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EMPHYSEMA: A DISEASE OF SMALL AIRWAYS OR LUNG PARENCHYMA?

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In 1984, the Division of Lung Disease at the NHLBI funded a workshop which led to what is still the most recent official definition of emphysema, i.e., “a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls, and without obvious fibrosis”¹. In this issue of *NEJM*, McDonough et al.² present a fascinating study showing a major obliteration of terminal bronchioles in COPD patients with emphysema, that seems to challenge this official definition. Indeed, when most people hear the word emphysema, they think of damaged or destroyed alveoli. Yet, in the McDonough paper, the major finding in patients with varying degrees of COPD is that there is a narrowing and almost total loss of terminal bronchioles, sometimes with minimal quantifiable damage in the distal parenchyma.

This study thus raises key issues related to the timeline of the pathology in COPD, particularly with regard to the interaction between the peripheral airways and parenchyma. It has been known for almost a century that there are bundles of elastic fibers that run the entire length of the airway tree from the trachea to the smallest airways². These elastic bundles are located in the mucosa just outside the basement membrane and give rise to the corrugated cross sectional appearance of an airway lumen. This axial structural linkage between the largest and smallest airways is essential for proper lung function. In emphysema, damage to this mechanical linkage could occur at different sites, and the question of which comes first, the loss of the terminal bronchioles or the loss of the acini, is important in understanding the pathologic etiology. The two possibilities are illustrated in Figure 1. If the axial fibers lose their tethering at their most distal ends (as with a loss of alveoli- Figure 1-panel A) they will recoil, and the resultant airway shortening could lead to the obstruction of small airways as observed. However, if the inflammation in the small airways leads to their own structural damage as has been described^{3, 4}, then the tethering of the distal acini will disappear, and the alveoli will lose the structural support that maintains normal architecture (Figure 1-panel B). Although McDonough et al.² argue that the small airway damage likely occurs first, their study was cross-sectional in a limited number of subjects, so causality cannot be proven. If alveolar walls were to weaken and become more distensible, this would be difficult to detect histologically or with micro CT, but it could contribute to narrowing of the inflamed bronchioles. It is worth noting that, unlike the major narrowing of small airways observed by McDonough et al., in their seminal histologic study,

Leopold and Gough⁴ found relatively few severely narrowed airways leading to emphysematous regions.

Regardless of the initiating cause, envisioning how the pathologic changes impact the 3 dimensional structure is neither simple nor intuitive. If terminal bronchioles disappear after being completely obstructed and degraded as dead tissue, then how do the larger airways connect to the remaining distal acini? And if one envisions small airways just disappearing, why do the larger upstream airways stay obstructed? One of the technical limitations of this study was that it was not possible to identify airways with lumens below the resolution of the CT images (about 1 mm), so it is very possible that there were still fibrous connections to the distal parenchyma. Further analysis of the novel and quite spectacular sequences of 16 μ m micro CT serial sections in the online supplement may be able to shed some insight on this 3 dimensional structural issue.

Finally, given this uncertainty regarding the pathologic progression for emphysema in COPD, it may be time to think about forming a panel to reconsider the definition of emphysema. A new 21st century definition will clearly need to include more about the involvement of small airways beyond their simply not being fibrotic. Based on the work of McDonough et al⁵, the permanent enlargement of the distal airspaces may only serve as a structural biomarker, being a secondary result of small airway inflammation and destruction.

References

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Figure 1.

Two models explaining the etiology of parenchymal airspace enlargement in COPD.

Panel A. Alveolar inflammation leads to destruction of alveolar walls and the elastic connective tissue fibers that link the acinus to the terminal airways. This allows the terminal bronchioles to recoil and obstruct.

Panel B. Inflammation in the terminal bronchioles causes wall thickening, obstruction, and ultimate severing or stretching of the elastic connective tissue fibers. This loss of support for

the distal acinus leads to folding (and ultimate destruction) of unsupported alveolar walls and enlargement of the duct.