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DUAL ENERGY COMPUTED TOMOGRAPHY BASED EVALUATION OF LUNG PERFUSION IN PATIENTS OF DIFFUSE INTERSTITIAL LUNG DISEASE

Dr Khanduri Sachin	Professor & Head Department of Radiodiagnosis Era's lucknow medical college & hospital , lucknow, uttar Pradesh
Dr Pandey Sushma	Junior resident-III ,Radiodiagnosis , Era's lucknow medical college & hospital , lucknow, uttar Pradesh
Dr Tyagi Ekta	Junior resident-III ,Radiodiagnosis , Era's lucknow medical college & hospital , lucknow, uttar Pradesh .
Dr Yadav Vivek K	Junior resident-III ,Radiodiagnosis , Era's lucknow medical college & hospital , lucknow, uttar Pradesh
Dr Yadav Harsh	Junior resident-III ,Radiodiagnosis , Era's lucknow medical college & hospital , lucknow, uttar Pradesh
Dr Imam Tariq A	Senior resident, Radiodiagnosis , , Era's lucknow medical college & hospital , lucknow, uttar Pradesh

ABSTRACT Dual energy computed tomography (DECT) lung perfusion is an encouraging option for early diagnosis of ILD with adequate accuracy, particularly in differentiation of UIP from non-UIP pathologies. Clinically Suspected cases of DILD aged 30-70 years were included . All the patients underwent blood investigations and pulmonary function test . DECT Somatom force machine was used for perfusion analysis . Final diagnosis was achieved by combining histopathology and findings of clinicoradiological follow up. Diagnostic efficacy of DECT perfusion was evaluated in terms of sensitivity, specificity, positive predictive value, negative predictive value and accuracy.Total 45 patients with mean age of 55.60+6.95 years were enrolled in the study. DECT perfusion was found to be 93.3 % accurate, 92.6% sensitive, 94.4% specific had 96.2% positive predictive value and 89.5% negative predictive value to diagnose the patients of UIP .

KEY WORDS : Dual energy computed tomography, Multidetector computed tomography, Usual interstitial pneumonia, Non usual interstitial pneumonia, pulmonary function test,virtual non contrast .

Introduction:

Diffuse interstitial lung disease (DILD) comprises a series of entities with similar clinical, radiologic and lung function presentations, in which the principal pathological alterations affect the interstitial alveolar structures.1 These are typically characterized by the presence of inflammation and altered lung interstitium, and specific forms of interstitial lung disease can be differentiated from one another when clinical data, radiologic imaging, and pathologic findings (if lung biopsy is needed) are combined to reach a confident diagnosis.2 The histopathologic changes in the lungs of patients with Interstitial lung disease(ILD) can range from granulomatous inflammation without parenchymal fibrosis in case of sarcoidosis to extensive pulmonary fibrosis with architectural distortion of the lung in idiopathic pulmonary fibrosis (IPF). Successful management of patients with ILD is dependent upon establishing an accurate and specific diagnosis.2 Accurate diagnosis requires careful evaluation of different etiologies and skillful integration of findings from clinical, radiologic, and pathologic examinations.3,4 High resolution CT (HRCT) thorax can provide invaluable information that strongly supports a specific diagnosis (e.g. typical changes of UIP) such that further biopsy is not required. Indeed, the HRCT has become a standard test for the evaluation of possible ILD.5 In general, a complete lack of pulmonary parenchymal changes on HRCT imaging virtually excludes a diagnosis of ILD, but lungs having microscopic involvement cannot be surely detectable by HRCT. Multi-detector computed tomography (MDCT) can scan the entire thorax with a single breath-hold maneuver and allow even better imaging than HRCT, and can facilitates differentiation among UIP, NSIP, and chronic HP patterns.6 HRCT is still considered the best investigation for the evaluation of pulmonary interstitium and to diagnose DILD. With the introduction of the MDCT, HRCT has provided a further insight to understand DILD better. The multidetector HRCT of the whole lung is based on volumetric imaging.7 Idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) reveals pathology of progressive irreversible fibrosis. Hence, the prognosis of IPF/UIP is unspeakable than that of other histopathologic types of DILD.8 However, sometimes HRCT patterns of fibrosis and active inflammation are indistinguishable, thus similar HRCT patterns of parenchymal abnormalities can leads to different treatment response.9,10

Dual-energy computed tomography (DECT) technique works on the principle of material decomposition thus can differentiate voxels of iodine substance from other materials. Iodine concentration quantification provides perfusion information about lung abnormalities.11 Hence, DECT can provide high resolution imaging with evaluation of lung perfusion .

With this background, the present study has been carried out to assess the role of dual energy computed tomography in evaluation of lung perfusion in patients of diffuse interstitial lung disease.

Material and Methods:

This study was carried out as a cross-sectional study with exploratory/descriptive design at Department of Radiodiagnosis in collaboration with Department of Pulmonary Medicine in Era's Lucknow Medical college & Hospital. During a period of eighteen months starting from November 2016 to May 2018.

Clinically Suspected cases of diffuse interstitial lung disease aged 30-70 years having normal kidney function tests willing to

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*Corresponding Author Dr Pandey Sushma

Junior resident-III ,Radiodiagnosis , Era's lucknow medical college & hospital , lucknow, uttar Pradesh . sushmapandey210sp@gmail.com ,

participate were included in the study. Patients with lung pathology other than interstitial lung disease and those allergic to contrast were excluded from the study. Clearance for carrying out the study was obtained from the Institutional Ethical Committee. An informed consent was obtained from all the patients.

Demographic information was noted. Subsequently, chief complaints, past history, treatment and drug history, family history and history of any allergy were also noted. All the patients underwent blood investigations and pulmonary function test evaluation.

For Dual Energy Computed Tomographic (DECT) assessment, we have used a DECT machine of 384 slice (Somatom force; Siemens Healthcare, Forchheim, Germany) with the dual-energy technique. The DECT system consists of two X-ray tubes and 2x192 row detectors with a perpendicular arrangement. CT images were acquired 90 s after intravenous contrast administration (100 mL of iopromide: ultravist 370) at a flow rate of 1.5 mL/s by using a power injector, followed by 20 mL saline flushing at a rate of 1.5 mL/ s with full inspiration.

The 90 kV, 150 kV and enhanced weighted average images were obtained from DECT. We had 1.5mm-slice-thickness virtual non-contrast (VNC) images and net iodine map images of the whole lung using DECT Liver VNC software and lung perfusion software (Syngo Dual Energy; Siemens Medical Solutions, Forchheim, Germany) respectively.

Total lung volume was calculated first by the perfusion software automatically. On VNC imaging patterns were labeled as follows: (normal, GGO, reticulation, consolidation, honeycombing). UIP cases were showing bilateral apico-basal areas of honeycombing and reticulation on VNC image (Figure 1a). Mean iodine values of particular pattern areas were obtained through iodine map by taking the iodine attenuation of particular region of interest(ROI)(Figure1b,) . Volume rendering technique of DECT contrast study can reveal extent of airway involvement of lung (Figure 1c).

Final diagnosis of patients was achieved by combining histopathological findings and findings of clinico-radiological follow up. Out of 45 patients only 37 were undergone biopsy, rest were proved by clinicoradiological follow up.The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD. Diagnostic efficacy of DECT perfusion was evaluated in terms of sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

Results: Age of patients enrolled in the study ranged from 39 to 67 years. Mean age of patients was 55.60+6.95 years. Majority of the patients were aged 51-60 years (51.1%), only 20.0% patients were aged ≤50 years, rest 28.9% were aged >60 years. Out of 45 patients enrolled in the study, 23 (51.1%) were females and rest 22 (48.9%) were males.

All the patients presented with signs and symptoms of Cough and Dyspnea, Wheezing was observed among 80.0% of the patients. Duration of illness ranged from 3 months to 5 years. Mean duration of illness was 1.95±0.98 years. Majority of the patients were suffering for >2 years (51.1%), duration of illness was ≤1 years among 31.1%, rest had duration of illness 1-2 years (17.8%). Severity of lung disease was assessed by pulmonary function test. Range of FVC among study population was 60-93% with mean value 80.33±8.32%.Range of DLCO was 45-89% with mean value 74.09±10.99%.

All the patients were subjected to DECT contrast study. Range of total lung volume of patients enrolled in the study was 767-3512 cc, mean total lung volume was 2713.80±601.97 cc. Contrast on DECT for normal lung ranged between 20 & 34 HU, mean contrast value of 28.69±3.79 HU. Contrast on DECT for reticulation in lungs ranged between 17.8-43.2 HU with mean contrast value of 35.47±7.80 HU. Range of contrast on DECT for Ground glass opacity was from 18.4 to 48.4 HU with mean value of 33.29+7.77 HU. Range of Contrast for consolidation was 11.2-38.1 HU and its mean value 20.90±8.04 HU.

Final diagnosis of patients was achieved by combining histopathological findings and findings of clinico-radiological follow up. However, out of 45 patients only 37 patients were undergone biopsy, rest of 8 patients were proved by clinico-radiological follow up .These 8 Patients had definite UIP pattern of bilateral apicobasal areas of subpleaural honeycombing and reticulation on follow up CT . Out of 45 patients, 27 (60.0%) were diagnosed as Usual interstitial pneumonia (UIP) on final diagnosis, 7 (15.6%) as Non-specific interstitial pneumonia and 4 (8.9%) as Cryptogenic organizing pneumonia (COP). One (%) patient each was diagnosed as Acute interstitial pneumonia (AIP), Pulmonary alveolar proteinosis & Respiratory bronchiolitis associated interstitial lung disease (RBILD) while 2 (%) patients each were diagnosed as Desquamative interstitial pneumonia (DIP) & Lymphocytic interstitial pneumonia (LIP) on histopathology and these 7 cases were classified as Other Non UIP diagnosis on DECT.

Total lung volume of patients diagnosed as others (3226±179 cc) was maximum followed by NSIP (3050±383 cc) while minimum values were found for UIP (2483±521 cc) followed by COP (2785±1115 cc). Difference in total lung volume of patients with above diagnosis was found to be statistically significant. Difference in contrast on DECT of normal lung of patients diagnosed as UIP (30.22±3.47 HU), NSIP (28.51±3.22 HU), COP (25.25±3.59) and Others (24.94±1.32 HU) was found to be statistically significant. Contrast on DECT for reticulation in lung was found to be significantly higher among patients diagnosed as UIP (40.18±3.47 HU) and NSIP (34.51±4.89 HU) as compared to COP (19.55±2.09 HU) and Others (27.33±4.50 HU). Contrast on DECT for ground glass opacity was maximum among patients diagnosed as UIP (37.24±6.27 HU) followed by Others (28.76±3.26 HU) and NSIP (28.69±7.16 HU) while minimum was for patients diagnosed as COP (22.58±5.38 HU). Contrast on DECT for consolidation of lung was maximum for patients diagnosed as COP (26.48±3.51 HU) followed by for UIP (20.87±8.56 HU) and NSIP (20.36±8.15 HU) minimum values were found for patients diagnosed as Others (18.37±7.46 HU) (Table 1).

Table 1: Correlation between final diagnosis and DECT perfusion Findings

Mean±SD

SN	Parameter	UIP (n=27)	NSIP (n=7)	COP (n=4)	Others (n=7)	Statistical significance
1.	Total lung volume (cc)	2483± 521	3050± 383	2785±1 115	3226+ 179	F=4.707; p=0.006
2.	Normal volume (HU)	30.22±3.4 7	28.51±3. 22	25.25±3 .59	24.94+ 1.32	F=6.740; p=0.001
3.	Reticulatio n (HU)	40.18±3.4 7	34.51±4. 89	19.55±2 .09	27.33± 4.50	F=48.14; p<0.001
4.	Ground glass opacity (HU)	37.24+6.2 7	28.69+7. 16	22.58+5 .38	28.76+ 3.26	F=10.82; p<0.001
5.	Consolidati on (HU)	20.87+8.5 6	20.36+8. 15	26.48+3 .51	18.37+ 7.46	F=0.875; p=0.462

Out of 45 patients enrolled in the study, DECT findings indicated 27 (60.0%) patients as UIP and rest 18 (40.0%) were indicated as non-UIP .

Out of 27 patients having final diagnosis of UIP, agreement of DECT diagnosis was found for 25 (92.6%) patients. Apart from this out of 7 patients having final diagnosis as NSIP, 2 (28.6%) were diagnosed as UIP by DECT. (Table 2). All the patients with final diagnosis of NSIP,

COP and Others were clubbed as non-UIP and DECT findings were compared .Comparison of Pulmonary function test and DECT findings among UIP and non-UIP patients was done.No significant difference in pulmonary functions (FCV and DLCO) of patients with final diagnosis of UIP or non-UIP was found. However, all the DECT parameters except Contrast consolidation (HU) of UIP and non-UIP showed statistically significant differences (Table 3).

Table 2: Agreement between Final Diagnosis and DECT Diagnosis

SN	Final Diagnosis	No.	Diagnosis by DECT perfusion	
			Correct	Incorrect
1.	UIP	27	25 (92.6%)	2 Diagnosed as NSIP
2.	NSIP	7	5 (71.4%)	2 Diagnosed as UIP
3.	COP	4	4 (100%)	Diagnosed as Non-UIP ie COP
4.	Other Non - UIP			
	AIP	1	1 Diagnosed as Non-UIP	
	DIP	2	2 Diagnosed as Non-UIP	
	LIP	2	2 Diagnosed as Non-UIP	
	Pulmonary alveolar proteinosis	1	1 Diagnosed as Non-UIP	
	RBILD	1	1 Diagnosed as Non-UIP	

Correlation of all the DECT parameters with both the pulmonary functions i.e. FVC & DLCO were found to be weak and non-significant (Table 4).

DECT perfusion was found to be 92.6% sensitive, 94.4% specific had 96.2% positive predictive value and 89.5% negative predictive value to diagnose the patients having histopathologically and clinico-radiologically established UIP. Diagnostic accuracy of DECT perfusion was found to be 93.3% .

Table 3: Association of final diagnosis with Pulmonary Function and DECT Findings

Mean±SD

SN	Parameter	UIP (n=27)		Non-UIP (n=18)		Statistical significance	
		Mean	SD	Mean	SD	't'	'p'
Pulmonary Functions							
1.	FVC	79.70	7.22	81.27	9.89	-0.615	0.541
2.	DLCO	73.09	8.88	75.60	13.71	-0.748	0.459
DECT Parameters							
1.	Total lung volume (cc)	2483.2	521.00	3059.7	558.26	-3.534	0.001
2.	Normal volume (HU)	30.22	3.47	26.40	3.09	3.777	<0.001
3.	Reticulation (HU)	40.18	3.47	28.39	7.12	7.412	<0.001
4.	Ground glass opacity (HU)	37.24	6.27	27.36	5.82	5.328	<0.001
5.	Consolidation (HU)	20.87	8.56	20.94	7.44	-0.028	0.977

Table 4: Pearson's correlation r to be calculated for Pulmonary Function & DECT Parameters

	FVC				DLCO			
	(r)	Level of correla-tion	'p'	Sig.	(r)	Level of correla-tion	'p'	Sig.
Total lung volume (cc)	0.242	Weak	0.109	NS	0.185	Weak	0.225	NS
Normal volume (HU)	-0.012	Weak	0.937	NS	-0.043	Weak	0.778	NS
Reticulation (HU)	-0.082	Weak	0.594	NS	-0.025	Weak	0.872	NS
Ground glass opacity (HU)	-0.090	Weak	0.559	NS	-0.259	Weak	0.086	NS
Consolidation (HU)	-0.274	Weak	0.069	NS	0.211	Weak	0.165	NS

Discussion: In view of the diagnostic difficulties in describing the diffuse interstitial lung disease pathologies, attempts have been made to focus on the approaches that provide a descriptive account of the underlying pathology with minimum discomfort and with a maximum accuracy. Dual energy computed tomography (DECT) is an advancement of HRCT and MDCT which further helps to diagnose lung parenchymal lesions using pattern and perfusion analysis of contrast material.12

Considering the high potential of DECT imaging in evaluation of diffuse interstitial lung disease, the present study was planned with an aim to assess the DECT based evaluation of lung perfusion in patients of diffuse interstitial lung disease.

For this purpose, total 45 patients with different suspected pathologies of diffuse interstitial lung disease were enrolled in the study. The age of patients ranged from 39 to 57 years. Interstitial lung disease is prevalent at all age groups. Considering the fact that ILD includes a spectrum of nearly 300 diseases, many of them are age-specific.13 In present study we focused on the mature adults aged >30 years with Male:female ratio of the study population was . In present study, the pulmonary function tests in general shows a restrictive pattern only with FVC values ranging from 60 to 93% (mean 80.33%) and DLCO from 45 to 89% (mean 74.09%).

On volumetric assessment total lung volume shows high variability (range 767 to 3512 cc). On perfusion analysis following use of contrast , the DECT values for normal lung (20 to 34 HU), reticulation (17.8 to 43.2 HU), ground glass opacity (18.4 to 48.4 HU) and consolidation (11.2 to 38.1 HU) show a considerable variability. These high variabilities for individual parameters indicated that the different perfusion patterns were being presented owing to diverse underlying DILDs.

After histopathology and clinic-radiological correlation, majority of cases were diagnosed as Usual Interstitial Pneumonia (UIP) (60%) followed by non-specific interstitial pneumonia (NSIP) (15.6%) and Cyrptogenic organizing pneumonia (COP) (8.9%) as mentioned. In their study, Moon et al.12 found UIP (n=11; %) to be less common than non-UIP ILDs (n=17; 60.7%). Although idiopathic pulmonary fibrosis (IPF) is not a synonym of UIP.14 However, the term is often used interexchangeably and a number of studies have shown it as a primary finding among ILDs in their study.15,16

In present study, DECT volumetric and perfusion analysis shows differential patterns for different final diagnoses. Volumetric analysis shows variable range of total lung volume in UIP and Non UIP cases. The perfusion values of iodine concentration (HU) somewhat varied from the volumetric assessment in terms of normal volume, reticulation and ground glass opacity values which were maximum in UIP and minimum in Non UIP cases. Evaluation of volumetric and perfusion patterns for differentiation between UIP and non-UIP pathologies also showed significant differences between two groups for all the variables except consolidation on perfusion-pattern assessment. In a previous study, Moon et al.12 also observed similar differences with sample size of (N=28; 17-non-UIP and 11 UIP). Compared to their study, in present study we had UIP as the dominant group (n=27/45; 60%) and hence more consistent findings resulting in a significant difference between group. We had included the definite UIP cases consisting of honeycombing pattern with subpleural and basal predominance on CT. Despite these promising results for differentiation of UIP, we must admit the limited usefulness of DECT perfusion in differentiation of different non-UIPs. While evaluating the agreement between DECT and final diagnoses, we found that out of 27 patients having final diagnosis of UIP, agreement of DECT diagnosis was found for 25 (92.6%) patients. Apart from this out of 7 patients having final diagnosis as NSIP, 2 (28.6%) were diagnosed as UIP by DECT. The present study showed that DECT perfusion alone was insufficient to differentiate among different non-UIP DILDs successfully. However, for diagnosis of UIP DECT perfusion was found to be 92.6% sensitive, 94.4% specific had 96.2% positive predictive value and 89.5% negative predictive value to diagnose the patients having histopathologically and clinico-radiologically established UIP and diagnostic accuracy of DECT perfusion was found to be 93.3%.

One of the problems in present study was that we focused mainly on the quantitative parameters of contrast enhancement . However, in their study Ferda et al.17 used qualitative analysis of DECT perfusion-pattern for identification of ILD. However, but they did not focus on the differential diagnosis of different ILDs as done in present study.

The present study did not find pulmonary function tests to be either useful in differentiation between UIP and non-UIP DILDs. However by Moon et al.12 in their study have found some satisfying and significant correlation between lung function parameters and volumetric and quantitative perfusion-pattern parameters, thus showed the disease extent and survival analysis by pulmonary function tests. It is an issue that needs further elaboration and shows that physiological impairment might be dependent on factors other than pathological changes evaluated by DECT.

The findings of present study; in turn shows that DECT based perfusion analysis are an emerging method for evaluation of diffuse interstitial lung diseases. Considering the relative clinical significance for identification of early UIP, the present study reveals the usefulness of DECT perfusion by analyzing iodine enhancement of particular pattern. Further studies to substantiate the findings of present study are recommended to consolidate the evidence further.

Conclusion: The findings of present study shows that DECT lung perfusion is an encouraging useful measure for evaluation of diffuse interstitial lung diseases, particularly in differentiation of UIP from non-UIP pathologies that can modify the treatment plan. DECT perfusion and pattern analysis helped to discriminate between early fibrosis and inflammatory changes in various diffuse interstitial lung diseases and shows a definitive advantage against lung function tests which in general remained non-differentiating.

Figure-1a : A Virtual noncontrast axial image showing extensive bilateral fibrosis, apico-basal honeycombing pattern with reticulation in 67 year male patient of UIP.

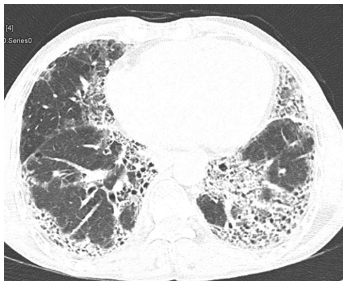


Figure-1b-Axial image of Perfusion iodine map showing increased contrast in the region of fibrosis and reticulation in bilateral basal region in same UIP case .

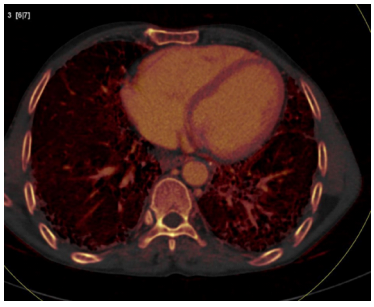
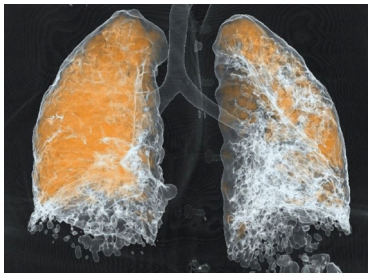


Figure-1c: Volume rendering technique ,showing increased extent of airway involvement in the bilateral lower lobe in same UIP case.



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