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

Caterina Salito, PhD; Livia Barazzetti, MSc; Jason C. Woods, PhD; and Andrea Aliverti, PhD

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 ΔSVgvariations 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 bronchopulmo-nary 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 ± 0.34 vs 0.15 ± 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. CHEST 2014; 146(6):1554-1565

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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

AFFILIATIONS: From the TBMLab (Drs Salito and Aliverti and Ms Barazzetti), Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy; the Center for Pulmonary Imaging Research (Dr Woods), Cincinnati Children's Hospital Medical Center, Cincinnati, OH; and the Department of Physics (Dr Woods), Washington University, St. Louis, MO.

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CORRESPONDENCE TO: Caterina Salito, PhD, Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, P.zza L. da Vinci, 32, 20133 Milano, Italy; e-mail: caterina.salito@polimi.it

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 endobronchially 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 endobronchial 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 × 0.625 × 1 mm, x-ray tube current 160 mA, kVp 120, pitch 1, and effective mAs 160 in CT images of healthy sub-jects. 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 sub-jects 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 recon-struction 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 seg-ment airway trees. The airways segmentation began by selecting a seed point in the trachea. The regions to be segmented were identi-fied by means of voxel connectivity and inclusion criteria. Consider-ing the seed point as the first point of the segmented region, the HU

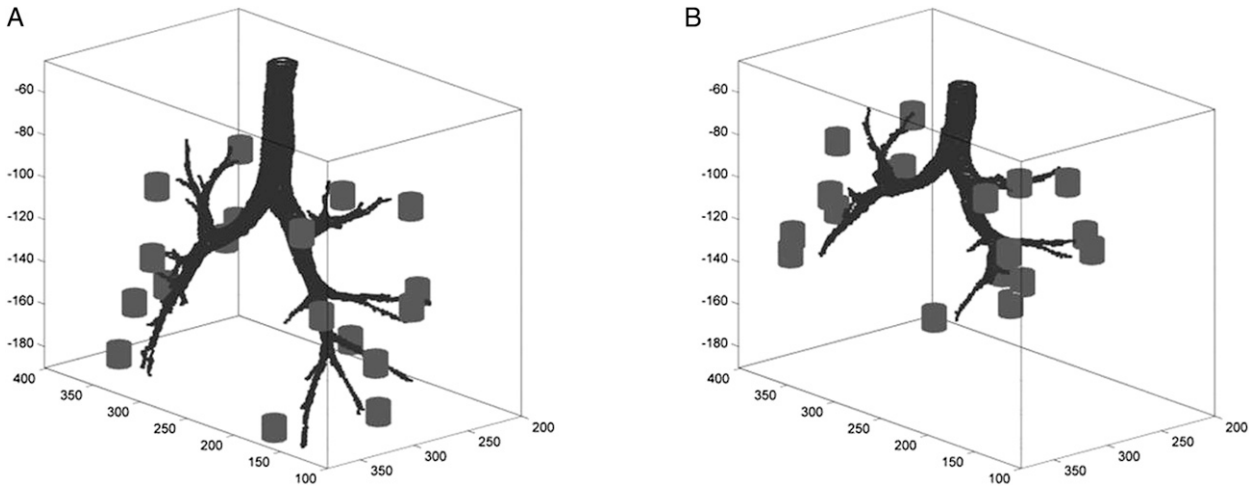

Figure 1 – *Example of a three-dimensional airway reconstruction used to define the cylindrical region of interest in all the bronchopulmonary segments at the two different lung volumes. A, TLC. B, RV. RV = residual volume; TLC = total lung capacity.*

intensity of each voxel belonging to a 26-member neighborhood of the seed point was checked and added to the segmented region if it was below a certain threshold.[17] The optimal intensity threshold was the maximum intensity threshold that did not result in parenchymal leakage (ie, the condition where the segmented region "leaks" out of the airways and includes a large number of voxels belonging to the parenchyma). The segmentation was completed by a morphologic closing and hole-filling step. The airway trees were reconstructed to the level of subsegmental bronchi, or later subdivisions in some cases.[17] The selected ROI in each segment was a cylinder constructed by choosing a circle on a selected slice, clearly within the bronchopulmonary segment of interest, with a diameter of 10 mm and extending 5 mm below and above this central slice. The circle was chosen distal to a segmental bronchus but not overlapping it and clearly avoiding the inclusion of voxels belonging to any airway.

Quantitative Analysis: All quantitative analysis was performed by a custom software developed in Matlab (The MathWorks, Inc).[7] Parenchymal analysis was performed for the entire lung, the different lobes, and all bronchopulmonary segments, in terms of SVg, defined as the difference between specific volume of tissue and gas and the specific volume of tissue and expressed as milliliters (gas)/grams (tissue).[6] Specific volume of tissue and gas is the inverse of density as measured from CT scan, which is calculated by adding 1,024 to the HU of each voxel and then dividing by 1,024.[6] The value used for the specific volume of tissue is the inverse of mean tissue density and calculated as specific volume of tissue = 1/1.06 mL/g.[18] For the calculation of SVg, voxels belonging to airways, blood vessels, and other structures of the lung were excluded, and only those belonging to the parenchyma (ie, with HU values < -600 HU) were considered. Changes of SVg ($\Delta SVg = SVg,TLC - SVg,RV$, expressed as mL/g, where SVg,TLC and SVg,RV are specific gas volume at TLC and RV, respectively) relative to the corresponding whole-lung volume variations ($\Delta V = V,TLC - V,RV$, expressed as mL, where V,TLC and V,RV are lung volume at TLC and RV, respectively) were calculated as $\Delta SVg/\Delta V$ and expressed per milligrams.

According to a recently published study,[19] the percentage of the voxels with attenuation values ≤ -950 HU (in CT images taken at TLC [LAA-950]) and ≤ -856 HU (in images taken at RV [LAA-856]) was calculated to estimate the extent of emphysema and gas trapping. To obtain global and lobar estimates, percentages were calculated respectively for the entire lung (LAA-950,total and LAA-856,total) and the different lobes (LAA-950,lobar and LAA-856,lobar), namely RUL, right lower lobe (RLL), left upper lobe (LUL), and left lower lobe (LLL).

For each subject, a plot including all the segments connecting the values of SVg (expressed as percentage of SVg,TLC) and of lung volume (expressed as percentage of predicted TLC volume) at TLC and RV for each bronchopulmonary segment was constructed (gray lines in Fig 2). In the same plot, the segment relative to the overall lung was included (black line in Fig 2). A heterogeneity index (HI) was then defined for each subject as

$$HI = \frac{\sqrt{\left(\sum_{i=1}^{N} d_i^2\right)/N}}{\Delta V}$$

where N is the total number of the considered bronchopulmonary segments; d_i is the vertical distance (in the diagram) between the end point of the i^{th} bronchopulmonary segment and the end point of the overall lung at RV; and ΔV is lung volume change.

Sensitivity Analysis on $\Delta SVg/\Delta V$: To evaluate the effects of the arbitrary selection of the ROI within a given bronchopulmonary segment on $\Delta SVg/\Delta V$, in three patients with COPD (P1, P2, and P3), nine different ROIs were considered for each bronchopulmonary segment, by varying ROI size (three sizes, diameter from 10-20 mm and height from 6-22 mm) and ROI position (three positions within the same segment). For each segment, the deviation from the average $\Delta SVg/\Delta V$ was calculated. The range of variability in $\Delta SVg/\Delta V$, exclusively due to the arbitrary selection of the ROI within a given bronchopulmonary segment, was then defined as the 25th to 75th percentile range of the overall distribution of the 432 (nine ROIs, 16 bronchopulmonary segments, three subjects) values obtained as described.

Statistical Analysis

To compare SVg data, a three-way analysis of variance was performed with volume (RV and TLC), lobe (upper and lower), and disease (healthy and COPD) as independent factors. To compare $\Delta SVg/\Delta V$ data, a two-way analysis of variance was performed with lobe and disease as independent factors. Post hoc tests were based on the Holm-Sidak method. Linear regression analysis was applied to analyze possible relationships between % low attentuation area (LAA) and SVg and ΔSVg. Significance was determined by P values $< .05$.

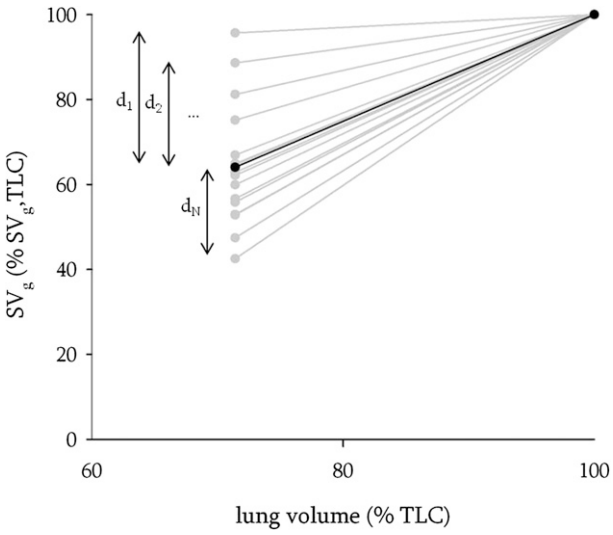

Figure 2 – *Representative plot including all the segments connecting the values of SV_g (expressed as percentage of SV_g at TLC, SV_g,TLC) and of lung volume (expressed as percentage of predicted TLC volume) at TLC and RV for each bronchopulmonary segment (gray lines) and the segment relative to the overall lung (black line). d = distance between the end points of each bronchopulmonary segment and the end point of the overall lung at RV. N = total number of the considered bronchopulmonary segments. SV_g = specifi c gas volume. See Figure 1 legend for expansion of other abbreviations.*

Results

Anthropometric characteristics, spirometric parameters, total LAAs, and lung volume (calculated from CT images) are reported in Table 1 for both patients with COPD and healthy subjects. Individual values of LAA-950 and LAA-856 in the diff erent lobes are shown in Table 2 . Individual total and lobar values of mean values of SVg at RV and TLC are shown in Table 3 . Th e group of healthy subjects (aged 41-62 years) had normal spirometry for their ages, FEV_1/FVC values 70%, and RV/TLC < 32%. Patients were characterized by values of total and lobar %LAA-950, %LAA-856, lung volumes, and RV/TLC ratio (> 65%) indicating severe and very severe emphysema, gas trapping, and a high degree of lung hyperinfl ation. [19] Absolute SVg values in patients with COPD were dramatically higher than healthy control subjects, in the whole lung and in all lobes, both at RV and TLC.

Figure 3 reports average values of SVg at TLC and RV in patients with COPD and healthy subjects for all the considered bronchopulmonary segments. In patients, the segments belonging to the right middle lobe (RB4 and RB5) were not included in the analysis because of the diffi culty in obtaining reliable segmentation in these regions. Th e average and intersubject variability (ie, SD) of SVg in the diff erent bronchopulmonary segments, both at TLC and RV, was much higher in subjects with COPD than in healthy subjects ($P < .001$). SVg values at TLC were significantly different than SVg values at RV in healthy subjects ($P < .001$) but not in subjects with COPD ($P = .067$).

In healthy subjects, SVg values in the upper lobes were not significantly different than those in the lower lobes ($P = .55$), whereas in COPD, SVg was significantly greater in the upper compared with the lower lobes ($P = .02$) (Table 3). The relationships between ΔSVg and lung volume variation were very similar in all healthy subjects. Conversely, a great intersubject variability was found in COPD.

Figure 4 illustrates two examples, a patient with COPD and a representative healthy subject. In the patient, a high variance of the slopes (both positive and negative) of the straight lines connecting SVg and volume values at TLC and RV was found. On the contrary, in the healthy subjects the slopes were very similar for the whole lung (black solid line), all lobes (black dashed lines), and bronchopulmonary segments (gray lines).

Figure 5 demonstrates that these findings can be generalized. In the same panel, the straight lines connecting SVg and volume values at TLC and RV, for the whole lung and the different lobes, averaged in all healthy control subjects and all patients with COPD, are shown. Although in the control subjects all straight lines were very similar ($P = .741$), in the patients with COPD the straight lines of the different lobes were more largely distributed around the line of the entire lung, with upper lobes being above (lower slope) and lower lobes below (greater slope) ($P < .001$). Interestingly, the slopes in the upper lobes were significantly greater in control subjects than in subjects with COPD ($P < .001$), whereas in the lower lobes the slopes were similar between healthy subjects and subjects with COPD ($P = .956$).

Figure 6 reports the values of ΔSVg/ΔV ("slopes") of all bronchopulmonary segments in all subjects. Although overall average values of slopes were very similar between healthy subjects and those with COPD (2.76/mg and 2.82/mg, respectively), overall variability was significantly higher in patients with COPD (SD = 3.80/mg, $P < .001$) and very low in the healthy (SD = 0.81/mg). In Figure 6A, the upper limit of significant negative values of slopes, calculated as the 25th percentile in the distribution of slopes exclusively due to ROI selection (−1.79/mg, dashed vertical line), is shown. Six out of 10 patients had bronchopulmonary segments with significantly negative slopes. Intrasubject

TABLE 1] Anthropometric Characteristics, Spirometric Parameters, Total Percentage of LAA-950 and LAA-856, and Lung Volume (Calculated From CT Images) for Patients With COPD and Healthy Subjects

Subjects	Sex	Age, y	Weight, kg	Height, cm	FEV_1, % Pred	FVC, % Pred	FEV_1/FVC, % Abs	% LAA-950	% LAA-856	V,TLC, mL	V,RV, mL
COPD											
P1	F	65	68	163	28	63	35	32	71	6,049	4,387
P2	F	55	50	163	16	38	33	37	81	4,624	3,891
P3	F	54	57	170	n/a	n/a	23	35	66	6,356	5,732
P4	M	65	46	168	19	47	32	60	85	6,997	5,489
P5	F	67	49	170	18	55	24	38	81	5,891	5,240
P6	F	62	59	165	20	42	37	34	69	5,858	4,879
P7	M	71	80	178	16	63	19	57	83	9,327	6,459
P8	M	65	69	180	15	47	11	45	80	8,979	6,518
P9	F	54	64	165	17	50	27	35	47	5,902	4,214
P10	F	n/a	n/a	n/a	18	74	20	43	50	4,668	3,722
Mean	…	62	60	169	18	52	26	42	71	6,465	5,053
SD	…	6	11	6	4	11	8	10	13	1,585	1,006
Control											
S1	F	54	76	173	135	140	78	24	19	6,028	1,873
S2	M	62	75	180	123	114	86	23	11	5,915	1,192
S3	M	46	78	178	97	102	78	13	12	4,360	1,762
S4	F	44	60	163	134	138	81	23	37	5,338	2,804
S5	M	49	114	201	93	108	70	27	21	9,383	2,777
S6	F	46	68	165	113	121	77	20	6	5,451	1,379
S7	F	41	81	155	91	96	80	14	1	3,728	949
S8	F	45	89	160	104	114	83	17	3	4,717	1,858
S9	F	42	89	173	108	127	71	24	4	5,560	1,356
S10	F	44	77	165	91	97	79	25	2	4,367	1,245
Mean	…	47	81	171	109	116	78	21	12	5,485	1,719
SD	…	6	15	13	17	16	5	5	11	1,560	640

abs = absolute; 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; n/a = data not available; pred = predicted; RV = residual volume; TLC = total lung capacity; V,RV = lung volume at residual volume; V,TLC = lung volume at total lung capacity.

TABLE 2] Lobar Percentage LAA-950 and LAA-856 in Patients With COPD and in Healthy Subjects

	RUL		RLL		LUL		LLL	
Subjects	%LAA-950	%LAA-856	%LAA-950	%LAA-856	%LAA-950	%LAA-856	%LAA-950	%LAA-856
COPD								
P1	35	79	17	77	33	71	26	58
P2	66	89	60	85	60	86	65	85
P3	41	76	35	68	34	69	25	49
P4	54	79	45	63	54	81	67	89
P5	30	81	52	88	34	84	27	70
P6	29	66	33	68	18	48	48	82
P7	61	89	26	48	58	88	35	52
P8	52	91	26	72	53	93	11	57
P9	34	50	46	84	28	64	21	50
P10	42	73	46	78	44	77	25	50
Mean	44	77	39	73	42	76	35	64
SD	13	12	13	12	14	13	19	16
Control								
S1	29	30	16	24	26	24	14	9
S2	29	14	15	8	30	11	13	3
S3	15	17	9	16	17	13	11	16
S4	28	62	16	11	34	63	15	20
S5	32	33	28	5	34	27	28	4
S6	30	8	25	2	23	4	16	4
S7	15	9	13	1	11	6	11	1
S8	14	20	12	3	14	17	13	5
S9	25	13	18	4	23	7	17	2
S10	24	15	20	4	24	2	20	12
Mean	24	22	17	8	24	17	16	7
SD	7	16	6	7	8	18	5	6

LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RUL = right upper lobe. See Table 1 legend for expansion of other abbreviations.

variability of ΔSVg/ΔV, expressed by the HI calculated in each subject, was significantly higher in COPD than in healthy subjects (respectively, 0.80 ± 0.34 and 0.15 ± 0.10; $P < .001$).

In Figure 7 , the relationships between lobar and total LAAs and the corresponding absolute values of SVg and ΔSVg/ΔV are shown both in subjects with COPD (fi lled symbols) and control subjects (open symbols). In Figures 7A-D, for each value of lobar LAA-950 and lobar LAA-856 (x-axis), the values of SVg and ΔSVg/ΔV of the differentbronchopulmonarysegmentsbelonging to a given lobe are indicated on y-axis. In Figures 7E and 7F, for each value of total LAA-950 and total LAA-856 (x-axis), the values of ΔSVg/ΔV of all the bronchopulmonary segments belonging to a given subject are indicated on the y-axis.

Discussion

CT imaging has been recognized as an important method for assessment of COPD. One of the approaches allowed by this technique is the calculation of specific volume of gas, which converts CT scan density into the physiologic meaningful index of volume of gas per gram of tissue. SVg is expected to change as a function of lung volumes. In the present work we measured SVg changes as lung volume decreases from a high volume close to TLC to a lower volume close to RV. The analysis was conducted not only for the overall lung but also locally, by considering the different lobes and by selecting small regions of interest corresponding to the different bronchopulmonary segments, in the same way that we envision future analysis for interventional targeting. This is of physiologic relevance, because total

TABLE 3] Lung Volumes and SVg Values in the Different Lobes in Patients With COPD and Healthy Subjects

	Whole Lung			RUL		RLL		LUL		LLL	
Subjects	SVg,TLC, mL/g	SVg,RV, mL/g	Δ SVg, mL/g	SVg,TLC, mL/g	SVg,RV, mL/g	SVg,TLC, mL/g	SVg,RV, mL/g	SVg,TLC, mL/g	SVg,RV, mL/g	SVg,TLC, mL/g	SVg,RV, mL/g
COPD											
P1	11.9	8.9	3.0	13.9	10.9	11.7	7.1	14.8	10.9	10.4	7.3
P2	38.6	35.5	3.2	56.2	58.1	33.6	25.5	46.8	45.0	29.4	22.6
P3	29.3	27.3	2.1	33.4	30.6	29.2	25.8	28.2	26.9	25.7	23.1
P4	41.6	33.1	8.5	40.1	32.5	35.7	28.3	38.9	31.6	47.4	39.4
P5	14.4	13.4	1.1	12.2	12.1	14.3	12.1	12.2	12.0	18.5	15.6
P6	17.3	14.1	3.2	11.8	9.5	24.7	21.1	10.0	6.9	21.9	18.2
P7	45.4	40.1	5.3	57.5	52.4	23.0	19.0	52.0	47.6	30.5	22.4
P8	20.5	17.2	3.3	24.1	21.6	17.7	11.3	25.1	23.0	13.0	10.5
P9	16.0	10.2	5.7	17.1	11.0	18.2	12.0	14.7	9.4	14.3	8.5
P10	37.5	34.7	2.8	35.7	33.1	43.7	42.7	36.8	34.0	34.3	29.6
Mean	27.2	23.4	3.8	30.2	27.2	25.2	20.5	28.0	24.8	24.6	19.7
SD	12.7	11.9	2.1	17.3	17.5	10.3	10.6	15.1	14.8	11.3	10.0
Control											
S1	13.5	3.8	9.8	14.6	4.3	12.0	3.3	15.5	4.3	12.1	3.1
S2	14.4	2.7	11.6	15.2	2.8	11.3	2.5	15.7	2.8	15.8	2.8
S3	8.4	3.4	4.9	9.0	4.1	7.3	3.5	9.7	3.3	7.6	2.6
S4	13.0	5.3	7.8	15.4	6.0	10.0	4.1	14.8	6.8	12.0	4.1
S5	14.3	3.4	10.9	14.6	3.9	15.2	3.1	13.6	4.0	13.6	2.8
S6	12.3	2.7	9.6	13.4	2.8	10.9	2.8	12.9	2.4	12.1	2.7
S7	9.6	2.6	7.0	9.8	2.8	9.3	2.4	10.3	2.8	8.9	2.3
S8	10.5	3.2	7.3	10.6	3.4	9.7	2.8	11.7	3.7	10.0	2.9
S9	14.3	3.1	11.2	16.2	3.9	13.3	2.9	14.4	3.0	13.1	2.4
S10	14.5	3.2	11.3	14.7	3.8	14.5	2.7	14.6	3.5	14.0	2.7
Mean	12.5	3.3	9.1	13.3	3.8	11.4	3.0	13.3	3.7	11.9	2.8
SD	2.2	0.8	2.3	2.6	1.0	2.4	0.5	2.1	1.3	2.5	0.5

All data are obtained from CT images taken at TLC and RV. SVg = specific gas volume. See Table 1 and 2 legends for expansion of other abbreviations.

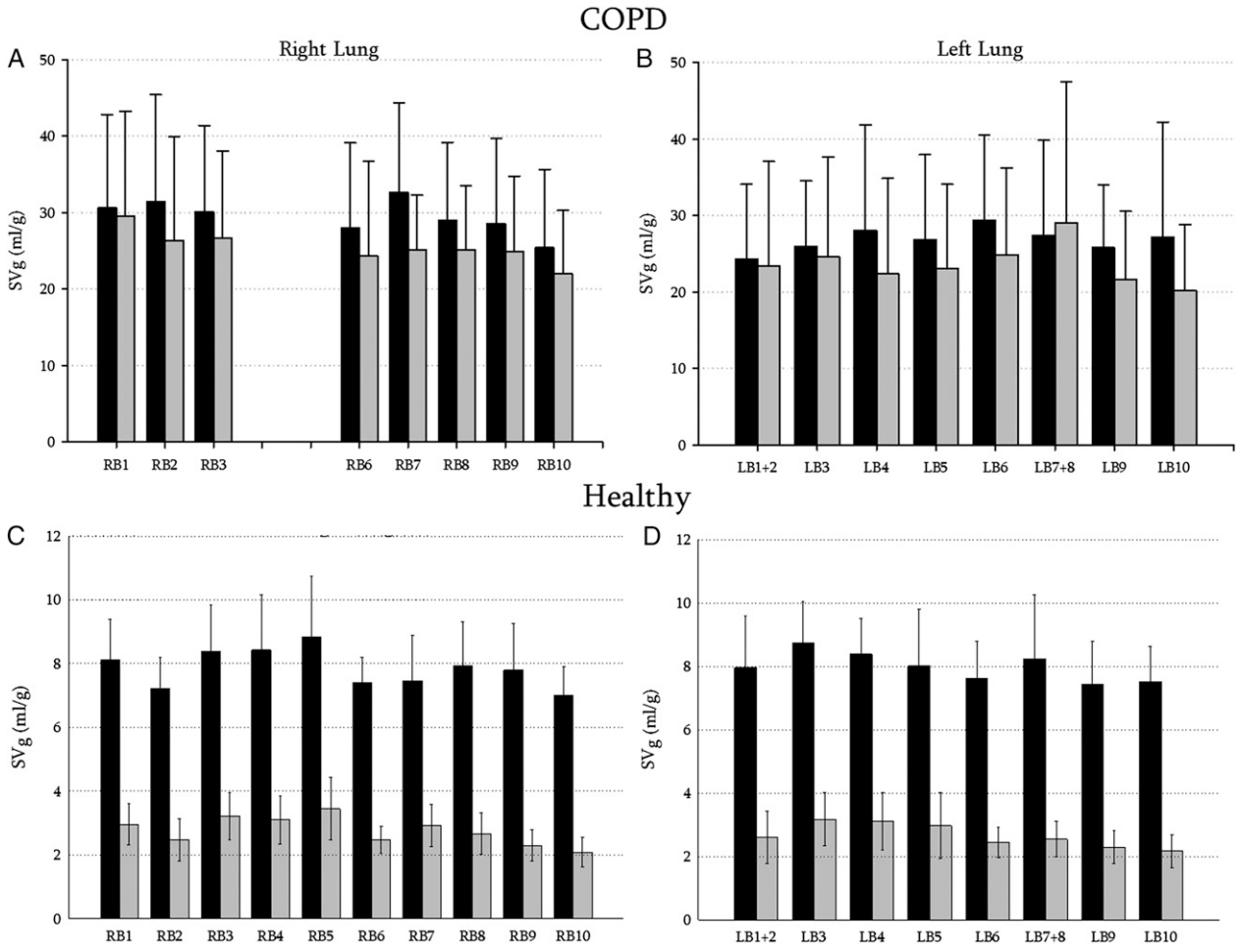

Figure 3 – *A-D, Average values of SV_g at TLC (black bars) and RV (gray bars) in patients with COPD (A, B) and healthy subjects (C, D) for all the considered bronchopulmonary segments. Data are reported as mean ± SD. See Figure 1 and 2 legends for expansion of abbreviations.*

specifi c gas volume of the lung represents an average of all "regional" (ie, either lobes or bronchopulmonary segments) specifi c volumes (SVg,r). If there are regions where SVg,r varies little with volume so that the slope of a plot of ΔSVg,r against overall lung volume variation (ΔV) is smaller than that for both lungs, there must be other regions where ΔSVg,r/ΔV is steeper, indicating a greater than average decrease in SVg,r with decreasing volume. In normal lungs, there is no gas trapping above closing volume, so that the spread of values of ΔSVg,r/ΔV around their mean value is small (Fig 5). Conversely, in patients with COPD we found a considerably larger range of slopes, as shown in Figure 5, and quantified by the higher values of the HI, that allows quantifying in a single parameter the degree of heterogeneity in terms of regional lung emptying. Our results also indicate that the regions where SVg,r varies little with volume are mostly localized in the upper lobes, whereas lower lobes show similar ΔSVg,r/ΔV values.

Figure 6 illustrates that in emphysema the distribution of ΔSVg,r/ΔV slopes in the different bronchopulmonary segments is very wide compared with normal lungs, with more emphysematous lung regions having low values of ΔSVg,r/ΔV (left tail of the distribution plot in the figure), other regions remaining normal, and other regions having higher values (right tail of the plot). In other words, from this point of view in COPD the lung can be considered as a three-compartment system, in which one compartment groups all units with severe emphysema (regions with gas trapping and low values of ΔSVg,r/ΔV), one groups all healthy units (regions with normal values of ΔSVg,r/ΔV), and one groups all units with higher-than-normal values of ΔSVg,r/ΔV. It is interesting to note that the occurrence of regions characterized by low values of ΔSVg,r/ΔV was similar in the different regions, with no significant differences between upper and lower lobes or between right and left lungs. As shown again in Figure 6 (left tail of the frequency distribution of ΔSVg,r/ΔV), a significant

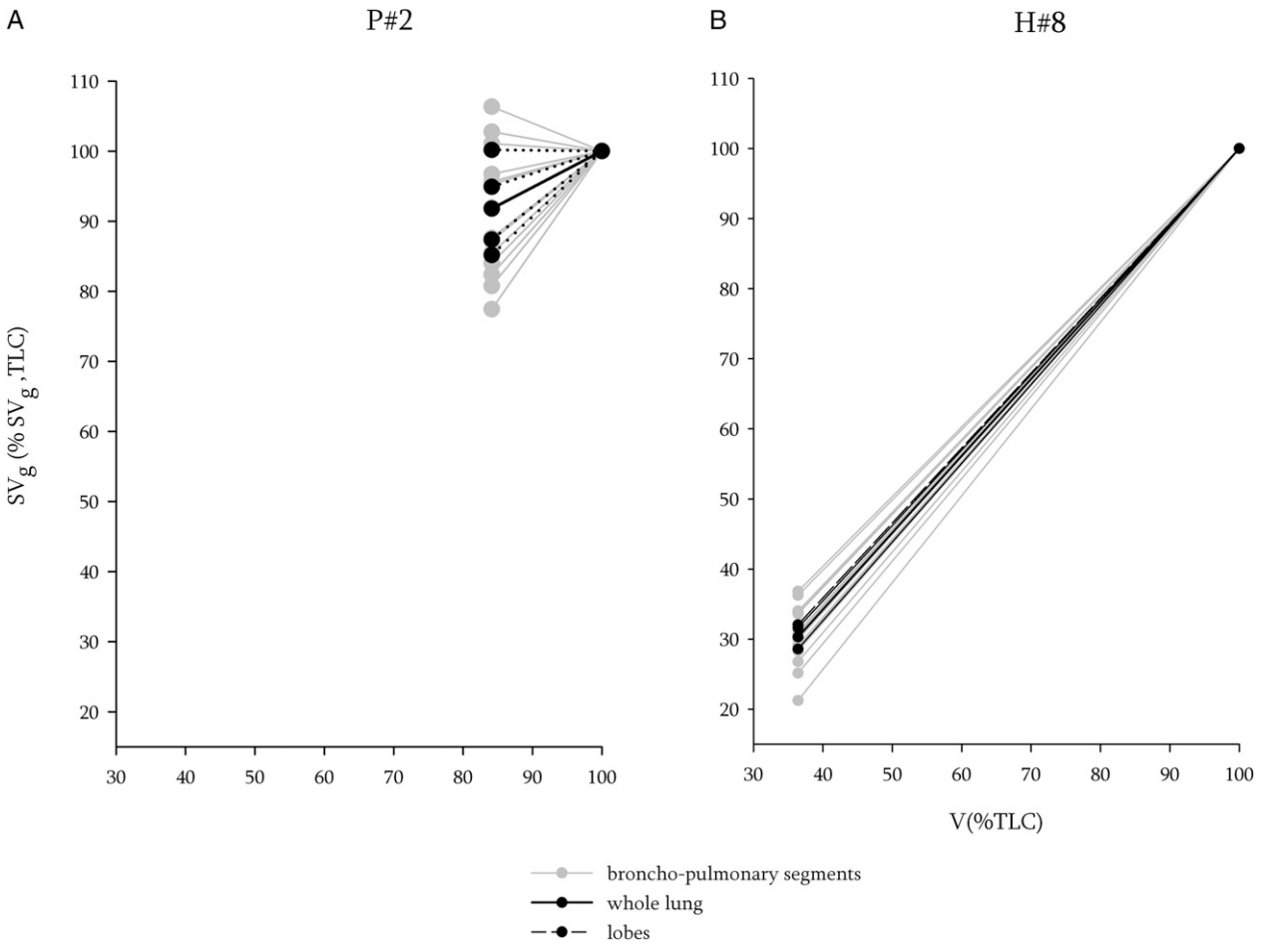

Figure 4 – *A, B, SV_g, expressed as % SV_g,TLC, as function of the lung volume (expressed as V[%TLC]) in one patient with COPD (P#2) (A) and in a representative healthy subject (H#8) (B). Gray lines: segments connecting SVg and volume values at TLC and RV in all bronchopulmonary segments. Dashed black lines: segments connecting SV_g and volume values at TLC and RV in the different lobes. Black lines: segments connecting SV_g and volume values at TLC and RV in the whole lung. V(%TLC) = %TLC volume. See Figure 1 and 2 legends for expansion of other abbreviations.*

number of bronchopulmonary segments in severe emphysema are characterized by significantly negative slopes in the ΔSVg,r/ΔV plot (ie, SVg increases when lung volume decreases). This is also visible in the representative example reported in Figure 4, where the straight lines of three bronchopulmonary segments are

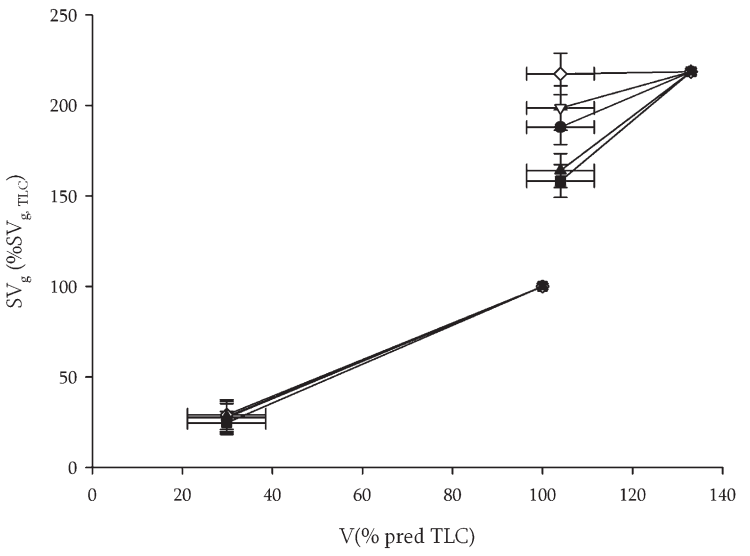

Figure 5 – *SV_g, expressed as $\%SV_{g,TLC}$ as function of the lung volume (expressed as pred %TLC volume). All segments connect SV_g and volume values at TLC and RV of the entire lung and all lobes. All points are reported as mean ± SD of all patients with COPD and all healthy subjects. LLL = left lower lobe; LUL = left upper lobe; pred = predicted; RLL = right lower lobe; RUL = right upper lobe. See Figure 1 and 2 legends for expansion of other abbreviations.*

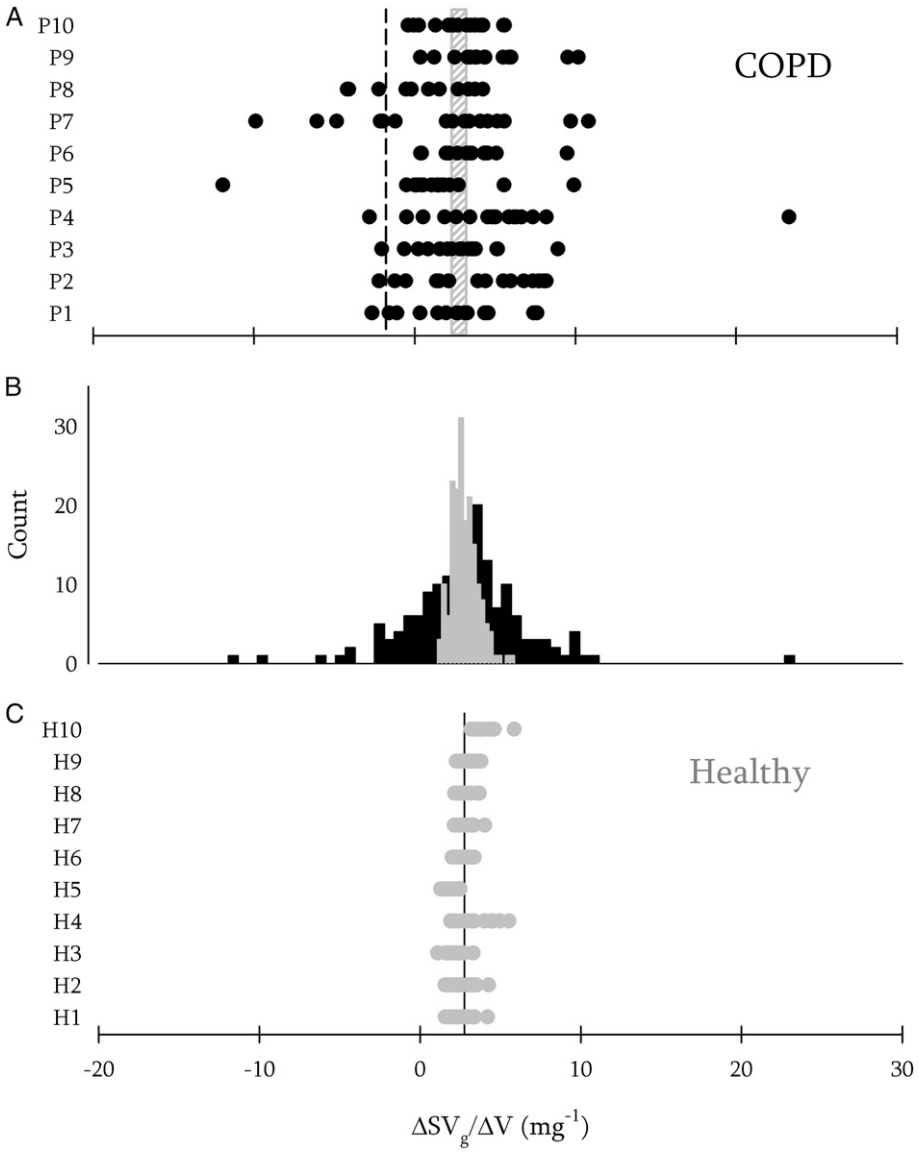

Figure 6 – *A-C, Values of* $\Delta SV_g/\Delta V$ *of all bronchopulmonary segments in all individual patients with emphysema (A) and in all individual healthy subjects (C). B, Frequency distributions of all* $\Delta SV_g/\Delta V$ *values in all patients with emphysema (black) and all healthy subjects (gray). Vertical solid lines = means of all* $\Delta SV_g/\Delta V$ *values. Dashed line: upper limit of significant negative values of slopes (see text). Gray area: range (25th-75th percentiles) of* $\Delta SV_g/\Delta V$ *values in healthy subjects.* $\Delta SV_g = SV_g,TLC - SV_g,RV$; ΔV *= total lung volume variations* ($\Delta V = V,TLC - V,RV$). *See Figure 1 and 2 legends for expansion of other abbreviations.*

characterized by a negative slope. As we pointed out,[20] a possible mechanism underlying this phenomenon is the presence of collateral flowthroughcollateralchannelsin the emphysematous lung.[20] On the contrary, as the collateral ventilation is uniformly low in the healthy lung since the resistance to airflowismuchgreaterthrough collateral channels than in the airway,[20,21] all bronchopulmonary segments are characterized by positive slopes in the ΔSVg,r/ΔV plots. Figure 7F demonstrates that negative slopes are present in patients with LAA-856 > approximately 60% (ie, the most severe in terms of total gas trapping)[19] irrespective of the global extent of emphysema (Fig 7E). These findings are evident only when considering the relationships between ΔSVg,r/ΔV and total (not lobar) LAAs. Therefore, the main strength of ΔSV/ΔV is to provide the chance to study lung function locally, a possibility not provided by using LAAs calculated on smaller regions of the lung.

A limitation of the current study is represented by the dimensions of the regions of interest, which were of limited size compared with the segments, and by their positions within the segments, which were chosen to avoid possible intersections with the airways. The total number of subjects is relatively small, although results in the healthy group are quite narrowly distributed. All patients were characterized by severe COPD, which made them a somewhat homogeneous group.

The results of the regression analysis between LAA-950 and SVg,TLC (Fig 7A) and LAA-856 and SVg,RV (Fig 7B) indicate that although in healthy subjects absolute values of SVg are obviously related to the amount of gas per

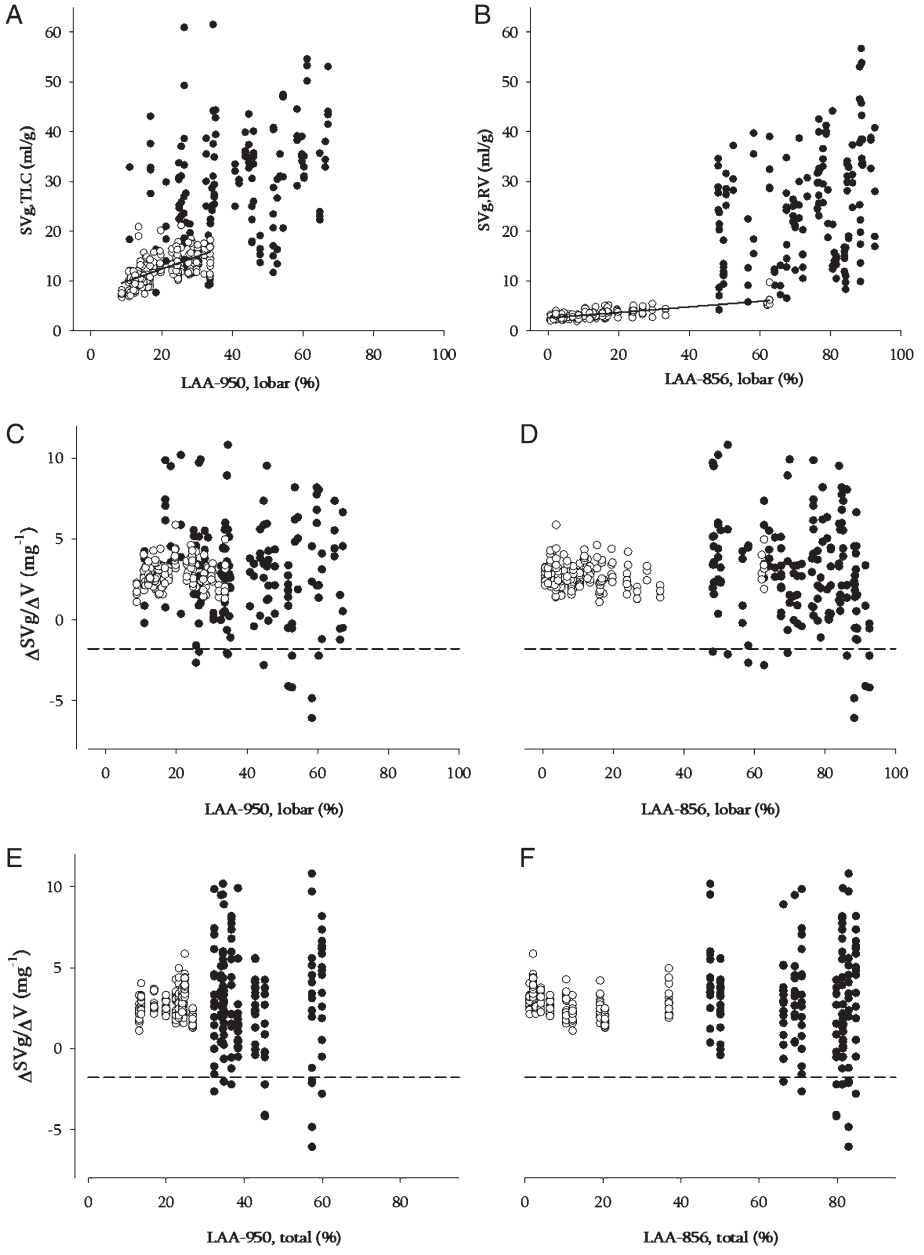

Figure 7 – *Relationships between LAA, SV_g, and changes of SV_g relative to the corresponding whole lung volume variations ($\Delta SV_g/\Delta V$) in COPD (closed symbols) and healthy control subjects (open symbols). LAA expressed as percentage of voxels with density < −950 HU within a lobe at TLC (LAA-950,lobar), density < −950 HU within the entire lungs at TLC (LAA-950,total), density < −856 HU within a lobe at RV (LAA-856,lobar), density < −856 HU within the entire lungs at RV (LAA-856,total). A, B, C, D, For each value of either LAA-950,lobar (A and C) or LAA-856,lobar (B and D), the values of SV_g and $\Delta SV_g/\Delta V$ of the different bronchopulmonary segments belonging to a given lobe are indicated on y-axis. In E and F, for each value of total LAA-950,total and LAA-856,total (x-axis), the values of $\Delta SV_g/\Delta V$ of all bronchopulmonary segments belonging to a given subject are indicated on y-axis. Dashed horizontal straight lines (C-F): upper limit of significant negative values of slopes (see text). HU = Hounsfield unit; LAA = low attenuation area. See Figure 1 and 2 legends for expansion of other abbreviations.*

lung tissue, in subjects with severe COPD they predict neither the extent of emphysema nor gas trapping. Only variations of SVg are able to describe functional abnormalities. In fact, the identifi cation of regions where ΔSVg/ΔV is low would help to identify and quantify regions (lobes and/or segments) where gas trapping is more pronounced. Th e i dentifi cation of regions where ΔSVg/ΔV is negative, instead, would help to identify regions where collateral ventilation is present. Theq uantifica tion of the heterogeneity index, fi nally, would be helpful to assess the patient in the diff erent stages of disease and before/after different treatments.

To our knowledge, this is the first study that characterizes the healthy lung in terms of SVg distribution measured from CT images of the lung at two different lung volumes. Therefore, the values here provided of SVg (in the small range of 14-10.24 mL/g at TLC and 4.65-3.01 mL/g at RV) and ΔSVg/ΔV (in the small range of 2.76 ± 0.81/mg) obtained in the group of healthy subjects represent a reference for future studies in which SVg and its changes with lung volume may be used as global and regional biomarkers for surgical planning and posttreatment evaluation of different techniques used for lung volume reduction in emphysema.

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