The Road to Precision Medicine in Chronic Obstructive Pulmonary Disease: Squeezing More Out of Chest Computed Tomography Scans

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease. The advances made in the last few years in COPD research have pushed the field into precision medicine, where individual therapeutic approaches are tailored to the distinct features of a patient's obstructive lung disease. The multiple pathophysiological derangements, factors, and etiologies that contribute to the airflow obstruction of COPD lead to diverse presentations and, for now, an unpredictable clinical course (1). This same heterogeneity is likely true in emphysema, where several different phenotypes have been described and are represented by the histological patterns of centrilobular, panlobular, and paraseptal emphysema (PSE). These are important distinctions because the natural history, appropriate therapies, and outcomes may vary by emphysema subtype. For example, adults with upper-lobe emphysema may benefit from lung volume reduction surgery (2), and the location of the emphysema is an important consideration when placing endobronchial valves (3).

Different endotypes have been described in emphysema characterized by a deficiency of alpha-1 antitrypsin; increased macrophages and neutrophils; release of matrix metalloproteinases, elastases, and collagenases (4); and parenchymal destruction and increased apoptosis, likely through the downregulation of the vascular endothelial growth factor pathway (5). A better understanding of emphysema

subgroups that integrates phenotypic signatures with distinct pathophysiological derangements is needed to identify "treatable traits." It is hoped that this approach will lead to more precise and tailored treatments for COPD.

Identification of treatable traits has become the standard of care in asthma, where patients' endotypes are now characterized as T-helper cell type 2-high and T-helper cell type 2-low subtypes. Treatable traits have led to a significant development of immune-altering medications to treat the different subtypes of asthma (6). In emphysema, identification of distinct subgroups is likely to have therapeutic relevance as well, but we currently lack well-studied and defined subtypes of patients. By defining subtypes of emphysema, physicians will be able to implement a precision medicine approach (7). From a research perspective, defining subgroups of emphysema will lead to identification of new drug targets and novel end points for clinical trials.

Currently, we are practicing in an era of medicine in which computed tomographic (CT) chest scans are widely obtained in patients with respiratory symptoms, especially in developed countries and in patients with a significant history of smoking tobacco. Emphysema is a frequent finding in adults who do not meet the spirometric criteria for COPD (8). Recent investigations based on the Multi-Ethnic Study of Atherosclerosis cohort have shown that emphysema is associated with

respiratory symptoms independently of the degree of airflow obstruction as measured by forced expiratory volume in 1 second (9). In current practice, physicians are only interested in knowing whether emphysema is present, without taking advantage of the breadth of quantifiable information contained within a CT scan. Our dichotomized view of emphysema is now being expanded by a growing body of chest CT quantification methods. For example, dual-energy CT imaging can identify regional perfusion heterogeneity in subjects with centracinar emphysema (10). Importantly, this modality can be used to monitor and document reversible vasoconstriction with sildenafil (11). Another modality, parametric response mapping (PRM), uses paired inspiratory and expiratory CT images to identify emphysema (PRM^{emph}) and functional small airway disease (PRM^{ISAD}). This methodology has been evaluated in two large multicenter cohorts (COPDGene [COPD Genetic Epidemiology] and SPIROMICS [Subpopulations and Intermediate Outcome Measures in COPD Study]) and has been shown to correlate with loss of lung function across different Global Initiative for Chronic Obstructive Lung Disease stages of COPD (12–14).

In this issue of the *AnnalsATS*, Copeland and colleagues (pp. 479–484) assess paired inspiratory and expiratory CT scans from 1,320 subjects enrolled in the COPDGene cohort (15). The authors evaluated the presence of paratracheal PSE

(Received in original form December 16, 2017; accepted in final form January 3, 2018)

Supported by the Flight Attendant Medical Research Institute (B.G.W.), a Stony Wold-Herbert Fund Fellowship (B.G.W.), and National Institutes of Health grants 5T32CA193111-03 and K23 AI102970 (L.N.S.).

Author Contributions: Drafted the manuscript for important intellectual content: B.G.W. and L.N.S.

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Ann Am Thorac Soc Vol 15, No 4, pp 428–429, Apr 2018

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DOI: 10.1513/AnnalsATS.201712-945ED

Internet address: www.atsjournals.org

(PT-PSE), a distinct form of PSE, defined as PSE of ≥ 0.5 cm located around the trachea and main stem airways. Prior investigations showed that centrilobular emphysema was associated with greater smoking history, and panlobular emphysema was associated with a reduced body mass index independently of forced expiratory volume in 1 second, whereas PSE seemed to be associated with fewer symptoms and physiological impairments (16). However, in the current investigation, PT-PSE was associated with expiratory central airway collapse (ECAC, defined by $\geq 50\%$ airway collapse during expiration). These findings have significant clinical relevance because in prior reports using the same multicenter cohort, ECAC was associated with worse pulmonary function, increased total and severe exacerbations requiring hospitalization, and overall decreased quality of life (17). In the current investigation, the authors showed that PT-PSE, but not other types of emphysema, was associated with ECAC in a multivariate model with an adjusted odds ratio of 1.98. The authors suggest that the loss of elastic recoil in the paratracheal area is

the dominant contributing factor to the collapsibility of the airways. Interestingly, obesity was also associated with ECAC in a multivariate analysis, suggesting that mechanisms other than loss of elastic recoil (e.g., mass loading and airway inflammation) may also be relevant for ECAC. PT-PSE was more frequent in patients with ECAC than in control subjects, with a prevalence of 16.6% and 11.8%, respectively ($P = 0.016$). Thus, the absolute difference in prevalence was only 5%, which makes the clinical utility of this parameter in isolation difficult to determine. However, when we consider the constellation of other radiographic parameters that have recently been identified as being significantly associated with disease progression or treatment response, we begin to see how precision medicine could be instituted to tailor therapeutic approaches to individuals with COPD.

This study supports the critical observation that not all types of emphysema are the same. Even within the commonly used histological categories (centrilobular, panlobular, and paraseptal) there are

subvariants that require further study. The road ahead for the clinically relevant use of the breadth of imaging data requires reproducibility and validation with other cohorts, where these parameters can be correlated with more relevant clinical outcomes (such as rate of lung function decline, exacerbation rate, response to treatment, morbidity, and mortality) or used to define subgroups of COPD with distinct pathophysiological endotypes that identify distinct treatable traits. Copeland and colleagues use PT-PSE to define a distinct clinical entity associated with ECAC that has a significant impact on measurable outcomes. Although the article may identify a small subgroup of subjects within the COPDGene cohort, the larger impact of this line of investigation is clear: uncovering distinct radiological features that will contribute to the precision of care in COPD. Ultimately, by pushing the field further down the road of precision medicine, the current study will succinctly add a few extra yards to the journey. ■

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

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