Preclinical vascular disease identifies smokers at risk for COPD

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Chronic obstructive pulmonary disease (COPD) is the only disease among the 10 leading causes of death in the United States with a prevalence that has steadily increased over the past four decades and for which no effective therapy has been developed to substantially blunt its progressive course. COPD has climbed to become the fourth leading cause of death in the United States, leading to the deaths of more than 120,000 people each year. Healthcare expenses and loss of work because of this disease have been estimated to cost over $37 billion annually. COPD is traditionally identified by the finding of an irreversible chronic airflow limitation. This limitation is thought to be present (diagnosed and undiagnosed) in up to 50 million people in the United States (1). Smoking has been clearly identified as the primary cause for COPD, but to date, there is no effective means to identify this disease before it becomes clinically manifested as airflow obstruction and impairs function or quality of life. The report by Alford et al. (2) in PNAS describes the use of ECG-gated multidetector row computed tomography (CT) perfusion imaging to identify vascular dysfunction in smokers with normal lung function and correlates this information with very early CT manifestations of centrilobular emphysema. This suggests a minimally invasive image-based biomarker that can identify subjects at high risk for developing COPD. Hopefully, this biomarker will stimulate new fields of research that could result in the development of preventative therapies for this poorly controlled disease epidemic.

Biomarkers for COPD

Although cigarette smoking is the primary cause of COPD, not all smokers are at the same risk for developing this disease. Only about one-quarter of heavy smokers develop clinically significant COPD (2). The basis for the differential susceptibility for this disease is poorly understood, although genetic factors, not yet defined, are thought to play a major role. A clinically relevant biomarker that can identify occult disease in individuals at high risk is badly needed. In the study by Alford et al. (2), all subjects had normal spirometry and normal lung densitometric measurements on CT. Those subjects with subtle visual evidence for centrilobular emphysema had a mean age of 46 years and had smoked an average of 31 pack years. The very earliest breakdown of lung tissue in emphysema occurs in the few alveoli surrounding the openings of terminal/respiratory bronchioles in the center of the lung lobule. Normal human lungs have about 20,000–25,000 terminal bronchioles, each of which serves a single lobule containing about 10,000–20,000 alveoli (3). The breakdown of a small number of these alveoli in the central region of the lobule can be seen as small holes on a chest CT scan, but this breakdown would not be sufficient to change the overall tissue density of the lung as shown by the normal Emphysema Index at −950 Hounsfield units in the smokers with centrilobular emphysema (CSE) subjects studied by Alford et al. (2). Thus, the increased heterogeneity of pulmonary perfusion identified by Alford et al. (2) is clearly in subjects with preclinical asymptomatic emphysema. This is the earliest biomarker of COPD identified to date.

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Remy-Jardin et al. (4) identified micronodules or areas of ground-glass opacity by CT in smokers that correlated with bronchiolitis or inflammation surrounding terminal bronchioles (5), and these micronodules show an early stage of the multifocal persistent inflammation that is characteristic of COPD. The absence of this type of finding in the study by Alford et al. (2) suggests that vascular changes and perfusion heterogeneity precede the more overt bronchiolitis pattern described by Remy-Jardin et al. (4).

Of great interest is that lung-perfusion heterogeneity is a biomarker that can reasonably be interpreted as being related to a likely fundamental mechanism underlying the pathogenesis of COPD (i.e., a unique, early vascular response of COPD-susceptible subjects to focal areas of smoke-induced inflammation). It is now recognized that underlying COPD is a substantial, chronic inflammatory response in the lungs. Macrophages, neutrophils, and CD8+ T cells are involved as well as multiple inflammatory mediators that have been found to be elevated in the serum or sputum of patients with COPD. The known inflammatory mediators include C-reactive protein (CRP), TNF-α, soluble TNF receptors (sTNF-R), neutrophil elastase, cathepsin, TGF-β, IL-6, IL-1β, IL-18, IFN-γ, GM-CSF, matrix metalloproteinase-9, prostaglandin (PG) E_2, and monocyte chemoattractant protein-1 (MCP-1) (6–10). This lung inflammatory reaction can be initiated by cigarette smoke and other inhaled irritants.

Early Vascular Abnormalities in COPD

Alford et al. (2) argue that their observation of enhanced areas of decreased perfusion found in subjects with early visual CT evidence of emphysema relates to a vascular abnormality in which hypoxic pulmonary vasoconstriction is not appropriately down-regulated, thus reducing vascular access of down-regulating immune modifiers and their effectiveness in controlling the local inflammatory responses around inflamed terminal bronchioles. A particularly interesting aspect of their finding is that this early vascular abnormality can precede any overt emphysematous tissue breakdown. Alford et al. (2) find perfusion heterogeneity in the lower lung lobes of subjects that had visual evidence of early emphysema in the upper lung lobes only and lower lungs that were otherwise functionally and structurally normal.

In COPD subjects, it is now becoming apparent that the inflammatory response is not limited to the lungs, and additionally, there is systemic inflammation with circulating inflammatory mediators, systemic oxidative stress, activated neutrophils and lymphocytes, and increased plasma levels of acute-phase inflammatory proteins (8). The result is a subtle, diffuse vascular injury and inflammation (10) that would explain the high risk of patients with COPD for comorbidities such as cardiovascular disease, osteoporosis, cachexia, lung cancer, depression, obstructive sleep apnea, and anemia (10–12). Cardiovascular disease actually

Author contributions: J.D.C. wrote the paper.

The author declares no conflict of interest.

See companion article on page 7485 in issue 16 of volume 107.

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accounts for up to one-half of all deaths in patients with COPD (11, 13, 14). The comorbidities associated with COPD have their greatest association with emphysema and airway disease rather than with the common risk factor of smoking. Thus, patients with COPD have about a 3-fold increase in ischemic heart disease and lung cancer compared with equivalent smokers without clinical findings of COPD. The chronic systemic inflammation associated with COPD is more likely the underlying factor driving the association. Support for this possibility comes from recent studies identifying links between COPD, systemic vascular dysfunction, and systemic inflammation (15, 16).

Thus, it would be reasonable to hypothesize that the early pulmonary vascular perfusion heterogeneity found in the study by Alford et al. (2) will also have a systemic correlate, because these same subjects are those with the greatest concurrent risk for ischemic heart/vascular disease. This issue would be worth pursuing, because early intervention and prevention can be effective in reducing the impact of this class of disease. Although current national and international guidelines for the treatment of COPD include recommending that clinicians consider comorbid conditions and their severity (17), there are no guidelines for prevention of either COPD or its comorbidities other than stopping smoking.

One important limitation in the interpretation of the current study by Alford et al. (2) is that all of the subjects were current smokers. Although this study identifies one of the earliest pulmonary vascular changes that occurs in smokers with preclinical emphysema, it will also be essential to learn if these abnormalities will persist in subjects who stop smoking. In contrast to many other forms of acute inflammation, inflammation typically continues after the acute stimulus (i.e., smoking) ends in the lungs of COPD patients (5, 7). It is common for the clinician to first see subjects for the clinical expression of COPD years or even decades after a heavy, chronic smoker stops smoking. Although, in many cases, the patients become tolerant to slowly progressing symptoms and complain only when limitations become severe, it also seems that a portion of heavy, chronic smokers develop a persistent inflammatory response involving the lungs that can progress and become severe independent of continued smoking. Thus, it will be important to determine the persistence of lung (and possible systemic) perfusion abnormalities in former smokers and if this biomarker of early vascular damage can be reversed or stopped with an appropriate early intervention.

Guidelines for the treatment of established COPD call for the use of inhaled corticosteroids in patients with advanced COPD only after optimizing long-acting β-agonists and long-acting anticholinergics (17). As the underlying characteristics of lung and systemic inflammation associated with COPD are better understood and the use of biomarkers identifying early, preclinical disease are validated, it should be possible to develop effective preventative strategies. This could involve the use of inhaled corticosteroids and/or the development of new antiinflammatory strategies that could be effective in early or preclinical COPD.

ACKNOWLEDGMENTS. Work on COPD is supported by National Institutes of Health Research Grants U01HL089897 and U01HL089856.

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