Title (2 pages)

In search for the parenchymal and vascular features in SSc-ILD: how to address the challenge of quantitative analysis of CT images and correlation with clinical and instrumental data

Abstract

Systemic sclerosis (SSc) is a rare connective tissue disease with abnormalities in vascular, immunological and fibrotic pathways. Pulmonary involvement is seen in more than 70% of patients with SSc. The two principal manifestations are interstitial lung disease (ILD) and pulmonary vascular disease leading to pulmonary arterial hypertension (PAH). Most patients have some degree of both conditions and any patient with scleroderma needs to be evaluated for both, with annual screening with lung function tests and echocardiography. Elevated systolic pulmonary arterial pressure (sPAP) at echocardiography has been shown to independently predicted PAH and diffusing lung capacity for carbon monoxide (DLco) reduction can be useful in monitoring ILD complicated patients and predicting development of PAH. Among other tests, nailfold capillaroscopy (with both qualitative and semi-quantitative assessment) was also shown to predict cardio-pulmonary involvement. As a screening tool for ILD, lung ultrasound for quantification of B-lines was proposed given the good association with computed tomography (CT) features and spirometry data. Moreover, renal resistive index was significantly increased in patients with SSc-ILD, correlates with elevated sPAP and can be considered a negative prognostic factor. Imaging in SSc patients can identify ILD patterns, such as ground-glass, reticular, and honeycombing images. However, qualitative analysis of CT scans suffers from low inter-observer agreement, being very subjective. Computer-based quantitative CT evaluation has the potential for greater precision than visual scoring in the estimation of the extent of diffuse parenchymal diseases. Pulmonary damage in SSc patients is not only due to parenchymal involvement, but also to the derangement of the pulmonary vessels. Today, the vascular CT quantitative data can be acquired by using lung automated computer-aided analysis. To date, in SSc no studies have been performed on the concomitant analysis of parenchymal and vascular CT data. Given that DLco decline and sPAP increase can be due to ILD and/or PAH, the aim to our study is to focus on both components by using quantitative CT tools to be correlated with clinical and instrumental disease features usually assessed in clinical practice.

To this aim, at least 50 SSc patients will be investigated with CT scans compatible to quantitative software analysis and the data will be correlated with clinical and instrumental parameters of both peripheral and central vasculopathy, pulmonary function tests, and lung ultrasound. This pilot study might pave the pathway to the assessment of pulmonary vasculature and the quantification of both parenchymal and vascular components. In fact, it might become a tool to be potentially employed in the evaluation of the anti-fibrotic immunosuppressive and vasodilating/vasoactive treatments effects, guiding the clinical approach to SSc patients in real life.
La sclerosi sistemica è una rara malattia cronica del tessuto connettivo caratterizzata dalla contemporanea presenza di fibrosi cutanea e degli organi interni, manifestazioni vascolari cardiache e digitali e infiammazione. Dato che le complicanze più gravi della malattia sono la fibrosi polmonare e l’ipertensione arteriosa polmonare, i pazienti vengono sottoposti a cadenza quantomeno annuale a esami di screening, quali l’ecocolor doppler cardiaco e le prove di funzionalità respiratoria. Alcuni parametri di questi esami, quali la diffusione del monossido di carbonio e la stima della pressione arteriosa polmonare sistolica, sono di aiuto per il reumatologo nel sospettare l’insorgenza di una delle complicazioni suddette. Tali parametri sono limitati dalla mancata capacità di dirimere tra le due manifestazioni, per cui sono necessari ulteriori strumenti oggettivi di valutazione e quantificazione del danno polmonare. Solo recentemente sono stati introdotti programmi informatici di analisi quantitative delle immagini ottenute tramite studio TC del torace e consentono di identificare e quantificare sia le alterazioni fibrotiche polmonari che le alterazioni vascolari polmonari, senza necessità di utilizzare mezzo di contrasto e di effettuare ulteriori acquisizioni. Pertanto, è quindi nostra intenzione studiare almeno 50 pazienti con SSc che abbiano già eseguito una TC torace ed analizzare tali scansioni con i programmi informatici suddetti, verificando poi se i dati risultati da tali analisi fossero in armonia con i valori ottenuti dalle analisi di routine e dalla valutazione clinica del paziente. Qualora i risultati ottenuti fossero significativi, si getterebbero le basi per ulteriori studi sulla quantificazione sia della fibrosi che dei vasi polmonari, soprattutto anche per valutare l’effetto delle terapie farmacologiche somministrate per combattere le manifestazioni cardio-polmonari legate alla sclerodermia.

**Key-words:** lung texture analysis, vascular analysis, capillaryscopy, CALIPER, diffusing capacity carbon monoxide, systolic pulmonary arterial pressure, interstitial lung disease.
**State of the art & Introduction to the project (2 pages)**

Systemic sclerosis (SSc) is a rare connective tissue disease with abnormalities in vascular, immunological and fibrotic pathways (Katsumoto et al., 2011). SSc proceeds from vasospastic episodes to fibrointimal proliferation of small vessels. The vasculo-vasospasm is referred to clinically as Raynaud’s phenomenon. Vasculopathy in the larger arterial vessels can manifest as pulmonary arterial hypertension (PAH) or sclerodema renal crisis. When progressive structural changes develop in the small blood vessels, blood flow is permanently impaired, which leads to prolonged episodes of Raynaud’s phenomenon and can result in ischaemic digital ulceration or infarction. Progressive structural changes can be seen by nailfold capillaroscopy (NVC) with typical findings being giant/megacapillaries, loss of capillaries, bushy capillaries and ramified capillaries (Cutolo et al, 2000). Given its diagnostic role for SSc, in particular for qualitative scoring, semi-quantitative assessment was also proven to detect changes in time, in particular indicating worsening of microangiopathy (Sulli et al, 2007) but also the ability of vasoactive treatment to determine an increase in capillary number (Trombetta et al, 2016). Pulmonary involvement is seen in more than 70% of patients with SSc. The two principal manifestations are interstitial lung disease and pulmonary vascular disease leading to PAH. Most patients have some degree of both conditions and any patient with scleroderma needs to be evaluated for both interstitial lung disease (ILD) and pulmonary hypertension (PAH) (Khanna et al 2013, Schoenfeld et al 2017). Pulmonary involvement is the most common cause of SSc-related death, as demonstrated by a study using data from the EULAR Scleroderma Trials and Research database (Tyndall et al., 2010). Annual screening with lung function tests and echocardiography is recommended as a screening for both ILD and PAH (Khanna et al 2013, Schoenfeld et al 2017): among echocardiography parameters measured with these two assessments, elevated systolic pulmonary artery pressure (sPAP) has been shown to independently predicted PAH, together with tricuspidal velocity (Frea et al, 2011). Among lung function tests variables, given the well-known indication for forced vital capacity (FVC) in restrictive diseases, diffusing lung capacity for carbon monoxide (DLco) value has been questioned for both prediction and follow-up. In fact, DLco value reflects both the conductance of alveolar-capillary membrane and the pulmonary capillary blood volume (Vc): Guarnieri et al showed that DLco reduction in ILD complicated patients was more suggestive for isolated ILD when both components were reduced, while more consistent reduction of Vc could raise the suspicion for ILD-associated PAH (Guarnieri et al 2015). Isolated DLco reduction in patients without cardio-pulmonary involvement is also possible, with higher risk for future development of PAH (Colaci et al, 2015). NVC, with both qualitative and semi-quantitative assessment, was also shown to predict cardio-pulmonary involvement: Markusse et al showed that increased risk for ILD, DLco decrease and increase of sPAP in case of NVC scleroderma pattern (Markusse et al, 2016). This is in line with other studies: Voillot et al showed that NVC scleroderma patterns and sPAP on both resting and exercise echocardiography were best predictors for development of PAH on follow-up visits (Voillot et al, 2016); Smith et al showed significantly increased risk for future severe peripheral vascular involvement with worsening of NVC SSc pattern, with OR progressively increasing from 1.90 for early pattern to 3.60 for the active pattern to 6.86 for the late pattern (Smith et al, 2013); finally Avouac et al confirmed the results for qualitative assessment of Smith et al, also demonstrating increased risk for lung vascular and skin fibrosis worsening and, moreover, showed that capillary loss during follow up was an independent predictor of overall disease progression, ischemic digital ulcers (DU), lung vascular progression, ILD and skin progression (Avouac et al, 2017). As a screening tool for ILD, lung ultrasound for quantification of B-lines was proposed as good association with computed tomography (CT) ILD findings (concordance rate 83%, sensitivity 100%, negative predictive value 100%) (Barakova et al 2012) and a moderate negative correlation with both FVC and DLco level (r=-0.63 and -0.48, respectively) (Gigante et al, 2016). Renal resistive index (RRI) is a semi-quantitative index representing the resistance that the blood flow encounter distally to the point where it is measured (Knapp 1995). Rivolta et al showed increased RRI values in SSc patients which correlated with...
disease duration and were significantly higher in small and medium calibre vessels (Rivolta 1996). Following studies demonstrated that RRI significantly correlated with glomerular filtration rate, progressive worsening of NVC pattern and history of DU (Rosato 2012). Moreover, RRI variation in time was shown to reflect the clinical evolution in a case of scleroderma renal crisis (Rosato 2013) and was sensitive to change during vasodilating treatment administration (Scorza 1997).

Recently, Bruni et al showed that SSc-Age-adjusted RRI values was more frequent in patients with ILD, late NVC pattern, skin fibrosis and digital ulcers and can be considered a negative prognostic factor for pulmonary, renal and cardiac involvement at follow-up (Bruni et al, 2017).

SSc patients with lung involvement can have subtle abnormalities at chest radiography, whereas CT can better depict the range of pulmonary damage. In particular, lung patterns of ILD, such as ground-glass, reticular, and honeycombing, have been described. However, the presence of such patterns is different from other forms of lung fibrosis, like idiopathic pulmonary fibrosis (IPF), and has specific characteristics that need to be studied. Desai et al. (Desai SR et al 2004) found that SSc patients in comparison to IPF patients have higher extent in ground-glass and less coarseness of reticulation. However, qualitative analysis of CT scans suffers from low inter-observer agreement, being very subjective. Computer-based quantitative CT evaluation has the potential for greater precision than visual scoring in the estimation of the extent of diffuse parenchymal diseases. A new generation of computer-based CT software tools have demonstrated similar results between computer quantitation and visual quantitative scoring in small-scale studies in patients with IPF, with distinct improvement in performance on older, less sophisticated software programs (Maldonado F et al. 2014) (Best AC et al 2008). A sophisticated quantitative CT software tool, called CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating), has been recently developed at the Biomedical Imaging Resource at Mayo Clinic (Rochester, MN, USA). CALIPER is a computational platform for the near-real-time characterization and quantification of lung parenchymal patterns on CT scans (Bartholmai BJ et al 2013). However, pulmonary damage in SSc patients is not only due to parenchymal damage, but endothelial dysfunction of pulmonary vessels plays an important role in the pathogenesis of disease.

Automated computer-aided analysis of lung vessels on CT scans has shown to yield promising results for non-invasive diagnosis of lung diseases. While pulmonary vascular tree segmentation has significantly improved and finally matured over the recent years (Rudyanto et al. 2014), a still largely unsolved problem is the fully automated separation of the pulmonary vascular tree into arteries and veins. Independent analysis of the arterial and venous pulmonary trees shows high clinical relevance in improving the diagnosis of lung diseases affecting both trees differently, as it occurs in patients with SSc. The main difficulty of labeling the two compartments (arterial and venous) is that it is not possible to distinguish arteries and veins based on their image intensity alone. Previous work has shown that artery/vein separation can be feasible but requires time-consuming explicit manual correction (Park S et al 2006) (Park S et al 2013). Fully automated approaches have recently been proposed and only two software programs are available worldwide (Charbonnier 2016) (Payer C et al 2015) (Payer C et al. 2016). So far these methods have not yet been used in evaluating patients with ILD in general and in particular SSc patients. Quantitative data on pulmonary vasculature obtained in a cohort of normal subjects stratified by age and sex have been presented by researchers of the Ludwig Boltzmann Institute for Lung Vascular Research (Graz, Austria) using one of the two available software programs for analysis of pulmonary arterial and venous compartments (ESTI meeting 2016 Krakow, submitted).

Both software programs do not require medium contrast administration nor additional CT scans, thus preserving the patient from exposure to further radiations.

Given that DLco decline and sPAP increase can be due to ILD and/or PAH, it is pivotal to assess both parenchymal and vascular components of the disease by using quantitative, objective and reproducible tools. To this aim, we intend to study both components by using quantitative CT tools to correlate with clinical and instrumental disease features usually assessed in clinical practice.
Aim of the study (1 page)

Our study aims at describing pulmonary vascular and parenchymal changes in SSc patients using a quantitative CT analyses.

Study objectives
1. to quantify radiological patterns of SSc related ILD (ground-glass, reticular, honeycombing)
2. to correlate quantitative CT data of lung parenchymal patterns to
   a. vascular CT data
   b. other parameters of peripheral (RRI, NVC qualitative and quantitative assessments, DU, telangiectasias) and central vascular involvement (sPAP)
   c. other instrumental parameters of ILD (FVC, DLco, B lines on lung ultrasound)
3. limited to patients with one available follow-up, to correlate changes in quantitative CT data of lung parenchymal patterns:
   a. change in vascular CT data
   b. change in other parameters of peripheral (RRI, NVC qualitative and quantitative assessments, DU, telangiectasias) and central vascular involvement (sPAP)
   c. Change in other instrumental parameters of ILD (FVC, DLco, B lines on lung ultrasound)
**Methods (3 pages)**

Patients attending the Rheumatology outpatient clinic of the dept of Rheumatology, AOU Careggi Firenze, classified as SSc according to the 2013 ACR/EULAR classification criteria for systemic sclerosis, will be eligible for the study.

Inclusion criteria:
1. Patients aged over 18 years-old
2. classified as SSc according to the 2013 ACR/EULAR classification criteria for systemic sclerosis
3. at least one available high resolution chest CT scan
4. written informed consent

Exclusion criteria:
1. ongoing treatment with oxygen supplementation at the time of chest CT
2. concurrent chronic obstructive pulmonary disease at the time of chest CT
3. unavailability of CT scans
4. CT acquisition parameters (i.e. type of acquisition, slice thickness, reconstruction kernels) inconsistent with post-processing imaging software algorithms
5. motion or beam-hardening artifacts on CT
6. co-existence of small airway disease, lung nodules, or masses.

Data on the following domains will be collected if available/performed within 3 months from chest HRCT scan.
1. demographics (gender, age, time from RP onset, time from first non-RP symptom, smoking exposure)
2. clinical data (height, weight, body mass index, skin subset according to Leroy and Medsger, modified Rodnan skin score -mRSS-, VEDOSS criteria fulfilment, current or previous history of DU, telangiectasia, history/diagnosis of PAH, ILD, scleroderma renal crisis, arthritis, presence of tendon friction rubs, gastro-oesophageal involvement, intestinal involvement, presence of dyspnoea by NYHA functional class, quality of life questionnaire)
3. instrumental data (NVC qualitative and semi-quantitative evaluation, ejection fraction, estimated sPAP and presence of diastolic dysfunction on chest echocardiography, FVC, DLco, FVC/DLCO ratio, RRI measured with renal artery echo Doppler, number of B-lines on lung ultrasounds)
4. imaging data (CT acquisition date, dose exposure, technical parameters of CT acquisition, post-processing imaging data obtained by using CALIPER software and vascular software)
5. serological data (NTproBNP, serum creatinine, creatinine clearance calculated with Cockroft Gault method (creatinine C-G), positivity for antinuclear antibodies-ANA-, anti-topoisomerase I antibodies – Scl70-, anti-centromere antibodies -ACA-, anti-RNA polymerase III antibodies -RNAPolIII)
6. previous and concomitant drug exposure (ACE-inhibitors, calcium channel blockers, angiotensin receptor blockers, diuretics, beta-blockers, steroids, immuno-suppressors, biologic treatment, bosentan, sildenafil, prostacyclin analogues, prostaglandin analogues).
If patient underwent a major change in the treatment after the CT scan (i.e. starting or dose modification of the immunosuppressant or starting or dose modification of a now major vasodilative/vasoactive treatment), a follow-up CT scan was performed and is available to the site, a second-time point analysis will be performed collecting data on the same above-mentioned parameters.

Chest CT scans will be analysed quantitatively by using two different software programs of post-processing image analysis: A. lung texture analysis (CALIPER software, developed at Biomedical Imaging Resource at Mayo Clinic, Rochester, MN, USA); B. quantitative vascular analysis (developed at Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria).

A. Lung texture analysis (CALIPER)
The potential for quantitative analysis to reliably characterize and quantify parenchymal abnormalities of HRCT in the setting of ILD is enormous. Ideally, computational tools can yield an objective biomarker that may allow for more consistent characterization of disease, with a mapping of specific characteristics and parenchymal abnormalities (Bartholmai BJ et al 2013). CALIPER is a CE approved computational platform for the near-real-time characterization and quantification of lung parenchymal patterns on CT scans (Bartholmai BJ et al 2013). This software program was validated by using pathologically confirmed datasets obtained through the Lung Tissue Research Consortium, a NIH/NHLBI sponsored, multi-site initiative dedicated to develop a repository of clinical and physiologic data, pathological specimens, blood and tissue characterization, CT scan data. CALIPER performs the lung parenchymal classification through texture analysis, computer vision-based image understanding of volumetric histogram features and 3D morphology of the classified voxels at CT. Artificial neural networks, Bayesian classifiers, support vector machines and k-neighbour classifiers are used to classify the parenchymal features. Outputs of the algorithm are lung patterns of disease, expressed as both color-coded voxels on CT images and quantitative data as relative volumes for each lung pattern (i.e. ground-glass, reticular, honeycombing, normal lung). Moreover, CALIPER provides a glyph similar to a radial space-filling plot as an iconic summary of the volumetric parenchymal classification. The glyph illustrates the relative volumes of the left and right lungs and further divided into three regions, each representing the individual lobes or upper/middle/lower lung zones. Thus, the glyph provides a global overview of parenchymal characteristics and lung volumes as well as distribution of the components that facilitates comprehension of the multidimensional source data.

B. Vascular Analysis
Analysis of the vasculature will be performed by using a novel quantitative software performing a fully automated separation of the pulmonary vascular tree into arteries and veins (Payer C et al 2016). Artery/vein separation allows better understanding of pulmonary structure and function, as it enables even localized studies of vascular alterations, which are closely related to endothelial dysfunction. The artery and vein segmentation is performed by fully-automated software. The input for the software is the contrast enhanced thoracic CT scan. After lung segmentation, subsequent processing is performed for both lungs independently. In the first step a multi-scale vessel enhancement filter produces images with a high response for tubular structures as well as the respective radius and a vessel orientation estimate. Next, regularly spaced local maxima of the vessel enhanced image are extracted for vessels between 2 and 10 mm diameter. These local
maxima are connected by edges in a local neighbourhood. For every edge, a path between its two endpoints is extracted, which penalizes path length and crossing regions with small tubularity values. This multitude of edges is filtered and the most likely edges are connected to individual vessel trees. Finally, the artery-vein labelling is realized by using two anatomical properties. First, the software exploits that arteries and veins are roughly uniformly distributed in the lung. Second, the software uses that bronchi which run in parallel and in close proximity to arteries. The algorithm results in morphologically characterized and properly labelled vessel segments. Validation of the artery/vein separation is performed by a thoracic radiologist. Visual inspection yields an estimation of the amount of wrongly labelled vessels.

The quantitative readouts of algorithm are the number of vessel segments in total and in certain diameter bins, the vessel density (number of vessel segments per lung volume), the total volume of the detected vessels normalised to the lung volume, and the tortuosity of the vessel segments.

Quantitative data obtained in normal subjects will be used as reference of normality.

Data will be analysed as follows:
The Shapiro-Wilk test will be used to test all data for normality. Continuous variables normally distributed will be expressed as mean (with standard deviation) and those non-normally distributed as median (25th to 75th percentiles). Percentages will be calculated for dichotomous and categorical data.

Correlations between continuous variables will be performed using Pearson’s correlation coefficient or alternatively Kendall Tau correlation coefficient.

In order to evaluate association between categorical variables Chi-square or Fisher’s test will be used.

To assess association between categorical and continuous variables ANOVA (after verifying the hypothesis using Shapiro-Wilk test for normality and Bartlett’s test for homoskedasticity) or Kruskal-Wallis test will be used.

The change for follow-up analysis will be calculated as the difference between after and before measurement. p-values smaller than 0.05 will be considered statistically significant.

Due to the observational nature of the study, no sample size calculation was performed but established according to previous similar studies.

For follow-ups only:
- Chi-squared between progression/stability + improvement at CALIPER and progression/stability + improvement at vascular CT
- Student t-test for paired samples between baseline and follow-up data for CALIPER and vascular CT data, FVC, DLco, sPAP.
**Study design and milestones (1 page)**

This is an observational study with a retrospective design. It will be held in a single referral tertiary centre for SSc care in the Dept. of Rheumatology, AOU Careggi Firenze. As a pilot study, we expect to enrol at least 50 patients with suitable CT scans for post-processing image analysis by both software programs.

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Milestones:

1. Patients enrolment. Meeting on February 16th, 2018 to state the number of enrolled patients and decide if prolonging the enrolment or moving to next phase.
2. Evaluation of feasibility of available chest CT scans with post-processing image software programs (lung texture analysis and vascular analysis). Meeting on April 27th, 2018 to state the number of CT scans available for post-processing image analysis, the number of scans included in the study, and the number of scans excluded in the study.
3. Post-processing CT scan analysis. Meeting on September 21st, 2018 to state the number of CT scans analysed and any type of error reported by the software.
4. Clinical data collection. Meeting on September 28th, 2018, to state the amount of data collected and if variable with prevalent missing data should be further included in the analysis.
5. Data analyses and results interpretation. Three meetings together with the statistician to address the analysis and go over the results obtained in a step-wise manner. Meetings on November 2nd, November 16th, November 30th, 2018.
6. Manuscript preparation, abstract submission, presentations. Starting December 2018 manuscript will be prepared and edited. Abstracts to conferences of both rheumatologic (EULAR, ACR, SIR) and radiologic (RSNA, ESTI, ECR, SIRM) conferences will be submitted.

**Costs estimates:**

- 10.000 € for technical analysis: vascular CT analysis (technical support and image data analysis) & CALIPER CT analysis (technical support)
- 10.000 € for human labour
- 2.500 € for statistical support and data analysis by a statistician
- 2.500 € for overhead to University of Florence

Grant Total 25.000 €
**Results and translation into clinical practice (1 page)**

We expect to:
- find a reduced relative volume of normal lung pattern
- be able to quantify relative volumes of reticular/ground glass/honeycombing patterns
- find negative correlation between CT data on parenchymal ILD and quantitative CT data on pulmonary vasculature
- be able to quantify pulmonary arterial and venous vessels and show a significant difference with normal population
- show a good correlation between lung vascular CT data and peripheral vessels semi-quantitative data
- find significant correlation between CT data on parenchymal ILD and functional lung tests
- find significant correlation between lung vascular CT data and functional lung tests, in particular DLco.

This would be translated into clinical practice:
- to dissect parenchymal and vascular components of DLco decline and sPAP elevation
- to study pulmonary vasculature without the use of contrast medium
- to predict pulmonary vascular involvement from peripheral microvascular parameters
- to support the clinician in evaluating treatment response both for parenchymal and vascular targeted treatments.
References


