

Establishing the entity of neonatal acute respiratory distress syndrome

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Contemporary definitions for acute respiratory distress syndrome (ARDS) including the Berlin definition in adults and the Pediatric Acute Lung Injury Consensus Conference (PALICC) definition in children exclude perinatal lung diseases and newborns in general (1,2). This is based on the assumption that newborns frequently develop acute hypoxemic respiratory failure due to conditions such as respiratory distress syndrome (RDS) and transient tachypnea of the newborn which differ patho-physiologically from ARDS. Since the treatment of these perinatal conditions and prognosis differ, it is prudent not to label them as ARDS. However, direct and indirect ARDS do occur in a subset of term and preterm neonates (3). A neonatal ARDS definition is thus justified to increase awareness of a common ARDS spectrum amongst different intensive care disciplines, facilitate research on this condition and the use of specific ARDS therapies for these patients.

De Luca *et al.* published a position paper with the main purpose of characterizing and defining neonatal ARDS (4). The group reviewed the literature to demonstrate the existence of neonatal ARDS, describe the similarities to pediatric and adult ARDS in biological and pathophysiological aspects and its necessity to guide therapeutic choices. This Montreux definition has similarities with the PALICC definition for pediatric ARDS in that it contains the same 5 criteria: (I) timing of injury; (II) risk factors; (III) lung imaging; (IV) exclusion of a

cardiac origin of edema; (V) oxygenation criteria by the oxygenation index (OI).

Unique factors of the Montreux definition are the inclusion of patients from birth to 4 weeks of age or 44 weeks' post-menstrual age regardless of gestational age or birth weight. It includes risk factors such as meconium aspiration syndrome (MAS), congenital pneumonias and perinatal asphyxia which are exclusively diseases of the newborn. RDS and transient tachypnea of the newborn are explicitly excluded, as are congenital malformations that affect the respiratory function. The Montreux definition also takes into account the effects of fetal hemoglobin and transfusion (adult hemoglobin) on the oxygen dissociation curve that may result in unpredictable oxygen saturation and partial pressure of arterial oxygen correlation. As such, the authors have proposed that pulse oximetry readings used to calculate oxygen saturation index or oxygen saturation to fractionated of inspired oxygen (FiO₂) ratio, not be used to evaluate oxygenation in neonates. As obtaining arterial blood gas might not be possible in all occasions, they have also proposed using transcutaneous arterial oxygen tension in place of arterial values when calculating OI.

The Montreux definition for neonatal ARDS is a step forward in recognizing the existence of ARDS in newborns. The strength of this definition is the detailed consideration of newborn/transition physiology. However, there remains some uncertainty on the applicability of this definition. The

first issue relates to the impact of arrested lung development in the extreme premature population, the so called “new bronchopulmonary dysplasia (BPD)”. Abnormalities of the lung microstructure including reduced and simplified alveolar structures, disrupted alveolar vasculature and fibroproliferation contribute to impaired oxygen diffusion which do not follow the usual trajectory expected in inflammatory ARDS with protein exudation (5).

Secondly, the preterm/newborn lungs are exquisitely susceptible to oxidative stress and any form of mechanical ventilation (6,7). Exposure to high FiO₂ concentration even for short periods can cause epithelial and endothelial necrosis by direct oxidative cell damage through production of reactive oxygen species, accumulation of inflammatory mediators (interleukins (IL)-1, -6, -8, transforming growth factor- β , tumor necrosis factor- α) and disordered vascular development (mediated by vascular endothelial growth factor and angiopoietins) within the lungs (6,8,9). Expressions of antioxidant enzymes in newborn lungs were demonstrated to be lower than in the developed lungs (7). The effects of mechanical ventilation are illustrated by a study in late-preterm infants showing that a short period (2 hours) of mechanical ventilation was sufficient to cause an imbalance of plasma cytokines (10). Tracheobronchial aspirate fluid in preterm neonates demonstrated increased levels and enhanced mRNA expression of pro-inflammatory cytokines (IL-1, -6, -8, and tumor necrosis factor- α) and reduced levels of anti-inflammatory cytokines (IL-10, IL-4, IL-12 and IL-13 or IL-1 receptor antagonist) (11-14). These studies also indicated that this pro- and anti-inflammatory cytokine imbalance was related to the chronological and gestational age of the infant (12,13). This indicates that meticulous precaution (perhaps more so compared to pediatric/adult ARDS) need to be taken while managing the neonate with ARDS including strict adherence to lung protective ventilation strategies, normoxia and early extubation.

The third consideration is the effect of intrauterine infection or chorioamnionitis on the developing lung. Acute chorioamnionitis can be a clinical diagnosis of maternal fever, elevated white blood cell count, tender uterus, and by amniotic fluid analyses for bacteria or can be a histopathological diagnosis in post-delivery findings of inflammatory cells and necrosis in the placenta (15). Clinicopathological correlation is not always present and the duration of exposure in this case may be unclear (15,16). Some women develop preterm labor and ruptured membranes, but after treatment, delivery may be delayed

—these women may carry fetuses with bacterial exposures for days to months obviating the first criteria of the Montreux definition (17). And indeed, some organisms like *Ureaplasma parvum* and *Mycoplasma hominies* which are normal vaginal flora in women of reproductive age may have prolonged exposures (18). Prolonged *Ureaplasma* infection in utero in the very preterm infant, together with postnatal consequences of ventilation and oxygen, results in a dysregulated inflammatory response that culminates in the ‘new BPD’ frequently seen in this population. Management of these infants will be different from other causes of neonatal ARDS.

Fourthly, just as early lung injury due to acute chorioamnionitis may be difficult to differentiate and attributed to RDS until the histopathological examination of the placenta is completed, some congenital/inherited lung disease may also be indistinguishable at the bedside (19). For instance, surfactant protein deficiency syndromes may present initially with RDS but later on, develop a similar recurrent decompensation which is no longer treated as RDS (20,21). Only a lung biopsy will differentiate this from other causes which mimic ARDS. However, the availability of lung biopsy is not widespread. Other conditions like congenital pulmonary lymphangiectasis and alveolar capillary dysplasia may also produce the same conundrum (22,23). Though rare, these entities present in the neonatal period and make the day-to-day diagnosis and management of ARDS challenging.

Lastly, although the Montreux definition advocates measuring pre-ductal partial pressure of oxygen in neonates with persistent pulmonary hypertension and patent ductus arteriosus, the effects of pathophysiological high pulmonary pressures in mal-transitioning newborns may exert complex effects which cannot be simply discounted by measuring the pre-ductal oxygenation. Pulmonary hypertension can occur in infants in 5 settings: (I) abnormally constricted pulmonary vasculature due to pulmonary parenchymal disease (e.g., RDS and MAS); (II) remodeled pulmonary vasculatures in the setting of normal lung parenchyma (e.g., idiopathic persistent pulmonary hypertension of the newborn); (III) structurally hypo plastic pulmonary vasculature (e.g., in lung hypoplasia, congenital diaphragmatic hernia); (IV) hyper viscosity syndromes (e.g., polycythemia) and recently described (V) altered pulmonary vascular growth, remodeling and tone in the new BPD (24-26). The first setting is a relevant consideration, affecting up to 10% of all causes of respiratory failure in neonates (25). Besides desaturation, pulmonary hypertension is more importantly

associated with right ventricular dilatation, septal flattening and eventually decreased left ventricular filling and output (25). Of note, traditional classification of severity of pulmonary hypertension utilizes different OI cut-offs (mild ≤ 15 , moderate ≤ 25 , severe ≤ 40 and very severe >40 vs. mild >4 , moderate >8 , severe >16 in the PALICC definition for PARDS) indicating that the degree of hypoxemia do not commensurate with lung inflammation as for pediatric and adult ARDS (27). This may be attributed in part to right-to-left shunting at the atrial level thus causing desaturation even at pre-ductal regions (28). It is also postulated that intra-pulmonary shunting occur more frequently in neonatal lung disease compared to children/adults and this is evident by the therapeutic efficacy of inhaled nitric oxide in this group (28,29). In addition, the left shift in the oxygen dissociation curve due to properties of the fetal hemoglobin has a significant effect on oxygenation and this too was acknowledged by De Luca and his team (30).

The recognition and development of a neonatal specific definition for ARDS is a commendable effort. However, there remain many challenges in the clinical applicability of this proposed definition. Intuitively, De Luca and his team have initiated a multi-center prospective observational study to determine the practical aspects of applying this definition. Before its use can become routine in clinical practice or research, it is important that this new definition is validated in the appropriate clinical setting across multiple centers and regions. A robust definition of neonatal ARDS should improve the detection of ARDS in infants without causing too much chaos and confusion to the clinician at the bedside.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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