Editorial

Neonatal ARDS: it's about time we take it to the next level

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With great interest I have read the position paper in a recent issue of the *Lancet Respiratory Medicine* from De Luca and colleagues defining acute respiratory distress syndrome (ARDS) in neonates (Montreux neonatal ARDS definition) (1). As a historical landmark, this welcoming of neonates to the ARDS community comes exactly fifty years after the first published description of ARDS in twelve critically ill patients by Ashbaugh *et al.* in 1967 (2). By modifying the "*A*" in ARDS from its initial "adult" into "acute" in the early 80s, children were already recognized as potential ARDS patients, and now ARDS finally spans the whole age spectrum, ranging from newborn to elderly.

The Montreux consensus definition of neonatal ARDS is comparable to the current adult (Berlin) and pediatric (Pediatric Acute Lung Injury Consensus Conference, PALICC) ARDS definitions (3,4), encompassing the following key elements: acute onset of oxygenation deficit with diffuse, (bilateral) opacities consistent with edema upon lung imaging, which is not fully explained by cardiac failure/congenital heart disease (1). The definition applies from birth until 44 weeks post-menstrual age or until 4 weeks post-natal age. Patients with specific neonatal diseases such as primary surfactant deficiency of prematurity (RDS), transient tachypnea of the neonate (TTN) and congenital anomalies are excluded when primarily responsible for the respiratory distress. Similar to adult and pediatric ARDS, neonates receiving non-invasive respiratory support can also fulfill the ARDS criterion, however there is no mandatory level of applied positive pressure. In contrast to PaO2-FiO2 ratio use in adult ARDS, neonatal and pediatric ARDS rely on oxygenation index (or oxygenation saturation index in children) calculation as a measure of the severity of the oxygenation deficit. Thus, while all three (neonatal, pediatric and adult) ARDS definitions share key criteria which grasp ARDS as a clinical syndrome of acute diffuse inflammatory lung injury, several differences exist between them, resulting from clinical and sometimes practical specificities of these age groups.

The effort of the international multidisciplinary collaborative project leading up to the Montreux neonatal ARDS definition certainly has considerable merit. In particular, the attempt to bridge the (often physically separated) disciplines of neonatal, pediatric and adult intensive care medicine deserves applause. Evidently, in an interdisciplinary approach we could learn much from each other's progress and mistakes in the daily clinical care and research of ARDS, facilitating the development of new treatment strategies. Although newborns with ARDS have been described already in 1989 (5), the current official recognition by the Montreux definition that neonates can indeed be diagnosed with ARDS will likely improve and broaden the whole ARDS field.

As stated in the paper from De Luca *et al.* there appears to be a strong pathophysiological argument that ARDS also exists in neonates (1). Many similarities in local and systemic activated inflammatory, coagulation, and cell death pathways, as well as histological features between ARDS and severe lung diseases in neonates have been found (1,6). In fact, one could even wonder why we would doubt the possibility of neonatal ARDS in the first place. Why would a

newborn not be able to develop diffuse damage to the lungs due to an excessive or dysfunctional inflammatory response to infection, aspiration, hemorrhage or transfusion? This injury may develop on top of underlying lung diseases such as RDS or chronic lung disease in preterm neonates, causing (additional) impairment in gas-exchange irrespective of the developmental stage of the lungs in these patients. Incomplete alveolarization would not be a valid counter argument in any way, as in humans this lung maturation process continues for many years into childhood (7). Similarly, the occurrence of distinct age-specific triggers of ARDS have so far not been a reason to exclude children, adults or elderly from having ARDS, so we should do the same for neonates.

In other words, why did it take us so long to recognize neonatal ARDS, which is rather (just) a new name than a new entity as announced by De Luca *et al.*? While incontestably a move forward for the ARDS field, the Montreux definition also painfully exposes the slow progress the critical care community has been making in identifying and characterizing ARDS in fifty years. In this day and age of advanced, high-output molecular tools for genetic and protein analysis, we are still modifying a set of non-specific clinical criteria in an attempt to sharpen the definition ARDS (1,3,4,8). Instead of applying one overall syndrome definition with several age-specific sub-criteria, we have now come up with three different age-related definitions of ARDS, and keep debating over seemingly minor (often practical) issues related to the level of applied pressure, measurement of oxygenation deficit, and the appearance of uni- or bilateral chest X-ray infiltrates, etc. This leads to considerable changes in ARDS incidence and outcome (9) and difficulty in comparing current to historical patient data. We are finding ourselves on a slippery slope when we keep debating these issues while we do not really have a clue of what ARDS actually is, at least in terms of the final common molecular pathways and series of events transcending differences in age. Now that we more or less have set a basic perimeter around the clinical picture of ARDS, a much stronger effort is needed to identify specific biomarkers, which upon inclusion in the ARDS definition, would really mean progress in the field.

In conclusion, the new Montreux consensus definition of neonatal ARDS published by De Luca *et al.* (1) is an important landmark, stimulating interdisciplinary collaboration in the field of critical care. At the same time, it shows we have to take it to the next level in more completely characterizing ARDS, in order to really be in sight of new treatment strategies and pharmacological therapeutics.

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Footnote

Conflicts of Interest: The author has no conflict of interest to declare.

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