledge derived from our experiments forms the basis for clinical tests and helps to

establish clinical protocols. As we used commercially available surfactant and technical equipment, a clinical protocol can be expected in the near future.

Our results regarding endotracheal administration of vitamin A are also promising regarding its clinical application. Our results identified the endotracheal route as a possible way to administer an innovative vitamin A preparation in parallel to surfactant replacement therapy. The obvious advantage of the endotracheal application is its delivery in close proximity to the target organ and its possible potential to increase the VA supply where it is needed most: at the alveolar septum. Our results contribute to the ongoing research for the optimal supplementation regime by adding a potentially new substance allowing for weight-targeted supplementation. In the context of our results regarding surfactant nebulization, our results bear the potential of vitamin A supplementation via the endotracheal route in a non-invasive manner. Further translational trials will enable us to improve means of vitamin A administration, while clinical trials and safety studies are warranted to help to investigate biological and clinical effects.

Our research also helps to extend the use of newly emerging techniques like closed-loop ventilation in neonatal care. First, our results showed safety and feasibility of closed loop oxygen control in a delivery room setting. Second, we obtained data about how biological parameters such as oxygen saturation are influenced by applying technical solutions. These findings are also a prerequisite for clinical application, and are especially important for caretakers on the neonatal intensive care unit. Meeting oxygen saturation ( $SpO_2$ ) targets by manually controlling the inspired fraction of oxygen is a difficult and time-consuming task. During routine NICU care,  $SpO_2$  target ranges are met during 50% of the time. Meeting  $SpO_2$  targets affects morbidity and mortality, depending on the target range chosen. Several clinical trials with different devices already have proven feasibility of automated closed loop  $FiO_2$  control in the NICU for various modes of ventilation, mixed populations, and by using different algorithms. In addition, an overall reduction of manual interventions during automated control was found in these studies, indicating facilitation of caretakers and nursing staff in clinical routine. The delivery of oxygen is also crucial in the delivery room setting. In this thesis, we could show that automated  $FiO_2$  control during mechanical ventilation was feasible in the delivery room setting with rapidly changing physiology of fetal transition to extra-uterine life and during surfactant replacement therapy, and helped to avoid hyperoxia. In conclusion, a closed-loop device for control of inspired oxygen can be tailored to meet the patient's needs directly after birth and to support the caretakers in the delivery room the best possible way. The use of a commercially available device will allow easily the next step by launching a clinical trial.

