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Chronic obstructive pulmonary disease: More imaging, more phenotyping...better care?

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In the current issue of the *Canadian Respiratory Journal*, Tulek et al (1) (pages 91-96) examined the concept that high-resolution x-ray computed tomography (CT) measurements of airway and parenchyma abnormalities in chronic obstructive pulmonary disease (COPD) could be used to classify patients into clinically relevant subgroups with resulting differences in lung function, markers of inflammation and exacerbation rates. In a relatively small group of COPD patients (n=80: small compared with the recently reported Genetic epidemiology of COPD [COPDGene (2)] and Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points [ECLIPSE (3) studies]), thoracic CT was acquired and visually evaluated by two experts using a modified Bhalla scoring system (4) – an approach more commonly used for cystic fibrosis imaging evaluations. On this basis, patients were classified into one of four groups: no imaging findings related to COPD; emphysema only; bronchiectasis/peribronchial thickening only; and emphysema in combination with bronchiectasis/peribronchial thickening. While 54 subjects demonstrated CT imaging evidence of emphysema or airway abnormalities, or both, 26 patients showed no CT abnormalities. Importantly, spirometry and other findings were worse for the subgroups with a CT-derived COPD phenotype than the subgroup with no findings. In addition, as might be intuitively expected (but not previously reported), the subgroup with only emphysema showed less severe pulmonary function results, inflammation and fewer exacerbations, whereas the group with both emphysema and airway abnormalities exhibited significantly lower lung function values, higher levels of C-reactive protein and erythrocyte sedimentation rates, and more exacerbations.

COPD is recognized as a regionally heterogeneous disease with underlying contributions from airway abnormalities (5) or, perhaps, airway obliteration (6) and emphysematous destruction. Recent pathological analyses using micro-CT have suggested that there is a loss of terminal bronchioles that temporally precedes emphysematous changes in COPD (6). It is well recognized that COPD is heterogeneous across individuals and regionally in the lung, and the exact temporal relationship of morphological changes in the airways and parenchyma has not yet been definitively established. What is clear, however, is that spirometry measurements provide less-than-ideal estimates or predictors of COPD onset and progression, response to treatment and exacerbation frequency (7). In light of this, CT has been proposed as a noninvasive method to provide regional measurements of the underlying morphological changes that directly result in COPD symptoms and exacerbations. Although the concept of COPD patient classification beyond forced expiratory volume in 1 s is decades old, it has recently been re-evaluated using CT in light of the large and exhaustive COPDGene (2) and ECLIPSE studies (3), and proposed as a way to discriminate patients with unique morphological, clinical and physiological characteristics. CT phenotyping provides a method to group or categorize patients based on imaging findings, and these can be statistically evaluated with respect to a myriad of laboratory findings, symptoms and other pathologies related to COPD; in addition, the underlying structure-function relationships that are determined can potentially be used to direct or at least guide treatment.

High-resolution CT images of airway morphology, parenchyma density and gross anatomy have been analyzed to determine phenotypes of COPD and classify patients into disease severity subgroups. For

example, using COPDGene data, Galban et al (8) developed an elegant approach to derive parametric response maps and identify CT phenotypes. Their results support the concept that airways disease precedes emphysema in early stage COPD, whereas when COPD progresses, both emphysema and airways disease are present. Using the same cohort of COPDGene patients, the relationship between exacerbation frequency and emphysema-predominant or airways disease-predominant CT phenotypes was evaluated (9). Here, exacerbation frequency was shown to be related to both emphysema and airway disease-dominant phenotypes and, in the case of mixed emphysema-airways disease phenotypes, exacerbation frequency was decreased but quality of life was much worse.

How can this information be used in the future? Do the risks and resources inherent in acquiring CT data outweigh the important information content and the potential to alter therapy decisions in COPD? In a resource-limited setting, outside of a major clinical trial, a careful clinical study involving a small group of smokers with COPD, such as presented by Tulek et al (1), provides intriguing evidence that CT phenotypes may help explain exacerbation risk, predict underlying inflammation and, perhaps, stratify patients. Indeed, the study by Tulek et al (1) demonstrates the importance of CT phenotyping, even in a small group of patients, and urges us to continue developing more robust, safer and less resource-intensive imaging phenotypes of COPD. Future steps necessarily include automated image analysis tools to reduce the time and variability inherent in manual analyses and finally, a randomized controlled trial to evaluate COPD outcomes based on therapy decisions made with and without imaging phenotype information.

Phenotyping promises potentially better therapy and outcomes for COPD patients, and this study makes it clear that now is the time to start making good on this promise.

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