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Chronic obstructive pulmonary disease (COPD) and emphysema are, jointly, the third leading cause of death in the United States. The MESA Lung Study found that percent emphysema on computed tomography (CT) was the major correlate of impaired left ventricular (LV) filling in the general population and that the total (i.e., artery and venous) pulmonary vascular volume (TPVV), a measure of the pulmonary macrovasculature on non-contrast CT had a wide distribution, was lower in COPD and emphysema, and was associated with reduced LV filling in a pattern often thought to reflect LV diastolic dysfunction. We also found that emphysema is common in the general population, often occurs without spirometrically defined COPD, and has a poor prognosis even in the absence of COPD. The major factors associated with progression of emphysema on CT among 4,472 participants followed for 10 years related to microvascular damage, endothelial adhesion molecules, endothelial-platelet interactions, and innate and adaptive immunity. Furthermore, medications interrupting some of these pathways were associated with slowed progression of emphysema. These longitudinal findings suggest that the pulmonary microvasculature may be critical to the development of emphysema. Pilot work suggests that this process may be mediated by purine (ATP and adenosine)-sensitive invariant natural killer T (iNKT) cells, cells in which the innate and adaptive immune systems intersect. For this renewal of the MESA Lung Study, we propose to perform contrast-enhanced, dual-energy CT to ascertain directly pulmonary microvascular blood volume (PMBV) in 1000 participants, assess emphysema subtypes, and spirometry among 2,000 participants, and measure iNKT cells in cases of emphysema, cases of reduced PMBV without obvious cause, and controls to test the following hypotheses: 1) PMBV is reduced and pulmonary artery volume is increased with percent emphysema and specifically in panlobular and centrilobular emphysema, suggesting that the site of resistance in these diseases is the pulmonary microvasculature; 2) immune activation is associated with emphysema progression and NKT-cell number and activation state are increased in emphysema and in participants with reduced PMBV; 3) lower regional and overall TPVV predicts progression of percent emphysema over 6 years among smokers and non-smokers. Innovative aspects of this proposal include the use of dual-energy CT scans to assess PMBV for the first time a large-scale study, longitudinal testing of the vascular hypothesis of emphysema among participants without COPD and among non-smokers, and assessment of iNKT cells in a multicenter study of emphysema. Confirmation of these aims in the MESA Lung Study, the only large, population-based, longitudinal study of emphysema, would provide a clear direction for strategies for the prevention of emphysema beyond smoking cessation and avoidance, a major new priority of the NHLBI/DLD, provide a potential imaging biomarker to facilitate early phase, short-term clinical trials, and suggest pulmonary vascular-related preventative and therapeutic strategies for emphysema.