

The First Golden Minutes of the Extremely-Low-Gestational-Age Neonate: A Gentle Approach

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Abstract

An increasing body of evidence has revealed that interventions performed during resuscitation of extremely-low-gestational-age neonates (ELGANs) may have a direct influence on the immediate survival and also on long-term morbidity. It has been proposed that interventions in the delivery room and/or hypothermia could trigger changes constitutive of chronic lung disease. New approaches in the first minutes of life using more gentle parameters of intervention are being studied. Thus, titrating inspiratory fraction of oxygen, the use of non-invasive ventilation to reduce trauma to the lung, the use of polyethylene/polyurethane wrapping to avoid hypothermia and delaying cord clamping altogether constitute promising initiatives. The first minutes of life are a valuable window for intervention. However, whilst these practice changes make sense and there are emerging data to support them, further evidence including long-term follow up is needed to definitively change resuscitation procedures in ELGANs.

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Morbidity and Mortality of Extremely-Low-Gestational-Age Neonates

In the last decade, improvement in the survival of infants born with gestational ages at or less than 28 weeks has been widely documented [1–10]: survival of infants born at 24 and 25 weeks' gestation rose from 25 and 50% in the early 90s to 40 and 60% 10 years thereafter in Europe and North America, respectively [3–10]. Of note, a similar improvement has also taken place in less developed countries, although the actual mortality rate is higher than that in developed countries [11]. The decrease in mortality rate has been attributed to a constellation of factors, and among them regionalization has been identified as one of the most relevant. Hence, volume of high-risk pregnancies and thus volume of patients admitted into the neonatal intensive care unit (NICU) have been underscored as determining factors to improved perinatal and neonatal care and the increasing survival [12–15]. Moreover, Phibbs et al. [15] predicted that up to 21% of the deaths of very-low-birth-weight infants in the year 2000 would have been potentially preventable if these infants had been born in a tertiary care regional medical centre. Notwithstanding, improvement in mortality seems not to be correlated to changes in the obstetric practice or neonatal resuscitation of the extremely-low-gestational-age neonates (ELGANs, defined as less than

or equal to 28 weeks' gestation). Hence, mortality in the delivery room has not substantially changed in the last decade, representing 15% of the live-born and 32% of the total deaths of ELGANs at discharge [9, 10]. In this regard, perhaps a pro-active or a restrictive approach to antenatal and perinatal treatment of the most immature infants could be a decisive factor to decreasing stillbirth rates and increasing the survival at 22–25 weeks' gestation [16, 17]. Other factors such as generalized use of prenatal corticosteroids, postnatal use of exogenous surfactant, new modalities of mechanical ventilation, use of inhaled nitric oxide, prevention of streptococcus B infection, and improvement in postnatal care in the NICU, have contributed to lowering mortality among extremely-low-birth-weight (ELBW, defined as less than or equal to 1,000 g) infants [6–8].

Interestingly enough, the improvement in mortality has not been paralleled by a decrease in ELGAN morbidity [1–10]. Prevalence of severe complications such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), septicaemia, severe intraventricular haemorrhage (IVH) or periventricular leukomalacia (PVL) have not substantially changed despite the increased use of prenatal corticosteroids and surfactant, implementation of indomethacin therapy and reduction in ductus arteriosus ligation, and decreased use of postnatal corticosteroids [7, 8, 10, 18, 19].

Fanaroff et al. [8] have indicated that the improvement in ELGAN survival would require determining, disseminating, and applying the best practices available, but also identifying new strategies and interventions. Recent research and clinical evidence suggest that interventions performed in the first minutes after birth may also have long-term consequences in addition to the short-term effects in the rate and quality of survival of ELGANs [20–26]. Accordingly, we will discuss basic aspects of postnatal adaptation related to ventilation, oxygenation, and temperature control. In addition, we will suggest how to apply present knowledge and technology in the delivery room (DR) to facilitate ELGAN adaptation to the extrauterine world and improve short- and long-term outcomes.

Ventilation

Initiation of Respiration in the Fetal to Neonatal Transition

To survive after birth, neuronal and muscular components of the respiratory system must be developmentally

advanced and functional to generate a rhythm that allows for gas exchange [27]. Hence, mechanisms responsible for this transition require the anatomical development of neuronal populations, onset of rhythmic respiratory neuronal populations, onset of rhythmic respiratory drive, and the actions of neuromodulators that control respiratory frequency, and functional development of the phrenic nerve and diaphragm musculature [28, 29]. During parturition, breathing movements are completely inhibited. Immediately after birth, respiratory activity which is intermittent in the fetus becomes continuous in the newly born infant. However, prematurity can alter the development and maturation of some of these mechanisms, and therefore most of the ELBW infants fail to establish sustainable and efficacious respiratory activity [30, 31]. Experimental findings suggest that the inhibitory role played by the placenta depends on prostaglandins [32]. Of interest is the importance of the Hering-Breuer inhibitory reflex, which is functional within the tidal breathing range and exerts a tight control on the breathing pattern of the term infant, is not altered by prematurity, and is thus vital in the first weeks of postnatal life [33]. However, excessive distensibility, distortion and compliance of the thoracic cage and weakness of the respiratory muscles may render respiratory efforts in the ELGAN inefficient [34].

After birth, alveolar hypoxia produces an immediate increase in ventilation followed by a later decrease. Conversely, high oxygen concentrations produce an immediate decrease in ventilation followed by hyperventilation [35]. In a recent study by Bookatz et al. [36], asphyxiated newborn rat pups were resuscitated with different oxygen concentrations. Time to onset of diaphragmatic activity was significantly shorter in the pups recovered in room air as compared to those ventilated with pure oxygen. Seemingly, a sustained increase in peripheral chemoreceptor drive during hypoxia will oppose central depression of respiration. Hence, hyperoxia during resuscitation could suppress peripheral chemoreceptor drive and delay re-initiation of breathing [37]. In a recent meta-analysis of studies performed in asphyxiated newborn infants, those resuscitated with room air established a spontaneous pattern of respiration significantly earlier than those resuscitated with pure oxygen [38].

There is a baseline concentration of CO₂ that is essential for the stimulation of pacemaker cells of central respiratory chemoreceptors. The level of CO₂ below which breathing ceases is known as the apnoeic threshold [39]. Interestingly, the apnoeic threshold of newborn infants is

very close to the baseline $p\text{CO}_2$ and therefore, hyperventilation caused by the use of high tidal volumes, high pressures or elevated respiratory rates would be sufficient to propel $p\text{CO}_2$ below threshold [40]. However, although hypercapnia increases respiratory muscle activity, the effect of this stimulus on the balance between upper airway and chest wall muscle activation is different. Upper airway muscles, as opposed to chest wall muscles, exhibit a high CO_2 threshold, thus explaining why some preterm infants develop obstructive apnoea [41].

Respiratory Adaptation of the ELGAN Immediately after Birth

Lung morphogenesis and repair are characterized by a complex sequence of cell-to-cell interactions of endodermal and mesodermal origins, which has evolved into an alveolar structure that can effectively exchange gases between the circulation and the alveolar space [42]. ELGANs are born at the end of the canalicular and beginning of the saccular stage of lung development. Their lungs therefore are formed by immature respiratory units called saccules. Saccules are characterized by lacking secondary septation, thus having a reduced gas exchange surface. In addition, alveolar type II cells are poorly represented and surfactant production is limited. It is important to note that septa between saccules are thick and contain two networks of capillaries rendering gas exchange difficult. Moreover, mesenchymal tissue contains low elastin and collagen, therefore having limited elastic properties [43–46]. Finally, the thoracic cage of ELGANs is extremely compliant, therefore having the tendency to collapse during forced inspiratory movements [34]. Taken together, these factors cause reduced lung compliance and limited thoracic expansion during inspiration, reduced elasticity and a lack of surfactant that may hinder the establishment of functional residual capacity (FRC). In addition, these factors also provoke a tendency towards airway and alveolar collapse (atelectasis) during expiration [47, 48]. As a consequence, most ELGANs will need positive inspiratory pressure immediately after birth to achieve lung expansion, and positive end-expiratory pressure (PEEP) to adequately establish FRC. In fact, recent reports indicated that 60–70% of the infants born at 26–28 weeks' gestation, and every baby born at or less than 25 weeks was intubated in the DR almost immediately after birth and received endotracheal intermittent positive pressure ventilation with end-expiratory pressure or non-invasive continuous positive airway pressure (CPAP) [49, 50].

Inflammatory Response of the Immature Lung to Stretch Forces

Experimental as well as clinical research has provided substantial evidence to infer that overstretching of the immature lung immediately after birth causes lung inflammation, which may increase morbidity and mortality in the ELBW infants [51, 52]. Of note is that most of the infants delivered before 30 weeks' gestation have been exposed to inflammatory or infectious processes in utero [51–56]. Further, resuscitation of ELBW infants still includes routine endotracheal intubation, positive-pressure ventilation, and high oxygen supplementation in many institutions [8, 11, 16, 18, 19, 25, 26, 57–59]. Recent surfactant trials have promoted the use of intubation and administration of surfactant directly in the DR as a protective strategy to avoid respiratory insufficiency [60, 61]. Although the use of prenatal corticosteroids has become the standard practice for preventing respiratory distress syndrome in preterm infants, its anti-inflammatory effect against prenatal lung inflammation and postnatal pro-inflammatory interventions such as oxygen, lung stretching or infection is still to be deciphered. Therefore, evaluating the consequences of resuscitation manoeuvres as a second inflammatory hit to the lung has become a matter of interest in recent years.

Using tidal volumes that would be considered adequate for a normal lung to initiate ventilation of the immature lung filled with fluid may cause lung injury secondary to overstretching [20–23, 60–62]. Indeed, administration of supraphysiological tidal volumes to immature lambs, even for short periods of time, inhibited the positive effect on lung mechanics of subsequently administered surfactant. However, disruption of lung mechanics was not accompanied by alterations in oxygen exchange, and paO_2 increased significantly in these animals [20–24]. Similar results were found for human infants given late rescue treatment of surfactant. There was no correlation between early improvement in oxygenation and lung volume changes [60]. These findings may be related to changes in ventilation-perfusion matching within the lung. Furthermore, newborn lungs with adequate surfactant content can be ventilated at high pressures (consequently large tidal volumes) at least for short time periods (10 min) with no undesired side effect, as the alveoli expand synchronously and the inspired gas is distributed uniformly in the parenchyma [63]. However, ventilation with high tidal volumes for very immature lungs at the end stage of the canalicular and beginning of the saccular phase, in the absence of sufficient surfactant in the alveolar surface and elasticity in the interstitium, will lead to

an uneven distribution of gas. Hence, some alveoli will alternatively overstretch (volutrauma) and collapse, while others will remain unexpanded (atelectotrauma). This result should be anticipated because the unventilated fetal lung with a high fluid content would not have time to recruit a sufficient number of alveoli that would approach the maximal lung volume [62, 64].

In addition to the physical injury to the immature lung, high-stretch ventilation using supranormal lung tidal volumes promotes the release of various inflammatory mediators into the alveolar space [65–68]. Among these inflammatory mediators, the pro-inflammatory cytokine tumour necrosis factor (TNF), which mediates CXC chemokine expression in models of lung inflammation, has received much attention, and its role remains controversial [69, 70]. Despite the strong evidence that TNF is able to influence the progression of pulmonary oedema by altering the function of epithelial and endothelial cells, the predicted net effects of TNF on pulmonary oedema formation are conflicting in the literature. Thus, TNF may either promote pulmonary oedema by increasing epithelial and endothelial permeability [71, 72] or oppose oedema by enhancing fluid re-absorption [73], depending on the differential signalling of TNF receptors, specifically p55 and p75. Both soluble TNF receptors, which are expressed by many different cell types such as alveolar, endothelial or epithelial cells, can signal through different intracellular pathways and may induce different cellular responses. For example, activation of p55 receptor favours high-stretch oedema formation, while p75 receptor activation may play an opposing role [74]. These results demonstrate a novel role for TNF signalling, specifically through the p55 receptor, in promoting high-stretch-induced pulmonary oedema, which is apparently independent of its effects on neutrophil recruitment. If confirmed, these findings could imply a novel therapeutic approach for high-stretch lung damage in the coming future by modulating the TNF-signalling pathway.

Clinical Interventions Meant to Reduce High-Stretch Damage to the Lung

Until a clear understanding of the intrinsic molecular mechanisms implicated in the development of inflammatory lung damage is achieved, some clinicians facing the necessity of ventilating ELBW infants have pursued the use of less aggressive and equally effective ventilation modalities.

CPAP was developed for infants with respiratory distress syndrome (RDS) by Gregory et al. [75] in 1971. How-

ever, since the introduction of surfactant and more efficient devices especially designed for mechanical ventilation of the newborn, the use of CPAP as primary therapy for RDS in preterm infants declined. Interestingly, CPAP has been again used as a first-choice therapy for neonatal RDS in recent years [59, 76–83].

CPAP is a technique of respiratory support that generates a continuous distending pressure to the lung and is delivered to spontaneously breathing infants with RDS or apnoea. Typically, a pressure of 4–8 cm H₂O is used to distend airways and alveoli, thus impeding lung collapse during expiration. Numerous advantages have been described in the use of CPAP. These include the improvement of lung volume expansion and the achievement of FRC. In addition, CPAP improves ventilation-perfusion matching while decreasing atelectasis and pulmonary vascular resistance, resulting in an improvement in oxygenation. Seemingly, the use of CPAP enhances the release of surfactant and helps maintain surfactant present on the alveolar surface. Of note, CPAP stabilizes the chest wall and dilates the airways. In doing so, it reduces inspiratory resistance, increases lung compliance, counteracts paradoxical movements and reduces thoraco-abdominal asynchrony of the chest wall. Consequentially, a larger tidal volume is possible for a given applied pressure and a lower inspiratory fraction of oxygen needed to attain adequate oxygenation, and therefore, the work of breathing could be substantially reduced [76–78]. However, there are some problems associated with the use of CPAP. Apparently, the incidence of air leak in the thoracic cavity (pneumothorax, pneumomediastinum, pneumopericardium) is increased, and there is a risk of overdistension in infants with adequate lung compliance. In addition, the use of CPAP does not allow the administration of prophylactic surfactant in the DR [76].

The question is whether it is possible to use early CPAP treatment in the DR for ELBW infants or ELGAN in an attempt to reduce acute complications associated with intubation, as well as long-term respiratory consequences of various types of trauma to the lung caused by mechanical ventilation. At birth, the lungs are unaerated and filled with fluid. Following delivery, aeration must occur to establish FRC. Commonly, ELGANs are not able to achieve FRC themselves. Either CPAP during spontaneous breathing or PEEP during ventilation helps establish FRC and improve oxygenation [77]. Finer et al. [49] randomized 104 ELBW infants of <28 weeks' gestation to CPAP/PEEP (n = 55) or no CPAP/PEEP (n = 49) in the DR during resuscitation immediately after delivery, avoiding routine intubation for surfactant administration. Al-

though most infants <24 weeks' gestation required intubation, Finer et al. demonstrated that over 50% of the infants in the experimental group were successfully randomized to CPAP in the DR. Other studies have confirmed the feasibility of using early CPAP in the DR in ELBW infants [26, 57–59]. Interestingly, in a recent randomized trial, combining early nasopharyngeal CPAP with sustained inflation to non-aggressively recruit the lung in ELBW infants immediately after birth was compared with the conventional approach of intubation [59]. The number of intubations at 72 h after birth and the number of doses of surfactant given were substantially reduced with less BPD developed in those ELBW infants treated with early CPAP compared to those with the conventional approach. To date, the CPAP or Intubation at Birth (COIN) Trial is the most extensive randomized, multicentre trial launched to compare the use of CPAP with early intubation in the DR [50]. In this study, 610 preterm infants born at 25 weeks' 0 days' to 28 weeks' 5 days' gestation who were able to breathe spontaneously at 5 min of age but still needed assistance, were assigned to either CPAP alone or intubation and ventilation [50]. CPAP was set at 8 cm H₂O, which is in the highest usual range in the DR. Of note is that there were no protocol requirements for the administration of surfactant for infants in either arm, and no specific extubation criteria. The rate of death or BPD at 36 weeks' gestation did not differ between both groups, although patients in the CPAP group needed less oxygen at 28 days after birth and had fewer days of ventilation. The CPAP group was associated with a greater incidence of pneumothorax, compared to those in the intubation group (9.1 vs. 3.0%, respectively; $p \leq 0.01$). As recently stated by Finer [84], although this study does not provide evidence of the superiority of CPAP over early surfactant, further studies will be needed to assess the best strategy for ventilation of ELGANs in the DR.

Oxygenation in the DR

Oxygen in the Fetal-to-Neonatal Transition

Fetuses have a partial pressure of oxygen of 15–25 mm Hg in the arterial blood [85], corresponding to an arterial oxygen saturation of approximately 50% [86, 87]. Several factors are important in the determination of oxygen content of the blood including oxygen saturation or binding with the haemoglobin. Importantly, these factors vary with gestational age of the fetus [88, 89].

Haemoglobin Concentration, Specifically the Concentration of Fetal Haemoglobin

Haemoglobin is the oxygen-carrying molecule in the blood, thus its concentration will affect the oxygen content of blood. Particularly, the haemoglobin concentration will increase when fetal hypoxia is present over a prolonged period. Conversely, in pathological conditions with fetal anaemia, such as fetal blood loss or haemolysis, the oxygen content of blood is greatly reduced. Further fetal haemoglobin (HbF), which has an increased oxygen-binding capacity with a left-shifted oxygen dissociation curve, constitutes the majority of haemoglobin and has physiological relevance for fetal growth and development under a low-oxygen (relatively hypoxic) environment. Indeed, ELBW infants have more than 90% of their red blood cells containing HbF [90].

Oxygen-Binding Capacity/Oxygen Dissociation Curve

Fetuses are growing and developing in a relatively hypoxic environment. To overcome such a disadvantageous condition, they produce HbF that can pick up the oxygen molecule from the maternal venous side (approximately 70% saturation) and deliver it to the target organs/tissues. HbF is composed of two α -chains and two γ -chains. The left-shifting of the oxygen dissociation curve of HbF indicates the increased binding between HbF and oxygen. This may be related to the decreased binding of 2, 3-diphosphoglycerate by HbF (γ -chains). Orzalesi and Hay [91] demonstrated that in whole blood, the *in vivo* effect of 2,3-diphosphoglycerate on the oxygen affinity of HbF was approximately 40% of that of adult Hb. Interestingly, the oxygen affinity of fetal blood decreases during gestation and depends on the relative proportions of adult Hb and HbF and on the level of red cell 2,3-diphosphoglycerate. However, Bard and Teasdale [90] showed that gestational age had no effect on 2,3-diphosphoglycerate levels and ΔpH between plasma and red cell. They therefore concluded that the decrease in fetal oxygen affinity as gestation progresses is related mainly to the increase in the amount of adult Hb, and the levels of 2,3-diphosphoglycerate or ΔpH between plasma and red cells are not a function of gestational age.

The Bohr Effect of HbF

The Bohr effect describes the reciprocal relationship between oxygen and acid reactive radicals in their interaction with haemoglobin. Kirschbaum [88] examined the Bohr effect over a range of saturation (10–87%) in human fetal blood samples and suggested that the difference in

the oxygen affinity to adult Hb and HbF was not attributable to differences between haemoglobin subtypes but to differences in the internal composition of erythrocytes. Thus, components that affect the proton content of erythrocytes, including CO₂, may influence oxygen-haemoglobin interaction.

After birth, the oxygen partial pressure rises to 50–80 mm Hg [87]. House et al. [92] showed that the mean arterial oxygen saturation was 59, 68, 82 and 90% at 1, 2, 5 and 15 min of life, respectively. For obvious reasons, depending on the concentration of oxygen being administered to the neonates, the degree and rate of the increase in oxygen saturation as well as the partial pressure of oxygen vary. The physiological importance of the degree and rate of increase in oxygen saturation during the transition from a low- to a high-oxygen environment is undetermined. Nonetheless, it is reasonable to 'smoothen' the transition in addition to the avoidance of excessive oxidative stress to the ELBW infants in this perinatal transition period.

Monitoring Oxygen Saturation in the First Minutes of Life

Rabi et al. [93], Kamlin et al. [94], and Mariani et al. [95] described the gradual increase in oxygen saturation measured by pulse oximetry in healthy neonates. Interestingly, in the study of Rabi et al. [93], infants delivered by caesarean section had 3% lower oxygen saturations and also took longer time to reach a stable oxygen saturation of $\geq 85\%$ when compared to infants delivered by vaginal delivery. Kamlin et al. [94] studied both term and preterm healthy infants ($n = 175$) who did not require resuscitation or supplementary oxygen. They reported that the median saturation at 5 min of life was 90 and 87% in term and preterm neonates, respectively. Furthermore, there was a significant gradient between the preductal and postductal oxygen saturations during the first 15 min of life, which was confirmed by the studies of Mariani et al. [95]. With regard to these changes in oxygen saturation after birth, Saugstad [96] commented that before initiating oxygen supplementation, care givers in the DR should be aware that median SpO₂ does not reach preductal levels of 90% until 5 min after cord clamping in vaginal deliveries. Moreover, in infants born by caesarean section and preterm infants, it may be delayed up to 2–3 min or even more in those infants in the lower range of normality to reach an SpO₂ of 90% or more [96].

Lowering Oxygen Concentrations

The transition from the fetal to neonatal life is associated with an increase in oxygenation and the inevitable

oxidative stress [96–100]. While the associated oxidative stress is a double-edged sword, the anti-oxidative capacity of the system plays an important role to facilitate the transition as well as to combat the potential oxidative stress induced injury. Indeed, the pro-oxidant state after birth may contribute to many metabolic and cellular functions of the neonate [101, 102]. Conversely, the compromised anti-oxidative capacity of the system may predispose to the occurrence of oxidative-stress-induced injury [103, 104]. Of note, the anti-oxidative system of the fetus matures late in gestation, and is especially compromised in ELBW infants [104]. Interestingly, these ELBW infants are at an increased risk of developing oxygen radical diseases of neonatology, including ROP, BPD, necrotizing enterocolitis (NEC) and IVH [105–107].

In order to avoid oxidative stress caused by excessive oxygen administration to the ELBW infant, several feasibility trials have been performed to prove whether resuscitation was possible using initial lower oxygen concentrations and titrating FiO₂ according to targeted values of SpO₂. Wang et al. [108] recently reported that the resuscitation of preterm neonates (24–31 weeks' gestation) with room air achieved a significantly lower oxygen saturation at 3 min of life than that when 100% oxygen was used (55 vs. 87%, respectively; $p < 0.05$) with no differences in neonatal mortality and morbidity. However, in a high percentage of cases FiO₂ had to be switched to 100% because infants did not meet targeted SpO₂. Escrig et al. [109] compared the effect of 30% oxygen used as initial FiO₂ in the resuscitation of ELBW infants (24–28 weeks' gestation) on the oxygen saturation with that when 90% oxygen was used. There was no difference in the minute-to-minute saturation where a stable oxygen saturation of 85% was reached by 5–7 min in both groups. Rabi et al. [110], in a study to compare the temporal changes in oxygen saturation in 106 preterm infants (mean gestational age of 29 weeks) using different oxygen administration strategies to target the oxygen saturation of 85–92% measured by pulse oximetry placed at the right wrist, confirmed the effectiveness of using a high starting oxygen concentration (100%).

The Neonatal Resuscitation Program and the International Liaison Committee on Resuscitation recently recommend the monitoring of oxygen saturation when preterm neonates need resuscitation and/or oxygen [111, 112]. The placement of pulse oximetry in ELBW infants is indeed feasible and provides useful information regarding the oxygenation of blood to guide the therapy, in addition to the understanding of the transition from fetal to neonatal life. While most studies were performed in

ELBW infants requiring resuscitation, it is essential to obtain normative data of the temporal profile of the oxygenation in blood. The trajectory of increasing oxygen saturation after birth in the non-resuscitated newborn infant would be the best available model to mimic during resuscitation.

When 100% or high oxygen concentration is being used to resuscitate ELBW infants, we believe that there may be an increased risk of injuries related to hyperoxia-induced oxidative stress. Indeed, Deulofeut et al. [113] reported that by avoiding hyperoxia, the short- and long-term outcomes of ELBW infants could be improved. Furthermore, in studies of term and near-term neonates, using 100% oxygen in the resuscitation has been associated with increased cardiac and renotubular damages [103] in addition to the increased oxidative stress shown in whole-blood markers (oxidized glutathione content) that persisted up to 28 days after birth [114]. In animal models of asphyxia, the increased oxidative stress has been related to impaired organ function and/or injury as in the heart, lung, brain, intestine, kidney, adrenal glands, and platelets [115–121]. Further, an epidemiological link between resuscitation with supplemental oxygen and childhood leukaemia has been suggested by Naumburg et al. [122] and Spector et al. [123]. Nonetheless, there is a lack of data on the effects of room air and oxygen in the resuscitation of preterm neonates.

However, some reports suggest that 100% re-oxygenation may be a beneficial therapy that was generally thought to be non-toxic and to have faster oxygen debt replenishment [124, 125], despite the greater oxidative stress. In the resuscitation of asphyxiated neonates, there is a delicate balance between oxidative-stress-related injury with the re-oxygenation/reperfusion process and persistent hypoxia/ischaemia damage. Resuscitation protocols using different oxygen concentrations may affect the balance between these two processes. While hyperoxic resuscitation exaggerates oxidative-stress-related injury and normoxic resuscitation may allow the continuation of anaerobic metabolism, both may result in more cellular damage/death. The oxidative-stress-related injury may be particularly important in ELBW infants who have a compromised anti-oxidant reserve system [99, 104]. The Neonatal Resuscitation Program and the International Liaison Committee on Resuscitation have indicated that there is insufficient evidence to specifically recommend an initial oxygen concentration for resuscitation of ELGANS; however, both adverted to the possible toxic effects of oxygen, especially in preterm infants, and recommended strict control of physical constants and

oxygenation [111, 112]. In recent years, the use of pulse oximetry as the guidance for the administration of supplemental oxygen has taken over the clinical evaluation of colour and has been encouraged [96].

Temperature Control in the DR

Tendency of the ELBW Infant to Hypothermia

ELBW infants experience limited capacity to control body temperature after birth. Moreover, low body temperature has been associated as an independent risk factor for mortality of preterm infants upon the admittance to the NICU [126].

In 1997, the World Health Organization provided the following definitions of normothermia and hypothermia for newborn infants [127]:

- Normal range: 36.5–37.5°C;
- Potential cold stress: 36.0–36.5°C; cause for concern;
- Moderate hypothermia: 32.0–36.0°C; danger, immediate warming of the infant, and
- Severe hypothermia: < 32.0°C; outlook grave, skilled care urgently needed.

The newborn infant exhibits an immature thermoregulation when compared to the older child or the adult. The difficulty in maintaining an adequate and stable core temperature is directly related to its gestational age and/or weight. Exhaustive studies performed by the group of researchers of Uppsala have described the peculiar physiological characteristics of the newborn infant which favour their thermal instability even under radiant heaters or incubators. Such characteristics include: (1) inability to shiver; (2) increased surface area to body weight ratio; and (3) extremely thin insulator subcutaneous tissue [128–133]. Of note, the heat loss by convection, evaporation and radiation usually far exceeds the heat production after birth. Thus, if measures are not promptly initiated to counteract this negative balance, body temperature will fall, independently of the environment temperature, during the first 12 h of life [128]. In addition, preterm infants are more prone than term infants to develop hypothermia, which is in part related to the thin subcutaneous fat for insulation to reduce heat loss. Moreover, preterm infants have less brown fat to produce heat and less glycogen store than term infants. The immature stratum corneum is relatively deficient in keratin content, resulting in an inadequate barrier to prevent large transepidermal heat and water losses soon after delivery. Further, preterm infants have an inefficient vascular control for thermoregulation [126].

Cold stress may negatively influence the physiology of fetal-to-neonatal transition. It has been shown that hypothermia can delay the initiation of spontaneous breathing and lead to respiratory distress and hypoxia [134, 135]. Hypothermia may also alter the circulatory changes which characterize adaptation from intra-uterine to extra-uterine environment, resulting in persistent pulmonary hypertension [136, 137]. Moreover, hypothermia causes negative metabolic effects such as hypoglycaemia [138–140] and metabolic acidosis [137], and impairs coagulation [141]. In infants with severe hypothermia, cold stress may lead to renal insufficiency, NEC and even death [138]. Recently, it has been shown that there is a relationship between reduced admission body temperature and both late-onset sepsis and in-hospital mortality [142].

In a study of the transepidermal water loss and heat exchange with the environment in relation with gestational age, Hammarlund et al. [129–131] found that preterm infants less than 30 weeks' gestation cared for in a humidity around 20% (that is present under the average radiant heater) continued to lose 20–75 g/m²/h of water by evaporation from the skin during the first day of life. This evaporative cooling effect equates to a heat loss of 13.3–50 W/m²/h. Thus, naked infants born before 28 weeks' gestation need 40°C in order to maintain a normal temperature in 20% ambient humidity, while increasing humidity to 60% can halve the evaporative losses.

Achievement of a Neutral Thermal Environment

A neutral thermal environment (NTE) is one in which standard metabolic rate or oxygen consumption is minimal. In an NTE, temperature regulation is exclusively achieved by non-evaporative physical processes [143]. Silverman et al. [144] were the first to show in a controlled study that thermal environment was important for the survival of preterm infants. They demonstrated that maintaining body temperature through the control of thermal environment during the first 5 days of life (Isolette temperature of 29 vs. 32°C, with relative humidity in both groups sets between 80–90% and resultant mean of the average axillary temperature 2.6°C higher in normothermic group) reduced mortality in low-birth-weight infants. Other clinical trials of preterm infants yielded similar observations [145].

Heat loss begins immediately after birth; therefore, caregivers in the DR should promptly intervene to reduce the risk of hypothermia. Hence, immediately after birth infants should be placed under radiant warmer and be wrapped and dried with warm cloths, especially the head.

These measures, which usually suffice in a term newborn, are insufficient for preterm infants, who inevitably lose heat in the DR and become hypothermic rapidly. Thus, admission temperature was <35°C in 40% of all infants born before 26 weeks' gestation within the United Kingdom and the Republic of Ireland during 1995 [1], and in 47% of preterm infants <1,500 g included in the 2002–2003 cohort of the Neonatal Research Network had less than 36°C at admission [8]. Different studies demonstrated that a convectively heated incubator was more efficient than an open radiant warmer in maintaining an NTE [146, 147], but placing a preterm newborn in an Isolette after delivery would make resuscitation manoeuvres difficult. Therefore, research was oriented towards the prevention of heat loss using wrappers of different materials. The first study in this area, reported by Baumgart et al. [148], compared the heat loss in classical warmer beds with plastic-walled chambers and that in thin, flexible and transparent plastic blankets aiming to diminish the infant's exposure to convective air currents. Interestingly, there was an important reduction in insensible water loss as well as a decreased radiant power demand in the group randomized to plastic blankets, suggesting that convection is an important factor influencing evaporation in neonates and this may be diminished by plastic wraps. Moreover, plastic blankets have shown to reduce metabolic derived heat loss; infants wrapped with plastic blankets had a substantial reduction in oxygen consumption and in heart rate [148, 149]. Seemingly efficacious, a series of different heat shields have been tested with variable success, such as plastic body hoods [150] or barriers made with another kind of material, like a semipermeable polyurethane membrane that allows free exchange of water and air [151]. Moreover, LeBlanc [152] showed that occlusive wraps made of polyethylene could transmit the long wavelength energy corresponding to radiant heat. Thereafter, several studies have demonstrated that polyethylene occlusive skin wrapping of the wet body applied immediately after birth diminished postnatal fall in temperature of very immature infants by reducing evaporative and convective heat loss [153, 154]. Theoretically, there is a risk of overheating ELBW infants when the polyethylene/polyurethane wraps are used. This may be of great concern to avoid hyperthermia (>38°C), especially in infants at risk of hypoxic-ischemic encephalopathy. Nonetheless, hyperthermia is an infrequent complication that may be reduced by the use of servocontrol thermoregulation during resuscitation [155].

In a recent Cochrane review, 6 interventions with 295 preterm infants randomized to different methods to pre-

vent hypothermia at birth were analysed [156]. It was concluded that plastic barriers were effective in newborns <28 weeks' gestation in the prevention of evaporative loss. In addition, thermal mattresses showed an equivalent effect in infants <1,500 g as that of plastic barriers. Additional measures, including the use of caps that had previously demonstrated to reduce heat exchange between head and ambient air, showed borderline effectiveness in reducing heat loss in the Cochrane review [156].

Delayed versus Early Cord Clamping

The optimal timing of cord clamping has not yet been established. However, delayed cord clamping may at least offer several theoretical advantages over early clamping of the cord, which has been postulated to put newly born infants at risk of hypovolaemic damage and iron loss, as well as of several blood disorders and type 2 diabetes, as a consequence of loss of haematopoietic stem cells or anaemia within the 6 first months of life [157–159]. On the contrary, delayed cord clamping may have possible complications resulting from overloading the neonatal blood volume, thus increasing the possibility of developing polycythaemia, respiratory distress or jaundice [160].

In a recent systematic review, researchers compared the effects of early (within 10 s after birth) versus delayed (after 3 or more minutes after birth or after the cord stopped pulsing) in 1,912 term neonates [161]. Delayed cord clamping was associated with an 80% reduction in the newborn's likelihood of being anaemic at 24–48 h and halved the risk of being anaemic at 2–3 months. However, the statistically significant differences between the two groups disappeared at 6 months. Moreover, haematological status as measured by haemoglobin, haematocrit or serum ferritin levels was improved in both short and long term. Interestingly, the risk of developing jaundice, respiratory distress, or admittance to the NICU was not increased [161]. Interestingly, although polycythaemia was more frequent in the delayed group, no physical signs were evident, and thus these infants did not require exchange transfusion [161]. Hutton and Hassan [161] concluded that delaying clamping of the umbilical cord in term neonates for a minimum of 2 min following birth is beneficial to the newborn, extending into infancy.

In the preterm infant, especially in the ELGAN, delaying cord clamping has some additional difficulties because the infant is immediately handed to the clinician to initiate resuscitation. However, in a recent systematic

meta-analysis of randomized trials including 454 infants below 37 weeks' gestation with delayed (30 s or more) or immediate (less than 20 s) cord clamping, it was concluded that delaying clamping for 30 s was a safe procedure, and offered major benefits with the reduction in blood transfusions and the incidence of IVH [162].

Conclusions

It is becoming more and more evident that medical interventions aiding ELBW infants to achieving a successful transition into the extra-uterine world is not exempt from short- and long-lasting complications. The use of excessive pressure or volume (overstretching) and oxidative aggression (reactive oxygen and nitrogen species) may cause acute damage to the lung and other organs. Moreover, it may induce structural modifications that will reduce functional capacity and promote chronic illness in the adult life. ELGANs are at a high risk of hypothermia and its deleterious consequences in the DR and during transport to the NICU; avoidance of cold stress should be emphasized. Delayed cord clamping for at least 30 s is a safe procedure and has apparently no negative effects.

We conclude that available technology may, in the near future, enable individualization of ventilatory and oxygenation needs, thus minimizing physical and oxygen-derived damage. In addition, cold stress can be avoided with a strict control of the infant's temperature. Achievement of these goals requires implementation of the concept of 'delivery room intensive care unit' (DRICU). The DRICU would provide the high-risk neonate with updated technology, as well as with highly qualified personnel, that can perform the optimal resuscitation at all times, thus improving the chance of a morbidity-free survival.

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