Mini-symposium: Alveolar and Vascular Transition at Birth

Managing Preterm Infants in the First Minutes of Life

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EDUCATIONAL AIMS

The reader will appreciate that:

- Preterm infants' postnatal adaptation is a complex process that often requires the intervention of especially trained caregivers.
- The cornerstone of a successful switch from a fetal to an adult type of cardiorespiratory circulation is to provide adequate lung ventilation. Both alveolar recruitment and achievement of a functional residual capacity are essential for establishing an adequate gas exchange.
- The use of non invasive ventilation and individual oxygen titration according to oxygen saturation provide the best and less aggressive means for achieving a successful postnatal adaptation of the preterm infant.

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SUMMARY

Premature infants often experience difficulties adapting to postnatal life. The most relevant ones are related to establishing an adult type cardiorespiratory circulation and acquiring hemodynamic stability, aerating the lung and attaining a functional residual capacity, performing an adequate gas exchange and switching to an oxygen enriched metabolism, and keeping an adequate body temperature. In recent years a body of evidence supports a trend towards gentle management in the delivery room aiming to reduce damage especially to the lungs in the so-called first golden minutes. Herewith, we describe and update four of the most relevant interventions performed in the delivery room: delayed cord clamping, non-invasive ventilation, individualized oxygen supplementation, and maintaining an adequate body temperature so as to avoid hyperthermia and/or hypothermia.

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INTRODUCTION

Experimental and clinical studies performed in recent decades have shown that interventions performed in the first minutes after birth, especially in very preterm infants could cause structural changes but also trigger inflammatory and pro-oxidant cascades injurious to most organs of the body and that could predispose to long-term conditions [1]. The 2010 ILCOR guidelines and recent consensus guidelines have underscored the advantages of delaying cord clamping for achieving hemodynamic stability, preventing brain damage, reducing the need of blood transfusions and improving iron status during the first year after birth [2,3]. In addition, non-invasive ventilation has been proposed to avoid or minimize possible damage to the lungs during postnatal adaptation in preterm babies who frequently need to be ventilated with positive pressure [2,3]. Of note, the use of individualized oxygen supplementation titrated according to individual response monitored using by pre-ductal oximetry is a new approach that tries to avoid damage caused by hyper- and/or hypoxia [4]. Similarly important is keeping an adequate body temperature which undoubtedly will influence mortality and morbidity of very preterm infants [3].

The aim of present review is to expand on these three newly evolving approaches meant to improve postnatal transition of very preterm babies to extra uterine life (Figure 1).
Allowing placental transfusion immediately after birth

In general there is agreement that delaying clamping of the cord is of benefit to the term and preterm infant. Maintaining blood supply to the heart (pre-load) while the lung vascular system gets replenished contributes to keeping an adequate left ventricular output, thus avoiding reduced blood flow to the CNS, coronary arteries, kidneys and the rest of the body [5]. Recent experimental studies in a sheep model of fetal to neonatal transition have clearly shown that delaying cord clamping after the initiation of positive pressure ventilation and establishment of a functional residual capacity favours myocardial stability, carotid flow, and brain oxygenation, thus prompting a smoother foetal to neonatal transition [6]. In 2010 ILCOR guidelines stated that for the term infant after a normal delivery there is evidence of the beneficial effects of delaying the clamping of the cord for at least one minute but it might be delayed until cessation of cord pulsation. In preterm infants, for uncomplicated deliveries, cord clamping should be delayed for a minimum of 30 seconds to 3 minutes after delivery. However, in extremely preterm infants or preterm infants who are born moderately to severely “depresed” there is no evidence as to whether delaying cord clamping would be of benefit instead of initiating the resuscitation manoeuvres immediately [2]. A recent systematic review comprising the available information since the publication of the 2010 ILCOR guidelines indicates that delaying cord clamping (DCC) up to 3 min in vigorous preterm babies significantly reduces hemodynamic instability, improves cerebral circulation, reduces intraventricular hemorrhage (IVH) all grades, necrotizing enterocolitis and the need for transfusions, although peak serum bilirubin was higher in the transfused group. However, no clear differences were found in the primary outcome of death, severe IVH or periventricular leukomalacia.

The optimal time to clamp the umbilical cord after delivery is still controversial. There are several small-randomized controlled trials (RCTs) that have compared early (20 s) to late (430 s) cord clamping following preterm birth as well as several prospective observational studies [7]. Of note, no conclusive data regarding the benefits of DCC in depressed infants and especially in very preterm infants are yet available. Although experimental studies support a positive effect on cardiorespiratory circulation, brain perfusion, and hemodynamic stability with delayed cord clamping, the setup needed to physically perform resuscitation maneuvers with an intact cord still constitutes an important impediment in most delivery rooms. In addition, in asphyxiated newborn infants there is a vasoconstriction of the placental vessels accompanied by vasoconstriction of the umbilical vessels, thus increasing the circulating blood volume in the foetus. However, pulmonary vasoconstriction and reduced myocardial contractility occur, which may prompt cardiac insufficiency and compromise recovery of the spontaneous circulation [8]. Under these circumstances cord milking has been suggested as a valid alternative. This manoeuvre consists of clamping the cord near the placenta and stripping (“milking”) approximately 20 cm several times (2 to 4) from the distal (placental) to the proximal (foetal) site of the cord. It can be performed in few seconds and provides the newly born with a substantial amount of blood that at least theoretically may contribute to hemodynamic stabilization. To date only three clinical trials have been performed in preterm infants, including a total of 100 babies. Cord milking resulted in increased placental transfusion and apparently appeared to be as effective as DCC.
Authors of these small trials concluded that cord milking may be an option when DCC is not an option because the newly born baby requires immediate resuscitation measures. However, there are still some questions that need to be answered. Hence, how rapid should the cord be stripped, or how often, or what’s the minimum or maximum length of the cord that should be stripped? In addition, there is some concern about the rapid perfusion of a significant blood volume into the infant’s circulation that does not resemble the physiologic flow of DCC [9].

Ventilatory support

Very preterm babies frequently experience difficulties initiating spontaneous effective respiration because of poor respiratory drive, poor muscle strength, surfactant deficiency, and high chest wall compliance. As a consequence, they need respiratory assistance to clear lung fluid, aerate the lungs, and establish a consistent functional residual capacity (FRC) to ensure gas exchange [10]. Failure to perform a uniform and functionally adequate lung expansion causes the coexistence of areas of atelectasis and over-distension which characterize respiratory distress syndrome (RDS) [3]. Preterm babies with RDS often need intubation and mechanical ventilation in the delivery room. These aggressive interventions although life-saving may cause trauma to the lung structure and lead to chronic lung disease [11].

Therefore, there is a search for ventilatory strategies in the delivery room (DR) capable of helping spontaneously breathing infants to adequately perform postnatal transition whilst reducing the risk of lung damage.

Ventilatory strategies that promote airway liquid clearance and alveolar recruitment

At birth a pressure gradient is required to overcome airflow resistance and move lung fluid distally through the airways; then to advance air to the terminal airspaces where the opening pressure is necessary to overcome the surface tension and open the alveoli [12]. This first lung recruitment maneuver (LRM) may be considered the pre-requisite to enable surfactant to reach a large proportion of alveoli, to begin its action, and to promote a more uniform lung volume [13]. This LRM is the first step of a high lung volume (“open lung”) strategy that is the key to protect the neonatal lung during mechanical ventilation [14]. Interestingly, the optimal technique of lung recruitment immediately after birth still remains unknown. To prompt lung expansion and establish an early functional residual capacity (FRC) the use of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) of at least 4-6 cm H2O has been advocated [15–18]. Thus, resuscitation guidelines underscore the efficacy of PEEP during resuscitation of preterm infants for the establishment and maintenance of an early FRC. FRC was achieved both by airway stabilization and prevention of alveoli collapse during expiration [2]. However, the use of fixed PEEP/CPAP in very preterm infants in the delivery room has not always been successful in establishing an adequate FRC. In a recent study, it was shown that a stepwise PEEP strategy after birth improved gas exchange, lung mechanics, and end expiratory volume without increasing lung injury in preterm lambs [19]. Delivery room management with stepwise increments of PEEP before giving surfactant has been satisfactorily applied via face mask in non-spontaneously breathing very preterm infants in order to reach a heart rate >100 beats per minute [bpm] and an SpO2 >85% within the first 10 minutes after birth, increasing the rates of survival and reducing morbidity [20]. In the study protocol sustained inflation (SI) maneuvers were employed before intubating the babies. In fact SI, defined as the application of an inflation pressure (e.g.: 25 cm H2O) for a period of time significantly more prolonged that the normal inspiratory time (e.g.: 15–25 s), is considered an alternative to clear fluid-filled lung and achieve an early FRC [20]. Immediately after birth, when the initial inflations are to be provided, it should be remembered that the fluid filled lung has a prolonged time constant. The first breaths of life in healthy term infants are characterized by a prolonged inspiratory time (4-5 s per breath, according to the long time constant of the fluid-filled lung), prolonged expiratory phase and high inflation pressure (30-35 cm H2O) along the major airways [21]. During these first “prolonged” inflations, the delta pressure moves the air/liquid interface distally towards the alveoli, thus facilitating direct lung aeration and clearance of lung liquid from the major airways within seconds after birth, that will be completed by the interstitial lymphatic and venous reabsorption (in the hours following the birth). In several minutes, by the achievement of an early FRC, the healthy term infant is able to maintain normal values of SpO2 while breathing in room-air [22].

Therefore to mimic the delta pressure generated by the high and prolonged inflation pressure of the newly born infant, a SI has been suggested for infants at high risk of respiratory failure. The application of a SI maneuver (prolonged inflation for 5 s) during resuscitation procedures was demonstrated to be efficacious in a population of asphyxiated term infants in relation to lung volume changes [23]. A rapid increase in heart rate and oxygen saturation reflected the efficacy of the resuscitation maneuvers [24,25].

Clinical observations of the first breath during mechanical resuscitation of preterm infants show that an initial inflating pressure around 20–25 cmH2O is generally effective in improving heart rate and chest expansion [2]. Nevertheless, the premature infant is often unable to generate such high inflating pressures within the first inspiratory excursions and is, therefore, incapable of achieving a homogeneous and generalized alveolar recruitment. As a consequence, many preterm infants need respiratory support and/or oxygen supplementation [26,27]. Intriguingly, SI maneuvers have not to markedly improved all the respiratory outcomes in clinical practice. Hence, the application after birth of SI maneuvers consisting of a peak pressure of 20-25 cmH2O for 10-20 seconds using a nasopharyngeal tube or an adequately sized mask and a Neo-puff (Fisher & Paykel Healthcare Ltd, Auckland, New Zealand) device, followed by the application of an adequate PEEP (e.g.: 5 cmH2O) were shown to be effective in the achievement of FRC and in improving short-term respiratory outcomes [reduction of tracheal intubation in DR and the need of mechanical ventilation (MV)] in preterm infants < 29 weeks’ gestation at risk for respiratory distress syndrome [28]. Recently, a study was launched which focused on the effect upon heart rate, SpO2 and cerebral tissue oxygenation of applying SI to a small group of preterm infants of <28 weeks’ gestation immediately after birth to enhance lung recruitment and consisted of three sustained inflations of 20, 25 and 30 cm H2O each of 15 sec duration followed by nasal CPAP. The majority of these infants needed more than one SI (with the application of growing pressures) because of persistent hypoxia or bradycardia. Sustained inflation did not negatively affect heart rate, arterial saturation or cerebral tissue oxygen saturation and a rapid increase in the infant’s heart rate and an increase in cerebral tissue oxygen saturation were observed [29]. The results of these small clinical trials seem to indicate that, under certain clinical conditions, SI could contribute to enhance alveolar recruitment and help to stabilize preterm infants in the DR without intubation. However, there are still many unanswered questions that need to be evaluated including appropriate setting of SI (duration and peak pressure), selection of patients (rescue or prophylactic procedure?), individually tailored setting of respiratory parameters used to manage the preterm infants, effects upon cerebral circulation,
management of a brisk increase in SpO2, and short and long-term outcomes of respiratory conditions.

**Oxygen supplementation**

**Oxygen in foetal life**

Foetal life elapses in an environment, which is relatively hypoxic compared to the extra uterine world. The arterial partial pressure of oxygen (pO2) in utero is $\approx 25-30$ mmHg (3.0-3.5 kPa) while in the first minutes after birth it will increase to 80-90 mmHg (10.5-12.0 kPa) [30]. Of note, oxygen delivery to tissue does not substantially differ in the foetus from the newborn. The reasons are: (i) the presence of foetal hemoglobin with a greater affinity for oxygen facilitates foetal oxygen uptake from the intervillous spaces from the placenta and increases oxygen saturation for a given pO2; (ii) extremely high foetal cardiac output as compared with adults (250-300 mL/kg/min); (iii) shunting from venous return coming from the placenta to organs with high oxygen needs ex-utero [31]. The intervillous partial pressure of oxygen is of 60 mmHg at 24-30 weeks’ gestation and of 45-48 mmHg at term. These values correspond to an SpO2 of 50%-60% in the foetus [32]. Interestingly, oxygen supplementation to the mother will cause a significant increase of foetal pO2 and oxidative stress. In addition, conditions of the mother causing foetal hypoxaemia, such as pre-eclampsia or insulin dependent diabetes, also cause oxidative stress to the foetus, and provoke postnatal maladaptation [32].

**Use of the pulse oximeter in the delivery room**

Pulse oximetry is now widely employed in the DR to objectively evaluate newborn postnatal arterial oxygen saturation instead of color, which has been traditionally employed but is subject to great individual variability [33]. Oxygen saturation (SpO2) reflects the percentage of oxy-hemoglobin present in the arterial blood. The pulse oximeter transforms, by means of specific algorithms, the degree of light absorption of oxygenated and deoxygenated haemoglobin at different infrared light spectra, compared to reference values of adult volunteers, and displays it as a percentage. This is the reason why no saturation values below 60%-70% are reliable. Pulse oximetry in the delivery room should be put at maximum sensitivity with averaging measurements every 2 seconds in order to detect minimal changes in a rapidly evolving clinical situation. The sensor is preferably put on the right hand or wrist to evaluate oxygenation of pre-duetal blood perfusing the central nervous system. Importantly, the sensor should be protected from intense light to avoid false readings. To achieve a rapid and reliable reading the oximeter should be turned on, then the sensor should be applied first to the baby and thereafter to the oximeter cable. In this way reliable readings can be mostly achieved with 60-90 seconds after birth. The presence of foetal hemoglobin, which represents almost 100% of the hemoglobin present in very preterm infants, may slightly alter the reading but lacks clinical relevance [34-36]. Pulse oximeters also display heart rate with great accuracy. This is extremely useful when evaluating the response to resuscitation since heart rate is probably the most practical clinical parameter reflecting a good or bad response [37]. For all the above-mentioned reasons, pulse oximetry together with an air/oxygen blender and a well-trained and sufficient human team round the clock altogether have optimised the resuscitation of term but especially very preterm infants [38].

**Postnatal oxygen saturation**

Immediately after birth the newly born infant has to aerate the lungs and establish a functional residual capacity to initiate an effective gas exchange. In order to do so liquid filling the airspaces has to be removed. The first inspiratory efforts cause an elevation of the negative intra-thoracic pressure that highly contributes to the passage of lung fluid to the interstitium. In addition, blockage of the active chloride mediated secretion and efficient Na+/K+ ATPase dependent pumps in type II alveolar cells both contribute to virtually clearing the fluid from the airways. Components of the lung fluid are cleared directly into the vasculature or via lymphatic from the lung interstitium over many hours. Processes that interfere with this mechanism such as prematurity, operative delivery and/or excessive sedation will delay airway fluid clearance and the establishment of effective gas exchange. Simultaneously, with the onset of labour, surfactant is secreted into the foetal lung fluid in large quantities. Surfactant deposition favouring alveolar distension upon expiration is essential for the establishment of a functional residual capacity (FRC) [10]. Preterm infants have delayed maturation of both, the Na+/K+ ATPase dependent pumps and surfactant metabolism, have a compliant chest wall and muscular weakness, or do not spontaneously initiate respiratory efforts [poor respiratory drive]. Altogether these factors will predispose preterm infants to respiratory insufficiency and the need for positive pressure ventilation and oxygen supplementation. In this scenario, the achievement of a stable pre-ductal SpO2 is substantially delayed even in healthy well-adapted preterm infants [10,37]. Recently, a group of researchers developed a SpO2 reference range for the first ten minutes after birth for term and preterm infants who did not receive any medical intervention in the delivery room. Three databases were merged, two from the Royal Women’s Hospital (Melbourne; Australia) and another from the University & Polytechnic Hospital La Fe (Valencia; Spain). Caregivers put a pre-duetal pulse oximeter (right hand or wrist) immediately after birth on all recruited babies and stored the data during the first ten minutes of postnatal adaptation. Pulse oximeters were adjusted to measure SpO2 every 2 seconds with maximum sensitivity. A total of 468 infants and 61650 data points were studied. Centile charts were elaborated for term, late preterm and very preterm infants. These charts can be used to monitor SpO2 after birth and intervene when titrating FiO2 individually according to the infant’s response [4]. Interestingly, term infants needed a mean of approximately 4.5 minutes to reach SpO2 of 90%; however, preterm infants needed 6–7 minutes to reach the same SpO2. Moreover, very preterm infants of <32 weeks needed almost 9-10 minutes to reach a similar SpO2 [4]. In addition, heart rate was simultaneously recorded and independently of the time needed to achieve SpO2 heart rate was above 100 beats per min indicating that cardiac oxygenation was adequate [39]. At present, Dawson’s nomogram is the best available reference for titrating FiO2 in newly born preterm infants in the delivery room. It is important to note that Dawson’s nomogram was made retrieving SpO2 in preterm babies spontaneously breathing air. However, a substantial number of preterm infants and especially those who are below 28 weeks gestation receive continuous positive pressure (CPAP) ventilation for stabilization in the first minutes after birth. In a recent study, it was shown that preterm babies breathing air, but supported with CPAP, achieve higher SpO2 significantly earlier than reflected in Dawson’s nomogram, and therefore caregivers in the DR should be aware of a rapid increase of SpO2 and avoid hyperoxaemia [40].

**Titrating oxygen in preterm infants in the first minutes after birth**

The initial steps once the baby is born are to achieve stabilization from a cardio-respiratory and thermal perspective following the ILCOR 2010 guidelines. This includes delayed cord clamping, keeping a neutral temperature, applying pulse oximetry on the right hand or wrist and non-invasive ventilation if the baby needs it [2]. Independently of the respiratory support needed, the
resuscitation team should be taking note carefully of the evolution of heart rate and SpO₂. SpO₂ should be individually titrated adjusting the FiO₂ according to the infant's response. The blender should be adjusted every 10–15 seconds aiming to keep the infant’s SpO₂ within the intended range. In this regard, the AAP in the 2010 recommendations suggested that the SpO₂ should be 60%–65% at 1 min, 65%–70% at 2 min, 70%–75% at 3 min, 75%–80% at 4 min, 80%–85% at 5 min and 85%–90% at 10 min [41]. The Dawson nomogram offers the possibility of adjusting SpO₂ within specific centiles. To avoid hypo- or hyperoxaemia the infant should be ideally kept within a safety range of SpO₂ between P10–25 and P50–75 centiles. Of note, it should be underscored that there is no proven evidence for establishing a definitive SpO₂ safety range during the period of stabilization of very preterm infants [42].

Keeping preterm babies warm

Thermoregulation after birth is highly dependent on the ability of the newborn infant to enhance heat production through the activation of thermogenesis using brown adipose tissue [43]. Unfortunately, preterm infants lack adequate brown adipose tissue deposition and are, therefore, not capable of achieving normal body temperature homeostasis with an unequivocal tendency towards hypothermia once they leave maternal milieu [44]. In the DR, maintenance of an adequate body temperature (target range of 36°C to 38°C) is one of the most important supportive therapies during fetal-neonatal transition especially for preterm infants. Both hypothermia and hyperthermia should be avoided during stabilization and upon admission to the neonatal intensive care unit. Of note, hypothermia at birth has been associated with an increased morbidity and mortality during hospital stay in preterm infants and/or very low birth (VLBW) infants. Therefore, specific interventions designed to prevent hypothermia are needed [45]. Hence, the delivery suite should maintain a temperature of at least 26°C when the birth of a very preterm infant (<28 weeks’ gestation) is expected. Moreover, all babies below 28 weeks’ gestation or <1500 g should be wrapped in polyethylene or polyurethane bags up to their necks at birth without previous drying to reduce heat loss and keep an adequate humidity. Nevertheless, when exothermic mattresses and radiant heaters are used, servo-control of the babies’ temperature should be mandatory especially after the first ten minutes after birth have elapsed and the risk of hyperthermia substantially increases [2,3]. For extremely preterm infants, polyethylene caps seem to be comparable with polyethylene occlusive skin wrapping to prevent heat loss after delivery [46]. Of note, careful monitoring of central and peripheral temperature is needed because effective temperature control under a radiant infant warmer (set in manual control) significantly varies among commercially available devices, suggesting that neonates can be easily put at risk of hypo- or hyperthermia [47]. Metabolic and haemodynamic changes due to hyperthermia (e.g. neonates born to febrile mothers) are at risk of adverse neurological outcomes [48], respiratory depression and increased mortality [49]. Therefore, every hospital delivering high risk neonates, especially extremely low birth weight infants, should have established protocols controlling room temperature, systematic use of plastic bags and/or caps, monitoring of temperature during resuscitation (preferably skin and central (rectal)) and during transport to the NICU trying to avoid hyper-and/or- hypothermia during the first golden minutes after birth [2,3,44–46].

DECLARATION OF CONFLICTS

None of the authors declares having conflicts of interest with the content of this manuscript

References


