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Whole-lung volume and density in spirometrically-gated inspiratory and expiratory CT in Systemic Sclerosis: correlation with static volumes at pulmonary function tests

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Abstract. *Background:* Spiral low-dose computed tomography (LDCT) permits to measure whole-lung volume and density in a single breath-hold. *Objective:* To evaluate the agreement between static lung volumes measured with LDCT and pulmonary function test (PFT) and the correlation between the LDCT volumes and lung density in restrictive lung disease. *Design:* Patients with Systemic Sclerosis(SSc) with(n=24) and without(n=16) pulmonary involvement on sequential thin-section CT and patients with chronic obstructive pulmonary disease(COPD)(n=29) underwent spirometrically-gated LDCT at 90% and 10% of vital capacity to measure inspiratory and expiratory lung volumes and mean lung attenuation(MLA). Total lung capacity and residual volume were measured the same day of CT. *Results:* Inspiratory [95% limits of agreement(95%LoA) -43.8% and 39.2%] and expiratory(95%LoA -45.8% and 37.1%) lung volumes measured on LDCT and PFT showed poor agreement in SSc patients with pulmonary involvement, whereas they were in substantial agreement (inspiratory 95%LoA -14.1% and 16.1%; expiratory 95%LoA -13.5% and 23%) in SSc patients without pulmonary involvement and in inspiratory scans only (95%LoA -23.1% and 20.9%) of COPD patients. Inspiratory and expiratory LDCT volumes, MLA and their Δs differentiated both SSc patients with or without pulmonary involvement from COPD patients. LDCT lung volumes and density were not correlated in SSc patients with pulmonary involvement, whereas they did correlate in SSc without pulmonary involvement and in COPD patients. *Conclusions:* In restrictive lung disease due to SSc there is poor agreement between static lung volumes measured using LDCT and PFT and the relationship between volume and density values on CT is altered. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 17-27)*

Key words: lung densitometry, pulmonary funtion tests, low dose computed

Introduction

Patients with restrictive lung diseases are usually evaluated with high resolution thin section computed tomography (CT) at deep inspiration for visual or densitometic assessment of the structural changes underlying the functional abnormalities (1-5).

Acquisition of CT scan at deep expiration, while it provides equal densitometric characterization of restrictive vs obstructive disease and healthy condition (6-7), offers the opportunity when combined with inspiratory scan, so called paired inspiratory/expiratory approach, to measure the changes of lung cross-sectional area and attenuation between maximal inspiratory and expiratory manoeuvre

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which were found to differentiate obstructive and restrictive lung disease (7-9).

Volumetric or spiral CT at standard or low dose enables whole-lung scan in a single breath-hold and offers two major advantages for evaluation of diffuse lung diseases with respect to sequential thin-section CT. First, it permits estimation of lung volume which is a major determinant of lung density. Second, it provides a more complete assessment of lung density since only a small fraction of lung parenchyma is examined in sequential thin-section CT (10-13). This is particularly valuable in view of longitudinal studies. In order to reduce the influence of the variable level of lung inflation or deflation during CT acquisitions, a spirometrically-gated CT technique has been developed and implemented on sequential thin-section or spiral whole-lung acquisitions to scan the lung at controlled and standardized volume in obstructive or restrictive lung disease (6, 14-21). In particular, it was demonstrated that spirometrically-gated whole-lung densitometry obtained with low dose CT (LDCT) was more reproducible and more closely correlated with pulmonary function tests (PFT) than visual assessment of sequential thin-section CT at standard dose in patients with restrictive lung disease due to pulmonary involvement in Systemic Sclerosis (SSc) (21). This justified optimism about the potential of whole lung densitometry performed on LDCT for longitudinal evaluation of this type of restrictive lung disease (21).

In healthy subjects and patients with obstructive lung disease, lung density is almost linearly influenced by the degree of inflation of the lungs (22) with greater volumes implying a reduced lung density. Hence, correction for individual inspiratory volume at the time of scanning has established as a fundamental methodological step for longitudinal densitometry assessment of emphysema with LDCT (23-26). Data about the density/volume relationship in whole-lung LDCT of restrictive lung disease are lacking.

In the present study we used spirometrically-gated spiral LDCT to measure inspiratory and expiratory whole-lung volume and density in patients with SSc and evidence of pulmonary involvement. The primary aims of the present investigation were: a) to assess the agreement between static inspiratory and expiratory lung volumes measured with LDCT and PFT in patients with a functional restrictive pattern of lung disease due to SSc and b) to measure the volume/density correlation in the same condition.

For comparison we considered two groups of patients. The first group was composed by SSc patients with normal PFT and no or trivial pulmonary involvement based on the results of visual assessment of sequential thin-section CT: they can broadly be assumed to be a "normal" control group. The second group had a functional obstructive pattern due to chronic obstructive pulmonary disease (COPD). Inclusion of the latter group enabled us to further explore in whole-lung spirometrically gated LDCT acquisition the capability of paired inspiratory/expiratory volumes and density parameters to differentiate patients with obstructive and restrictive lung disease (7).

Methods

Patients selection

We studied 40 consecutive outpatients with SSc and 29 consecutive outpatients with COPD enrolled at the Careggi University Hospital of Florence, Italy.

SSc patients underwent clinical and laboratory evaluations as requested by international guidelines (27) and were classified as limited (n=27) or diffuse (n=13) disease (28). Eight out of 40 SSc patients (5 with limited and 3 with diffuse disease) had mild pulmonary arterial hypertension (PAH) based on the Doppler Echocardiography (DE) results (29).

Patients with COPD were enrolled according to the presence of not fully reversible airways obstruction as stated in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program (30).

CT examination and PFT were obtained in the same day.

The hospital ethical committee approved the study and the patients gave their informed consent to participate.

CT examination

CT examinations were performed on a single detector scanner (Siemens Somatom Plus 4, Erlangen, Germany) equipped with a spirometer (14) which was calibrated with a 3 L syringe before each

test. All subjects were examined in the supine position.

To identify patients with pulmonary involvement according to a visual score system (2, 3), SSc patients were preliminarily examined by ungated sequential thin-section (1 mm collimation) CT, at end inspiration, standard dose (219 mAs, 140 Kv) and sharp (AB91) reconstruction filter (5, 7, 20).

To evaluate whole-lung volumes and density all patients underwent spirometrically-gated volumetric LDCT (19-21). After a spirometric-gated scout, whole-lung low dose (43 mAs and 140 Kv) spiral scans were obtained, with 10 mm collimation and pitch 1.5, the smallest possible field of view and sharp (AB91) reconstruction filter, at 90% of patient's vital capacity (VC). Scan duration time of 15-20 s allowed to acquire the entire lung volume in a single breath-hold. The scout and the whole-lung acquisition were repeated at 10% of patient's VC corresponding to maximal expiration.

CT Data analysis

Visual evaluation in SSc patients.

The pattern of pulmonary involvement in SSc is usually that of nonspecific interstitial pneumonia (NSIP) with additional honeycombing cystic spaces in an 11-37% of subjects (31)

The presence and severity of pulmonary involvement in SSc patients were visually evaluated on thin-section CT by the same observer (IO) using a modification of the 0-30 score scale proposed by Warrick et al. (2).

In particular, the scale includes a score of severity and a score of extension combined. Five parenchymal abnormalities were considered and a point value was assigned to each abnormality as follows: ground glass appearance = 1; irregular pleural margins = 2; septal and subpleural lines = 3; honeycombing = 4; subpleural cysts = 5. Since distinction between subpleural cysts and honeycombing with large cystic air spaces can be difficult, we considered as score 5 presence of macro honeycombing that was arbitrarily defined as cystic air spaces greater than 10 mm (32).

For each patient, the score of severity of disease was obtained by adding these point values. Accordingly, the severity of disease had a possible range between 0 (normal) and 15 (all abnormalities present). The score of extent of disease was obtained by counting the number of broncho-pulmonary segments involved for each abnormality. Involvement of 1 to 3 segments implied a score = 1; 4 to 9 segments a score = 2; more than 9 segments a score = 3. The extent of disease score had thus a possible range between 0 (no segment involved by any abnormality) and 15 (plus more than 9 segments showing all 5 abnormalities). Finally, severity and extent of disease scores were added to form a total thin-section CT score ranging from 0 (lack of any pulmonary abnormality) to 30 (maximum severity and extension of lung disease).

The visual scale showed a "very good" interoperator reproducibility in a prior study (3). In the same study Diot et al. (3) evaluated the relationship between PFT and visual score indicative of pulmonary involvement and found that a visual score of 7 on thin section CT offered the best compromise between sensitivity and specificity with a positive predictive value of 0.82. Hence we assumed that SSc patients with an individual cumulative visual score $\geq$7 on thin-section CT had evidence of pulmonary involvement, whereas SSc patients with an individual cumulative visual score <7 could be considered to have no or trivial pulmonary involvement.

Volume and density evaluation

LDCT acquisitions were examined on a remote console (Leonardo, Siemens, Erlangen, Germany) using a software for a semi-automatic computerized evaluation of lung density (Pulmo, Siemens, Erlangen, Germany) (14). The boundaries of the lungs on each spiral section were determined automatically by a density-discriminating computer program. Manual corrections of lung contour were performed by the same operator (I.O.) and were usually needed to exclude the main bronchovascular branches and to include gross subpleural abnormalities as honeycombing that the software tend to assimilate to the thoracic wall. The software automatically provided the value of the inspiratory (InspVol) and expiratory (ExpVol) lung volume. Using a custom made software we computed mean lung attenuation (MLA) (17, 18) of the whole lung histograms acquired at 90% and 10% of VC.

Changes between inspiration and expiration for volumes and MLA were calculated as Δs= inspiratory value - expiratory value.

PFTs

We measured static [functional residual capacity (FRC)] and dynamic [forced expiratory volume in 1 second (FEV_1)] lung volumes by a body plethysmograph equipped with a Vmax 22 spirometer (V6200 Autobox D_L Sensor Medics, Yorba Linda, California) and calculated residual volume (RV) and total lung capacity (TLC). All the above parameters were expressed either as absolute value or as percentage of the predicted values according to American Thoracic Society standards (33, 34). Notably, in order to compare InspVol and ExpVol at LDCT, obtained at 90% and 10% of VC, with volumes measured at PFTs we defined the TLC corrected according to the formula cTLC = RV+90%*VC and RV corrected according to the formula cRV = RV+10%*VC.

Statistical analysis

As recommended, we used the Bland and Altman method (35) to assess the agreement between static lung volumes measured by spiral-LDCT with those measured by PFTs. To have a term of comparison with previously reported data (13) also the r coefficient of linear regression analysis was calculated for InspVol and cTLC and for ExpVol and cRV.

The differences between groups for the LDCT volumes and density measurements obtained at 90% and 10% of VC and for their inspiratory-expiratory variations (Δs) were assessed by one-way analysis of variance (ANOVA) and Bonferroni post-test for multiple comparisons.

Linear regression analysis was finally used to correlate volume and density measurements. Statistical significance was set at $p<0.01$.

Results

Twenty-four SSc patients with an individual cumulative visual score ≥7 on thin-section CT were considered to have pulmonary involvement (mean visual score 15±6, range 7-26). The most severe parenchymal changes in terms of micro or macrohoneycombing were present in 4 (16.6%) of the patients. Sixteeen SSc patients with an individual cumulative visual score <7 on thin-section CT were considered not to have pulmonary involvement (mean visual score 3±2, range 0-6). Two of the latter patients had mild PAH.

Table 1 summarizes demographic and PFT data of the three groups of patients. As expected, the SSc patients with pulmonary involvement had varying degree of reduction of static lung volumes consistent with restrictive lung disease, SSc patients without pulmonary involvement had an almost normal functional pattern and patients with COPD had varying degree of hyperinflation and not reversible airflow obstruction consistent with obstructive lung disease.

Figure 1 shows the results of Bland-Altman plot evaluation of the agreement of Insp Vol with cTLC and of ExpVol with cRV in SSc patients with pulmonary involvement (plots A and B) in SSc patients without pulmonary involvement (plots C and D) and in COPD patients (plots E and F). In SSc patients with pulmonary involvement inspiratory (-43.8% and 39.2%) and expiratory (-45.8% and 37.1%) lung volumes measured on LDCT and PFT showed the widest 95% limits of agreement. A substantial agreement of inspiratory (95% limits of agreement -14.1% and 16.1%) and expiratory (95% limits of agreement -13.5% and 23%) volumes was

Table 1. Demographic, antropometric, and PFT data in SSc patients with pulmonary involvement (PI) (n=24), in SSc patients without PI (n=16) and in COPD (n=29) patients

	SSc with PI Mean±SD (range)	SSc without PI Mean±SD (range)	COPD Mean±SD (range)
Age (yrs)	56±15 (18-80)	60±10 (42-74)	61 ±6 (50-81)
Gender (F/M)	19/5	16/0	9/20
FEV_1(%)	81±19 (50-122)	99±16 (70-126)	58±23 (27-106)
FEV_1/VC	80±8 (68-98)	75±7 (61-85)	48±13 (25-75)
FRC(%)	79±22 (45-127)	97±19 (67-136)	137±26 (83-190)
RV(%)	76±27 (32-141)	95±16 (70-126)	151±41 (90-239)
TLC(%)	77±18 (51-113)	98±15 (63-127)	114±13 (82-141)

FEV_1(%): forced expiratory volume in 1 second (% of predicted value); FEV_1/VC: Tiffeneau index; FRC(%): functional residual capacity (% of predicted value); RV(%): residual volume (% of predicted value); TLC(%): total lung capacity (% of predicted value)

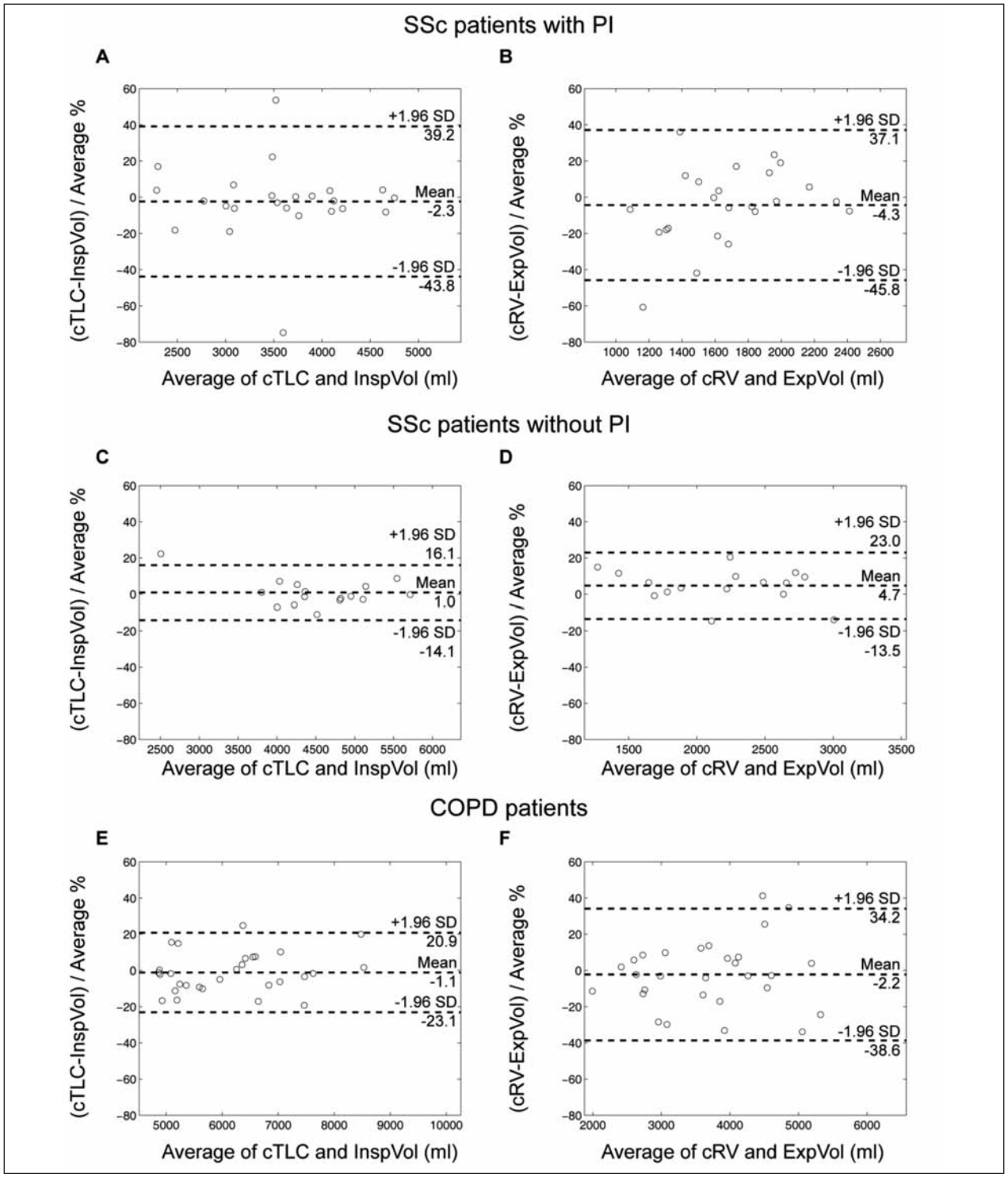

Fig. 1. A-F. Bland and Altman plots showing the agreement between cTLC and InspiratoryVolume and between cRV and Expiratory Volume in SSc patients with pulmonary involvement (PI) (panel A and B), in SSc patients without PI (panel C and D) and in patients with COPD (panel E and F). Dotted lines represent the mean of the difference of measurements obtained by PFT and spiral LDCT and the mean of the difference ±1.96 SD. Note in panel F that the most severely hyperinflated COPD patients were those with the lowest agreement between the expiratory volume measured by means of PFT and by means of spiral LDCT

observed in SSc patients without pulmonary involvement and, although to a lesser degree, for inspiratory volume only (95% limits of agreement -23.1% and 20.9%) in COPD patients. The linear regression analysis showed significant correlation ($p<0.01$) between Insp Vol and cTLC and between ExpVol and cRV in all three groups of patients with lowest *r* values for SSc patients with pulmonary involvement (inspiratory volumes $r=0.57$; expiratory volumes $r=0.66$), intermediate *r* values for COPD patients (inspiratory volumes $r=0.81$; expiratory volumes $r=0.68$) and highest *r* values for SSc patients without pulmonary involvement (inspiratory volumes $r=0.92$; expiratory volumes $r=0.89$).

Table 2 and Figure 2 show the distribution of LDCT determined inspiratory, expiratory and Δs volumes and MLA in the three groups of patients. As compared to SSc patients without pulmonary involvement, SSc patients with pulmonary involvement had smaller volumes and higher densities and patients with COPD had greater volumes and lower densities. The ANOVA showed significant ($P<.0001$) differences among the three groups for all these variables. In particular, Bonferroni post hoc analysis showed that inspiratory and expiratory LDCT volumes, but not their Δs, differentiated either SSc patients with or without pulmonary involvement from COPD patients. Only inspiratory volume differentiated SSc patients with from those without pulmonary involvement. Inspiratory and expiratory MLA differentiated the three groups of subjects, while ΔMLA differentiated COPD patients from SSc patients with or without pulmonary involvement.

Table 3 reports the relationship between inspiratory and expiratory volumes measured on LDCT, MLA and their Δs within each of the three groups of patients. In the SSc patients with pulmonary involvement, no significant correlation between any of the LDCT determined volumes, MLA and their Δs was observed. In SSc patients without pulmonary involvement, InspVol correlated with inspiratory MLA, ExpVol correlated with expiratory MLA and ΔMLA and Δvolume correlated with inspiratory MLA. In COPD patients ExpVol correlated with expiratory MLA and ΔMLA and Δvolume correlated with expiratory MLA and ΔMLA.

Discussion

In this study, we addressed two relevant issues for application of spiral CT scanning to evaluation of patients with restrictive lung diseases, namely the degree of agreement of the static inspiratory and expiratory volumes measured by means of CT and PFT and the relationship between CT volume and density measurements. Notably, in view of the application of the CT to the longitudinal evaluation of progressive conditions such most of those underlying restrictive lung disease, we used low-dose scanning techniques.

The lung volumes measured on LDCT scans obtained with spirometric gating at 90% and 10% of the vital capacity were not in agreement, although being correlated, with the corresponding inspiratory and expiratory volumes measured at PFT in patients with restrictive lung disease due to pulmonary in-

Table 2. Volume and density measurements computed from whole lung low dose volumetric acquisition at 90% (inspiratory scans) and at 10% (expiratory scans) of vital capacity and their modifications Δ=inspiratory scans-expiratory scans in SSc patients with pulmonary involvement (PI), SSc patients without PI and COPD patients

	Inspiratory scans (Mean±SD)	Expiratory scans (Mean±SD)	Δ (Mean±SD)
SSc with PI			
Volume (mm^3)	3596±809	1702±340	1894±721
MLA (HU)	-770±52	-578±70	-192±55
SSc without PI			
Volume (mm^3)	4499±810	2132±542	2366±635
MLA (HU)	-834±27	-672±76	-161±62
COPD			
Volume (mm^3)	6187±900	3730±969	2457±873
MLA (HU)	-870±18	-784±45	-85±38

MLA: mean lung attenuation; HU: Hounsfield Units

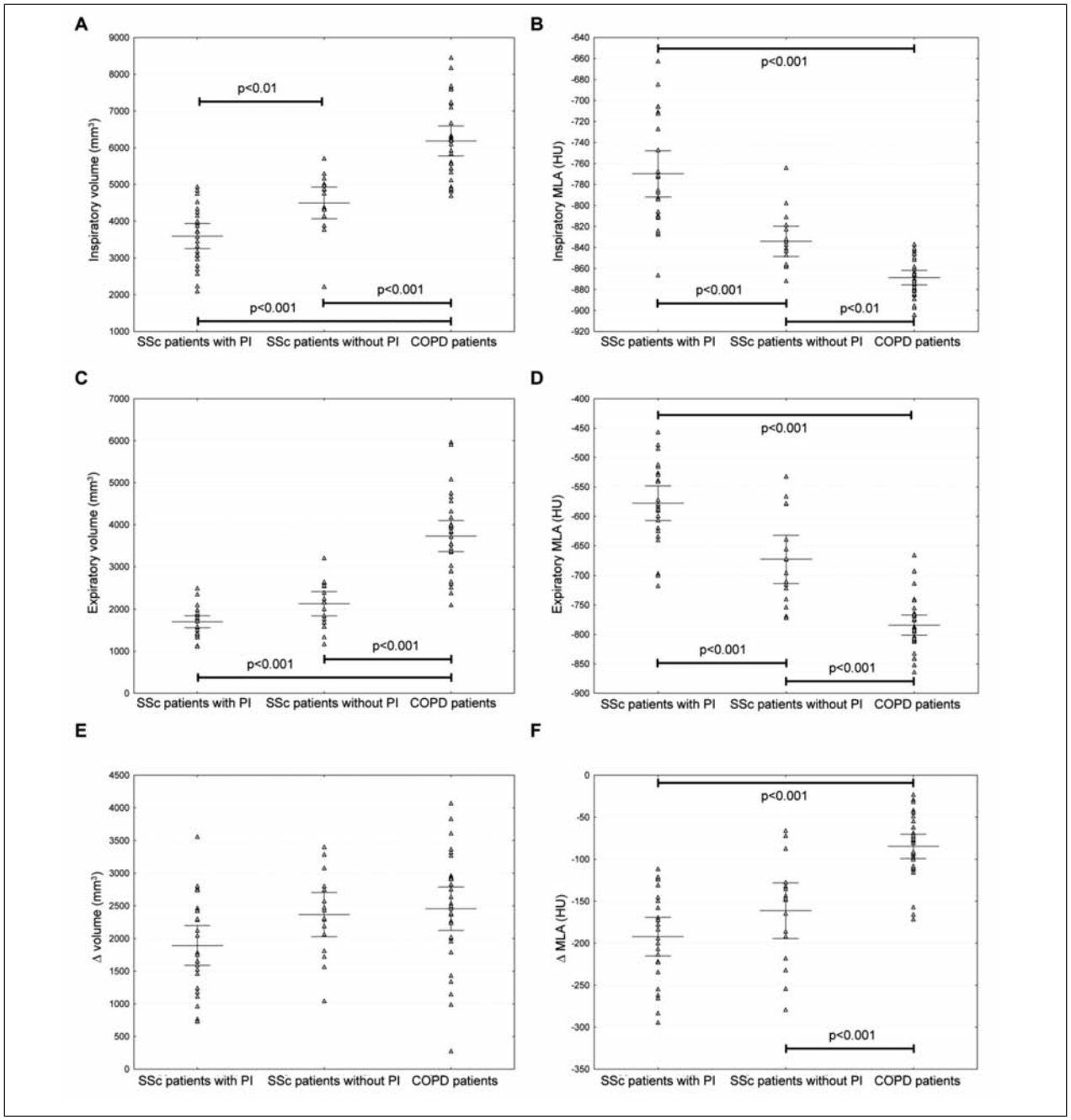

Fig. 2. A-F. Distribution of the inspiratory, expiratory volumes measured on LDCT, MLA and their differences (Δ) in SSc patients with pulmonary involvement (PI), SSc patients without PI and COPD patients. The large transverse line indicates the mean values and the smaller transverse lines its 95% confidence interval

volvement in SSc. In particular, the 95% LoA indicated a poor agreement (35). Such a discrepancy between the measurements at LDCT and PFT of inspiratory and expiratory lung volumes in SSc patients with pulmonary involvement is not unexpected and can be explained with the impaired mechanic properties of lung parenchyma and chest wall which might be exacerbated by the different positions in which the respiratory manoeuvre is performed on LDCT and PFT.

Table 3. Correlation of Inspiratory Volume, Expiratory Volume and Δvolume with densitometric data in SSc with pulmonary involvement (PI), SSc without PI and COPD patients.

	Inspiratory Volume (mm^3)			Expiratory Volume (mm^3)			Δ Volume (mm^3)		
	SSc with PI	SSc without PI	COPD	SSc with PI	SSc without PI	COPD	SSc with PI	SSc without PI	COPD
Inspiratory scans									
MLA (HU)	NS	r=-0.84 p<.001	NS	NS	NS	NS	NS	r=0.64 p<.01	NS
Expiratory scans									
MLA (HU)	NS	NS	NS	NS	r=-0.89 p<.001	r=-0.69 p<.001	NS	NS	r=0.51 p<.001
Δ									
MLA (HU)	NS	NS	NS	NS	r=0.86 p<0.001	r=0.74 p<.001	NS	NS	r=-0.71 p<.0001

MLA: mean lung attenuation; HU: Hounsfield Units

This poor agreement in restrictive lung disease is at variance with what we observed in SSc patients without pulmonary involvement and for the inspiratory volumes in COPD patients in whom a substantial agreement between lung volumes at LDCT and PFT was observed.

While no data in healthy subjects are available, a high correlation coefficient for both inspiratory and expiratory volumes at CT and PFT was previously reported in COPD patients (13).

Theoretically, the poor agreement between expiratory volume at LDCT and PFT in COPD patients may be accounted for by the fact that CT measurements are obtained in supine position that influences lung volumes by modifying the configuration of the diaphragm. This body position can ameliorate expiratory flows in less obstructed patients but increases airflow limitation in those more severely obstructed. In addition, in the supine position there is a tendency of airways to collapse with consequent hyperinflation proportional to the severity of obstruction. The above two explanations are confirmed by the Bland and Altman plot (Figure 1F) showing that the most severely hyperinflated patients in our study were those with the lowest agreement between the expiratory static volumes. Moreover, at least two factors can explain the apparent discrepancy between our findings and those previously reported concerning the relationship between expiratory lung volumes at CT and PFT in COPD patients (13). First, the poor agreement indicated by the Bland and Altman method in our series corresponded to a 0.68 *r* value which is comparable to the 0.83 *r* value reported in the previous study (13). Second, we adopted respiratory gating at 10% of vital capacity and the expiratory volumes achieved in static expiratory scans by COPD patients are generally higher than those obtained with spirometric gating (personal unpublished observations).

The present investigation also demonstrates that the almost linear relationship between lung volume and density CT values observed in subjects with normal lung structure and function and in patients with obstructive lung disease (22) is severely altered in patients with restrictive lung disease due to pulmonary involvement in SSc. This can be due to the presence in these patients of regions of ground glass opacities with increased density and regions of honeycombing with mixed decreased and increased density. In particular, the latter areas could be relatively "stiff" and resistant to density and size modifications during maximal inspiratory and expiratory maneouvers.

Possible implications of the poor correlation between static volumes at LDCT and PFT and the loss of the volume/density correlation in restrictive lung disease due to SSc include the following. First, because of the poor agreement with TLC, the inspiratory volume measured even with spirometrically-gated LDCT cannot be used as a marker of progression of restrictive lung disease. For the latter purpose, TLC and diffusion capacity for CO (DLCO) (5) have to be preferred also in consideration of the use of ionizing radiations in LDCT.

Second, the loss of the density/volume correlation in restrictive lung disease suggests caution about

judgement of progression of disease using visual rating score of thin-section CT in which the reduced cross-sectional area of the lung can influence the morphological changes that are visually rated. This is indirectly confirmed by the practical recommendation not to use visual scales for a blind rating of serial CT examinations but to directly compare images obtained at the same anatomic level in serial CT examinations trying to incorporate in the visual rating the modifications of the cross sectional area associated with restrictive lung disease (personal unpublished observation). The subjectivity of this procedure cannot be ignored.

Third, in several prior studies densitometry of pulmonary involvement in restrictive lung diseases was carried out on sequential inspiratory thin section CT without consideration of the lung volume variations typical of these conditions (1, 4, 5, 36). The present results indicate that if the full potentials of densitometry for the staging and follow-up of interstitial lung disease have to be exploited, measurement of lung volume must be carried out beside computation of lung density in the LDCT assessment. In fact, both the decreased static volume and the abnormal volume/density relationship in paired inspiratory and expiratory scans might represent additional information to the typical increase of density reflected in the visually rated morphological changes, although admittedly the interplay among these three variable is probably much complex. In fact, decreased lung volume might reflect the fibrosis but at the same time it tends to increase the lung density that is the hallmark of fibrosis. On the other hand, chest abnormalities in SSc might be responsible of decreased inspiratory and expiratory volumes at CT, independently from lung morphological changes.

Finally, our data, obtained with spirometrically-gated whole lung CT, confirm that, in general, paired inspiratory/expiratory volumes and density parameters enable to differentiate patients with obstructive and restrictive lung disease better than corresponding data obtained in inspiratory scans only. This capability of CT was previously reported by Kauzcor et al. (7) who calculated MLA and cross-sectional area on sequential thin-section CT at three anatomic levels at standard dose and without spirometric gating. In our study, we employed a low dose protocol by combining thick collimation and reduction of the tube-current (19). Since low current affects the computation of relative area as quantitative index of emphysema (19, 37, 38), we simply computed MLA which is a robust density measurement also in the evaluation of pulmonary fibrosis (1, 6, 7, 19, 20, 36).

In particular, we observed that whole-lung volume and MLA in expiratory scans improve the differentiation between COPD patients and SSc patients without or with pulmonary involvement, as compared to inspiratory scans (7-9). In addition, also in line with previous data (6,7) expiratory MLA was significantly higher in SSc patients with than in SSc patients without pulmonary involvement. Conversely, the expiratory volume did not differentiate SSc patients with and without pulmonary involvement (7) and volume Δs did not differentiate among the three patient groups. Finally, the MLA Δs differentiated COPD patients from SSc patients with and without pulmonary involvement but not the latter two groups. Overall our findings seem to indicate that the contribution of the expiratory scans for such a differentiation is per-se rather than due to the possibility of computing the inspiratory/expiratory differences.

Although lung volume and attenuation at paired LDCT obtained at full inspiratory/expiratory position can be used to characterize different types of ventilatory impairment, admittedly, at the present time the exact clinical role of this capability of LDCT is unclear, especially with respect to the information provided non-invasively by PFT (7).

We recognize some limitations of our study.

First, it was performed using a spiral CT scanner with a single row of detectors. This forced us to use thick collimation sections to obtain whole-lung scanning in a single breath-hold. This hindered visual evaluation of morphological alterations (and emphysema in COPD patient) which required additional sequential thin-section CT. Multi-detector spiral CT scanners, enabling whole-lung examination with thin collimation sections and double reconstruction with thin section and sharp kernel for visual assessment and with thick section and smooth kernel for densitometry (13,39) have overcome this limitation. Second, we assumed that SSc patients without significant pulmonary involvement might represent healthy control subjects. This is clearly an approximation. However, these SSc patients, who underwent CT to detect subclinical lung disease, had

no or trivial morphological changes on sequential thin-section CT and normal lung function (flows, volumes and diffusing capacity) at PFT. On the other hand, concern about radiation exposure is a strong argument against examining healthy subjects even using LDCT. Third, the evaluation of the thin section sequential CT sections to classify SSc patients in the subgroups with and without pulmonary involvement was performed by one observer only. However, the visual scale adopted showed a substantial inter-operator reproducibility using the weighted kappa statistics in a prior investigation in a larger sample of SSc patients included in the present study (5). Fourth, it is unsettled to what extent our findings obtained in group of SSc patients with a predominantly NSIP pattern of pulmonary involvement can be extended to other restrictive lung diseases, in particular those with usual interstitial pneumonia pattern. Finally, we included in the group of SSc patients without pulmonary involvement few patients with mild PAH. While we cannot exclude that PAH has influenced some density measurements (40) it is not expected that it affects evaluation of lung volumes and volume/density relationship which were the primary objectives of this investigation.

In conclusion, static inspiratory and expiratory lung volumes measured on LDCT and PFT are different and the lung volume/density relationship is altered in patients with restrictive lung disease due to SSc. Paired inspiratory/expiratory LDCT can differentiate patients with restrictive and obstructive lung disease.

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