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Review

Hyaline membrane disease or respiratory distress syndrome? A new approach for an old disease

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Proceedings

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The role of the clinical pathological dialogue in problem solving
Guest Editors: Gavino Faa, Vassilios Fanos, Peter Van Eyken

Abstract

The term "hyaline membrane disease" refers to the histological aspect of the most frequent pulmonary pathology in preterm newborn patients. The lung of the preterm baby is morphologically and functionally immature. Surfactant deficiency in the immature lungs causes alveolar instability and collapse, capillary edema and the formation of hyaline membrane. Thus, the hyaline membranes are epiphenomena and are not the cause of respiratory failure in infants with immature lungs. This definition is presently used to indicate surfactant deficit alone and should not be used for other causes of respiratory distress. Clinicians prefer to talk of "respiratory distress syndrome" (RDS).

Improvement in neonatal treatment has changed the natural course of the illness, its clinical and radiological features and has enabled extremely low birth weight newborns (ELBW) to survive. Alveoli paucity and pulmonary interstitial thickness in ELBW impair gas exchange and may necessitate prolonged ventilation treatment, increasing the risk of ventilator-induced lung injury (VILI) and bronchopulmonary dysplasia (BPD). RDS, therefore, is a complex illness where pulmonary immaturity and surfactant deficit play a role together with other pathological conditions that determine the course of the illness and both short and long-term results.

Keywords

Continuous positive airway pressure, hyaline membrane disease, mechanical ventilation, preterm infant, respiratory distress syndrome, surfactant therapy.

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Introduction

Respiratory distress syndrome (RDS) is the primary cause of mortality and morbidity in preterm newborns. Rate and degree are related to the gestational age (GA) and weight of the newborn baby.

EuroNeoStat Annual Report for Very Low Gestational Age Infants 2010 indicates a rate of 92% for RDS in newborn babies with a GA of 24-25 weeks, 88% at 26-27 weeks, 76% at 28-29 weeks and 57% at 30-31 weeks [1]. Other risk factors can derive from maternal diabetes and perinatal asphyxia and can frequently be complicated by other pulmonary and extra-pulmonary pathologies (pneumonia, patent ductus arteriosus, extra-pulmonary area collection, pulmonary hypertension and pulmonary hemorrhage). RDS risk variability in the various races, ethnic groups, and mono or hetero zygotic twins have suggested genetic causes. Mutations and variations of the genes that directly codify the production and the structure of surfactant or that contribute to the regulation of pulmonary development of the inflammatory response might be risk factors for the development of RDS [2].

Pathological features

Surfactant deficit and immature lung structure with reduced alveolization and excess connective tissue matrix produce alveolar instability, collapse, capillary leak edema, alveoli necrosis, inflammation up to the hyaline membrane that invade the bronchial terminals and the alveoli ducts.

Thus, hyaline membranes are epiphenomena and not the cause of respiratory insufficiency in newborns with immature lungs and may classify a variety of primary bronchial damage. Delayed pulmonary fluid absorption, a great permeability of alveoli epithelium to the plasmatic proteins and inefficient cardio-pulmonary transition also condition surfactant synthesis and function.

RDS physiopathology is characterized by alterations in the pulmonary mechanism (low compliance, reduced capacity functional residue (CFR) with alveolar instability and an irregular tendency to collapse, atelectasis, acidosis and hypoxia. The work of breathing is aggravated by the reduced flow volume for pulmonary hypo-expansions, and increase of the dead space.

Clinical symptoms are tachypnea, grunting, intercostals and epigastrium retraction, apnea, cyanosis and severe breathing insufficiency. According to Vermont Oxford Network Neonatal a newborn is affected by RDS if it has a PaO_2 < 50 mmHg (< 6.6 KPa) in room air, central cyanosis in room air or requires supplementary oxygen to maintain PaO_2 > 50 mmHg (> 6.6 KPa) [3] and has typical radiographic alterations. The "reticulogranular" texture of the lung opacities, decreased lung expansion, symmetric generalized consolidation of variable severity, effacement of normal pulmonary vessels, air bronchograms up to dense, bilateral symmetric lung consolidation (the so-called white out) completely effacing the cardio-mediastinal and diaphragm contours are rare; instead it is more frequently a framework respiratory better than expected. Increasingly infants of extremely low weight despite immaturity and incomplete lung development are able to survive with little aggressive ventilatory support.

The fetal and neonatal adaptation phenomena defined as developmental plasticity are influenced by prenatal steroid treatment and by fetal exposure to inflammation [4]. The role of glucocorticoids in lung growth is therefore enigmatic: they alter normal alveolarization, but promote the structural maturation through the thinning of the mesenchyme and induce pulmonary surfactant production through increased biosynthesis of phosphatidylcholine. Actually, glucocorticoids and inflammation seem able to modulate lung maturation both positively (inducing growth/maturation) and negatively (a predisposition to asthma and bronchopulmonary dysplasia [BPD]).

Advances in clinical management of respiratory distress syndrome

Despite the increase in preterm births, also in relation to the phenomena of multiple pregnancies, the elaboration of global assistance strategies other than the administration of surfactant, have reduced the rate and degree/severity of RDS also modifying the extent of short and long-term results [5].

The change in some obstetrician's approaches (antibiotics during prolonged rupture of membranes [PROM], administration of progesterone, magnesium sulfate and tocolitics) and neonatal well-being/welfare evaluation improvements enable better births for these infants. The antenatal use of antibiotics aims at reducing the chorioamnionitis-induced inflammation; however, this procedure demonstrates marginal benefits, moreover the possibility of worsening the neuro-developmental outcome must be taken into account. IL-1, IL-6, IL-8, TGF-beta, VEGF and TNF-alpha appear to play a crucial role in this condition.

Prenatal administration of steroids (betametasone) in all pregnancies < 34 weeks GA, significantly reduces neonatal mortality [6] without adverse maternal effects and with minimal short-term fetal effects and carries out a protective action from 24 subsequent hours up to one week from administration [7]. At birth establishing the vital parameters [8], plus other helpful methods such as delayed clamping of the umbilical cord [9], control of the ambient air and newborn's temperature [10], heating and humidification of the gases [11], pulse-ox preductal target above or equal to 85% at 10 minutes from birth [12] can greatly affect neonatal outcome.

Generally speaking a careful pulse-ox/saturation control while in intensive care unit can reduce the risk of ROP and, although to a lesser extent, also of BPD [13]; avoiding values that are too low and seem to be connected to a higher mortality rate it is wise to maintain saturation targets from 90 to 95% and avoid SaO_2 fluctuations in the post-natal period, particularly in newborn babies of less than 27 gestational weeks [14]. In actual fact, the greater part of < 32 week GA newborn babies, in the case of spontaneous respiration, may be continuous positive airway pressure (CPAP) assisted with 21-30% FiO_2 leaving the use of greater oxygen concentrates to persistent bradycardia and hypoxia. Only large multi-centre studies on short-term and long-term results will be able to assist in the best approach.

At birth few premature babies require intubation [15] although the reduced residual functional capacity and the irregular alveoli recruitment require an efficient and soft stabilization strategy. Controlled flow volumes are given and in the case of peak inspiratory pressure (PIP) on patients with apnea always using end expiration pressure and minimum and controlled inspiration pressure to avoid lung damage.

At present the administration of CPAP, precocious and controlled, represents the best approach for stabilizing the premature newborn babies at birth [16] and reduces the need for mechanical ventilation (MV) and surfactant treatment. A more rapid alveoli recruitment would be possible and an adequate flow volume by combining the use of constant and controlled positive end-expiratory pressure (PEEP) to the administration of a single inflation of approximately 25 cmH_2O for 15 seconds (sustained lung inflation [SLI]) [17, 18].

Substitute therapy with surfactant

When necessary, the use of surfactant is to be timely and possibly followed by non-invasive ventilation (NIV) [19, 20] so as to reduce the risks of mortality and short and long-term morbidity. Surfactant, preferably natural, is administered to all newborn patients under 26 weeks GA with $FiO_2 > 0.30$ and those over a GA of 26 weeks with $FiO_2 > 0.40$ [21]. Dosage for preventive purposes is to be at least 100 mg/kg, although clinical and pharmacokinetic data indicate 200 mg/kg as ideal [22].

Early administration using INSURE (INtubate – SURfactant – Extubate to CPAP) technique reduces the need for MV and subsequent BPD. Administration of multiple doses is more efficient with respect to a sole administration in terms of mortality and air leak [23-25].

Inter-tracheal administration may also be with inter-tracheal sounding tube (less invasive surfactant administration [LISA]) for those patients in spontaneous breathing sustained by CPAP throughout administration, totally avoiding intubation and PIP ventilation [26]; but this technique is still experimental and does not seem to have any particular effect on the long-term prognosis. The administration of surfactant by means of nebulizers [27] and surfactants containing budesonide are still under study for early prevention of BPD [28].

Non-invasive ventilation

The use of early nasal CPAP at birth (ENCPAP) is able to stabilize the pulmonary volumes [29, 30] and to favour reabsorption of the pulmonary fluid and thus it should be applied to all < 30 weeks GA newborn patients at risk for RDS [31]; the procedure would reduce the need for intubation, highly intensive treatment and results would be less harmful for the lungs. One every 25 newborns

treated with ENCPAP, without intubation and MV does not develop BPD [32, 33].

Unfortunately ENCPAP is aggravated by a remarkable failure rate (50%) in low GA newborn and low birth weight babies where steroids are or not administered in the prenatal phase [34, 35]. In these cases, although accepting relatively high CO_2 (permissive hypercapnia) and high end expiration pressure, but not haemo-dynamically dangerous, the use of MV becomes inevitable.

At present predictive factors in ENCPAP failure are suggested as being the need to reanimate with $FiO_2 > 0.30$, a CPAP pressure of 6.4 (± 1.2) cm H_2O, the need for FiO_2 of 0.40 in the first four hours of life (0.30 if < 26 weeks), and clinical situations requiring the use of surfactant.

In alternative to CPAP other NIV methods can be taken into consideration. In particular nasal intermittent positive pressure ventilation (NIPPV) seems particularly valid in treating some apneas and in problematic weaning. Less certain results exist on the validity of nasal synchronization.

Mechanical ventilation

The scope of MV (conventional, synchronized to volumetric target or high frequency oscillatory ventilation [HFOV]) [36, 37] is to supply an adequate correction of the blood gases with minimum pulmonary risk and to stabilize pulmonary volume without creating hemodynamic alterations or other side effects. In this moment there is not method of ventilation without risk of lung injury. Short-term pulmonary damage essentially related to air leak (pneumothorax, interstitial emphysema, pneumomediastin) plays an important role in the development of long-term complications (BPD).

PEEP should be increased based on oxygenation, CO_2 levels, lung function, and hemodynamic response of the patient thereby avoiding hypo or pulmonary hyperinflation.

Hypocapnia should always be avoided as associated to BPD and peri-ventricular leucomalacia [38]. During guaranteed MV flow volume the utmost attention has to be paid to the flow volume (4-5 ml/kg) that tends to increase particularly in tiny babies as the weeks go by. Removal of the endo-tracheal tube is to be sought whenever possible [39] avoiding MV being maintained at minimum parameters for too long. There are clear correlations between MV duration and BPD [40] or neurological complications.

A number of strategies exist to increase NIV success or removal of endo-tracheal tube such as precocious administration of caffeine during MV [41], use of hypercapnia and the use of low dose desametasone (< 0.2 mg/kg/day) or very low (0.05 mg/kg/day) in babies under MV after 1-2 weeks from birth [42-44]. Many centres use hydrocortisone that has less side-effects [45].

Other paramount aspects in global approach strategy for RDS are neonatal care (Kangaroo mother care, temperature control, posture control and pain control), treatment of bacterial infections, anti-mycosis preventive medicine, anemia control, "forced" nutrition and moderate water restriction particularly in ELBW [46-48]. Hypoperfusion and hypotension are not strictly connected, particularly in the first 3 days after birth owing to transition circulation. Cerebral blood flow measurements are similar in well hypotensive compared to normotensive ELBW. The ideal blood pressure is not known and many clinicians aim to maintain the mean arterial pressure above the GA in weeks. In actual fact when hypotension determines a hypoperfusion needs to be treated [49]. During RDS, hypoperfusion and hypotension are related to hypovolemy, owing to flow subtraction on the part of a large duct, or left-to-right atrial shunt or to a myocardial malfunction: in this case a functional bed-side echocardiography may prove useful.

In the case of hypovolemy or where the particular case is unclear, fluid expansion is required with small bolus of physiologic solution. Dopamine is more valid than dobutamine in treating hypotension in preterm newborn, as concerns short-term outcome although dobutamine may be a more rational choice in cases of myocardial malfunction and low systemic blood flow. Where there is no response or it is partial, epinephrine or hydrocortisone may be used [50].

Milrinone does not seem to improve perfusion in preterm babies. Cyclooxygenasis inhibitors (indomethacin or ibuprofen) are to be considered for the PDA closure when perfusion is poor, an ample shunt from left to right and a baby whose weaning from the respiratory support is problematic. Preventive indomethacin treatment reduces patent ductus arteriosus PDA and inter-ventricular hemorrhage, but there is no difference in long-term outcome. Indomethacin and ibuprofen are equally valid, although ibuprofen has less side-effects and may be administered orally while surgical ligature seems correlated to more severe side-effects [51, 52].

Several large randomized controlled studies of inhaled nitric oxide in preterm babies with respiratory distress, hypoxic respiratory failure or early evolving BPD have failed to demonstrate clear benefits in terms of survival or reduced BPD [53, 54]. Until further studies have been performed, inhaled nitric oxide cannot be recommended for the prevention of BPD in preterm infants.

For technical reasons ECMO treatment can only be used on > 34 weeks GA patients and a weight > 2,000 g.

Conclusions

Advances in perinatal medicine and neonatology have altered the natural history of lung disease in premature newborns, while introducing a new era of radiologic and clinical complexity. There are still many points under debate with regard to pulmonary development/growth mechanism in fetal life and the newborn patients but a lot has already been learnt. Organ development and plasticity during the fetal stage and in newborn babies may increase the chances of survival in "miracle babies" but the extremely high costs and the biological aspects that enable these babies to survive are still being investigated. Only a correct and global approach not forgetting knowledge on the impact of neonatal treatment, may reduce the rate of BPD.

Declaration of interest

The Authors declare that there is no conflict of interest.

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