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Review

Pulmonary insufficiency of extreme prematurity (PIEP) and surfactant deficiency disease (SDD) – It is time to classify respiratory distress syndrome (RDS) in preterm neonates

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Abstract

Respiratory distress in premature neonates is the consequence of various pathophysiologic conditions.

The respiratory distress syndrome (RDS) is commonly considered as the consequence of pulmonary surfactant deficiency; these babies generally respond well to exogenous surfactant.

In extremely premature babies, overall physiological immaturity of the lungs secondary to prematurity itself plays a significant role in respiratory illness; the therapeutic response to continuous airway distending pressure or surfactant is not very impressive in these babies, who continue to need an extended period of respiratory support and eventually end up in developing bronchopulmonary dysplasia.

This article aims to highlight the importance of the difference between primary surfactant deficiency disease (SDD) and pulmonary insufficiency of extreme prematurity (PIEP).

This classification may help in drawing up more appropriate treatment plans and reduce the gestation-related skewed outcomes in future research.

Keywords

Respiratory distress syndrome, surfactant deficiency disease, pulmonary insufficiency of extreme prematurity, preterm, neonates.

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Introduction

Respiratory distress syndrome (RDS) is a common diagnosis in neonatology. Lower gestational age carries an increased risk of mortality and morbidity [1, 2]. Identification of the cause of respiratory distress is crucial for the diagnosis, appropriate management, and a favourable outcome.

Respiratory distress *per se* is the consequence of various pathophysiologic conditions in premature newborns.

The commonest one is pulmonary surfactant deficiency [3]; these babies respond well to surfactant, which improves alveolar recruitment and gas exchange [4].

In extremely premature babies, the respiratory distress is due to overall physiological immaturity (pulmonary insufficiency) of the lungs; the therapeutic response to continuous airway distending pressure or surfactant is generally insufficient and they need an extended period of respiratory support [5].

Unless one recognizes these two conditions as different clinical entities, clinicians continue to "manage" all cases of RDS with a mix and match of therapeutic options and the research outcomes will be greatly influenced by the gestational skew of the study population.

In the subsequent sections, we have attempted to make a distinction between pulmonary insufficiency of extreme prematurity (PIEP) and surfactant deficiency disease (SDD) based on available literature.

Anatomical and physiological aspects

The development of the lung in the fetus is a continuum of anatomical growth and physiological maturity, which continues for a couple of years even after birth. It is important to note that embryologically (**Fig. 1**), the lungs attain a certain level of maturity for adequate

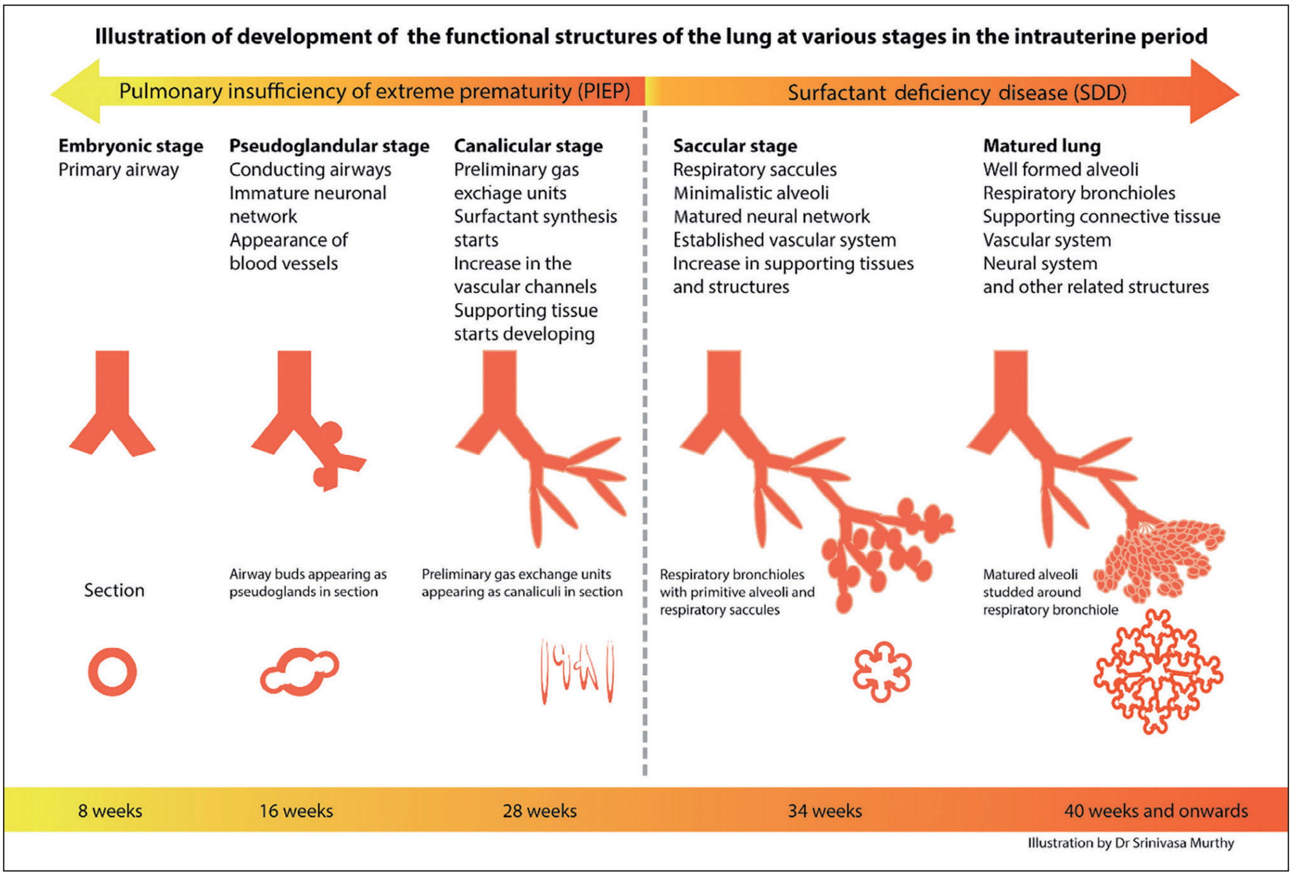

Figure 1. Development of functional structures of the lung at various stages in the intrauterine period.

exchange at around 28 weeks of gestation. Developmentally, lung histology of extreme premies is limited to the canalicular stage. There are neither differentiated gas-exchanging structures for functioning nor supporting structures for anatomical resilience. This extreme immaturity of the lung leads to precarious physiologic function and exponentially increased vulnerability to iatrogenic injury. This contrasts with babies born after 28 weeks of gestation. Saccules in their lung tissue are sufficiently differentiated to take part in gas exchange. The blood vessels are developed to perfuse the ventilated areas and actively contribute to the gas exchange. A similar finding in an animal model is explained by Fu et al. [6]. An extensive review of human lung development is presented by Laudy and Wladimiroff [7].

Therapeutic response

The ability of the immature lung to sustain adequate gas exchange with respiratory support is the primary limiting factor that determines the survival of premature babies. The severity of the pulmonary illness is generally assessed from clinical and radiological observation. Quantification of response to treatment has emerged as another interesting approach in recent times [8, 9]. The requirement of oxygen in Downes' score was the first one with this approach [10]. Other assessment tools include gasometrical analysis, oxygenation index, arterial alveolar oxygen difference, PaO_2:FiO_2 ratio, etc. The recent addition is the saturation oxygen pressure index (SOPI) validated for use in babies on continuous positive airway pressure (CPAP) support [11].

From a perspective of respiratory support, extremely premature babies (< 28 weeks) have increased needs compared to their more mature counterparts. This emanates from structural, histological, and functional immaturity, which are more profound than mere deficiency of surfactant. The need for long-term positive pressure ventilation (PPV) rather than continuous airway distending pressure alone, despite surfactant administration, stands out as the hallmark of PIEP. Added to this, the therapeutic response for respiratory support is less predictable, increases therapy-related complications, and has less favorable pulmonary and non-pulmonary outcomes [5].

Gestation-related respiratory issues and other outcomes

Below is the analysis derived from the data published in various scientific papers in the last decade (**Tab. 1**) [12-15]. The gestational age of 28 weeks stands out as an inflection point beyond which both pulmonary and general outcome improves significantly. The need for intubation at birth and the use of surfactant in babies born at less than 28 weeks of gestation has always been high with odds stacked against them. The same trend continues despite the best of the treatment available for these babies and is shown as a high odds ratio (OR) with respect to chronic lung disease and death. This makes the extremely premature babies a unique and vulnerable group with respect to their respiratory illness, which is more of overall lung immaturity rather than surfactant deficiency alone. Other associated morbidities such as sepsis, necrotizing enterocolitis and intraventricular hemorrhage follow a similar trend [16, 17]. However, for the sake of keeping this discourse focused they are not discussed in detail.

Table 1. Gestation-associated need for respiratory support and outcome in various studies.

	NICHD, 2010 [12]	NICHD, 2016 [13]	EPIPAGE-2, 2017 [14]	CNN, 2020 [15]
PPV < 28 weeks of GA	75.4%	57.1%	-	57.1%
PPV > 28 weeks of GA	47.0%	10.0%	-	18.7%
OR – PPV	**3.5**	**12**	**-**	**5.78**
Surf < 28 weeks of GA	81.0%	-	89.0%	77.8%
Surf > 28 weeks of GA	65.0%	-	42.6%	30.3%
OR – Surf	**2.3**	**-**	**10.9**	**8.06**
BPD < 28 weeks of GA	55.0%	44.3%	20.7%	69.3%
BPD > 28 weeks of GA	23.0%	11.2%	4.6%	34.6%
OR – BPD	**4.1**	**6.3**	**5.4**	**4.3**
Death < 28 weeks of GA	35.0%	18.2%	35.2%	19.0%
Death > 28 weeks of GA	8.0%	1.2%	1.1%	1.6%
OR – Death	**6.2**	**18.3**	**48.8**	**14.4**

BPD: bronchopulmonary dysplasia; CNN: Canadian Neonatal Network; EPIPAGE-2: Epidemiological study on small gestational ages; GA: gestational age; NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development; OR: odds ratio; PPV: positive pressure ventilation; Surf: surfactant. The data in this table is consolidated from the elaborative tables of the corresponding studies.

Treatment challenges

The action of surfactant is to reduce surface tension at the alveolar level. For an immature lung in the canalicular stage, the surfactant may not make much difference as the high surface tension at the air-fluid interface is just non-existent.

Application of higher driving pressure to the lung fails to yield good results as the respiratory membrane is not developed and canaliculi are poorly perfused. The immaturity of the respiratory center resulting in prolonged periods of apnea further complicates the picture. The brain chemoreceptors do not respond to changes in the oxygen or carbon dioxide in the blood appropriately. The challenges posed by these features are overwhelming for both the neonate and the treating physician. Unlike SDD, in PIEP, the therapeutic measures become more and more idiosyncratic. The combination of the tailored therapeutic approach and variable response for the same by the neonate makes it hard to compare this group with those with SDD, who have a more predictable response to a protocolized management plan.

This necessitates distinct categorization of these extremely premature neonates with respect to respiratory pathophysiology, respiratory management, research, and resource allocation. This reclassification can help in a focused approach, which would eventually translate into better clinical outcomes and research opportunities.

Pulmonary insufficiency of extreme prematurity

PIEP is a condition characterized by impaired gas exchange at the lungs due to the underdevelopment of all the necessary structures, such as the airway, air receptacles, blood vessels, and supportive neural and connective tissue. Neonates born before 28 weeks of gestation generally fall into this category. The severity is inversely proportional to the gestation. These babies are either born apnoeic or with significant chest retraction and grunting. The respiratory distress is severe, with either Downes' score > 4. These babies respond poorly to CPAP and need PPV for some period. On CPAP, they rapidly deteriorate and their SOPI increases to > 1.6 within a few hours of birth, needing escalation of respiratory support. Response to surfactant is only marginal. The dramatic and sustained response to exogenous surfactant seen in surfactant deficiency goes against this diagnosis. The chest X-ray can show a complete white-out picture due to the absence of air secondary to underdeveloped lungs. Conversely, the lung parenchyma can be very minimal, and only airways show up on chest X-ray, resulting in a small volume but "normal" looking lung. Hypoxia with mixed acidosis on blood gas analysis and significantly elevated right ventricular systolic pressure on Echo are common features. They will need a prolonged duration of ventilatory support despite surfactant administration. These neonates, unfortunately, have a higher risk of developing pneumothorax, pulmonary hemorrhage, and chronic lung disease.

Surfactant deficiency disease

In contrast to PIEP, SDD is typically seen in babies born after 28 weeks of gestation. The initial Downes' score may not be different from those with PIEP. These neonates respond well to CPAP support. A small proportion of these babies can progress with SOPI reaching 1.6 over the next few hours, requiring surfactant administration and mechanical ventilation for a brief period of 24 to 48 hours. Chest X-ray is typical of RDS, with a ground glass appearance and air bronchogram. Blood gas analysis is either normal or shows mild hypercapnia. An echo shows normal to mildly elevated right ventricular pressures for the age. Surfactant administration has an impressive effect, which results in the de-escalation of respiratory support within a couple of days. Complications such as pneumothorax, pulmonary hemorrhage, and chronic lung disease are minimal.

Discussion

The immature lungs can be supported in many ways, including surfactant, CPAP, non-invasive ventilation, conventional mechanical ventilation (CMV), and high-frequency ventilation. The treating clinicians generally use an appropriate combination of all these modalities available to successfully support premature babies.

It has been consistently shown that the outcomes improve with increasing gestation. As the gestation increases, the maturity of the lung improves and so its ability to successfully exchange gas with different modes of respiratory support provided. Response to surfactant and success rate of CPAP in babies born after 28 weeks compared to those born earlier has been impressive. As a result, studies have unambiguously demonstrated better overall outcomes in babies born after 28 weeks of gestation compared to those born before 28 weeks.

The developmental maturity of preterm babies depends primarily on gestational age. Birth weight is one of the attributes which is partly dependent on gestation. Hence, the studies that have reported outcomes based on gestational age at birth are more relevant for this discussion rather than birth weight *per se*. A detailed study by EPIBEL (Extremely Preterm Infants in Belgium) [18] team on babies less than 26 weeks of gestation reported the need for mechanical ventilation to be above 90%, three-fourths of them needed surfactant, and two-thirds of them had air leaks, and the survival rate varied from zero to 54%. A recently published MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) report [19] describes a mortality of 46% in preemies born before 28 weeks of gestation compared to 28.9% otherwise (OR of 2.1).

A better insight into this issue can be obtained from the data published by the Canadian Neonatal Network™ *Annual Report 2010* [5]. More than 40% of babies less than 30 weeks needed endotracheal intubation and resuscitation at birth. This rate was inversely proportional to the gestational age, and more than 75% needed endotracheal tube insertion for resuscitation at birth if the gestational age was less than 26 weeks. This rate was reduced to < 20% if the gestational age was greater than 31 weeks. Definitive RDS was diagnosed in more than 80% of babies born at gestation less than 30 weeks. Though there has been an enormous improvement in the management of extreme preemies in the last decade, this difference still exists.

We suggest that PIEP should be differentiated from SDD and considered as a clinical diagnosis at birth. This could help in drawing up appropriate treatment protocols, providing better care, and facilitating more refined research in the future.

A neonate born after 28 weeks of completed gestation with respiratory distress that responds promptly to continuous distending pressure/surfactant and does not need a driving pressure (invasive or non-invasive PPV) respiratory support following initial improvement can be categorized as having SDD. De Luca et al. have used similar criteria for neonatal RDS, to exclude babies for their definition of neonatal acute RDS, which is due to lung injury from various causes [20]. A neonate who is born at less than 28 weeks of gestation and requires driving pressure support (CMV or nasal intermittent positive pressure ventilation [NIPPV] or high-frequency oscillatory ventilation [HFOV]) despite surfactant administration can be considered to have PIEP.

The term “lung immaturity” is not limited to alveoli and hence using this term as synonymous with “surfactant deficiency” should be avoided. Pulmonary immaturity is a spectrum and includes the whole of the lung as an organ, be it cartilage, smooth muscle, blood vessels, or endothelial lining. Surfactant deficiency is on the favourable end of this spectrum, where respiratory units are formed but remain collapsed due to deficiency of surfactant. PIEP, on the other hand, falls on the non-favourable side of the spectrum, as it involves structural and functional immaturity of all the components, such as smooth muscles, cartilage, blood vessels, etc.

One of the points we have discussed earlier, which may come under intense discussion among neonatologists, is the gestational age at which PIEP should be considered. Pathophysiology of the lung in preterm is a continuum, and hence introducing a binary perspective is very difficult and tricky. As noted earlier, we have zeroed in on 28 weeks, as there are a good number of available literature suggesting this could be the inflection point. However, as neonatal care is advancing every day, it may be revised in the future.

Declaration of interest

The Authors declare that there is no conflict of interest. Funding source: self-funded.

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