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Original article

Lung recruitment strategies and surfactant in neonatal intensive care unit

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Abstract. Several studies in the lamb model have shown that hyperinflation of the lungs early in life may cause a blunted response to surfactant with signs of lung injury and any attempt to recruit lung volume in the surfactant deficient preterm infant by large lung inflations at birth should be potentially dangerous. As regards the situation when surfactant is given later, as rescue treatment for established RDS, the evidence for a clinically beneficial effect of a recruitment maneuver is yet insufficient and, hopefully, future studies will gather more data on this aspect. (www.actabiomedica.it)

Key words: surfactant, HFOV, premature neonates, lung recruitment

Introduction

In the beginning of the surfactant era, various more or less elaborate procedures were performed at the time of surfactant instillation, including chest-positioning, manual ventilation, and changes in ventilator settings (1). These procedures were thought to facilitate surfactant spreading but were largely undocumented and have gradually come out of fashion. Surfactant is now often given as one or two rapid boluses in the trachea during a short disconnection from the ventilator, and it is generally thought that the different techniques are probably similar in terms of outcome (2). However, the poor documentation does not necessarily mean that these techniques are ineffective. In adults with acute lung injury or collapsed lungs during anesthesia, lung recruitment maneuvers can very effectively remove atelectasis and improve lung function (3). Surfactant deficient preterm infants have a decreased stability of air spaces in expiration. During mechanical ventilation, this may lead to lung collapse if PEEP is set too low and if expiration time is excessively long. Such collapsed air spaces would, at least in theory, be recruitable if a sufficiently high end-inspiratory pressure is applied. If this is done before and during surfactant instillation, surfactant would be expected to spread into a larger part of the lung. Air spaces, temporarily stabilized by the recruitment maneuver, could be more permanently stabilized by surfactant, and the net result would be an improved effect of treatment.

Lung lavage of previously healthy mature animals will induce a severe surfactant deficiency, decreased stability of air spaces, and widespread alveolar collapse. Such animals have a markedly reduced FRC, while inspiratory capacity (the volume change of the lungs from 0 to 30 cm H_2O, i.e. the equivalent of vital capacity as measured in spontaneously breathing subjects) initially remains unchanged (4). The atelectatic lung parts are relatively easy to open and are less unstable than in other models (5). The good effect of the recruitment maneuvers is therefore not surprising.

The pathophysiology of human RDS is often described in similar terms, i.e. alveolar collapse and low

FRC, but the true situation is probably more complicated. Krause et al. state that the lack of improvement in dynamic compliance immediately after surfactant treatment of human infants with RDS suggests that a substantial compartment of unventilated air spaces still exists (6). This may be true, but it does not necessarily follow that these air spaces would be recruitable before surfactant administration. An unventilated compartment could be explained by atelectasis, which might be opened by a recruitment maneuver. Such maneuvers are certainly often used with good effect, e.g. after disconnections from the ventilator and endotracheal suctioning. However, in severe RDS, an unventilated compartment could also be caused by e.g. edema, hyaline membranes, or inflammatory infiltrates, which may not be eliminated by pressure alone.

In preterm monkeys, the major cause for the loss of lung capacity is the presence of proteinaceous alveolar edema rather than alveolar collapse (7). This results in a proportionally greater reduction in inspiratory capacity than in FRC. Similar lung mechanical findings have been reported in human infants with severe RDS (8), suggesting that a substantial portion of the unventilated lung compartment is probably not recruitable.

Krause et al. suggest that the RDS lung consists of populations of alveoli with varying degrees of instability and collapse (6). An alternative model would be that a large part of the lung is fluid-filled and does not take part in gas exchange, while some of the ventilated lung parts may have relatively normal mechanical properties. If the latter model is true, large tidal volumes may lead to overdistension of the aerated lung parts, while the fluid-filled parts cannot be recruited.

Surfactant is now often given shortly after birth as prophylaxis against RDS. At birth, the lung is fluid-filled rather than atelectatic, and experimental studies do not support the use of lung recruitment. In preterm lambs, surfactant spreads less homogeneously in a ventilated lung than when given before the first breath (9), and this inhomogeneity is particularly pronounced following a recruitment maneuver at birth (10). Moreover, several studies in the lamb model have shown that hyperinflation of the lungs early in life may cause a blunted response to surfactant and signs of lung injury (11-13). All these aspects regarding the best way to deliver surfactant by promoting a more homogeneous distribution and its consequent best efficacy, are particularly important in the era of early application of continuous positive airway pressure (CPAP) and in general, of a non-invasive respiratory support to avoid mechanical ventilation, because their deep understanding contribute to reduce the risk of ventilator-induced lung injury and chronic lung disease (CLD).

The findings from the COIN (14), SUPPORT (15), and VON DRM trials (16) - comparing Early CPAP versus standard care (intubate, surfactant, mechanical ventilation) - are remarkably consistent. No single trial was able to demonstrate a statistically significant difference in the risk of death or CLD when infants were managed initially with CPAP. From the results of these 3 studies, it is clear that initial stabilization on CPAP and provision of rescue surfactant only when necessary is at least as beneficial and quite possibly preferred over the standard therapy of intubation of all infants at risk in the DR and subsequent support with mechanical ventilation. However, the optimal respiratory care of newborns with respiratory distress syndrome (RDS) may involve yet another choice. As potential alternative, the INSURE (INtubate, SURfactant, Extubate) approach is very attractive. Recently, several studies have investigated the effectiveness of the association between non-invasive ventilation and surfactant, administered by transient intubation (INSURE), showing that it is effective in preventing the need for mechanical ventilation. The findings from the CURPAP (17) and VON DRM trials (16)- comparing Early INSURE **versus** Early CPAP as initial stabilization - showed no differences in mortality, CLD or any other outcome. Nevertheless, in VON DRM trial 51% of infants in INSURE Group was later intubated.

Although beneficial in clinical practice, the INSURE method cannot be universally applied to all preterm neonates with RDS and is unsuccessful in a particular section of this population. The INSURE failure rate reported in the literature widely ranges from 9% to 50%. The reported independent risk factors conditioning a failure of INSURE are low birth weight (BW) <750-1000 grams and the severity of initial respiratory disease (ratio a/ApO_2 <0.20 to 0.44 on the first blood gas analysis (18). Prophylactic or early rescue surfactant administration before alveolar recruitment probably achieves a non-uniform surfactant distribution, result-

ing in poor clinical response to the first surfactant treatment and the immediate positive effects of surfactant on oxygenation may be primarily attributable to the stabilization of already open alveoli, and not due to recruitment of collapsed ones. Alveolar instability refers to the tendency for an alveolus to switch abruptly between the inflated state and the collapsed state. When instable alveoli have been stabilized by surfactant repletion they deflate progressively without collapse so that they retain gas volume at end-expiratory pressures below their critical closing pressure. The lung model on which this hypothesis is based assumes the presence of three compartments that differ in ventilation and stability: 1) a compartment of alveoli that are not ventilated, 2) a compartment of alveoli that are ventilated, but are instable and collapse during expiration, and 3) a compartment of alveoli that are ventilated and do not collapse during expiration.

The importance of lung recruitment before surfactant administration has been demonstrated by Krause MF et al. (6) in a piglet model of lung injury where a volume recruitment by means of moderately increased tidal volumes or increased PEEP or both, leads to augmentation of alveolar ventilation, thus improving gas exchange and lung function owing to more homogeneous surfactant distribution within the lungs. Volume recruitment was proven by improved compliance and increased functional residual capacity (FRC) in all the intervention groups.

More recently, the interrelationship between the role of surfactant and a sustained inflation (SI) to aid ex utero transition of the preterm lung has been investigated (19). The applied pressure of the SI needs to be sufficient to overcome the high resistance and long time constant of the liquid-filled respiratory system at birth. Thereafter, ventilation strategies need to account for the low compliance state of the surfactant-deficient lung. It is plausible to expect that the therapeutic benefits of exogenous surfactant therapy will be maximized by quickly and uniformly aerating the lung beforehand. In preterm rabbits, an SI of 20 seconds and inflating pressure of 35 cm H_2O was sufficient to fully aerate the lung at birth. Whether these parameters translate to other animal models or to newly born humans remains unclear. It has been in fact demonstrated that excessively large inflations can cause lung injury and negate the benefits of subsequent surfactant therapy (20). Ten newborn lambs with a gestational age of 127 days were randomized to receive surfactant either before the first breath or immediately after a lung recruitment maneuver consisting of five sustained inflations of 8, 16 or 32 ml/kg. Functional residual capacity was measured by sulfur hexafluoride washout, and inspiratory capacity as well as maximal compliance were obtained from a static expiratory pressure-volume curve after the lungs had been inflated to 35 cm H_2O. As main result, the authors found that lung recruitment at birth does not improve the response to surfactant in immature lambs, but may instead have an adverse effect on lung function and morphology.

The same Authors examined whether a lung recruitment maneuver just before surfactant would affect the response to rescue treatment in immature lambs with established respiratory distress syndrome (21). Five pairs of preterm twin lambs with gestational age 127 days were delivered by cesarean section and supported by pressure-limited mechanical ventilation for 4 h. At 30 min of age, when all the lambs were in severe respiratory failure, they were treated with porcine surfactant, 200 mg x kg^{-1}. One lamb in each pair was subjected to a lung recruitment maneuver consisting of five sustained inflations of 20 ml x kg^{-1} just before surfactant instillation. At 10 min after surfactant treatment, all the lambs showed a large improvement in oxygenation and an increase in inspiratory capacity and static compliance. Except for a transiently better oxygenation after surfactant therapy in the recruitment group ($P < 0.05$), there was no significant between-group differences in gas exchange or lung mechanics at any time point during the study. There was no difference in post mortem intrapulmonary air volume or alveolar expansion in histologic lung sections between groups. This small study does not show any positive or negative effect of a lung recruitment maneuver on the response to rescue surfactant therapy in immature animals with RDS.

Conclusions

From all available data it is clear that no definitive evidence exists about a positive effect of recruitment

before surfactant instillation, but a rationale exists for testing the following hypothesis: a lung recruitment maneuver performed with a step-by-step CDP increase during HFOV (and not with a SI) could have a positive effects in terms of both increased FRC values and of surfactant distribution in an immature animal model of RDS? Could this hypothesis be tested in newly born humans to compare the INSURE approach (INtubate, SURfactant, Extubate) vs the INRECSURE approach (INtubate, RECruit the lung, SURfactant, Extubate)? This represents our next challenge.

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