[Original Research]

CHEST

A Longitudinal Cohort Study of Aspirin Use and Progression of Emphysema-like Lung Characteristics on CT Imaging

The MESA Lung Study

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BACKGROUND: Platelet activation reduces pulmonary microvascular blood flow and contributes to inflammation; these factors have been implicated in the pathogenesis of COPD and emphysema. We hypothesized that regular use of aspirin, a platelet inhibitor, would be associated with a slower progression of emphysema-like lung characteristics on CT imaging and a slower decline in lung function.

METHODS: The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled participants 45 to 84 years of age without clinical cardiovascular disease from 2000 to 2002. The MESA Lung Study assessed the percentage of emphysema-like lung characteristics (< –950 Hounsfield units) ("percent emphysema") on cardiac (2000-2007) and full-lung CT scans (2010-2012). Regular aspirin use was defined as 3 or more days per week. Mixed-effect models adjusted for demographics, anthropometric features, smoking, hypertension, angiotensin-converting enzyme inhibitor or angiotensin II-receptor blocker use, C-reactive protein levels, sphingomyelin levels, and scanner factors.

RESULTS: At baseline, the 4,257 participants' mean (± SD) age was 61 ± 10 years, 54% were ever smokers, and 22% used aspirin regularly. On average, percent emphysema increased 0.60 percentage points over 10 years (95% CI, 0.35-0.94). Progression of percent emphysema was slower among regular aspirin users compared with patients who did not use aspirin (fully adjusted model: –0.34% /10 years, 95% CI, –0.60 to –0.08; $P = .01$). Results were similar in ever smokers and with doses of 81 and 300 to 325 mg and were of greater magnitude among those with airflow limitation. No association was found between aspirin use and change in lung function.

CONCLUSIONS: Regular aspirin use was associated with a more than 50% reduction in the rate of emphysema progression over 10 years. Further study of aspirin and platelets in emphysema may be warranted.

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KEY WORDS: COPD; CT; platelets

ABBREVIATIONS: COX = cyclooxygenase; MDCT = multidetector CT; MESA = Multi-Ethnic Study of Atherosclerosis; PD15 = 15th percentile of lung density

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COPD and emphysema are jointly the third leading cause of death in the United States and the world.[1,2] Emphysema is defined as destruction of alveolar walls distal to the terminal bronchioles on pathologic specimens[3] and has also been measured on CT imaging as the percentage of emphysema-like lung characteristics (hereafter referred to as "percent emphysema"). Percent emphysema has been associated with lower left ventricular filling[4] and reduced daily activity,[5] as well as increased respiratory and all-cause mortality in COPD[6] and in the general population without airflow obstruction.[7,8]

The pathogenesis of COPD and emphysema is incompletely understood, but altered pulmonary blood flow and inflammation may be relevant factors.[9,10] Pulmonary capillaries are damaged in emphysematous lung in humans,[11,12] and factors that inhibit angiogenesis lead to emphysema in animals.[13,14] Platelet activation is increased in the setting of vessel injury and inflammation,[15] and in animal models of acute lung injury, platelet activation reduces pulmonary microvascular blood flow and increases lung neutrophils,[16,17] findings that are improved with aspirin.[17,18] Additionally, platelet factor 4, which is released on platelet activation, increased the extent of neutrophil elastase-induced emphysema in an animal study.[19] Finally, platelet activation was found to be increased in patients with COPD compared with control subjects[20] and during exacerbation among those with COPD,[21] and thrombocytosis was associated with increased mortality after hospitalization for COPD, a finding that was not present for those taking aspirin.[22] These findings suggest a potential role of platelets in emphysema and COPD; however, it is unknown whether aspirin use alters the progression of emphysema or the decline in lung function.

We hypothesized that regular use of aspirin would be associated with slower progression of percent emphysema seen on CT over 10 years. We also examined the change in lung function over 5 years. We tested this hypothesis in a general population sample with mostly subclinical emphysema, as doing so may provide insights into strategies for treatment and prevention.

Methods

Multi-Ethnic Study of Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study that recruited 6,814 participants in 2000 to 2002 from six US communities; they were aged 45-84 years and were free of clinical cardiovascular disease.[23] The MESA Air Pollution Study recruited an additional 257 participants using the same criteria in 2004 to 2007.[24] The MESA Lung Study enrolled 3,965 MESA participants in 2004 to 2006 (at the second and third visits).[25] All MESA Air participants were at one site. An additional 410 MESA participants were enrolled in 2010 to 2012 (e-Fig 1). The protocols of MESA and all studies described herein were approved by the institutional review boards of all collaborating institutions and the National Heart Lung and Blood Institute. All participants provided written informed consent.

Aspirin Use Assessment

Medication use was assessed at each visit by a medication inventory.[26] Participants were instructed to bring all prescription and over-the-counter medications used in the preceding 2 weeks to the visit; staff recorded the name, strength, and frequency. Participants were separately asked whether they were taking aspirin, and if so how many days per week.

The primary exposure was regular use of aspirin at baseline, defined as use of any aspirin dose 3 or more days per week, as even 81 mg every 3 days inhibits platelet activation.[27] Additional analyses evaluated any aspirin use at baseline, regular aspirin use at each visit, time-varying aspirin use, and doses of 81 and 300 to 325 mg.

Measurement of Percent Emphysema

All participants underwent cardiac CT scans at baseline following a standardized protocol at full inspiration on electron beam tomography and multidetector CT (MDCT) scanners.[28] Participants were coached to total lung capacity, and two scans were obtained. Lung volumes on replicate cardiac CT scans were highly correlated ($r = 0.95$), and unless image quality differed, the scan with the greatest lung volume was selected for analysis. Follow-up cardiac CT scans used the same protocol. Forty-five off-protocol scans and 312 acquired on Aquilion scanners (Toshiba), which produce unreliable lung density measures, were excluded. Full-lung scans were performed on 3,204 MESA Lung participants at the 10-year follow-up examination at full inspiration on MDCT scanners following the

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