Computed Tomography Assessment of Airways Throughout Bronchial Tree Demonstrates Airway Narrowing in Severe Asthma

Pierre-Yves Brillet, MD, PhD, Marie-Pierre Debray, MD, Jean-Louis Golmard, MD, PhD, Yahya Ould Hmeidi, MD, Catalin Fetita, PhD, Camille Taillé, MD, PhD, Michel Aubier, MD, Philippe A. Grenier, MD

Abbreviations and Acronyms

AUC area under the receiver operating characteristics curve

CT computed tomography

FEV_1 forced expiratory volume in 1 second

FVC forced vital capacity

LA lumen area

MDCT multidetector row computed tomography

WA wall area

WA% WA expressed as a percentage of total bronchial area (LA + WA)

Rationale and Objectives: To analyze airway dimensions throughout the bronchial tree in severe asthmatic patients using multidetector row computed tomography (MDCT) focusing on airway narrowing.

Materials and Methods: Thirty-two patients with severe asthma underwent automated (BronCare software) analysis of their right lung bronchi, with counts of airways >3 mm long arising from the main bronchi (airway count) and bronchial dimension quantification at segmental and subsegmental levels (lumen area [LA], wall area [WA], and WA%). Focal bronchial stenosis was defined as >50% narrowing of maximal LA on contiguous cross-sectional slices. Severe asthmatics were compared to 13 nonsevere asthmatic patients and nonasthmatic (pooled) subjects (Wilcoxon rank tests, then stepwise logistic regression). Finally, cluster analysis of severe asthmatic patients and stepwise logistic regression identified specific imaging subgroups.

Results: The most significant differences between severe asthmatic patients and the pooled subjects were bronchial stenosis (subsegmental and all bronchi: $P < .002$) and WA% ($P < .0003$). Stepwise logistic regression retained WA% as the only explanatory covariable ($P = .002$). Two identified clusters of severe asthmatic patients differed for parameters characterizing airway narrowing (airway count: $P = .0002$; focal bronchial stenosis: $P = .009$). Airway count was as discriminant as forced expiratory volume in 1 second/forced vital capacity ($P = .01$) to identify patients in each cluster, with both variables being correlated ($r = 0.59$, $P = .005$).

Conclusions: Severe asthma–associated morphologic changes were characterized by focal bronchial stenoses and diffuse airway narrowing; the latter was associated with airflow obstruction. WA%, dependent on airway caliber, is the best parameter to identify severe asthmatic patients from pooled subjects.

Key Words: Asthma; airway remodeling; multidetector computed tomography; imaging; three-dimensional.

Acad Radiol 2015; ■:1–9

From the University Paris 13, Sorbonne Paris Cité, Bobigny, France (P.-Y.B.); Department of Radiology, APHP, Hôpital Avicenne, Bobigny, France (P.-Y.B., Y.O.H.); Department of Radiology, APHP, Hôpital Bichat, Paris, France (M.-P.D.); Department of Biostatistics, APHP, Hôpital Pitié–Salpêtrière, Paris, France (J.-L.G.); Department ARTEMIS, CNRS UMR 8145, Telecom SudParis, Evry, France (C.F.); Université Paris Diderot–Paris 7, Paris, France (C.T., M.A.); INSERM U700, Faculté de Médecine Bichat, Paris, France (C.T., M.A.); Department of Pulmonology, APHP, Hôpital Bichat, Paris, France (C.T., M.A.); Université Pierre et Marie Curie, INSERM U678, Paris, France (P.A.G.); and Department of Radiology, APHP, Hôpital Pitié–Salpêtrière, Paris, France (P.A.G.). Received October 2, 2014; accepted December 29, 2014. **Address correspondence to:** P.A.G. e-mail: philippe.grenier@psl.aphp.fr

http://dx.doi.org/10.1016/j.acra.2014.12.026

Asthma is a heterogeneous condition, which may be characterized in terms of clinical, functional, and biological phenotypes (1,2). Approximately, 5%–10% of asthmatic patients have severe disease (3), associated with airway inflammation that induces structural changes over time. These changes are known as airway wall remodeling (4) and include subepithelial fibrosis, enlarged mucous glands, smooth muscle hypertrophy and hyperplasia (5,6). Remodeling in severe asthma has functional consequences, with decreased forced expiratory volume in 1 second (FEV_1) (7) and persistently increased bronchial hyperresponsiveness (3). However, whether functional alterations are associated with three-dimensional (3D) in vivo bronchial

geometry modifications due to airway narrowing remains to be demonstrated.

Bronchial remodeling can be assessed quantitatively on bronchial biopsy specimens but histologic examination does not provide information on its variability throughout the bronchial tree (8). Moreover, data on bronchial tree geometry are sparse, mainly based on examination of rubber casts of airways (9). Nowadays, the morphologic consequences of remodeling in severe asthma need to be better understood as it would contribute to choosing the best adapted among new emerging treatments (10).

Computed tomography (CT) represents a valuable, noninvasive method for assessing airways throughout the bronchial tree. Most CT studies have focused on bronchial dimensions of proximal airways and evaluation of airway wall area (WA) in asthma (11). That quantification has also been considered a biomarker of remodeling (12) through WA measurement and calculation of WA as a percentage of total bronchial area [WA% = WA/(LA + WA) × 100] (11,13–17). However, data on lumen area (LA) changes all along the bronchial tree are lacking. Multidetector row CT (MDCT) and automated software (18) advances make such assessments possible and provide information on remodeling distribution and severity, from the bronchus origin to its distal divisions, and its consequences on the airway lumen caliber (19). Those findings would be relevant to help phenotype the disease and select appropriate treatment, such as, bronchial thermoplasty (20) (aiming to reduce the airway smooth muscle and induce bronchodilatation).

The primary study objective was to analyze bronchial tree morphologic changes, including airway wall thickening and airway narrowing, that can be visualized and measured with 3D/2D multiparametric airway analysis derived from the MDCT acquisitions of severe asthmatic patients. The second goal was to investigate whether airway morphologic parameters could identify specific subgroups of severe asthma patients.

MATERIALS AND METHODS

Patients

The study was approved by the appropriate institutional and ethics committees according to French law. Written informed consent was obtained from each patient. Thirty-two patients with severe asthma, according to the World Health Organization definition (21), were prospectively recruited by a Department of Respiratory Medicine between July 2009 and February 2012. Their clinical and functional data are summarized in Table 1. These patients underwent MDCT scans as part of their standard workup, temporally far (>6 weeks) from any exacerbation or infection. Seven patients with milder asthma, recruited during the same period by the same pulmonologists (blinded, blinded), also underwent MDCT scans according to the same protocol. Six nonasthmatic subjects, who underwent MDCT for atypical thoracic pain ($n = 4$) or to rule out pulmonary metastasis ($n = 2$) and having no pulmonary abnormality on MDCT, were also included. The latter two groups were pooled to serve as controls.

MDCT Acquisitions

Acquisitions were obtained on a 64-channel MDCT (LightSpeed VCT; GE Medical Systems, Milwaukee, WI), according to a standard acquisition protocol (120 kVp; automated mA exposure with a noise index of 35 and z-axis modulation) and 0.625-mm collimation (0.984 pitch). The dose × length product was always <250 mGy/cm. No contrast material was used. Overlapping 0.625-mm reconstructions every 0.3 mm were obtained to have near-isotropic images, using a bone kernel. No iterative reconstruction was used. Images were focused on the right lung because of potential cardiac motion artifacts in the left lower lobe lingula which could impair measurement. A 512^2 pixel matrix was used, giving a constant pixel length (0.42–0.5 mm).

Airway Computations

The volumetric, high-resolution CT lung data sets were analyzed with a dedicated workstation using BronCare software (ARTEMIS Department, Telecom SudParis, Evry, France). This software automatically processes MDCT data for 3D airway lumen segmentation (22,23), central-axis computation of the airway tree (skeletonization), and 2D reconstruction of manually selected bronchi in a cross-sectional plane orthogonal to this axis, with automatic computation of LA, WA, and WA% (24). To study bronchial LA geometry, the interval between each reconstructed slice was <1 mm. Finally, to generate the 3D color-coded LA caliber map, corresponding to every point on the lumen surface, the lumen dimension at each point is measured and colored. It reports the radius of the maximal sphere inscribed in the lumen volume and tangent to its surface at this point (25) (Fig 1).

Bronchus Analysis

Two radiologists (both blinded) reviewed 2D reconstructed slices and 3D-lumen caliber images of the bronchi to consensus, in a random order. That analysis described the geometry of the distal airway tree (airway count) and the proximal bronchi (with evaluation of LA, WA, WA%, and detection of bronchial stenoses). First, from the skeletonization of the airway tree, the number of ≤3-mm-long bronchi (to exclude artifacts mainly due to bronchial diverticula) segmented by the software was counted from the main bronchus. The derived parameter (airway count) served as a surrogate of distal airway caliber. The underlying concept is that the segmentation algorithm uses detection of airway candidates, followed by constrained propagation, which retrieves the distal airway segments (23). In the case of airway obstructions