The Relationship between Small Pulmonary Vascular Alteration and Aortic Atherosclerosis in Chronic Obstructive Pulmonary Disease:

Quantitative CT Analysis

Shin Matsuoka, MD, PhD, Tsuneo Yamashiro, MD, Alejandro Diaz, MD, Raúl San José Estépar, PhD, James C. Ross, PhD, Edwin K. Silverman, MD, PhD, Yasuyuki Kobayashi, MD, Mark T. Dransfield, MD, Brian J. Bartholmai, MD, Hiroto Hatabu, MD, PhD, George R. Washko, MD

Rationale and Objectives: The relationship between chronic obstructive pulmonary disease (COPD) and atherosclerosis has been suggested; this association may relate to systemic inflammation and endothelial dysfunction, which can lead to alteration of small pulmonary vessels. The relationship between atherosclerosis and small pulmonary vessel alteration, however, has not been assessed in COPD patients. We tested the hypothesis that the severity of thoracic aortic calcification measured by computed tomography (CT) would be associated with the total cross-sectional area of small pulmonary vessels (CSA) on CT images.

Materials and Methods: The study was approved by the institutional review board and was Health Insurance Portability and Accountability Act–compliant. Informed consent was waived. For 51 COPD patients enrolled in the National Heart, Lung, and Blood Institute Lung Tissue Research Consortium, we calculated the percentage of total CSAs of less than 5 mm^2 for the total lung area (%CSA<5). Thoracic aortic calcification, quantified by modified Agatston score, was measured. The correlations between thoracic aortic calcification score and %CSA<5, pulmonary function, and extent of emphysema were evaluated. Multiple linear regression analysis using aortic calcification score as the dependent outcome was also performed.

Results: The %CSA<5 had a significant negative correlation with the thoracic aortic calcification score ($r = -0.566$, $P < .0001$). Multiple linear regression analysis showed significant correlation between the aortic calcification score and %CSA<5 ($P < .0001$) independent of age, pack-years, extent of emphysema, and FEV1%.

Conclusions: Atherosclerosis, assessed by aortic calcification, is associated with the small pulmonary vascular alteration in COPD. Systemic inflammation and endothelial dysfunction may cause the close relationship between atherosclerosis and small pulmonary vessel alteration.

Key Words: Chronic obstructive; systemic inflammation; pulmonary artery; atherosclerosis; computed tomography.

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From the Department of Radiology (S.M., T.Y., H.H.), Pulmonary and Critical Care Division(A.D., E.K.S., G.R.W.), Surgical Planning Laboratory, Laboratory of Mathematics in Imaging (R.S.J.E., J.C.R.), and Channing Laboratory (E.K.S.), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Department of Pulmonary Diseases. Pontificia Universidad Católica de Chile, Santiago, Chile (A.D.); Department of Radiology, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan (S.M., Y.K.); Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham (M.T.D.); Department of Radiology, Mayo Clinic College of Medicine, Rochester, MN (B.J.B.). Received January 16, 2010; accepted August 1, 2010. Supported by National Institutes of Health (Grants K23HL089353-01A1, U01 HL089856-0), and a grant from The Parker B. Francis Foundation. **Address correspondence to:** S.M. e-mail: shin4114@mac.com

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Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory disorder (1–4) in which inflammation may be associated to the development of cardiovascular diseases (5,6). Although the underlying mechanisms remain unknown, cardiovascular disease contributes significantly to morbidity and mortality in COPD (7,8). Atherosclerosis is the principal cause of cardiovascular diseases, including coronary heart disease, stroke, and peripheral vascular disease (9,10), and it is thought to be associated with systemic inflammation and endothelial dysfunction (11–14). Prior investigations suggested that systemic inflammation in COPD may promote atherosclerosis (12), and recent studies have reported relationships between atherosclerosis and COPD (15–20).

The development of arterial calcification is an active process seen at all stages of atherosclerotic plaque development, and is closely associated with vascular injury (21,22). Many researchers have reported the relationship between aortic calcification and an increased risk of cardiovascular events (23–26). Patients with calcification in the thoracic aorta have 3.8 times the relative risk for obstructive coronary artery disease independent of age (26). In addition, a recent study showed that the severity of thoracic aortic calcification measured by computed tomography (CT) strongly correlates with inflammatory markers such as interleukin-6 (27).

Small pulmonary vascular alteration is a characteristic feature of COPD. Recent studies suggest that both pulmonary and extrapulmonary vascular alterations in COPD patients closely relate to systemic inflammation and endothelial dysfunction (15–19,28–30). Previously we have demonstrated that the total cross-sectional area of small pulmonary vessels (CSA) can provide clinically relevant data regarding pulmonary vascular disease in COPD (31,32). We sought to determine if this same CT-based measure of pulmonary vascular disease is related to accepted measures of arteriosclerosis in COPD. The principal purpose of this study was to evaluate the relationship between the severity of thoracic aortic calcification and CSA, each measured on CT images. To our knowledge, the relationship between systemic and pulmonary vascular alteration has not been assessed in COPD patients. Further, although correlations between atherosclerosis and the extent of emphysema and airflow obstruction have been reported (15–20), a relationship with thoracic aortic calcification has not been assessed. Thus, we also evaluated those relationships.

METHODS

Subjects

We retrospectively evaluated CT scans and clinical data collected as part of the National Heart, Lung, and Blood Institute Lung Tissue Research Consortium (LTRC). Further information on LTRC is available on the website www.ltrcpublic.com. This retrospective study was approved by the institutional review board at our institution, and performed in compliance with the Health Insurance Portability and Accountability Act guidelines. All subjects gave written informed consent. Subjects were evaluated for inclusion in our study if they had both a diagnosis of COPD (a ratio of postbronchodilator forced expiratory volume in 1 second to forced expiratory vital capacity, FEV1/FVC < 0.7) and high-resolution CT scans available for quantitative analysis. The LTRC cohort has CT images scanned in two different tube current protocols; subjects with the protocol using an automated dose modulation were excluded. The subjects with chronic heart failure, diabetes mellitus, or chronic renal failure were excluded from this study. Additional exclusion criteria included 1) obvious abnormal lung parenchymal lesions other than emphysema on the CT images used for analysis; 2) other potentially confounding abnormalities including pneumothorax, pleural effusion, cardiomegaly, findings suggestive of suggesting cardiac failure, or postoperative status; or 3) excessive image noise preventing image analysis.

All subjects underwent standardized spirometric lung function measurements according to American Thoracic Society guidelines (33). Postbronchodilator FEV1 and FVC were recorded in liters and expressed as percentages of predictive values (FEV1% predicted). Single-breath diffusing capacity for carbon monoxide was also obtained and expressed as percentages of predictive values (DLco% predicted).

Multislice CT Scanning

All subjects were scanned with 16-detector CT (Light Speed 16 or LightSpeed Pro16, GE Medical Systems, Milwaukee, WI) at full inspiration, without receiving contrast medium. Images were obtained using 140 kV and 300 mA. Acquisition time was 1 second or less and the matrix size was 512 × 512 pixels. Images were reconstructed with bone algorithm at a slice thickness of 1.25 mm and interval of 0.625 mm.

CT Measurement of Small Pulmonary Vessels

CT measurements of the pulmonary CSA has been described elsewhere (31,32). In brief, the following procedures were performed. First, the lung field was segmented using a threshold technique with all pixels between −500 and −1024 Hounsfield units (HU) on each CT image (Fig 1a). Next, segmented images were converted into binary images with a window level of −720 HU (Fig 1b). We measured CSA at sub-subsegmental level; the range of CSA of each vessel was defined as less than 5 mm^2 at the sub-subsegmental level (34). After these settings, CSA of each vessel was calculated (Fig 1c). Finally, we totaled the CSA of vessels measured on each set of three CT slices, and those totals were abbreviated as follows: CSA<5 for the total cross-sectional area of vessels that ranged <5 mm^2. The total area of the lung in the three selected slices was obtained using threshold values between −500 HU and −1024 HU, and the percentages of CSA<5 (%CSA<5) for the total area of the lung were calculated.

CT Measurement of the Thoracic Aortic Calcification

Reconstructed sagittal CT images were used for the assessment of thoracic aortic calcification. A calcified lesion in the thoracic aorta was defined as an area within an aortic wall with CT attenuation above a threshold of 90 HU (35). The thoracic aorta was defined as the region from the ascending aorta to the descending aorta at the level of the cardiac apex. Regions of interest around all lesions in each slice were placed by an experienced radiologist and were automatically analyzed by the OsiriX image processing software (Version 3.5.1; available at http://www.osirix-viewer.com).