CHEST

# Heterogeneity of Specific Gas Volume Changes
## A New Tool to Plan Lung Volume Reduction in COPD

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**OBJECTIVE:** The aim of this work was to investigate if regional differences of specific gas volume (SVg) in the different regions (lobes and bronchopulmonary segments) in healthy volunteers and patients with severe emphysema can be used as a tool for planning lung volume reduction (LVR) in emphysema.

**METHODS:** CT scans of 10 healthy subjects and 10 subjects with severe COPD were obtained at end-inspiration (total lung capacity [TLC]) and end-expiration (residual volume [RV]). For each subject, ΔSVg (ΔSVg = SVg,TLC − SVg,RV, where SVg,TLC and SVg,RV are specific gas volume at TLC and RV, respectively) vs ΔV (ΔV = V,TLC − V,RV, where V,TLC and V,RV are lung volume at TLC and RV, respectively) was plotted for the entire lung, each lobe, and all bronchopulmonary segments. For each subject, a heterogeneity index (HI) was defined to quantify the range of variability of ΔSVg/ΔV in all bronchopulmonary regions.

**RESULTS:** In patients with COPD, SVg,TLC and SVg,RV were significantly higher and ΔSVg variations lower than in healthy subjects ($P < .001$). In COPD, ΔSVg/ΔV slopes were lower in upper lobes than in lower lobes. In healthy subjects, the entire lung, lobes, and bronchopulmonary segments all showed similar ΔSVg/ΔV slopes, whereas in COPD a high variance was found. As a consequence, HI was significantly higher in subjects with COPD than in healthy subjects ($0.80 \pm 0.34$ vs $0.15 \pm 0.10$, respectively; $P < .001$).

**CONCLUSIONS:** SVg variations within the lung are highly homogeneous in healthy subjects. Regions with low ΔSVg/ΔV (ie, more pronounced gas trapping) should be considered as target areas for LVR. Regions with negative values of ΔSVg/ΔV identify where collateral ventilation is present. HI is helpful to assess the patient in the different stages of disease and the effect of different LVR treatments.

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**ABBREVIATIONS:** HI = heterogeneity index; HU = Hounsfield unit; LAA = low attenuation area; LAA-856 = lung pixels with an attenuation of ≤ −856 HU on expiratory CT scan; LAA-950 = lung pixels with an attenuation of ≤ −950 HU on inspiratory CT scan; LLL = left lower lobe; LUL = left upper lobe; LVRS = lung volume reduction surgery; ROI = region of interest; RLL = right lower lobe; RUL = right upper lobe; RV = residual volume; SVg = specific gas volume; SVg,r = regional specific gas volume; TLC = total lung capacity

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In the past years there have been intense research efforts to develop precise imaging biomarkers relevant to COPD and other lung diseases. Analysis of lung ventilation is explored via MRI with hyperpolarized gases, such as $^{3}He$[1-3] or $^{129}Xe$.[4] CT imaging allows densitometric measurements of the lung, and its ability to quantify trapped gas has been shown.[5-8]

Research into new biomarkers has been mirrored by efforts at trapped-gas reduction via new invasive and minimally invasive interventions, such as stent-supported airway bypass[9] and ronchially installed, one-way exit valves.[10] Endobronchial treatments are still in investigational phases; preliminary results are varied and may suffer from the lack of a precise imaging biomarker. Recently, it has been shown that quantitative CT scan target volume[11] and regional perfusion[12] analysis may help to identify lobar exclusion and to select the most responsive patients to ronchial valve treatment. Measurements of changes in specific gas volume (SVg) via CT scan may not only be an excellent biomarker but may also provide specific regional information that can aid in surgical planning and evaluation posttreatment. SVg is defined as volume of gas per gram of tissue (mL/g) and is derived pixel-by-pixel from CT images of lung density.[6,8] It can be extracted from CT images by converting the Hounsfield unit (HU) value to a measure of specific volume, which is a more physiologically meaningful measure. This method has been introduced by Coxson et al[5,6] in studies assessing regional lung volumes and by Salito et al[8] in studies on an animal model of airway obstruction and on emphysematous lungs in vivo.[7] SVg is necessarily quantitative, and it can be used regionally[13] and globally.

The aim of this work was to evaluate if heterogeneity of SVg and its changes with lung volume can be considered a useful tool for planning lung volume reduction surgery (LVRS) in patients with severe emphysema who are candidates for LVRS. We hypothesized that in the different regions of normal lungs, variations of SVg with lung volume are very similar throughout the lung. Conversely, in emphysema there are regions where gas is trapped, and regional SVg should vary little with volume, in contrast to other regions where regional SVg variations are greater than normal and the heterogeneity of variations of SVg with lung volume would be larger. Therefore, our hypothesis was that regional SVg variations are able to identify target areas for LVRS, to quantify their extension, and to assess their connection with other regions. To verify these hypotheses, we analyzed SVg in the entire lung, in the different lobes, and in selected regions of interest belonging to all bronchopulmonary segments in healthy volunteers and patients with COPD in whom CT images were taken at high and low lung volumes.

## Materials and Methods

### *Subjects*

CT imaging was performed on 10 healthy volunteers with no history of smoking or lung disease and 10 patients with severe COPD belonging to a pretreatment assessment database of a clinical trial.[14] The institutional review board of Washington University approved the protocol for healthy humans (HRPO n. 09-0602), and informed written consent was obtained from each subject. Local institutional review board approval was obtained, and written informed consent was obtained from all patients with COPD.

### *CT Imaging*

All subjects underwent scanning with a multidetector CT scanner (SOMATOM Sensation; Siemens AG). After coaching, CT scan was performed during a breath-hold in both deep inspiration (approximating total lung capacity [TLC]) and deep expiration (approximating residual volume [RV]) with the subject in the supine position. The subjects were instructed on the importance of breath-holding and immobility during scanning and on attaining reproducible maximum inspiratory and expiratory breath-hold.

The voxel size was $0.625 \times 0.625 \times 1$ mm, x-ray tube current 160 mA, kVp 120, pitch 1, and effective mAs 160 in CT images of healthy subjects. CT images of patients with COPD had a variable slice thickness (0.6-2 mm). All the CT images were reconstructed with a standard reconstruction filter (b50f). The resulting radiation dose was approximately 2.4 and 2.5 to 2.7 mSv per scan, respectively, in healthy subjects and patients.

### *Image Analysis*

**Lung/Lobes Segmentation and Volume Calculation:** CT images of the lung were first segmented by means of an automatic algorithm based on the method proposed by Hu et al.[15] Left and right lungs were separated by detecting the anterior and posterior junctions, and lung boundaries along the mediastinum were smoothed. The lobes were segmented using MIPAV software (National Institutes of Health, http://mipav.cit.nih.gov/). As in some cases the fissure was not clearly visible, right middle lobe was grouped with the right upper lobe (RUL). The voxels with intensity below $-600$ HU were considered to be parenchymal, and the volume of the whole lung (tissue and airspace) was computed as the sum of the volumes of the voxels in each segmented slice, calculated as the product of the pixel size and the reconstruction interval spacing between slices.[5]

**Region of Interest Selection:** A three-dimensional airway reconstruction was used to choose a region of interest (ROI) in each lung segment (see later) at the two different lung volumes (Fig 1). An automatic algorithm using a region-growing approach, based on the iterative algorithm proposed by Kiraly et al,[16] was developed to segment airway trees. The airways segmentation began by selecting a seed point in the trachea. The regions to be segmented were identified by means of voxel connectivity and inclusion criteria. Considering the seed point as the first point of the segmented region, the HU