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Review

Sustained inflation: Prophylactic or rescue maneuver?

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SUMMARY

Application of nasal continuous positive airway pressure (nCPAP) in the delivery room is a valid alternative to mechanical ventilation in the management of respiratory failure of preterm infants, with reduced occurrence of bronchopulmonary dysplasia and death. nCPAP at birth is still burdened by a high failure rate. Sustained inflation appears to be an intriguing approach to allow the respiratory transition at birth by clearing the lung fluid, thus obtaining an adequate functional residual capacity. This may enhance nCPAP success. Sustained inflation reduces the need for mechanical ventilation in the first 72 h of life, with no changes in the incidence of bronchopulmonary dysplasia and death. The efficacy of sustained inflation seems to be related to the presence of open glottis with active breathing of the infant. Further studies are needed to recommend the application of sustained inflation during delivery room management of preterm infants at risk of respiratory distress or with clinical signs of respiratory failure.

1. Introduction

Preterm infants often need respiratory support at birth, despite noticeable efforts to start spontaneous breathing. In particular, the extremely low for gestational age (ELGA) infants fail to achieve and to maintain an adequate lung volume.

Mechanical ventilation (MV), formerly considered the best respiratory approach for preterm infants with respiratory failure, has a proven and direct correlation with bronchopulmonary dysplasia (BPD), especially when it is prolonged in time or when it is applied without accurate control of tidal volumes or adequate positive end-expiratory pressure (PEEP) [1].

For this reason, the use of non-invasive respiratory support (e.g. nasal continuous positive airway pressure, nCPAP) in the management of the respiratory distress of preterm infants became a standard of care. Recently, the use of nCPAP has been compared to the use of MV as primary approach to neonatal respiratory distress syndrome (RDS), with or without surfactant replacement. Recent randomized controlled trials (RCTs) concluded that nCPAP seems to be a valid alternative to MV [2–4].

A non-invasive respiratory approach in the delivery room, in order to avoid MV, may lead to a small but significant reduction in the rate of BPD in very premature infants [5,6]. The recently published guidelines on resuscitation from the International Liaison Committee on Resuscitation and the European Resuscitation Council have endorsed an approach of using CPAP first [7,8].

Nevertheless the nCPAP failure rate still remains high: 50% of infants initially managed with nCPAP need to be intubated and mechanically ventilated [2–4]. In some cases we can hypothesize that this failure is a consequence of the application of insufficient continuous distending pressure (CDP). For this reason, the setting of the optimal CDP, obtained with stepwise increments of CPAP level, has been suggested in the preterm infants with RDS [9,10]. In spontaneously breathing infants the achievement of an early and adequate functional residual capacity (FRC) at birth seems to be a prerequisite for the success of the non-invasive management of the respiratory failure.

2. Sustained inflation for respiratory support

At birth the lung is fluid-filled and the reabsorption of the liquid from the lung past was formerly attributed primarily to the epithelial sodium channels. It is now thought to be initially due to a pressure generated by the first breaths. Respiratory activity then moves the lung fluids in the airways towards the alveoli,

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where the fluid is pushed into the interstitium and reabsorbed by the lymphatic and vein vessels in the few hours following birth [11].

Immediately after birth, normal term infants show some prolonged inspirations (three or four deep inspirations, some of which are maintained for 5 s), generating a pressure gradient required to overcome airflow resistance and move fluid distally through the airways [12]. These first breaths are usually "prolonged" because the fluid-filled lung is characterized by a long time constant. The largest component of the inspiratory pressure then advances gas to the terminal airspaces, where the opening pressure is necessary to overcome the surface tension and open the alveoli [13]. This initial lung recruitment allows the surfactant to spread in the alveoli. This enables surfactant to exert its action and promotes a more uniform lung volume [14]. Moreover it is now demonstrated that the first inspirations that create an early lung recruitment actively contribute to the fall in pulmonary arterial resistance and the rise in pulmonary blood flow with a rapid improvement of the fetal–neonatal transition [15].

The preterm baby, especially if ELGA, is unable to generate these initial deep and prolonged inspirations to achieve an adequate FRC and a uniform lung aeration. Therefore the application of CPAP at birth by face mask, nasopharyngeal tube or nasal prongs, in many cases does not guarantee a normal gas-exchange. Then the preterm infants may need a positive pressure ventilation (PPV) delivered by face mask or tracheal tube in order to effect the lung opening. Unfortunately the application of a PPV without a prior FRC gain may damage the airways, producing a non-homogeneous lung filling, so initiating lung damage, even if it is delivered with controlled pressure (peak and PEEP) by using a T-piece device.

During the first phase of the respiratory transition the airways are filled with fluid, so that no lung gas-exchange can occur. The respiratory support should then be focused on clearing the gas-exchange regions of liquids. This is the primary rationale to the application of sustained inflation (SI) at birth. This maneuver can mimic the first prolonged inspirations performed by term infants to generate the delta pressure to move the fluid distally through the airways [11].

In a preterm rabbit model it has been demonstrated that an initial SI (delivered after tracheal intubation) followed by PEEP improved FRC formation and uniformity of lung aeration [16] and reduced markers of lung injury when compared with volume-targeted ventilation and PEEP [17].

In preterm lambs a prolonged SI (15–20 s, delivered after tracheal intubation) at birth recruited a variable FRC and showed a minimal increase of lung inflammation when compared to CPAP alone, but showed a significant reduction of this inflammation when compared to MV. This protective effect of SI disappeared when the SI was followed by MV [18].

Three RCTs have compared prolonged SI to routine PPV in terms of capacity to reduce the need for MV in the first 48–72 h of life in preterm infants [19–21]. Lindner et al. and Te Pas and Walther investigated one approach of a 'rescue SI maneuvre' in infants with signs of respiratory failure. By contrast, Lista et al. studied a prophylactic SI approach in preterm infants at risk for RDS. Lindner's study showed no differences in terms of primary outcome between the two groups of preterm infants of 25.0–28.9 weeks GA); the studies of Te Pas and Walther (preterm infants of 25^{+0}–32^{+6} weeks GA) and Lista et al. (preterm infants of 25^{+0}–28^{+6} weeks GA) showed a significant reduction of need for MV in the infants assigned to the SI group and also of BPD occurrence (Te Pas and Walther). In all of these studies SI was not associated with significant side-effects; Lista et al.'s study registered a non-significant tendency towards an increase of pneumothorax (PTX) in the SI group (6% vs 1%). PTX occurred at a median age of 70 h of life (70 h after the maneuver). The majority of these PTXs were mechanically ventilated with a "non-protective" modality (pressure-controlled ventilation) before the onset of the PTX. No direct relation of the PTX occurrence with the maneuver was found. These authors now believe that since an effective SI ensures the achievement of a good FRC and the improvement of lung compliance, once the infant is in the neonatal intensive care unit the appropriate tidal volume and PEEP levels should be applied both in non-invasive respiratory support and MV in order to avoid the risk of over-inflation.

Two meta-analyses [22], one of which is a Cochrane review [23], and the guidelines for the neonatal resuscitation [7] have recently reviewed the available literature.

In the two meta-analyses, infants initially treated with SI showed improved short-term respiratory outcomes, with reduced need of tracheal intubation and MV within 72 h of life (NNT = 10) [22], with no improvement of BPD and/or death occurrence [22,23]. The rate of patent ductus arteriosus was higher in the SI group [22,23], but it is not clear why.

The meta-analysis of Schmolzer et al. suggests restricting the use of SI to randomized trials until future studies demonstrate the efficacy and safety of this lung aeration maneuvre [22].

The Cochrane review concluded that "at present there is insufficient evidence from clinical trials to determine the efficacy and safety of initial SI for newborn infants resuscitated with PPV. RCTs comparing PPV with and without sustained inflations at neonatal resuscitation are warranted" [23].

The authors of the neonatal resuscitation guidelines largely agree in stating that they are [7] "against the routine use of initial SI (>5 s duration) for preterm infants without spontaneous respirations immediately after birth, but an SI may be considered in individual clinical circumstances or research settings."

These guidelines suggest that a short SI (<5 s) could be considered in case of absent or inadequate breathing efforts. Therefore it should be applied only as rescue intervention in infants with signs of respiratory failure.

An international multicentre RCT (Sustained Aeration of Infant Lungs – SAIL trial) is now comparing initial SI with PEEP to initial IPPV with PEEP in extremely preterm infants (23^{+0}–26^{+6} weeks GA) requiring resuscitation/respiratory intervention in order to determine the efficacy of these interventions in preventing BPD or death [24].

In the era of a tailored individualized ventilatory support, we hypothesize that not all the SIs have to be delivered with the same pressures and duration since not all preterm infants will react as a homogeneous group with a uniform behavior.

A critical role is played by the presence of open or closed glottis that allows or denies the air to enter the lung during the maneuver.

The fetal glottis is closed for >50% of fetal life to reduce the energy expenditure and to maintain the fluids produced by the pneumocyte type 2 into the lung. Moreover the fetal glottis is tonically adducted during apnea [25].

The asphyxiated term infant has hypotonic/atonic laryngeal muscles, which leads to an open glottis. In these infants an initial pressure of 30 cmH_2O maintained for ~5 s for the first inflation is able to generate a volume entering the lung comparable to spontaneous breaths and an adequate FRC in term infants [26]. Therefore in the asphyxiated term infants studied, the anatomy of the vocal cords at birth (open) favours the efficacy of one or more short SIs; the duration of the maneuver (5 s) was set to follow the inspiratory time of the first breaths at birth of term infants.