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Intercellular adhesion molecule 1 and progression of percent emphysema: The MESA Lung Study

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Summary
Background: Endothelial intercellular adhesion molecule (ICAM) 1 binds neutrophils and facilitates their transmigration into the lung; E-selectin facilitates leukocyte rolling. As neutrophils contribute to tissue destruction in emphysema and chronic obstructive pulmonary disease, we hypothesized that soluble ICAM-1 (sICAM-1) and E-selectin (sE-selectin) would be associated with longitudinal progression of emphysema and lung function decline.
Methods: The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled participants 45–84 years old without clinical cardiovascular disease in 2000–02. The MESA Lung Study assessed percent

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emphysema (<−950 Hounsfield units) on cardiac (2000−07) and full-lung CT scans (2010−12), and spirometry was assessed twice over five years. sICAM-1 and sE-selectin were measured at baseline. Mixed-effect models adjusted for demographics, anthropometry, smoking, C-reactive protein, sphingomyelin and scanner factors.
Results: Among 1865 MESA Lung participants with measurement of sICAM-1 and percent emphysema the mean log-sICAM-1 was 5.5 ± 0.3 ng/mL and percent emphysema increased 0.73 percentage points (95% CI: 0.34, 1.12; $P < 0.001$) over ten years. A one SD increase in sICAM-1 was associated with an accelerated increase in percent emphysema of 0.23 percentage points over ten years (95% CI: 0.06, 0.39; $P = 0.007$). No significant association was found for sE-selectin, or between any adhesion molecule and lung function.
Conclusions: Higher levels of sICAM-1 were independently associated with progression of percent emphysema in a general population sample.

Introduction

Chronic obstructive pulmonary disease (COPD) is defined by spirometric airflow obstruction that does not fully reverse and is the 3rd leading cause of death worldwide [1]. Emphysema is defined pathologically as the permanent enlargement of airspaces and destruction of alveolar walls [2]. Emphysema occurs in the majority of patients with COPD [3] and is not infrequent among smokers without COPD or older never smokers [4]. Emphysema assessed quantitatively on computed tomography (CT) has been associated with increased hospitalizations and mortality in those with and without COPD [5−7]. However, the pathogenesis of COPD and emphysema remains incompletely understood and there are no medications targeting emphysema outside of alpha-1 antitrypsin deficiency.

Neutrophils, which are involved in the pathogenesis of emphysema and COPD, migrate into the lung via tight adhesion to intercellular adhesion molecule (ICAM) 1, an adhesion protein on endothelial cells [8,9]. E-selectin, an adhesion molecule expressed on activated endothelial cells, contributes to leukocyte rolling and thereby facilitates tight adhesion [8]. ICAM-1 blocking antibodies reduce neutrophilic pulmonary inflammation by two-thirds in animals, suggesting that ICAM-1 may be critical in neutrophil access to the lung [10]. Small studies have found altered ICAM-1 and E-selectin in COPD [11,12], and cross-sectional studies have found inverse associations between soluble ICAM-1 (sICAM-1) and lung function [13,14]. However, no longitudinal study has assessed the relationship between ICAM-1 or E-selectin and the progression of emphysema or decline in lung function.

Since endothelial ICAM-1 correlates with plasma levels of sICAM-1 [15], we tested the *a priori* hypotheses [16] that sICAM-1 and soluble E-selectin (sE-selectin) are associated with longitudinal increases in the percentage of emphysema-like lung on CT and decline in lung function with the goal to understand subclinical disease progression. We tested this hypothesis in a general population sample with mostly subclinical emphysema as it likely represents a biologically-relevant early stage in COPD pathogenesis, and may provide insight into strategies for disease prevention [17]. In addition, subjects with clinical disease are more likely to have characteristics that may confound the relationship of interest (e.g., active infection, corticosteroid use). In order to test the specificity of the associations, we also examined soluble vascular cell adhesion molecule (sVCAM)-1, soluble L-selectin (sL-selectin), and soluble P-selectin (sP-selectin), adhesion molecules that increase with inflammation but are less relevant to neutrophil recruitment [8,9].

Methods

Multi-Ethnic Study of Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA) recruited 6814 participants ages 45−84 years and free of clinical cardiovascular disease in 2000−02 from six U.S. communities [18]. Exclusion criteria were weight over 300 lbs, pregnancy, and impediments to long-term participation. The MESA Air Pollution Study recruited an additional 257 participants under the same criteria in 2004−07 [19].

The MESA Lung Study enrolled 3965 MESA participants in 2004−06 who had flow-mediated dilation measured and consented to genetic analyses [20], all MESA Air participants at one site, and an additional 408 MESA participants in 2010−12. The current analysis includes participants in the MESA Lung Study with measurement of sICAM-1 and baseline percent emphysema.

The protocols of MESA and all studies described were approved by the institutional review boards of collaborating institutions and the National Heart, Lung, and Blood Institute. Written informed consent was obtained from all participants.

Measurement of adhesion molecules

Plasma sICAM-1 was measured at baseline among 2621 MESA and the MESA Air participants using an ELISA assay (Parameter Human sICAM-1; R&D Systems, Minneapolis, MN). The coefficient of variation (CV) was 5.0%. Serum sE-selectin was measured at baseline for 998 MESA participants and the MESA Air participants (Parameter Human sE-selectin Immunoassay; R&D Systems; CV 5.7−8.8%).