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Parametric Response Mapping as an Indicator of Bronchiolitis Obliterans Syndrome after Hematopoietic Stem Cell Transplantation

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The management of bronchiolitis obliterans syndrome (BOS) after hematopoietic cell transplantation presents many challenges, both diagnostically and therapeutically. We developed a computed tomography (CT) voxel-wise methodology termed parametric response mapping (PRM) that quantifies normal parenchyma, functional small airway disease (PRM^{fSAD}), emphysema, and parenchymal disease as relative lung volumes. We now investigate the use of PRM as an imaging biomarker in the diagnosis of BOS. PRM was applied to CT data from 4 patient cohorts: acute infection (n = 11), BOS at onset (n = 34), BOS plus infection (n = 9), and age-matched, nontransplant control subjects (n = 23). Pulmonary function tests and bronchoalveolar lavage were used for group classification. Mean values for PRM^{fSAD} were significantly greater in patients with BOS (38% ± 2%) when compared with those with infection alone (17% ± 4%, $P < .0001$) and age-matched control subjects (8.4% ± 1%, $P < .0001$). Patients with BOS had similar PRM^{fSAD} profiles, whether a concurrent infection was present or not. An optimal cut-point for PRM^{fSAD} of 28% of the total lung volume was identified, with values >28% highly indicative of BOS occurrence. PRM may provide a major advance in our ability to identify the small airway obstruction that characterizes BOS, even in the presence of concurrent infection.

INTRODUCTION

Pulmonary complications, both infectious and noninfectious, are a common cause of morbidity and mortality after hematopoietic cell transplantation (HCT). Within this context, bronchiolitis obliterans syndrome (BOS) remains particularly problematic, characterized clinically by fixed airflow obstruction of small airways and pathologically by progressive circumferential fibrosis of terminal bronchioles. BOS is extremely heterogeneous in its presentation, due in part to the nonuniform diagnostic criteria historically used to define the condition [1–3]. The development of National Institutes of Health consensus criteria (NIH-CC) over the past decade has been a major advance in our recognition and categorization of the disorder [2,4]. NIH-CC–defined clinical parameters for the diagnosis of BOS depend on a combination of clinical and radiographic findings, including diminished forced expiratory volumes in 1 second (FEV_1), evidence of air trapping on high-resolution computed tomography (HRCT), the absence of active pulmonary infection, and the presence of chronic graft-versus-host disease in another organ.

Using the NIH-CC definition, the criteria for BOS are often not met until a patient exhibits significant airway obstruction, with FEV_1 values typically less than 60% predicted at the defined onset [3,5]. Once present, the prognosis of affected patients is poor, with 5-year overall survival < 20% [5]. Therapeutic options for BOS are minimal, with responses measured as disease stabilization rather than functional

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improvement [6,7]. Early recognition of the disorder, before the development of irreversible airway changes, may potentially lead to improvements in therapeutic responses and overall survival.

The parametric response mapping (PRM) technique has been developed at our center as a quantitative imaging biomarker for the assessment of obstructive lung disease. PRM is a voxel-based approach that provides detailed information on disease phenotype otherwise unattainable by conventional CT-based quantitative measures. Using biphasic (inspiratory and expiratory) HRCT, PRM is able to determine the severity, phenotype, and spatial heterogeneity of the pulmonary pathology using a methodology distinct from other CT-based measures [8–11]. PRM was first demonstrated on HRCT data from patients with chronic obstructive pulmonary disease, allowing quantification of the degree of functional small airway disease (fSAD) and emphysematous changes in relation to normal lung parenchyma [8]. Commonly used CT metrics for the diagnosis of lung disease have historically used tissue volumetric summary statistics of lung fields, including the mean lung density. PRM, however, classifies local variations in lung function based on a voxel-by-voxel comparison of lung attenuation changes from coregistered inspiratory and expiratory CT scans, providing both global and localized evaluations of lung pathology.

We now report on the application of PRM to patients with BOS after HCT, specifically adapted to quantify the relative contribution of fSAD in affected individuals irrespective of the presence of acute infection. A comparison of PRM in patients with BOS, at the time of initial diagnosis of BOS (based on NIH-CC) and during episodes of secondary infection, is now examined.

METHODS

Retrospective clinical data, pulmonary function analysis, and HRCT images at inspiration and expiration were obtained from 3 groups of HCT recipients at the University of Michigan Medical Center: group 1, infection, no BOS; group 2, BOS, no infection; and group 3, BOS, with infection. Group 1 patients were early post-HCT (<120 days), with an acute infectious pneumonitis and no clinical or radiographic features of BOS. Group 2 patients were selected at the time of NIH-CC–defined onset of BOS, without active pulmonary infection. Group 3 patients previously met the NIH-CC for BOS but now exhibited an infectious pneumonitis.

Bronchoalveolar lavage (BAL) studies, including BAL special stains, PCR assays for viral pathogens, and cultures for bacteria, fungi, viruses, and mycobacteria, were performed to establish the presence (or absence) of an infectious pneumonitis in patients in all groups. Pulmonary function tests (PFTs) including measurements of FEV_1, forced vital capacity (FVC), FEV_1/FVC ratio, residual volume, and lung diffusion capacity were obtained, with measurements expressed as percent predicted values. Modified NIH-CC were required to establish the diagnosis of BOS, including a $FEV_1 < 75\%$ predicted, signs of obstructive airway disease (FEV_1/FVC ratio <.7, residual volume >120% predicted, or evidence of air trapping on HRCT), absence of infection, and the presence of chronic graft-versus-host disease in another organ [4]. NIH lung function scores were determined, based on published methodology [4].

Bronchoscopy was performed within 14 days (group 1) or 28 days (groups 2 and 3) from the defined HRCT. PFTs were performed within 28 days of the HRCT in group 2 and 3 patients. Paired PFTs and HRCT were not available in group 1 patients, given the early post-transplant time course of this group. FEV_1, FEV_1/FVC, and lung diffusion capacity were acquired as part of the study design and analyzed in this study. In addition, a single case from group 2 was identified as having 5 interval CT examinations. Data were analyzed and presented to demonstrate the use of PRM to monitor pulmonary complications and disease progression. All transplant subjects signed an institutional review board–approved informed consent for data collection and analysis.

Additional age-matched, nontransplant, healthy subjects (group 4) were analyzed for this study to serve as negative control subjects (n = 23). These subjects, accrued as part of a separate clinical trial at the University Medical Center Groningen (NORM Study, NCT00848406), were individuals >40 years of age who did not smoke during the last year and had <.5 pack years smoking history. Pulmonary function measurements (FEV_1 and FEV_1/FVC) were acquired in all age-matched control subjects.

Parametric Response Mapping

The PRM method consists of 3 key steps: image acquisition, image processing, and voxel classification (Figure 1) [8].

Image acquisition

Internal CT data at the University of Michigan were obtained as whole lung volumetric CT scans at full inspiration (total lung capacity) and incremental scans at relaxed expiration (functional residual capacity) on GE scanners (GE Healthcare, Little Chalfont, UK) and reconstructed using a bone reconstruction kernel. Slice thicknesses were 1.25 mm for all scans, with slice numbers on average around 220 for inspiration scans and around 15 for expiration scans. All CT scans were linearly Hounsfield unit (HU)-corrected based on aortic blood (50 HU) and central air (−1000 HU) as described previously [12].

NORM Study CT data (for control subjects) were obtained as whole lung volumetric acquisitions both at full inspiration and forced expiration (residual volume) on a Somatom scanner (Siemens, Munich, Germany) with 1-mm slice thickness and a reconstruction index of .7 mm. A standard kernel (B30f) was used for image reconstruction. HU values of aortic blood (37 HU) and central air (−995 HU) were determined to check for scanner drift on all NORM data. All data were found to have negligible drift; as such, no HU corrections were performed.

Image processing

Image processing consisted of lung parenchymal segmentation followed by deformable volumetric registration, which spatially aligns the inspiration scan to the expiration scan such that both share the same spatial geometry. The lungs from expiratory CT scans acquired at the University of Michigan were segmented from the surrounding anatomy (ie, bronchus, heart, and chest wall) using in-house algorithms developed in a mathematical programming language (Matlab, Natick, MA). User verification and manual corrections were applied as necessary. Whole lung volumetric inspiration data were registered to the interval expiration data, allowing presentation of the PRMs. Inspiratory scans were coregistered to expiratory scans for all subjects and time points. Image registration was performed using a cost function of mutual information and thin-plate spline warping deformations [13]. Upon completion of image registration, the images share the same geometric space. Each voxel, the smallest unit of volume in a 3-dimensional image data set, consisted of a pair of HU values: 1 HU value at inspiration and 1 HU value at expiration. For reference, air and water attenuation values are −1000 and 0 HU, respectively.

The NORM trial acquired whole lung volumetric CT scans at both inspiration and expiration, with CT data processed by our group as described above. One distinction between the CT scans from the NORM trial and CT scans from group 1, 2, and 3 subjects was the direction of scan registration (geometric alignment), given differences in spatial arrangements between inspiratory and expiratory views. In the NORM Study, expiration scans were registered (aligned) to the inspiration scans [8], whereas CT scans for group 1, 2, and 3 subjects did the converse, aligning the inspiratory scans with the expiration scans.

Voxel classification

Classification of the voxels from attenuation maps into discrete zones allows quantification of normal lung parenchyma, fSAD, emphysema, and parenchymal disease characteristic of infection (Figure 1, Table 1). Three thresholds are used to classify individual voxels into 1 of 4 categories with the following color codes: emphysema (red voxels), fSAD (yellow voxels), normal parenchyma (green voxels), and parenchymal disease (purple voxels). Voxels with HU values less than −950 on the inspiration scan and at least −856 on the expiration scan have been identified previously as having a weak correlation to pulmonary function (ie, FEV_1) [8]. As such, no analysis was performed on this measure. In addition, parenchymal tissue with voxel values above −500 HU on the inspiration scan were not analyzed in this study. Global PRM measures were calculated by normalizing the sum of all voxels within a classification by the total lung volume, which include all parenchymal voxels over the full range of HU. The nomenclature of these measures for normal lung parenchyma, fSAD, emphysema, and parenchymal disease were PRM^{Normal}, PRM^{fSAD}, PRM^{Emph}, and PRM^{PD}, respectively.

Thresholds of −950 HU and −856 HU on the inspiration and expiration scans, respectively, were defined as specified by the COPDGene study [14]. The upper limit on the inspiration CT (−810 HU) was determined using inspiration CT scans from the age-matched control subjects (group 4; n = 23) obtained from the NORM Study. Briefly, the CT lung density data were normalized by taking their natural logarithm. A bi-Gaussian fit was performed on the normalized CT data and the 95% confidence interval (1.96 × standard deviation) of the principle peak that resides in a range of −1000 to −500 was determined.