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Back to the Future: Building Up the Case for Exploring Red Blood Cell Morphology in Pulmonary Arterial Hypertension

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In 1910, Cecil Price-Jones at Guy's Hospital (London, UK) published the first report on red blood cell width variability, noting that the diameter of these biconcave anucleate cells ranged between 4 and 12 μm , analyzed using classical methylene blue-stained blood films (1). This early-era finding demonstrated wide distribution of the mean red blood cell width (RDW) within a single aliquot from healthy individuals, affected further by simple factors such as diurnal variation. However, it was also noted that RDW was modulated by hemorrhage, giving rise to the possibility that RDW could be a useful parameter for profiling hematological disorders, and, ultimately, its *bona fide* role distinguishing hypoxic microcytic anemia (and others) from β -thalassemia trait (2). Because hemoglobin biochemistry is both central to the pathogenesis of many diseases and affected by red blood cell geometry (3), RDW has emerged as an attractive and easily measured parameter for prognostic considerations clinically.

Indeed, anisocytosis is a reproducible determinant of adverse outcome in large clinical studies focusing on patients with congestive heart failure (4), stroke (5), chronic obstructive pulmonary disease (6),

pneumonia (7), and pulmonary arterial hypertension (PAH) (8) among others. This trend is to some extent predictable, as pathophysiology and risk stratification underlying these conditions aligns with factors regulating red blood cell rheology, including interplay between inflammatory, nutritional, and genetic determinants, as well as disrupted iron metabolism, renal dysfunction, and hepatic dysfunction. Thus, it remains unknown whether the association between RDW, disease, and outcome (or disease severity) is uniform across subpopulations of at-risk patients. Understanding this may be useful, in turn, for prioritizing which circumspect clinical phenotypes warrant more detailed study of RDW clinically.

Once regarded primarily as a disease confined to plexogenic remodeling of distal pulmonary arterioles, PAH is now viewed as a heterogeneous syndrome involving right ventricular dysfunction, dysregulated hypoxic and metabolic signaling pathways, and abnormal circulating levels of neurohumoral and sex hormone vascular effectors (9, 10). Despite improvement in clinical outcome with the availability now of 14 drug therapies approved by the US Food and Drug Administration, PAH remains highly morbid, costly, and associated with substantially decreased quality of life (11). Thus, understanding biological intermediaries that reflect changes in specific or integrated pathophysiological pathways has important implications for

PAH diagnosis, prognosis, and potentially patient selection for clinical trial enrollment or treatment. Although RDW has been studied in this context previously (8), unbiased comparative analyses quantifying the strength of association between RDW and clinical diagnosis remained lacking. This uncertainty has hampered knowledge on the extent to which RDW may be important in PAH relative to other cardiopulmonary diseases.

In this issue of *AnnalsATS*, Thayer and colleagues (pp. 589–598) aimed to stratify the association between RDW level across specific clinical diagnoses (12). The authors hypothesized that the strength of RDW–disease associations is inhomogeneous across the medical spectrum, despite an RDW-altering pathophysiological thread that is part of many clinical diagnoses included in the study (e.g., heart, lung, inflammatory, nutritional diseases, etc.). A phenomewide association study (PheWAS) approach was used, which leverages the frequency of a particular observation in a large population segregated by phenotype to infer clinical (or biological) significance of a specific measurement.

The study analyzed the association between RDW values with 263 phenotypes (*International Classification of Diseases, Ninth Revision*, diagnostic categories) in a nonanemic discovery cohort of 121,530 individual patients, and focused on 48 phenotypes that were replicated further in a validation cohort of 2,039 individual

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patients after stratifying by sex. From this approach, the odds ratio for the phenotype association with RDW per 1% level increase was strongest in both cohorts among patients (regardless of sex) with a PAH diagnosis, although other diagnoses linked previously to RDW variability were well represented in the analysis, providing a measure of quality control for the PheWAS methodology. This work then diverged from past reports on the topic by confirming these population data on a granular level; that is, the investigators identified a positive association between RDW level and PAH-related echocardiographic and invasive cardiopulmonary hemodynamic measurements, including right ventricular cavity dilation, pulmonary artery pressure, pulmonary vascular resistance, and diastolic pressure gradient. Results from subgroup analyses imply that RDW level may exert useful discriminatory power for identifying patients with precapillary pulmonary hypertension (e.g., intrinsic pulmonary vascular disease) from patients with at least a component of postcapillary pulmonary hypertension.

Overall, this work is an important contribution to the field for several reasons. First, the meticulous methodology used by the authors underscores the importance of coupling patient-level data to support findings from unbiased analytic studies in unselected populations. This accomplishment requires particular mention, as unverified findings from genome-wide association studies, for example, are an important limitation to translating derivative results clinically (13). The authors address and meet this metric by confirming RDW variability in patients with pulmonary hypertension, using echocardiography and right heart catheterization, which are the screening and gold standard diagnostic tests, respectively. Second, using the PheWAS method permitted simultaneous comparisons between different patient populations relative to the exposure (e.g., RDW level). This approach confirmed prior reports indicating that RDW variability is linked to numerous different diseases, but sheds important insight to warrant recognizing cardiopulmonary disease, perhaps PAH more specifically, as phenotypes for which this association is particularly strong. Third, as suggested in the manuscript, this work illuminates abnormal RDW, often overlooked in clinical practice, as a potential window into underlying cardiopulmonary disease.

It is important to emphasize that association studies do not imply causation, despite the use of sound epidemiological methods, nor could all factors that affect RDW be controlled using the authors' study

design. Inferring importance based solely on the frequency of an observation may, in turn, overlook wider pathways underlying the pathogenesis and biological profile of a disease (14). In the case of PAH and right heart failure, this is particularly important because of the convergence of numerous different molecular mechanisms, nuances in clinical presentation, and temporal trends in clinical trajectory (15). Thus, the authors' measured view on the implications of these data are spot on: abnormal RDW may imply a hidden cardiopulmonary pathophenotype, and should be recognized as such, although data presented here do not inform on the role of RDW as a true biomarker in PAH, and alternative comorbid diseases associated with increased RDW should be considered at point of care.

In summary, work from Thayer and colleagues demonstrates internal consistency between PheWAS and patient-level clinical data identifying the unique relevance of RDW to the clinical profile of PAH. In doing so, this work illustrates the strength of comparative analyses across different phenotypes, focusing on easily acquired clinical measurements, which in the case of RDW are often overlooked and potentially underused. This work aligns well with prior studies in the PAH field, suggesting that greater attention is warranted to understanding the pathobiological implications of abnormal red blood cell rheology in patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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The Final Frontier: Preschool Asthma Severity—The Silent Years No More

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Asthma is the most common cause of hospitalization in children. Most of the burden of this disease is found in very young preschool children. It is exceedingly common for preschool children to experience severe wheezing episodes resulting in either an oral steroid course or an emergency room visit before they receive a diagnosis of asthma (1, 2). Despite advances in reducing severe asthma exacerbations in older children and adults, preschool asthma continues to be characterized by recurrent severe exacerbations. Reasons cited for these observations include a lack of objective measures to aid in the diagnosis, heterogeneity in preschool wheezing phenotypes and responses to therapy, and difficulty in symptom assessment due to a reliance on surrogate reporting rather than direct history,

leading to inadequate therapy or misdiagnosis.

In this issue of *AnnalsATS*, Arianto and colleagues (pp. 599–605) attempt to shed light on one aspect: the ability of preschool lung function tests to improve asthma diagnosis (3). The focus on lung function is not surprising given the increasing evidence that asthma in early life alters lung growth (4–6), impairing peak adult lung function, which in turn is a notable risk factor for early respiratory compromise and morbidity. Furthermore, there is some evidence that interventions within 1–2 years of disease onset that decrease the number of overall exacerbations may promote healthy lung growth (7). Taken together, these studies raise the question of whether earlier diagnosis and improved monitoring can be used to optimize preschool asthma treatment and thereby prevent the cycle of ongoing asthma exacerbations, worsening lung function, and poor lung growth.

The results reported by Arianto and colleagues are sobering. In their study, they followed 646 children from the general population during the first 6 years of life and performed whole-body plethysmography and multiple breath washout (MBW) in all of the children starting at age 3. Notably, at age 3 years, only a quarter of the children were able to perform MBW, and one-fifth (19%) were able to complete whole-body plethysmography. Success rates increased significantly thereafter, such that by age 4

the majority of the children (58–60%) were able to perform both preschool tests. By 5 years of age, 80% of the children were able to perform MBW and plethysmography, and spirometry attempted for the first time was successful in 50%. Given that most adults with persistent asthma (75%) can trace their symptom onset to the first 3 years of life, the ability of lung function to inform the diagnosis by age 3 years is important (8). However, Arianto and colleagues report that none of the assessed lung function tests were useful for diagnosing asthma in a general population cohort.

At issue is the heterogeneity of wheezing phenotypes and the lack of a gold standard diagnosis for asthma. Although partly true at every age, this is particularly problematic in the preschool population, as most wheezing disorders will resolve without sequelae by school age (9, 10). The challenge in this age group is to prospectively identify symptomatic children who will suffer from severe exacerbations or continue to suffer from persistent symptoms well into the future, requiring treatment. Here, Arianto and colleagues's data provide some insight. All of the children were assessed by study physicians for a diagnosis of asthma at age 6 years. The complicated diagnostic criteria included a recurrent history of "lung symptoms" (cough, wheeze, and/or dyspnea) for at least 3 days within 6 months, typical symptoms of asthma (exercise-induced symptoms, nocturnal symptoms, or cold air-induced

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