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SCLERODERMA (J VARGA, SECTION EDITOR)

Novel Imaging Approaches in Systemic Sclerosis-Associated Interstitial Lung Disease

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Abstract

Purpose of the Review Novel imaging approaches, such as quantitative computed tomography (CT), magnetic resonance imaging (MRI), and molecular imaging, are being applied to interstitial lung diseases to provide prognostic, functional, and molecular information. Here, we review such imaging approaches and their applicability to systemic sclerosis-associated interstitial lung disease (SSc-ILD).

Recent Findings Quantitative CT can be used to quantify the radiographic response to SSc-ILD therapy. Due to advances in MRI sequence development, MRI can detect the presence of SSc-ILD with high accuracy. MRI can also be utilized to provide functional information as to SSc-ILD and paired with molecular probes to provide non-invasive molecular information. MRI and ultrasound have promising test characteristics for diagnosing ILD in SSc without the use of ionizing radiation.

Summary Novel imaging approaches can detect SSc-ILD without the use of ionizing radiation, provide non-invasive functional and molecular information, and quantify treatment response in SSc-ILD. These techniques hold promise for translation into clinical care and clinical trials.

Keywords Systemic sclerosis · Interstitial lung disease · Pulmonary fibrosis · High-resolution computed tomography · Magnetic resonance imaging · Molecular imaging

Introduction

Interstitial lung disease (ILD) is a well-known complication of systemic sclerosis (SSc) affecting over 60% of patients with SSc [1, 2]. SSc-ILD is most accurately diagnosed using computed tomography (CT) of the chest given the high false-negative rates of pulmonary function testing (PFT) as a screening modality for ILD [2]. Recognition of SSc-ILD is crucial because a diagnosis of SSc-ILD carries important prognostic and treatment implications. The mortality associated with SSc-ILD is increasing given a decline in the mortality associated with scleroderma renal crisis and advances in the treatment of pulmonary arterial hypertension [3]. ILD is now the leading cause of death in patients with SSc by some estimates [3]. Despite many advances in our understanding of SSc-ILD, several important challenges remain. First, individual disease courses are difficult to predict. While certain features have been associated with more rapid progression, prognostication of an individual's ILD disease course is challenging due to the considerable heterogeneity of disease progression. Pulmonary function testing (PFT) and CT can assess the degree of pulmonary function impairment and the extent of disease involvement but are not able to inform as to disease activity unless performed repetitively over time. Determination of response to ILD-targeted treatment can be difficult as well. While some patients may have a more robust response to immunosuppressive therapies, for others response to treatment may be more subtle and very difficult to determine based on PFT and CT-based assessments alone. Lastly, the demonstrated benefit from currently utilized SSc-ILD

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treatments, including cyclophosphamide and mycophenolate mofetil, is modest [4, 5], and more effective treatments are needed.

Novel imaging and analysis techniques hold great potential for addressing some of the unmet needs within the field of SSc-ILD. Advanced imaging modalities such as magnetic resonance imaging (MRI) and positron emission technology (PET) have been utilized to obtain important biomarker information as to disease activity and treatment response in the fields of cardiac disease, neurodegenerative disease, and oncology and are beginning to be applied more often to pulmonary diseases, including ILD. In addition, advanced analysis techniques, such as quantitative CT, are emerging as important methods of providing prognostic information as to ILD with potential for their use as imaging-based biomarkers for clinical trials [6•]. While within the field of ILD many of these novel imaging and analysis-based techniques have been applied to the ILD of idiopathic pulmonary fibrosis (IPF), due to similarities between IPF and SSc-ILD such methodologies may prove equally meaningful across both conditions. Here, novel imaging approaches as applied to SSc-ILD will be reviewed with a focus on recent advances in the fields of quantitative CT, MRI, and molecular imaging. In addition, radiation dose reduction techniques for CT and non-radiation-based imaging modalities for SSc-ILD screening will also be highlighted.

High-Resolution Computed Tomography

High-resolution CT (HRCT) is currently the imaging modality of choice for ILD (Table 1). With HRCT, thin-sliced cross-sectional imaging of the lung is obtained that provides detailed anatomic assessment of the airways and the secondary pulmonary lobule. HRCT performed at expiration enables the presence of air trapping to be determined. While HRCT informs as to the extent of ILD and the radiographic pattern of such, the radiation dose required is not trivial. Depending on the type of CT scan used the radiation dose from one CT acquisition can be greater than that provided by over 100 chest X-rays [7]. Concerns exist as to the amount of radiation exposure afforded with CT and the potential adverse long-term effects [7], especially in a patient population like SSc-ILD where repetitive imaging is usually needed [8]. Low-dose CT confers lower radiation exposure than HRCT but the anatomic resolution is less.

Slice-reduced HRCT has been proposed as a means of performing HRCT with a reduced radiation exposure yet still affording high diagnostic quality images for the assessment of ILD [9]. Slice-reduced HRCT using a total of nine axial slices had a sensitivity of 88.3% for diagnosing ILD in patients with SSc with the highest diagnostic characteristics for extensive disease extent [10]. Of the nine predefined slices, the majority were located in the basilar portion of the lungs—the anatomic location most likely to be affected in SSc-ILD. This reduction in the number of slices to nine would have resulted in a reduction in the mean radiation exposure per CT acquisition from 2.09 to 0.08 mSv [10]. In another study, slice-reduced HRCT with a total of nine axial slices detected ground glass, subpleural lines, and honeycombing to a similar degree as HRCT in SSc-ILD; however, the ability to detect bronchiectasis was reduced [11]. The main advantage of a slice-reduced technique is the substantial reduction in radiation exposure, to that on par with a chest radiograph [10, 11]. The main disadvantage, however, is the potential for lung nodules to go undetected. Given that patients with SSc are increased risk of lung cancer [12], a sliced-reduced HRCT technique may fail to detect potentially important incidental abnormalities.

Quantitative Computed Tomography

Quantitative CT employs the use of computerized algorithms to perform precise and objective quantification of CT findings of interest, for example the extent of fibrosis. Quantitative CT analysis techniques, including adaptive multiple features

Table 1 Imaging modalities for use in SSc-ILD

Modality	Use in SSc-ILD	Advantages	Disadvantages
Computed tomography (CT) – including high-resolution CT (HRCT)	-Standard of care for ILD imaging, including SSc-ILD	-Very high spatial resolution, especially HRCT -Established quantitative CT algorithms for advanced CT analyses	-Ionizing radiation exposure -Limited functional information provided
Magnetic resonance imaging (MRI)	-Mainly investigational at current time	-No radiation exposure -Can provide functional information -Can be paired with molecular probes	-Spatial resolution is less than CT -Lung MRI less readily available than chest CT
Ultrasound	-Mainly investigational at current time	-No radiation exposure -Low cost -Easily performed	-Primarily informs as to pleural and subpleural space

method (AMFM) and computer-aided lung informatics for pathology evaluation and rating (CALIPER), have been demonstrated to provide important information as to the risk of subsequent disease progression and mortality in IPF [13, 14]. Quantitative CT has been utilized to assess the effects of immunosuppressive treatment in SSc-ILD [15, 16••]. Quantitative lung fibrosis (QLF) scoring was performed using a texture-based analysis to determine CT changes at 12 months in a subgroup of patients enrolled in the Scleroderma Lung Study [15]. Patients treated with cyclophosphamide had a decrease of 2.6% in QLF scores from baseline compared to the placebo group who had an increase of 9.1% in QFL scores. Similarly, quantitative CT was performed to assess the treatment effects of cyclophosphamide or mycophenolate mofetil in the Scleroderma Lung Study II participants for whom baseline and 24-month HRCT were available [16••]. The extent of total lung fibrosis as determined by the quantitative interstitial lung disease (QILD) score was reduced by 2.51% in both treatment groups with no difference in the degree of reduction with cyclophosphamide versus mycophenolate mofetil. The change in whole lung QILD correlated inversely with the absolute change in FVC and DLCO at 24 months within each treatment group. These data support a potential role for imaging-based biomarkers as determinants of treatment response for SSc-ILD.

Magnetic Resonance Imaging

While CT, especially high-resolution CT (HRCT), remains the diagnostic test of choice for evaluation of the lung parenchyma due to its superior ability to obtain detailed morphologic information, CT is limited in its ability to provide functional information. Thus, MRI emerges as a promising alternative to CT as it can provide functional as well as structural information without the use of ionizing radiation (Table 1). Proton lung MRI has traditionally been difficult to perform because of the low density of water protons in the lung compared to other tissues and air-water interfaces forming magnetic susceptibility gradients that cause rapid signal decay and image artifacts [17]. Advances in MRI sequence development now allow for the pulmonary parenchyma to be imaged with enhanced resolution and improved clarity at short acquisition times through use of ultrashort time-to-echo (UTE) sequences. Such UTE techniques have been employed in patients with cystic fibrosis to enable structural assessment of the lung parenchyma without radiation exposure [18, 19].

Use of MRI of the lung to image pulmonary fibrosis has been investigated in several studies with results promising as to the ability of MRI to detect structural changes associated with ILD [20–24]. The ability of MRI, performed using a half-Fourier single-shot turbo spin-echo sequence, to determine the presence and degree of ILD was assessed retrospectively in 18 patients with SSc who underwent MRI of the chest and HRCT within a 12-month interval [23]. For SSc patients with greater than 0.5% parenchymal involvement on MRI, MRI could detect ILD with a very high sensitivity (93%) and perfect specificity (100%). The degree of MRI-detected ILD inversely correlated with the pulmonary function testing parameters, forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) and positively correlated with the amount of ILD on HRCT. However, MRI under-measured the degree of ILD as compared with HRCT. Whether or not current MRI sequences can image the lung with enough clarity and resolution to enable the underlying radiographic pattern to be determined, for example determining the presence of a usual interstitial pneumonia pattern, remains to be demonstrated. Given that the spatial resolution of MRI remains lower than CT, ongoing MRI sequence development is likely needed for determination of the radiographic pattern with high accuracy and confidence. MRI has the potential to become a viable alternative to CT to assess for the presence of ILD without conferring any radiation exposure. Ongoing research is needed to determine the sensitivity of MRI to detect interval morphologic changes over time or with ILD-targeted treatment.

A major advantage of MRI is its ability to provide functional information that would not be available with conventional CT. Using the UTE sequence, spiral volume interpolated breath-hold examination (VIBE), MRI of the lung was performed in seven SSc-ILD patients, nine SSc without ILD patients, and nine healthy volunteers [25]. Images were acquired during a breath hold after inspiration and after expiration with the differences in two images analyzed with elastic registration algorithms. With fibrosis, affected lung tissue should be less distensible and thus determination of voxel changes with respiration may serve as a surrogate measure for detecting areas of fibrosis. When compared to healthy volunteers and SSc without ILD patients, SSc-ILD patients had an absence of what the authors define as “marked deformation” (specifically a lack of a marked decrease) when comparing the change in voxel size from inspiration to expiration in the poster lower lung regions with these regions corresponding to areas of HRCT-determined fibrosis as reported by the authors. These results demonstrate that functional MRI can detect regional lung changes in SSc-ILD. MRI has been utilized to detect early functional changes with treatment in multiple disease processes including cystic fibrosis [26], and further research is needed to determine if MRI can be employed in a similar fashion to detect early treatment-related changes in SSc-ILD as related to perfusion, permeability, and ventilation.

MRI can also be performed with inhalation of hyperpolarized xenon gas to obtain detailed regional functional information as to ventilation and ^{129}Xe transfer across the interstitial space and into red blood cells [27]. ^{129}Xe MRI was

performed using the technique of chemical shift saturation recovery (CSSR) in four SSc-ILD patients, four IPF patients, and ten healthy volunteers to assess alveolar microstructure by measuring barrier thickness [28]. Both IPF and SSc patients had increased alveolar septal thickness compared to healthy volunteers; however, when corrected for age, only the difference in septal thickness between IPF and healthy volunteers remained significant. ^{129}Xe MRI has been demonstrated to detect changes in gas diffusion over time in patients with IPF [29]. While ^{129}Xe MRI studies have predominately focused on IPF, its application to SSc-ILD may elucidate important functional information not otherwise obtainable.

Molecular Imaging

Molecular imaging enables non-invasive characterization of molecular processes in vivo. A molecular probe can be combined with an imaging modality, such as MRI, single photon emission computed tomography (SPECT), or positron emission technology (PET) and utilized to visualize and quantify the location and expression of a molecular target of interest. Growing interest exists in the use of molecular imaging for non-invasive visualization of aberrant molecular pathways in fibrosis [30•, 31]. Molecular probes have been developed that target molecular pathways involved either directly or indirectly in fibrosis pathogenesis. Several of these molecular probes have been utilized in animal models of pulmonary fibrosis or in humans with pulmonary fibrosis including SSc-ILD.

Endothelial injury is central to the pathogenesis of SSc and results in increased capillary permeability or vascular leak [32]. While a normal response to tissue injury [33], increased capillary permeability has been shown to contribute to the development of pulmonary fibrosis [34]. Using the clearance rate of the inhaled radiolabeled molecule, technetium-labeled diethylenetriamine pentaacetate (^{99}Tc-DTPA), as a measure of the integrity of the alveolar capillary membrane, patients with SSc-ILD had fast ^{99}Tc-DTPA clearance rates consistent with increased permeability of the alveolar capillary membrane [35]. In addition, the rate of ^{99}Tc-DTPA clearance associated with risk of SSc-ILD disease progression, as determined by subsequent change in FVC, in two independent studies [36, 37]. Using the albumin-binding gadolinium-based contrast agent, gadofosveset, molecular MRI was performed on six patients with pulmonary fibrosis (one SSc-ILD and five idiopathic pulmonary fibrosis) and four healthy volunteers to determine the degree of lung albumin extravasation [38•]. Albumin extravasation, as a surrogate measure of lung vascular leak, was increased diffusely in patients with pulmonary fibrosis compared to healthy volunteers with the degree of increase similar across upper, middle, and lower measured lung regions. Comparisons with CT revealed that albumin extravasation occurred in areas of "normal" lung in addition to areas with interstitial abnormalities in both IPF and SSc-ILD (Fig. 1).

Ongoing endothelial injury and immune system activation result in fibroblast activation, a key feature of fibrosis pathogenesis in systemic sclerosis as well as fibrosis in other disease processes [39, 40]. The end result of activated fibroblasts is excessive deposition of extracellular matrix, central to which is type I collagen [40]. ^{68}Ga-CBP8 is a PET tracer specific for type I collagen [41]. ^{68}Ga-CBP8 was demonstrated to bind with high specificity to collagen in the lungs of bleomycin-treated mice. ^{68}Ga-CBP8 accurately quantified the degree of collagen present in both mouse models of pulmonary fibrosis and explanted lung tissue from IPF patients. In addition, ^{68}Ga-CBP8 was sensitive to detecting treatment response in a vascular leak dependent model of pulmonary fibrosis. First-in-human studies are underway to assess the ability of ^{68}Ga-CBP8 to detect increased collagen in IPF (ClinicalTrials.gov Identifier: NCT03535545). As increased type I collagen is also a key pathogenic feature of fibrosis in SSc, including SSc-ILD, ^{68}Ga-CBP8 has the potential for applicability to SSc-ILD for non-invasive collagen detection. While administration of PET tracers, including ^{68}Ga-CBP8, do confer radiation exposure, PET can be paired with MRI as opposed to CT thus limiting the total radiation dose per imaging session.

Other fibrosis-specific molecular probes have potential for use in patients with pulmonary fibrosis, including SSc-ILD, though many are still in the preclinical phase of development at this time. The formation of mature collagen is dependent on lysyl oxidase-mediated collagen cross-linking. Lysyl oxidase gene expression is upregulated in fibroblasts from both SSc-ILD and IPF patients [42]. Two MRI probes, Gd-Hyd and Gd-OA, have been developed to detect lysyl oxidase activity by targeting allysine, an amino acid formed in collagen by the action of lysyl oxidase [43, 44]. Both probes detected active fibrosis generation, i.e., fibrogenesis, as well as response to treatment with a lysyl oxidase inhibitor in the bleomycin mouse model. Allysine imaging represents a potential non-invasive biomarker of disease activity for use in fibrotic diseases, like SSc-ILD.

The most readily available PET probe is fluorodeoxyglucose (^{18}F-FDG) which is utilized to quantify glucose uptake in tissues. While its main application is for oncologic indications, ^{18}F-FDG PET has been employed in fibrotic lung diseases. Increased ^{18}F-FDG uptake was demonstrated in patients with diffuse parenchymal lung disease, some of whom had connective tissue disease-associated ILD [45] with higher uptake associating with mortality in IPF [46]. ^{18}F-FDG PET was recently utilized to provide pharmacodynamic information as to an investigational IPF therapy, omipalisib, in an early stage trial in IPF patients [47]. ^{18}F-FDG PET detected a decrease in glucose uptake with pirfenidone administration in the bleomycin model; however, no change in ^{18}F-FDG uptake was detected in patients treated with pirfenidone or nintedanib at 3 months [48]. As

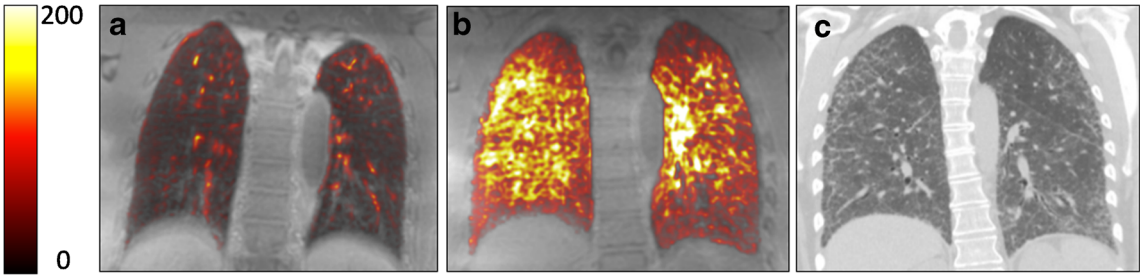

Fig. 1 Molecular imaging of albumin extravasation in systemic sclerosis-associated interstitial lung disease. Fused MRI color overlay images (baseline pre-contrast images subtracted from images obtained 10–12.5 min post-contrast injection super-imposed on baseline image) for **a** healthy volunteer and **b** SSc-ILD patient. **c** CT scan of the SSc-ILD patient. For the healthy volunteer (**a**), the majority of the lungs are unenhanced with higher areas of signal intensity correspond to the location of blood vessels. Findings are similar to an angiogram as gadofosveset is bound to albumin in the blood. For the SSc-ILD patient (**b**), signal intensity is markedly increased throughout the lung parenchyma consistent with increased pulmonary albumin extravasation or pulmonary vascular leak in the SSc-ILD patient. Albumin extravasation was increased across the entire lung including areas that were "normal" on CT scan performed within 5 months of MRI (**c**). Images provided courtesy of Sydney Montesi. Study results published in Montesi SB, Rao R, Liang LL, Goulart HE, Sharma A, Digumarthy SR, et al. Gadofosveset-enhanced lung MRI to detect ongoing vascular leak in pulmonary fibrosis. Eur Respir J. 2018; 1800171 [38•]

interest in molecular imaging of fibrosis grows and more probes are translated into humans, additional fibrosis-specific probes will likely become available to allow early detection of response to antifibrotic therapies in ILD patients. Use of molecular probes may enable a precision medicine approach to be applied to ILD patients similar to that which is beginning to be used in oncology [49, 50].

Other Imaging Modalities

Lung ultrasound has been investigated as an imaging screening modality for the detection of ILD. Lung ultrasound offers several advantages as an imaging modality as it is performed without the use of ionizing radiation, is less costly than either CT or MRI, and can be accomplished in a very short amount of time (Table 1). Lung ultrasound to assess and quantify the number of B lines, hyperechoic artifacts extending vertically from the pleura that move in parallel with lung movement, has been utilized to detect the presence of ILD with high accuracy in connective tissue disease-associated ILD [51, 52]. Lung ultrasound was initially performed in SSc patients to assess the number of ultrasound lung comets, now referred to as B lines, with good correlation demonstrated between the total number of ultrasound lung comets and severity of ILD, as measured by the Warrick score [53]. Lung ultrasound was performed on 58 SSc patients who had undergone HRCT [54]. SSc-ILD patients had a significantly increased number of B lines compared to SSc without ILD. HRCT and lung ultrasound has a concordance rate of over 80% for the detection of ILD. Using HRCT to define the presence of ILD, lung ultrasound had a sensitivity of 100% and a specificity of 84.2% in a cohort of 48 SSc patients, 29 of whom had SSc-ILD [55]. The number of B lines correlated with the extent of ILD as determined by the Warrick score and inversely correlated with FVC and DLCO. Together, these data suggest that lung ultrasound may serve as an alternative to CT for detecting the presence of ILD. However, lung ultrasound is limited in its ability to provide morphologic information and informs primarily as to abnormalities in the pleural space and subpleural region of the lung. Whether or not lung ultrasound is sensitive enough to detect changes in the extent of ILD over time remains to be determined.

Optical imaging uses light to enable in vivo microscopy imaging. It is performed with non-ionizing as opposed to ionizing radiation as is utilized with CT. Optical coherence tomography performed endobronchially was able to detect traction bronchiectasis and honeycombing in patients with ILD who underwent lung biopsy via video-assisted thoracoscopic surgery [56]. Optical imaging has the potential to be combined with fibrosis-specific molecular probes to enable in vivo molecular imaging of fibrosis on a microscopic level [57]. Optical imaging using probe-based confocal laser endomicroscopy (pCLE) has been utilized to image the alveolar space in diffuse lung disease such as pulmonary alveolar proteinosis [58].

Future Directions

While considerable advances have occurred in the development and application of novel imaging modalities for SSc-ILD, ongoing sequence development, especially for MRI and translational of fibrosis-related molecular probes are needed. Molecular imaging, in particular, has been proposed to address several key unmet needs within the fields of fibrosis research and clinical care [30•]. Such a modality, by enabling direct visualization and non-invasive quantification of specific molecular pathways critical to fibrosis pathogenesis, has potential for utilization as a disease activity measure to better

inform as to SSc-ILD prognostication. Preclinical data for several of the fibrosis-specific molecular probes, including the ones discussed here [41, 43, 44], demonstrate their ability to detect changes with treatment. The ability to determine early response to current and investigational SSc-ILD treatments would greatly inform patient care, such that individual treatment plans can be tailored accordingly, and accelerate drug development to advance that care by improving clinical trial feasibility.

Conclusions

Recent advances have occurred in the development of novel imaging approaches for SSc-ILD. These advances represent important steps in the use of MRI to provide structural, functional, and molecular information in SSc-ILD, the application of quantitative CT to determine and quantify treatment response, and the development of alternative imaging modalities for SSc-ILD screening that are radiation-free or radiation-reduced compared to conventional HRCT. Ongoing research is needed to apply these and other techniques to obtain personalized information as to disease activity and treatment response in patients with SSc-ILD to guide prognostication and optimal selection of ILD-targeted treatments for individual patients.

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Compliance with Ethical Standards

Conflict of Interest Sydney Montesi receives research support paid to her institution from United Therapeutics. She has received funding from Promedior though her institution. Peter Caravan has > 5% equity in Collagen Medical, Factor 1A LLC, and Reveal Pharmaceuticals. He receives research support from Pfizer, Pliant Therapeutics, Indalo Therapeutics, and has been a consultant to Collagen Medical. He is a named inventor on issued or pending patents that cover ^{68}Ga-CBP8, Gd-Hyd, and Gd-OA.

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Human and Animal Rights Statement All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines). Figure 1 has not been published previously; however, the results from this image were published as part of Montesi et al. [38•] with all appropriate informed consent obtained.

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