How to Detect Tobacco-related Vasculopathy: Are We There Yet?

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Not only has tobacco use been estimated to cause up to 1 billion deaths in the 21st century (1), it has been identified as the most important causative factor for the development of chronic obstructive pulmonary disease (COPD), which has become the third leading cause of death globally. On the basis of these observations, more research is needed to help screening, diagnosing, and treating smoking-related diseases.

It has been well established that COPD is a chronic inflammatory airway disease, but recent reports have shown that pulmonary hypertension (PH), a common feature and prognostic factor of COPD, increases the risk for acute COPD exacerbations (2, 3). A COPD-associated pulmonary vascular phenotype has been proposed, which consists of precapillary PH, moderate airway obstruction, and severe diffusion limitation (4). Multiple reports using clinical samples and experimental rodent models demonstrate that cigarette smoke can induce pulmonary vascular remodeling, even while lung function remains normal (5–7). In patients with COPD, the prevalence of PH is more difficult to determine because these patients are generally stable and do not undergo right heart catheterization. Nevertheless, early detection can improve treatment and quality of life. Therefore, the question remains whether a tobacco-related pulmonary vasculopathy exists, and if so, whether this would be predictive for the development of COPD-related PH disease in larger adult populations that are seemingly healthy.

In this issue of *AnnalsATS,* Synn and colleagues (pp. 698–706) conducted a retrospective data analysis using the Framingham Heart Study cohort to hypothesize that tobacco exposure is associated with lower pulmonary blood volumes and vascular pruning (8). Data from 2,410 participants who had undergone volumetric whole-lung tomography were used, and an automated algorithm generated 3-dimensional reconstructions of the pulmonary vascular tree and calculated the total volume of all intrapulmonary vessels. These results were analyzed using a multivariable linear regression model to assess associations between these computed tomography (CT) metrics and cigarette smoke exposure after adjustment for demographic covariates. Interestingly, and in contrast with previous studies, cigarette smoke consistently correlated with higher absolute pulmonary blood vessel volume with a linear effect increase when comparing never, former, and current smokers. These findings did not change when results were adjusted for lung function parameters including percentage predicted forced expiratory volume in 1 second (FEV_1), sex, physical activity or cardiovascular disease, and related comorbidities. The authors concluded that although there is evidence of a histologically defined tobacco-related vasculopathy, radiographically detected vascular pruning may not be a surrogate, at least when characterizing a "healthy" population of smokers.

Despite a robust design with sufficient power and valid statistical analysis, several questions remain: Why is there such discrepancy between previous studies and this study on hand? Is the radiographic analysis of pulmonary vascular assessment not sensitive enough? Or is this analysis tool even valid? Therefore, it is important to look at previous studies in more detail that also employed CT metrics to assess pulmonary vascular volume. Several of these studies, which included individuals diagnosed with severe emphysema and PH, showed that quantitative CT measures of cross-sectional areas of small pulmonary vessels correlated with emphysema, and could even differentiate between patients with COPD with and without PH (9–11). Another study, led by investigators of the Multi-Ethnic Study of Atherosclerosis (MESA), described the analysis of pulmonary blood volume in 2,303 participants (12). Noncontrast CTs in full inspiration after the SPIROMICs protocol using a high-spatial-contrast algorithm for reconstruction were used (13), in addition to contrast-enhanced magnetic resonance imaging measures assessing pulmonary vascular blood volume, to determine an association between lower pulmonary microvascular blood volume and impaired left ventricular (LV) filling and relaxation in ever-smokers (12). Among the 4,717 participants in the MESA study, 2,303 completed both cardiac MRI and full-lung CT and were therefore included in this subgroup study with 53% of ever-smokers (10% current smokers), 27% airflow limitation, and 10% emphysema on CT. The authors excluded participants who had significant cardiovascular disease. The main finding of this study demonstrated an association between a lower pulmonary vascular volume with lower LV filling and dyspnea among ever-smokers including those without smoking-related lung disease. Therefore, one of their conclusions was that low pulmonary vascular blood volume may lead to impaired LV filling and contribute to dyspnea in ever-smokers without significant cardiopulmonary disease.

In another study, Estepar and colleagues also analyzed pulmonary vascular volume with CT metrics, using a subset of the COPDGene cohort, which included 359 smokers and 85 never-smokers with normal lung function (14). Smokers in this cohort had an average predicted percentage FEV_1 of 59% and a significant emphysema score (%LAA-950 [percent of computed tomography low attenuation area less than 950 Hounsfield units] average of 6.33). When the authors divided the smoker cohort into subgroups according to COPD severity, using Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages, they could not measure a significant difference in median blood vessel volume between never-smokers and the smoking (current or former) control patients, but the measures of the aggregate blood vessel volume in vessels <5 mm^2 in cross-section and nonvascular tissue volume were

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significantly decreased in individuals with higher GOLD stages (14). All these studies share an important limitation with regard to the method of image analysis, as there is no differentiation between the pulmonary artery or the venous vasculature; furthermore, there is no distinguishing among vessel lumen, vessel wall, or interstitial inflammation and fibrosis adjacent to the vessel wall. Nevertheless, most of the studies presented here used comparable volumetric CT analysis modalities and algorithms and do not explain the differences in outcomes.

Could these differences be explained by the choice of study population? As stated here, Synn and colleagues did not use a novel analysis modality, but their study is the first one to apply it and its algorithm to a large representative and relatively healthy cohort (8). This would also explain why they found an association of smoking with higher pulmonary blood volume, which is the opposite of the previous studies. Low blood volume and/or pruning of the vasculature might be a hallmark of the patient with COPD with significant emphysema with or without PH, and not a characteristic feature of a smoker with preserved lung function. The MESA substudy, however, implied that ever-smokers without lung disease had lower pulmonary blood volumes as well, but they demonstrated a strong association with impaired LV filling, a phenomenon that could be a result of concentric LV remodeling or increased LV stiffness, characteristics that might have not been evident in the Framingham Study Cohort. Another explanation for the smoking-associated increase in pulmonary blood volume was explained by the authors of the study on hand as being a result of a larger appearance of the pulmonary vasculature on imaging by an increased recruitment resulting from a stronger inspiratory effort in healthy smokers. Nevertheless and despite these limitations, Synn and colleagues can reliably conclude that smoking is associated with a higher average total pulmonary vascular volume when compared with nonsmokers in the Framingham study cohort by the use of volumetric imaging (8). In the future, more studies using this modality of larger prospective cohorts of smokers are needed to determine the prognostic relevance. ■

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

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