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⊗ Pulmonary Vascular Disease in Premature Infants Early Predictive Models of Late Respiratory Morbidity

Pulmonary vascular disease (PVD) and established pulmonary hypertension (PH) are common associations of bronchopulmonary dysplasia (BPD) (1). Although the reported incidence of PH is 14–44% in infants with recognized BPD (2, 3), recent evidence indicates that up to 20% of extremely low gestational age neonates without BPD will develop some degree of PVD during the neonatal period (2, 3). The mechanistic interrelation of both pathologies in more prematurely born infants is informed by the tandem development of the alveoli and microvasculature (4). BPD and PH share similar risk factors and overlapping symptoms, with some pointing to early PVD as an essential causative factor in the pathobiology of BPD (2) and others suggesting that PVD could be a distinct feature of prematurity, rather than a manifestation of BPD (5–7). Regardless of its association with BPD, it is more likely that PVD is just one of many factors leading to impaired respiratory function after preterm birth. It is not surprising that early identification of PVD, independent of the diagnosis BPD, may predict later pulmonary dysfunction, especially because preterm birth is associated with an increased risk of PH in childhood, adolescence, and adulthood (8).

Improved echocardiographic assessment of PVD has led to increased recognition that disrupted pulmonary vascular growth in preterm infants may contribute to the pathogenesis of late respiratory disease (LRD) (2, 7). The diagnosis of PVD and the true prevalence of PH in preterm infants has been difficult to discern because of the paucity of reliable noninvasive measures to evaluate pulmonary hemodynamics (1) and an underappreciation for the practice of screening for PVD in extremely low gestational age neonates, with a focus primarily on infants with BPD (9). However, preterm infants without a diagnosis of BPD also remain at risk for respiratory morbidities and abnormal lung function into childhood, emphasizing the need to focus on alternate measures that explore differing mechanisms of disrupted pulmonary vascular and airway growth after prematurity (10).

In this issue of the *Journal*, Mourani and colleagues (pp. 1020–1027) leveraged a multicenter cohort of preterm infants to demonstrate that echocardiographic evidence of PVD at 7 days of age was associated with a higher incidence of LRD in early childhood (11). This builds on their previous report demonstrating that early

echocardiographic findings of PVD are strongly associated with the development and severity of BPD and late PH at 36 weeks (2). They also found that maternal diabetes and invasive mechanical ventilation support at 1 week of age were associated with LRD. Although BPD was predictive of LRD, there were 32 infants (14%) who did not have echocardiographic evidence of early PVD, late PH, or clinical BPD, but did have LRD. The article pursues the “vascular hypothesis,” which states that pulmonary vascular disturbances can contribute to later pulmonary dysfunction in former preterm infants. These data show that early identification of PVD, independent of later development of BPD, may contribute to the pathobiology of longer-term respiratory morbidity in former preterm infants.

The study is timely, as the ability of a BPD diagnosis to predict the impact of prematurity on respiratory disease beyond the neonatal period has been questioned. Similar to the large, prospective multicenter cohort study from the NIH PROP (Prematurity and Respiratory Outcomes Program) (12), these data identify those preterm infants at risk of developing late respiratory morbidity in the first week of life. Although prediction of late morbidity by perinatal risk factors and BPD alone in the PROP cohort exceeded that of the current study, it is likely that both perinatal and postnatal factors affect the airspaces and the pulmonary vasculature, driving the clinical trajectories of children born prematurely. The identification of high-risk infants earlier in their course may provide a critical window for applying established or emerging therapies to prevent progressive PVD and PH and to improve late respiratory morbidities (12).

Significant challenges exist in the noninvasive assessment of pulmonary hemodynamics and thereby in the identification of key adaptive mechanistic underpinnings of PVD in premature infants (9). Traditional echocardiographic markers of PH have relied on a combination of qualitative assessments (interventricular septal wall motion and right ventricular [RV] morphological changes) and quantitative estimates based on the tricuspid regurgitant jet velocity. Echocardiographic evidence of PVD often precedes the onset of overt clinical signs, symptoms, and detection of PH. In the pulmonary circulation, the key components of RV afterload, resistance and compliance, evolve together, but in opposite directions in both health and disease (13). In early PVD, a small increase in PVR is accompanied by a significant reduction in vascular compliance, an initial response that may not result in an immediate change in pulmonary arterial pressure, limiting the applicability of many of the current screening modalities that only rely on detecting an increase in pressure. With more advanced stages of PVD (i.e., PH), vascular stiffness will reach its maximum limits, and any further increase in PVR is not associated with further reduction in compliance. The recognition of alterations in septal

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wall morphology and function at 7 days in some preterm infants is indicative of elevated pressures seen in PH (2, 14). Emerging, noninvasive indices of PVD (e.g., RV systolic time intervals [7], measures of RV function [e.g., strain parameters (14)]) that more broadly capture components of RV performances and afterload (pressure, resistance, and compliance) may prove to be more informative than pressure estimates alone.

Early evidence of PVD in preterm infants adds to the growing list of complications of being born premature that may increase susceptibility or be a marker for greater risk of late pulmonary disease beyond the neonatal period and into early childhood, adolescence, and adulthood (8, 15). Adding these results to their previous work, Mourani and colleagues have now shown that echocardiographic evidence of PVD at 1 week of age is an early predictor of BPD, late PH, and late respiratory disease (11). Newborns with PVD may be particularly susceptible to secondary insults; future studies should use these early risk factors as predictive biomarkers toward enrolling the highest-risk infants into clinical intervention trials (6). ■

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Ⓜ Healing Pulmonary Rehabilitation in the United States A Call to Action for ATS Members

There is a paradox in the field of pulmonary rehabilitation (PR). There is now vast literature showing evidence that PR is safe, effective, and cost-effective (1, 2). Furthermore, PR improves

exercise tolerance, reduces dyspnea, and enhances quality of life likely better than any other available therapy (3), and has been shown to shorten hospital admissions in chronic obstructive pulmonary disease (COPD) (4). Despite the documented benefits of PR, the increasing prevalence of COPD, and the availability of Medicare and other insurance coverage, there is mounting concern that poor PR reimbursement in the United States may accelerate the decline in PR availability, further jeopardizing the limited availability of a key intervention in chronic lung disease. A recent analysis demonstrated that

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