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Original Research

Measure of lung dielectric proprieties in patients with Idiopathic Pulmonary Fibrosis: correlation with clinical, radiological and pulmonary functional parameters

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ABSTRACT

Background: Dielectric properties of biological tissues are biophysical parameters; in lung they change with amount of air, blood and parenchyma. Remote Dielectric Sensing (ReDS™) technology measures dielectric properties of lung tissues quantifying the content of fluids inside the scan volume. We aimed to evaluate the reliability of ReDS™ measure in Idiopathic Pulmonary Fibrosis (IPF) patients and in healthy volunteers, and to investigate the correlation of ReDS™ score with clinical, radiological and functional parameters.

Methods: We conducted a prospective observational study, including 52 patients with diagnosis of IPF and 17 healthy volunteers; for each patient we recorded: complete functional evaluation, dyspnoea score (mMRC scale), Usual Interstitial Pneumonia (UIP) Computed Tomography (CT) pattern (UIP definite or probable) and ReDS™ measure (expressed in %).

Results: ReDS™ measure was reported as correct both in patients and controls, the firsts with higher scores (33.8% vs 29.1%, $p = 0.003$). In IPF patients we observed a significant inverse correlation with ReDS™ score and Forced Vital Capacity (FVC), Vital Capacity (VC) and Total Lung Capacity (TLC) measures and, when we considered only patients with UIP definite CT pattern, the correlation was inverse with FVC, VC, TLC, DLCO. In IPF patients the higher was mMRC dyspnoea index, the higher was ReDS™ score. No significant correlations were observed between ReDS™ score and functional parameters in healthy controls.

Discussion: We demonstrated a correlation of ReDS™ scores with some functional (mainly indicative or diagnostic for restriction) and clinical parameters in IPF patients; the score was correlated with density of tissues possibly quantifying tissue fibrosis in IPF patients.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonia and at histopathologic examination presents features of usual interstitial pneumonia (UIP) [1]. IPF causes worsening dyspnoea and progressive loss of pulmonary function with a median survival time of approximately 3–5 years [2].

Pulmonary function tests (PFT) and high-resolution CT (HRCT) are fundamental for the diagnosis of IPF [3,4]. Typical UIP pattern on HRCT is defined by the presence of honeycombing and reticular opacities, with or without traction bronchiectasis, in subpleural and basal predominance in both lungs [1]. The presence of typical UIP pattern on HRCT is

Abbreviations: CPI, composite physiologic index; CT, computed tomography; DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HRCT, high resolution computed tomography; mMRC, modified Medical Research Council; ReDS, Remote Dielectric Sensing; TLC, total lung capacity; VC, vital capacity; UIP, usual interstitial pneumonia; VA, alveolar volume.

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enough for the diagnosis of IPF in the appropriate clinical setting [1].

IPF is characterized by a spirometric functional restrictive pattern, defined by a reduction of total lung capacity (TLC); nevertheless, due to its reproducibility, forced vital capacity (FVC) has been used as the standard spirometric measure of pulmonary function in IPF for many decades. Longitudinal change in serial measures of lung volume (either FVC or vital capacity VC) is a widely accepted hallmark of disease progression in patients with IPF and is commonly used as primary endpoint in therapeutic studies in IPF [5]. FVC is generally accepted as a surrogate of disease severity and progression, though does not appear to either correlate with any specific radiological feature or present CT pattern [5].

Lung volumes determined by functional respiratory imaging directly correlate with FVC as their relative changes: loss of lobe volumes, increase of fibrotic tissue and airway radius measured at TLC correlated with changes in FVC, but these already occur in the lower lobes when FVC is still within normal limits [6].

In lung fibrosis CT measurements, including densitometric measures, quantitative interstitial score, quantitative honeycombing measure and visual fibrosis score were strongly correlated with both FVC and diffusion lung capacity for carbon monoxide (DLCO): in particular, there is an inverse correlation between quantitative densitometry of lung and FVC as well as percentage of [7].

The dielectric properties of a biological tissue are basic biophysical parameters [8]: in the lung, they change mainly with the amount of air, blood and parenchyma [8,9]. The dielectric coefficient of a material is represented by a frequency-dependent number describing its interactions with electromagnetic energy, including absorption, reflection and transmission of the energy. The dielectric coefficient of the intact lung is very sensitive to the ratio between respectively volumes of air and water; thus this number is a direct measure of fluid concentration [8]. Remote Dielectric Sensing (ReDS™) technology (Sensible Medical Innovations Ltd. Kfar Neter, Israel) measures the dielectric properties of tissues by quantifying the content of fluids inside the scan volume. Low power electro-magnetic signals are emitted across the thorax through the lung and the characteristics of the signals received after passing through the tissue are related to their dielectric properties, which are mostly determined by the lung's fluid content [9].

Amir et al. provided a direct validation of the accuracy of ReDS™ when compared to CT in patients with acute and chronic congestive heart failure: the authors demonstrated that ReDS™ and CT have comparable accuracy to determine fluid content [9].

In lung fibrosis, the volume of air is reduced and the tissue volume is increased compared to a normal lung; it's also known that the more fibrosis increases, the more FVC, TLC and DLCO are reduced because FVC and TLC are proportional to fibrosis [3].

Given the proven correlation between CT and ReDS™, we aimed to: 1) verify the physical hypothesis that underlies the use of ReDS™ measure in IPF patients; 2) evaluate the reliability of ReDS™ measure in IPF patients and in healthy volunteers; 3) evaluate differences of ReDS™ measure scores among IPF patients and healthy volunteers; 4) investigate the correlation of ReDS™ score and clinical, radiological and functional measures in patients with IPF and healthy subjects.

2. Material and methods

2.1. Study population

We conducted a single centre prospective observational study, including all consecutive patients with a diagnosis of IPF, followed at Interstitial Lung Diseases Ambulatory of our centre, a middle-size teaching hospital in the North-West of Italy. Recruitment period started at 1st September 2021 and finished at 30th April 2022. This study was conducted in accordance with STROBE statement for observational cohort studies [10], and it was approved by our Institutional Ethical Committee (CE132/2022).

We included all patients with a high confidence diagnosis of IPF based on international guidelines [2] and who underwent as outpatient, to a complete clinical and functional evaluation, and at the same time to ReDS™ measure. We excluded those patients who had a diagnosis of combined pulmonary fibrosis and emphysema, a previous history of pulmonary arterial hypertension (Group 1, 2 or 3) [11], congestive heart failure and those who were unable to perform the spirometric evaluation at the enrolment time.

As a control group, we included healthy, non-smokers, volunteers, without history of respiratory diseases; these subjects underwent the same clinical and functional evaluations and then ReDS™ measure.

For each patient we recorded: demographics (age, gender, height and weight), long term oxygen therapy (LTOT), CT pattern (UIP definite, UIP probable), dyspnoea score measured with mMRC scale and respiratory functional data. In particular we measured: FVC (in L/min and %predicted value), vital capacity (VC, in L/min and %predicted value), forced expiratory volume in the first second (FEV1, in L/min and %predicted value), FEV1/FVC (in %), TLC (in L and %predicted value), DLCO (in ml/min/mmHg and %predicted value), alveolar volume (VA, in litres) and DLCO/VA (in ml/min/mmHg/L and %predicted value). For each patient we also calculated composite physiologic index (CPI) reflecting the morphologic extent of pulmonary fibrosis: extent of disease on CT = 91.0 - (0.65 x DLCO%) - (0.53 x FVC%) + (0.34 x FEV1%) [12].

Each patient, at the enrolment time, underwent ReDS™ measurement; ReDS™ Wearable System (Sensible Medical Innovations Ltd., Netanya, Israel) is composed by two sensors integrated in a wearable vest which is applied to the thorax of the patient. After having worn it, the two sensors are located on the front and on the back of the thorax and no need of direct skin contact. The measurement starts when the upfront sensor inflates and last for nearly 60 s after which the results is displayed on ReDS™ screen (Fig. 1).

The two sensors analyse signal that reflects dielectric proprieties of the section of the lung interposed between the two sensors; dielectric coefficient of a material is represented by a frequency-dependent number describing its interactions with electromagnetic energy. Water has a high dielectric coefficient and dielectric coefficients of tissues are determined mainly by their fluid content. In particular, the dielectric coefficient of pulmonary tissue is determined by the dielectric coefficient of its components (air, blood, parenchyma) and their relative concentrations. In normal conditions, it is accepted that lung is primarily composed of air and water components: the dielectric coefficient of the intact lung is very sensitive to the ratio between the volumes of air and water, thus this number is a direct indicator of fluid concentration. The measure result is reported as percentage of fluid content in the scan volume: derived from its clinical validation use, ReDS™ score normality ranges between 20 and 35% [13].

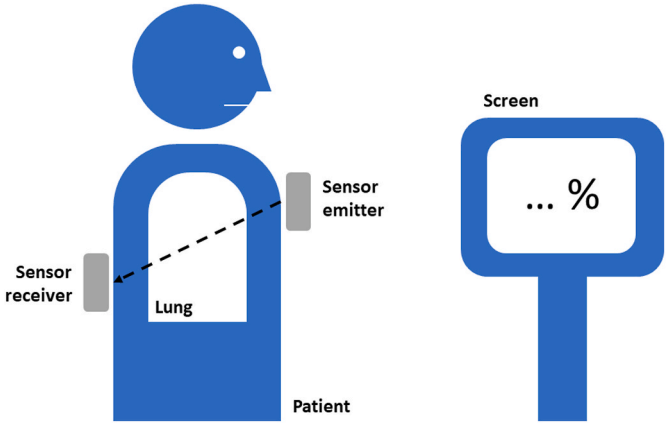

Fig. 1. ReDS™ instrument: the signal is emitted by the sensor located in the front of the patient's thorax, passes through the tissues and is received by the one located in the back. The result of the analysis is displayed on the screen.

2.2. Statistical methods

Categorical variables are presented as absolute value and percentage, while for continuous ones we reported mean ± SD or median and interquartile range [IQR], minimum and maximum values [min, max], as appropriate. We applied the paired *t*-test or non-parametric signed-rank test to test differences between quantitative parameters. We performed ordinary one-way ANOVA for comparison of three or more means, and Tukey test for multiple comparisons when appropriate. Correlation between functional parameters or clinical continuous variables and ReDS™ results were calculated using Pearson correlation coefficient (R and 95% confidence intervals, IC). A two-tailed test was considered for the hypothesis testing procedure and statistically significant values were considered to reach a P value < 0.05. Statistical analysis was performed using MedCalc (MedCalc Software Ltd, Belgium).

3. Results

We included in our analysis 52 patients affected by IPF corresponding to 52 ReDS™ measurements and 17 healthy subjects as controls. Among 52 patients, 40 were male (76.9%), 39 (75%) had a UIP definite pattern and 13 (25%) a UIP probable one. All patients had a restrictive pattern (mean TLC 58.19%) with a moderate DLCO impairment (mean DLCO 42.40%) (Table 1).

All of ReDS™ measurements were reported automatically as "correct" by the instrument, in both patients and controls, without the need to repeat the measurement.

ReDS™ score was higher in IPF patients with a mean score of 33.83% (min 21%, max 52%), whereas among healthy volunteers was 29.12% (min 23%, max 35%) ($p = 0.003$).

In our cohort, we observed a significant inverse correlation between ReDS™ score and several functional parameters: in particular the correlation was more significant with TLC% and FVC%, both indicative of restrictive functional pattern, respectively with $R = -0.486$ (95%CI = −0.723 to −0.145, $p = 0.007$) and $R = -0.465$ (95% CI = −0.710 to −0.119, $p = 0.010$). Conversely, we observed a positive correlation between ReDS™ score and FEV1/FVC ($R = 0.516$, 95% CI = 0.185 to 0.742, $p = 0.004$) and CPI ($R = 0.497$, 95% CI = 0.224 to 0.698, $p = 0.0009$) (Table 2, Fig. 2).

When we considered only patients with HRCT UIP definite pattern, we recorded a significant correlation among ReDS™ score and: FVC%, VC%, FEV1/FVC, TLC, TLC%, DLCO, DLCO%, VA, VA% and CPI (Table 3, Fig. 3).

On the contrary, when we evaluated only patients with UIP probable pattern, we found a significant correlation only between ReDS™ score and CPI (Table 4).

When we stratified patients for severity of their functional deficit using different parameters, we observed higher scores in patients with a more severe restriction measured with TLC% ($p = 0.040$) but only among mild (≥60%) and severe (<40%) deficit; similar results were obtained for lower FVC% (FVC≥50% vs <50%, $p = 0.007$) and lower DLCO% values (DLCO 40–59% vs <40%, $p = 0.035$). Moreover, we observed that patients with worse dyspnoea scores measured with mMRC scale had higher ReDS™ scores ($p = 0.027$), in particular among patients with mMRC 2 *vs* 3 grades, independently from the radiologic pattern ($p = 0.044$). Finally, patients in LTOT treatment (11 patients) had higher ReDS™ scores ($p = 0.026$) (Table 5).

For completeness, we conduced same measure in healthy controls we observed no statistical correlations between ReDS™ scores and functional parameters (Table 6).

Table 1
Clinical, functional and radiological characteristics of IPF patients and healthy subjects.

	IPF patients	Healthy subjects
Number of subjects	52	17
Number of ReDS™ measures	52	17
Age (mean ± SD), in years	75.62 ± 5.05	76.82 ± 5.26
Sex: male/female	40 (76.9%)/12 (23.1%)	7 (41.17%)/10 (58.82%)
UIP HRCT pattern		
• Definite	39 (75%)	
• Probable	13 (25%)	
mMRC dyspnea scale	2.04 ± 0.71	
• mMRC 1	12 (26.1%)	
• mMRC 2	26 (56.5%)	
• mMRC 3	14 (30.4%)	
FVC (L/min)	2.74 ± 0.83	4.78 ± 1.19
FVC %	76.94 ± 17.95	98.18 ± 11.77
VC (L/min)	2.80 ± 0.83	4.80 ± 1.20
VC %	78.83 ± 17.89	99.06 ± 10.91
FEV1 (L/min)	2.21 ± 0.65	4.10 ± 0.92
FEV1%	82.75 ± 18.76	100.59 ± 11.84
FEV1/FVC	81.67 ± 8.82	86.42 ± 8.82
TLC (L)	3.69 ± 1.04	5.74 ± 1.23
TLC %	58.19 ± 13.36	91.76 ± 8.18
DLCO (ml/min/mmHg)	10.00 ± 4.15	29.24 ± 6.72
DLCO %	42.40 ± 15.94	89.24 ± 10.22
VA (L)	3.56 ± 1.05	5.58 ± 1.20
VA %	60.54 ± 16.13	91.65 ± 8.40
DLCO/VA (ml/min/mmHg/L)	2.94 ± 0.97	5.29 ± 0.65
DLCO/VA %	72.63 ± 18.91	98.24 ± 13.29
CPI	52.36 ± 12.78	
ReDS™ score %	33.83 ± 6.44	29.12 ± 3.17

Abbreviations: CPI, composite physiologic index; DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HRCT, high resolution computed tomography; mMRC, modified Medical Research Council; ReDS, Remote Dielectric Sensing; TLC, total lung capacity; VC, vital capacity; UIP, usual interstitial pneumonia; VA, alveolar volume.

4. Discussion

Our study demonstrated that an inverse correlation was observed between the main functional parameters indicative for restrictive functional impairment and the parameter extrapolated from the instrument, whose value, expressed in %, could be indicative of tissue density. This correlation was particularly present in IPF patients with definite UIP-type CT patterns.

ReDS™ measures the combination of dielectric proprieties (relative

Table 2
Correlation results among functional parameters and ReDS™ score in IPF patients.

	R	95% CI for R	p
FVC	−0.277	−0.584 to 0.099	0.145
FVC%	**−0.465**	**−0.710 to -0.119**	**0.010**
VC	−0.280	−0.586 to 0.096	0.141
VC%	**−0.474**	**−0.716 to -0.130**	**0.009**
FEV1	−0.142	−0.484 to 0.236	0.459
FEV1%	−0.285	−0.590 to 0.090	0.132
FEV1/FVC	**0.516**	**0.185 to 0.742**	**0.004**
TLC	−0.310	−0.607 to 0.063	0.101
TLC%	**−0.486**	**−0.723 to -0.145**	**0.007**
DLCO	−0.267	−0.577 to 0.109	0.161
DLCO%	−0.348	−0.634 to 0.024	0.063
DLCO/VA	0.029	−0.340 to 0.391	0.879
DLCO/VA%	−0.113	−0.460 to 0.264	0.559
VA	−0.336	−0.625 to 0.034	0.074
VA%	−0.349	−0.634 to 0.020	0.063
CPI	**0.497**	**0.224 to 0.698**	**0.0009**

In bold, statistically significant results. Abbreviations: CPI, composite physiologic index; DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ReDS, Remote Dielectric Sensing; TLC, total lung capacity; VA, alveolar volume; VC, vital capacity.

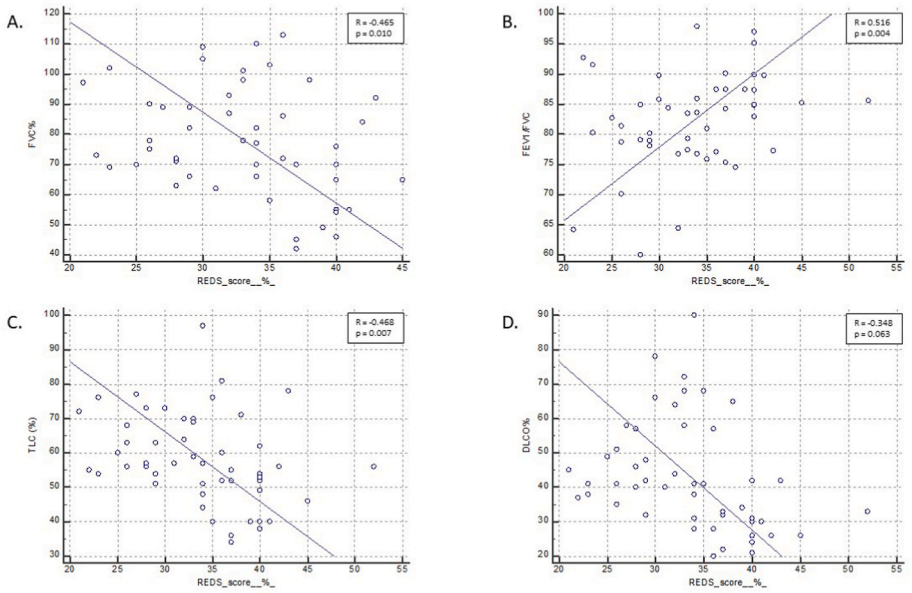

Fig. 2. Correlation results among mail functional parameters and ReDS™ score in all IPF patients.

Table 3
Correlation results among functional parameters and ReDS™ score in IPF patients with UIP definite pattern.

	R	95% CI for R	p
FVC	−0.029	−0.551 to 0.023	0.069
FVC%	**−0.374**	**−0.613 to -0.070**	**0.017**
VC	−0.290	−0.552 to 0.023	0.069
VC%	**−0.376**	**−0.615 to -0.073**	**0.016**
FEV1	−0.144	−0.436 to 0.175	0.374
FEV1%	−0.228	−0.503 to 0.089	0.156
FEV1/FVC	**0.342**	**0.031 to 0.594**	**0.032**
TLC	**−0.382**	**−0.620 to -0.080**	**0.014**
TLC%	**−0.474**	**−0.684 to -0.191**	**0.002**
DLCO	**−0.377**	**−0.616 to -0.074**	**0.016**
DLCO%	**−0.397**	**−0.631 to -0.098**	**0.011**
DLCO/VA	−0.161	−0.453 to 0.162	0.326
DLCO/VA%	−0. 106	−0.408 to 0.216	0.519
VA	**−0.377**	**−0.619 to -0.060**	**0.017**
VA%	**−0.374**	**−0.617 to -0.066**	**0.018**
CPI	**0.469**	**0.123 to 0.712**	**0.010**

In bold, statistically significant results. Abbreviations: CPI, composite physiologic index; DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ReDS, Remote Dielectric Sensing; TLC, total lung capacity; VA, alveolar volume; VC, vital capacity.

permittivity and conductivity) of the lungs which are determined by the volumetric concentrations of fluids. Nopp et al. [14] defined that the filling factor (F) is the ratio of air volume (Va) to lung tissue volume (Vc):

$$F = Va \,/\, Vc$$

Filling factor (F) and relative permittivity and conductivity are inversely correlated; the decrease of conductivity and relative permittivity was explained by alveolar walls thinning as well as the deformation of the epithelial cells and blood vessels caused by the expansion of the alveoli [8].

Based on the assumption that in lung fibrosis *Va* is reduced and *Vc* is increased, as demonstrated by the comparison between CT images and functional evaluations [15], for formula F = *Va/Vc*, F is directly proportional to FVC and therefore FVC is inversely proportional to dielectric properties (conductivity and permittivity).

If the equation of ReDS™ measurement is:

$$\text{ReDS™ score} = 1 \,/\, (1 + F)$$

and, after simplifications:

$$\text{ReDS™ score} = Vc \,/\, (Va + Vc)$$

Then, if lung air volume is reduced as measured in FVC (or TLC and VA) ReDS™ is higher, and if *Vc* increases and *Va* decreases due to fibrosis, therefore ReDS™ score increases even more. This would demonstrate the reason why in our patients the ReDS™ score increases with the reduction of FVC and TLC (and collaterally also DLCO).

This correlation has never been demonstrated before in the literature although other studies evaluated permittivity on tissues from animal models in which fibrosing damage was induced, verifying that as the amount of fibrotic tissue increased, it corresponded to an increase in permittivity [16]. More recently, cirrhotic liver has been shown to have higher permittivity and conductivity than normal liver tissue. Indeed, the authors surmise that both hepatic fibrous tissue deposition and edema due to increased resistance to hepatic portal vein flow may both contribute to the increase in dielectric properties in the cirrhotic liver [17]. Finally, based on a variety of techniques and measurements, including dielectric measurements, water sorption, longitudinal acoustic velocity, dynamic mechanical spectroscopy and heat capacity, it is known that water molecules are tightly bound to specific sites on collagen chains [18], and fibrillar collagen deposition is the dominant architectural feature of human lung fibrosis [19].

The second objective of the study was verified since the measurements were performed correctly, and all were reported as regular by the instrumentation without the need for repetition nor interaction of the patient with the instrumentation.

We demonstrated an inverse correlation between the ReDS™ score and some functional parameters: specifically, we observed an inverse correlation with FVC%, VC%, TLC% which are typically reduced in patients with IPF and correlate with the degree of fibrotic tissue extension in IPF [5–7]. Moreover, we also found a direct correlation between ReDS™ score and CPI which quantifies the functional defect attributable to pulmonary fibrosis, excluding the component ascribable to emphysema [12]. A possible physical and pathophysiologic explanation for these findings may be searched in the anatomopathological and functional characteristics of IPF patients: as demonstrated in some studies

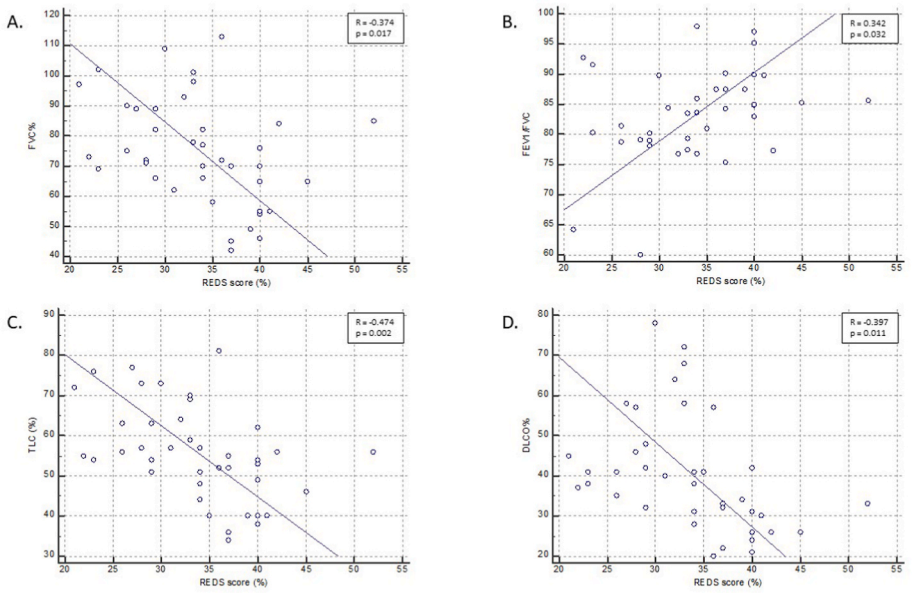

Fig. 3. Correlation results among mail functional parameters and ReDS™ score in IPF patients with UIP definite pattern.

Table 4
Correlation results among functional parameters and ReDS™ score in IPF patients with UIP probable pattern.

	R	95% CI for R	p
FVC	0.413	−0.248 to 0.811	0.206
FVC%	−0.330	−0.336 to 0.776	0.321
VC	0.501	−0.141 to 0.846	0.116
VC%	0.451	−0.203 to 0.827	0.163
FEV1	0.297	−0.368 to 0.761	0.375
FEV1%	0.179	−0.471 to 0.703	0.597
FEV1/FVC	0.068	−0.586 to 0.669	0.851
FEV1/VC	−0.001	−0.630 to 0.628	0.996
TLC	0.381	−0.283 to 0.798	0.247
TLC%	0.175	−0.474 to 0.701	0.606
DLCO	−0.002	−0.601 to 0.598	0.994
DLCO%	−0.125	−0.674 to 0.513	0.713
VA	0.319	−0.347 to 0.771	0.338
VA%	0.096	−0.534 to 0.658	0.778
DLCO/VA	−0.363	−0.791 to 0.302	0.271
DLCO/VA%	−0.289	−0.757 to 0.375	0.388
CPI	**0.597**	**0.035 to 0.872**	**0.040**

In bold, statistically significant results. Abbreviations: CPI, composite physiologic index; DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ReDS, Remote Dielectric Sensing; TLC, total lung capacity; VA, alveolar volume; VC, vital capacity.

Table 5
Mean ReDS™ score results stratified for different functional and clinical parameters.

	Mean (±SD) ReDS™ score	p
UIP definite	33.82 ± 6.71	0.640
UIP probable	33.36 ± 5.78	
TLC ≥60%	31.36 ± 5.65[a]	[a]0.040
TLC 40–59%	34.20 ± 7.12	
TLC <40%	38.20 ± 1.30[a]	
FVC ≥50%	33.34 ± 6.88	0.007
FVC<50%	38.40 ± 1.34	
DLCO ≥60%	33.12 ± 2.64	[a]0.035
DLCO 40–59%	30.70 ± 5.89[a]	
DLCO <40%	36.56 ± 6.77[a]	
mMRC1	32.58 ± 6.44	[a]0.044
mMRC2	32.30 ±5–97[a]	
mMRC3	37.71 ± 6.05[a]	
LTOT	36.63 ± 4.98	0.026
No LTOT	32.10 ± 5.74	

[a] Indicates the significant paired comparison. DLCO, diffusion lung capacity for carbon monoxide; FVC, forced vital capacity; LTOT, long term oxygen therapy; mMRC, modified Medical Research Council; ReDS, Remote Dielectric Sensing; TLC, total lung capacity; VC, vital capacity.

using CT images, in IPF the air volume is reduced, while the volume and density of fibrotic tissue increase compared with a normal lung [15]. We also know that the more fibrosis increases, the more FVC, TLC, and DLCO are reduced, and that the reduction in FVC and TLC is proportional to the extent of fibrosis (as demonstrated by comparative analysis of chest CT imaging) [5–7].

Interestingly, when considering the entire population of patients with IPF, the ReDS™ score was found to be directly related to the dyspnea score measured with the mMRC scale. Previously published data have shown that the degree of dyspnea, measured with the mMRC scale, correlated with the main functional parameters FVC, TLC, DLCO and survival in IPF patients [20,21].

Similar surprising results were obtained when we stratified patients according to definite or probable UIP pattern. In the group of patients with definite UIP patterns, we demonstrated an inverse correlation between the ReDS™ score results and the main functional parameters indicative of restrictive alteration, namely FVC%, VC%, FEV1/FVC, TLC, TLC%, DLCO, DLCO%, AV, AV%. In contrast, in the group of patients with probable UIP pattern, no correlation was found between the ReDS™ score and the functional parameters but only with the CPI. A direct correlation between radiologic pattern (UIP definite *vs* probable) and extent of functional abnormalities has never been demonstrated in the literature [22,23]; nevertheless, a correlation between densitometric measures assessed at HRCT and functional parameters such as FVC and DLCO has been widely demonstrated [6,15,24]. Even in our cohort of patients FVC, TLC and DLCO were similar between the two groups without significant differences.

We can therefore hypothesize that the differences in correlation between the ReDS™ score of patients with definite and probable UIP patterns may be due to the different disposition of the alterations in the parenchyma: in particular, the electromagnetic waves are emitted in the upper part of the chest, frontally, and pass through the lung until they reach the sensor located in the lower part of the chest, dorsally [9]. The electromagnetic wave beam then goes through the portion of the lung

Table 6
Correlation results among functional parameters and ReDS™ score in healthy controls.

	R	95% CI for R	p
FVC	−0.198	−0.620 to 0.311	n.s.
FVC%	0.121	−0.381 to 0.568	n.s.
VC	−0.205	−0.624 to 0.305	n.s.
VC%	0.129	−0.374 to 0.574	n.s.
FEV1	0.118	−0.566 to 0.384	n.s.
FEV1%	0.273	−0.238 to 0.666	n.s.
FEV1/FVC	0.287	−0.224 to 0.674	n.s.
TLC	−0.323	−0.696 to 0.185	n.s.
TLC%	−0.128	−0.573 to 0.375	n.s.
DLCO	−0.499	−0.790 to 0.025	n.s.
DLCO%	−0.523	−0.802 to 0.057	n.s.
DLCO/VA	−0.280	−0.670 to 0.321	n.s.
DLCO/VA%	−0.355	−0.714 to 0.151	n.s.
VA	−0.320	−0.690 to 0.189	n.s.
VA%	−0.103	−0.556 to 0.396	n.s.

Abbreviations: DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ReDS, Remote Dielectric Sensing; TLC, total lung capacity; AV, alveolar volume; VC, vital capacity.

that is most affected by fibrotic tissue: in fact, in the definite UIP pattern, fibrotic changes have an apico-basal gradient and a ventro-dorsal distribution [1,2]. Furthermore, it can be hypothesized that the different ReDS™ scores are due not only to the distribution of fibrosis but also to its composition: the definite UIP pattern has honeycombing and alveolar changes, both conditions absent in the UIP probable pattern; honeycombing consists of the presence of cystic spaces with thickened walls, in which there is excessive deposition of fibrotic tissue around the cysts leading to increased tissue density [1,2], potentially affecting the passage of electromagnetic waves emitted by the instrumentation. The differences of correlations among two patterns indicate that the ReDS™ system performs a quantitative measurement and not a qualitative one; however, this result could be influenced by some factors, mainly the sample size and the absence of quantification of anatomical damage detectable on CT.

Finally, we also conducted same measurements on healthy subjects: in our population ReDS™ values ranged between 23% and 35%, similar to those previously reported in the literature [13]; although we observed a small overlap in the measured values between the healthy and pathological populations, we demonstrated a significant difference in the mean score value between the two different populations. As expected, we did not identify any significant correlation between functional data and ReDS™ % score in healthy subjects.

To further improve the correlation between HRCT and the ReDS™ measurement, it might also be appropriate to use CT instrumentation that is capable of quantifying the percentage of fibrosis relative to healthy lung parenchyma. This would make the correlation between the two investigations even more sensitive and meaningful [25–27].

Moreover, based on our preliminary findings, this measure could be used also in patients affected by any form of ILD with a UIP definite or probable pattern, such as connective tissue disease (CTD)-associated ILD [28]. Finally, a longitudinal functional evaluation conducted on the same patient, comparing the results with the percent change from baseline in each of the respiratory functional parameters, would allow us to assess the concordance of the measurements and a possible prognostic value.

Our pilot study has some limitations.

- the first one lies in the small number of patients enrolled: increasing the sample size would allow for a reduction in the standard deviation of the measurement potentially better identifying the reference values for both the healthy population and the subjects with IPF;
- another limitation lies in the HRCT acquisition process and classification of UIP patterns: HRCTs dated no more than six months before measurement with ReDS™ were used in the study. Although the time period is limited and usually does not allow for consistent disease evolution, it would be useful to perform HRCT within 24 h of measuring with ReDS™ and performing spirometry, so that the measurement result can be correlated with a radiological picture as recent as possible;
- the measurement is conducted on one lung only, the right lung, without considering any different anatomical distribution of the damage evident on CT: nevertheless, the functional damage assessed by spirometry reports to us the overall function of the pulmonary system, without considering anatomical differences, ipsi- or contralateral to the assessment conducted with the ReDS™.

5. Conclusion

In conclusion, we demonstrate a correlation of ReDS™ scores with some functional (mainly indicative or diagnostic for a restrictive pattern) and clinical parameters in patients with IPF; the score is correlated with the density of tissues that the electromagnetic waves emitted by ReDS™ pass through, reflecting their dielectric proprieties. Due to its ease to use, invasiveness and non-necessity of patients' collaboration to obtain an adequate measurement, ReDS™ could be used as an adjunction to classical spirometric evaluation in IPF patients. Larger and longitudinal studies are needed to confirm these promising preliminary results.

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CRediT authorship contribution statement

Filippo Patrucco: Conceptualization, Conception and design of the work, Funding acquisition, Formal analysis, Acquisition, analysis and interpretation of data, Writing – original draft, Drafting the article and revision, Final approval of the version to be published: all the authors. **Carlo Albera:** Writing – original draft, Drafting the article and revision, Final approval of the version to be published, all the authors. **Mattia Bellan:** Funding acquisition, Formal analysis, Acquisition, analysis and interpretation of data, Final approval of the version to be published: all the authors. **Martina Zava:** Funding acquisition, Formal analysis, Acquisition, analysis and interpretation of data, Final approval of the version to be published: all the authors. **Francesco Gavelli:** Funding acquisition, Formal analysis, Acquisition, analysis and interpretation of data, Final approval of the version to be published: all the authors. **Piero Emilio Balbo:** Conceptualization, Conception and design of the work, Writing – original draft, Drafting the article and revision, Final approval of the version to be published: all the authors. **Paolo Solidoro:** Writing – original draft, Drafting the article and revision, Final approval of the version to be published: all the authors.

Declaration of competing interest

No conflict of interest.

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