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Evaluation of visual and computer-based CT analysis for the identification of functional patterns of obstruction and restriction in hypersensitivity pneumonitis

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SUMMARY AT A GLANCE

In hypersensitivity pneumonitis, computer-derived (CALIPER) variables are stronger predictors of restriction and obstruction than visual CT scores as judged by correlations between morphology and functional indices. The pulmonary vessel volume demonstrated the strongest correlations of all CT variables with restrictive indices and may represent a new measure of interstitial damage.

Abstract

BACKGROUND AND OBJECTIVE: To determine whether computer-based quantification, (CALIPER software) is superior to visual CT scoring in the identification of CT patterns indicative of restrictive and obstructive functional indices in hypersensitivity pneumonitis (HP).

METHODS: 135 consecutive HP patients had CT parenchymal patterns evaluated quantitatively by both visual scoring and CALIPER. Results were evaluated against: FVC, TLC, DLco and a composite physiologic index (CPI) to identify which CT scoring method better correlated with functional indices.

RESULTS: CALIPER-derived scores of total interstitial disease extent correlated more strongly than visual scores: FVC (CALIPER R=0·73, visual R=0·51); DLco (CALIPER R=0·61, visual R=0·48); CPI (CALIPER R=0·70, visual R=0·55). The CT variable that correlated most strongly with restrictive functional indices was CALIPER pulmonary vessel volume (PVV): FVC R=0.75, DLco R=0.68, CPI R=0.76.

Ground glass opacity quantified by CALIPER alone demonstrated strong associations with restrictive functional indices: CALIPER FVC R=0·65; DLco R=0·59; CPI R=0·64; visual=not significant. Decreased attenuation lung quantified by CALIPER was a better morphological measure of obstructive lung disease than equivalent visual scores as judged by relationships with TLC (CALIPER R=0·63, visual R=0·12). All results were maintained on multivariate analysis.

CONCLUSION: CALIPER improved on visual scoring in HP as judged by restrictive and obstructive functional correlations. Decreased attenuation regions of the lung quantified by CALIPER demonstrated better linkages to obstructive lung physiology than visually quantified CT scores. A novel CALIPER variable, the pulmonary vessel volume, demonstrated the strongest linkages with restrictive functional indices and could represent a new automated index of disease severity in HP.

KEY WORDS

QUANTITATIVE COMPUTER ANALYSIS

HYPERSENSITIVITY PNEUMONITIS

VISUAL CT ANALYSIS

PULMONARY VESSEL VOLUME

AIR TRAPPING

SHORT TITLE

PFT links with CT scores in HP

INTRODUCTION

As computer technology continues to advance, modern quantitative computer tools have reached a level of sophistication that has allowed the extents of various parenchymal patterns indicative of fibrosing lung disease (FLD) to be characterized on CT imaging [1, 2]. Computers have been taught to mimic the identification of CT patterns that are familiar to radiologists, and the result has been the quantitation of features including ground glass opacification, reticular pattern, decreased attenuation lung and honeycombing extents. However new unexpected markers of disease have also been uncovered such as the pulmonary vessel volume (PVV) which represents the volume of pulmonary arteries and veins excluding vessels at the lung hilum[3].

In patients with idiopathic pulmonary fibrosis (IPF), computer quantitation of CT parenchymal patterns have been shown to outperform visual CT scores with regard to correlations with restrictive functional indices[3] and mortality prediction[4]. However the applicability of such tools to other FLDs is as yet unclear. Furthermore, in diseases such as hypersensitivity pneumonitis (HP) where mixed obstructive and restrictive disease is the rule rather than the exception[5, 6], the strength of automated tools in characterizing interstitial involvement and air-trapping has not been evaluated. Accordingly, the current study aimed to evaluate, the strength of visual and computer quantitation of CT patterns reflecting restrictive and obstructive functional indices in patients with HP. A second aim was to validate the functional correlations of CALIPER pulmonary vessel volume in a population of HP patients.

METHODS

Study population and clinical information

All consecutive patients with a multidisciplinary team diagnosis of HP, presenting over a four and a half year period (January 2007 to July 2011) were identified. Patients with a non-contrast, supine, volumetric thin section CT were included, and subsequent exclusions are shown (as per flowchart in Supplementary Figure 1). CT, pulmonary function test (PFT) and echocardiography protocols have been previously described [3]. A smoker was defined as someone with a greater than 1 pack-year smoking history. An ex-smoker was defined as someone who had not smoked a cigarette for over 12 months. This study of clinically indicated CT and PFT data was approved by the Institutional Ethics Committee of the Royal Brompton Hospital and the Institutional Review Board of the Mayo Clinic Rochester.

CT visual evaluation

Each CT scan was evaluated independently by two radiologists (RE, ALB) with 5 and 7 years thoracic imaging experience respectively, blinded to all clinical information. Visual CT scoring and consensus derivation have been previously described[3, 7, 8]. CT patterns scored visually on a lobar basis included ground glass opacities, reticular pattern, honeycombing, consolidation, gas trapping (which comprised separate scores of emphysema and mosaic attenuation [the decreased attenuation component]) and traction bronchiectasis[9].

CALIPER CT evaluation

CALIPER evaluation of CT data[3] involved algorithmic identification and volumetric quantification of every voxel volume unit into one of seven radiological parenchymal features: normal lung, three grades of CALIPER gas trapping (grade 1=mild, 2=moderate 3=marked)[1], ground glass opacification, reticular pattern, honeycombing and the pulmonary vessel volume. Volumes for all eight parenchymal features were converted into a percentage using the total lung volume also measured by CALIPER. The pulmonary vessel volume (PVV) score quantified the volumes of pulmonary arteries and veins excluding vessels at the lung hilum as a percentage of lung volume. The sum of Grade 2 and 3 gas trapping was designated as representing overt emphysema[3]. Grade 1 gas trapping which contained areas of normal appearing lung, air-trapping and emphysema was designated non-specific gas trapping.

For both visual and CALIPER scores, overt fibrosis extent was taken as the sum of reticular and honeycomb percentages whilst total interstitial disease extent additionally summed ground glass opacity percentage.

Functional measures

The PFTs that were examined included forced expiratory volume in one second (FEV1), forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLco), carbon monoxide transfer coefficient (Kco), residual volume (RV), total lung capacity (TLC) and composite physiologic index (CPI)[10].

Statistical analysis

Data are given as means with standard deviations, or numbers of patients with percentages where appropriate. Interobserver variation for visual scores was assessed using the single determination standard deviation. Correlations between the extents of parenchymal patterns and individual PFTs were examined using Pearson's product moment correlation. Univariate and multivariate analyses were undertaken to investigate relationships between CALIPER or visual CT evaluation and PFTs. In all study analyses, a p-value of <0.05 was considered significant. Models were formally tested for heteroscedasticity to confirm that the assumptions of parametric analysis had been satisfied. Statistical analyses were performed with STATA (version 12, StatCorp, College Station, TX, USA).

RESULTS

Baseline data

The initial study population comprised 135 consecutive patients with a final MDT diagnosis of HP based on a compatible clinical history and review of the following data: antigen exposure history (positive in 57/135 (42%) of patients: avian n=22, fungus n=24, combined avian and fungus n=9, dusts n=2), precipitating antibodies (identified in 39%), bronchoalveolar lavage (BAL) findings (performed in 56%), CT imaging (100%) and histopathology from lung biopsy (44%). Age, gender, mean visual scores, CALIPER scores and PFTs are shown in Supplementary Table S1. Interobserver variation scores are shown in Supplementary Table S2.

Visual scores identified more total ILD extent (61.3%) than CALIPER scores (21.6%). ILD extent predominantly comprised ground glass opacities when evaluated using visual or CALIPER scores. Honeycombing totaling over 1% of the lung volume was identified in only 11/135 (8%) patients using CALIPER but was recorded in 29/135 (21%) patient with visual scoring.

Relationships between visual and CALIPER scores

Linkages between visual and CALIPER scores for shared interstitial CT patterns were strongest for honeycombing (R=0.77) and fibrosis extent (R=0.62) and weakest for ground glass opacities (R=0.21). There was no significant linkage between total decreased attenuation lung scored visually and by CALIPER. Accordingly functional relationships between ground glass opacities and parenchymal decreased

attenuation scored visually and by CALIPER were individually examined in greater detail (see below).

All three types of CALIPER-derived decreased attenuation lung demonstrated linkages to visual emphysema scores but not to visual mosaicism scores. Grade II and III decreased attenuation demonstrated strong linkages with visual emphysema scores confirming that the two CALIPER variables probably reflect overt emphysematous damage. Grade I decreased attenuation had the weakest relationship with visual emphysema scores, yet represented approximately 18% of the total lung volume indicating that the score captures a combination of emphysema, air-trapping and normal lung.

Strong linkages were shown between CALIPER PVV and CALIPER ILD extent (R=0.80) and CALIPER overt fibrosis extent (R=0.73), but not right ventricular systolic pressure (Table 1). The results suggest that the PVV variable may in part reflect a measure of interstitial damage rather than pulmonary hypertension severity.

Relationships between CT variables and PFTs

Of all the visual CT scores, fibrosis and reticulation extent and traction bronchiectasis severity demonstrated the strongest relationships with FVC, DLco and CPI (Table 2). Visual emphysema and mosaicism demonstrated only weak linkages with PFTs.

On CALIPER CT analysis, total ILD extent demonstrated stronger linkages with FVC, DLco and CPI than corresponding visual CT scores. However of all CT variables scored visually or by CALIPER, PVV that showed the strongest links with PFTs (Table 3).

Ground glass opacity scored by CALIPER showed strong associations with PFTs in contrast to visual ground glass opacity scores which had no significant relationships with functional indices. In a simple bivariate analysis comparing ground glass opacity and fibrosis extent against TLC in separate visual and CALIPER models (Supplementary Table S3), CALIPER ground glass opacity was a stronger measure of interstitial disease than visual ground glass opacity scores.

Multivariate relationships between CT variables and PFTs

Following correction for patient age and gender, PVV remained the strongest independent CT predictor of FVC, DLco and CPI (Supplementary Table S4). When CALIPER and visual measures of ILD extent were examined in separate models alongside PVV, both measures of ILD extent independently linked to FVC, DLco and CPI. The concordance of the two independent measures of ILD extent in the models incorporating PVV implies that PVV does not solely reflect damage to the pulmonary interstitium.

Relationships between decreased attenuation lung and PFTs

Decreased attenuation lung parenchyma scored by CALIPER (Figure 1) was strongly associated with a reduced CPI and an elevated FVC, DLco and TLC on univariate analyses (Table 3). However when the components of visually scored decreased

attenuation lung (emphysema and the decreased attenuation component of a mosaic attenuation pattern) were separately examined, at most, only weak functional correlations were identified (Table 2).

Overall decreased attenuation lung quantified by CALIPER demonstrated a strong linkage to physiological measures of obstruction (TLC) on multivariate analysis (Supplementary Table S3). The results were maintained when the same CALIPER variables were examined against DLco. Visual quantitation of total decreased attenuation lung had no relationship to TLC or DLco in separate models (Supplementary Table 3).

DISCUSSION

Our evaluation of computer-based CT analysis in patients with hypersensitivity pneumonitis has identified several new findings. Firstly, CALIPER variables correlate more strongly with PFTs than visually scored CT variables. Specifically, ground glass opacities, which are commonly found in HP, when quantified by CALIPER, correlate more strongly than visual CT scores with restrictive functional indices. Decreased parenchymal attenuation on CT, a hallmark of HP, also demonstrated stronger linkages with obstructive functional indices, when quantified by CALIPER rather than with visual CT scores. Intriguingly, of all the CT variables examined, it was the pulmonary vessel volume that demonstrated the strongest linkage with FVC, DLco and CPI.

Computer analysis of CT imaging in FLD is increasingly being used as a robust method of quantifying disease extent, and is free from the inter-observer variation that impairs visual CT quantification. To date there have been no studies investigating computer CT analysis in patients with HP. Disease characterization by CT in HP can be challenging because of differing proportions of fibrosis, lymphocytic infiltrate, and obstructive disease secondary to bronchiolitis or emphysema which may coexist[6, 11-13].

Ground glass opacification can be extensive in HP and represents a CT pattern that is prone to considerable observer variation, as seen by the limited interobserver agreement in the current study and in previous HP series[14, 15]. The co-existence of air-trapping amidst regions of increased lung density may result in the

misclassification of normal regions of lung parenchyma as either ground glass density or air-trapping. Accordingly, the strong links between CALIPER-defined ground glass opacities and functionally restrictive lung disease in the current study are encouraging and indicate that computer analysis of interstitial patterns on CT may prove to be superior to traditional visual scoring of CT patterns in HP.

Automated tools have to date struggled with characterizing regions of decreased attenuation in patients with FLD[16, 17]. The morphological similarities shared by honeycomb cysts, traction bronchiectasis and emphysema, that limits visual CT agreement among even experienced radiologists[18], similarly represents a complex classification conundrum for computer tools. Nevertheless, in our study we found that decreased attenuation lung captured by CALIPER reflected physiologically obstructive parenchyma, as measured by TLC, in contrast to the lack of similar relationships with visually quantified decreased attenuation lung.

Though there remains limited specificity in the type of parenchyma classified by CALIPER as decreased attenuation lung (which probably incorporates emphysema, air-trapping and normal lung), the CALIPER variable demonstrates improved functional relationships when compared to visual CT scores. The ability of CALIPER to appropriately distinguish functionally obstructive regions of lung in the context of a FLD represents an impressive advance in computer-based characterisation.

The degree of interobserver variation for mosaic attenuation and ground glass opacity scores in the current study are similar to historic series [6, 14, 15]. Furthermore,

linkages between visually-scored mosaic attenuation and RV/TLC ratio in the current study are in line with previous observations in patients with HP[6] and are of similar strength to the relationship between RV/TLC ratio and CALIPER-derived decreased attenuation. The agreement with prior studies suggests that the reported strengths of CALIPER over visual scores in the current study are not a consequence of anomalous visual CT scores peculiar to the current study. Additionally, the improved functional links for CALIPER scores over visual CT scores mirrors findings in a previous study of patients with IPF[3] attesting to the robustness of computer-based CT analysis across FLD subtypes.

Discordances between CALIPER and visual scores of ground glass opacification have been explored in previous analyses[3]. CALIPER characterizes regions of increased density with superimposed reticular lines as ground glass opacity, based on the patterns ascribed by radiologists in the original training dataset for the tool. The visual scorers however classified the same pattern as reticulation. A further source of discordance between CALIPER and visual CT scores is related to the differing scoring methodologies utilized by CALIPER and visual lobar CT scores. In the former, CT patterns in shrunken areas of lung can be under-represented by scores relying on purely volumetric quantitation of disease patterns. Lobar visual scores however, will ascribe equal weight (as a proportion of total lung disease extent) to individual pattern extents within both a normal appearing lower lobe and a shrunken fibrotic upper lobe.

CT features of the pulmonary vasculature have not previously been linked with functional indices in patients with HP. In the current study PVV and ILD extent, scored visually and with CALIPER, were independently predictive of FVC, DLco and CPI, replicating findings in IPF[3]. Whilst the pathophysiological basis of the CALIPER PVV signal is unclear, the results of the current study support previous findings in IPF[3] and connective tissue disease-related ILD[7] that suggested that the PVV signal may reflect a combination of both interstitial extent and vascular damage. As previously stated[4], whilst the majority of the PVV signal arises from the vasculature, in cases with more extensive fibrosis, the PVV measure may capture some perivascular fibrosis or peripheral reticulation, which may be reduced with refinement of the tool.

There are limitations to the current study. Firstly, not all cases had histopathological proof of diagnosis. However restricting analyses to biopsy proven cases would not, in the era of multi-disciplinary team diagnosis, reflect a real world HP population. Secondly, although grade II and III decreased attenuation lung appeared to reflect visually scored emphysema, the majority of decreased attenuation lung scored by CALIPER was classified as grade I decreased attenuation and probably represents a mixture of emphysema, air-trapping and normal lung. A potential caveat to the utility of CALIPER in classifying decreased attenuation lung in HP is that a strict distinction between air-trapping and emphysematous lung cannot currently be attained. However when mosaicism and emphysema extents were separately characterized visually, the results did not link significantly with functional measures of obstruction. Nevertheless, a future aim would be to further refine the CALIPER

variable to increase the specificity with which individual CT patterns are characterized within parenchyma of decreased attenuation.

In conclusion, we have demonstrated that in HP, CALIPER measures of restrictive and obstructive lung disease patterns relate more strongly to functional indices than visual CT scores. Specifically, the pulmonary vessel volume showed the strongest links with functional indices reflecting pulmonary fibrosis and may be a new index in the evaluation of patients with hypersensitivity pneumonitis.

Disclosure statement

JJ reports personal fees from Boehringer Ingelheim unrelated to the work in the current manuscript.

BJB, RK, SR report a grant from the Royal Brompton Hospital during the conduct of the study; another from Imbio, LLC, was outside the submitted work; and all have a patent: SYSTEMS AND METHODS FOR ANALYZING IN VIVO TISSUE VOLUMES USING MEDICAL IMAGING DATA licensed to Imbio, LLC.

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Table 1. Linear Regression analyses demonstrating relationships of CALIPER variables with various CT scores and RVSP.

Independent variable	CALIPER CT variable	Beta Coefficient	95% Confidence Interval	P value	Model R value
ILD extent	ILD extent	0.49	0.36, 0.63	<0.0001	0.53
Fibrosis extent	Fibrosis extent	0.15	0.12, 0.19	<0.0001	0.62
GGO	GGO	0.19	0.04, 0.34	=0.01	0.21
Reticular pattern	Reticular pattern	0.13	0.09, 0.17	<0.0001	0.51
Honeycombing	Honeycombing	0.08	0.07, 0.09	<0.0001	0.77
Low attenuation lung	Low attenuation lung			NS	
Emphysema	Grade 1 DA	0.53	0.07, 0.99	=0.02	0.20
Emphysema	Grade II DA	0.10	0.08, 0.12	<0.0001	0.69
Emphysema	Grade III DA	0.04	0.03, 0.05	<0.0001	0.62
Mosaicism	Grade 1 DA			NS	
Mosaicism	Grade II DA			NS	
Mosaicism	Grade III DA			NS	
CALIPER ILD extent	PVV	0.07	0.06, 0.08	<0.0001	0.80
CALIPER Fibrosis extent	PVV	0.31	0.26, 0.36	<0.0001	0.73
RVSP	PVV			NS	

Linear regression analysis demonstrating relationships (R values) significant to a level of 0.05 between CT parenchymal patterns representing interstitial disease characterized by visual and CALIPER scores (light grey) and between CT parenchymal patterns representing airspace disease characterized by visual and CALIPER scores (light blue). Relationships between pulmonary vessel volume (PVV) and CALIPER and echocardiographic variables are also demonstrated (white background). CT=computed tomography, ILD=interstitial lung disease, Fibrosis extent= sum of reticular pattern and honeycombing, GGO=ground glass opacity, DA=decreased attenuation, PVV=pulmonary vessel volume, RVSP=right ventricular systolic pressure, NS=not significant.

Table 2. Linear regression analyses demonstrating relationships between functional indices and visual CT scores

PFT (patient numbers)	Interstitial disease				Gas Trapping	
	ILD	Fibrosis	GGO	TxBx	Mosaic	Emph
FEV1 (129)	-0.40*	-0.49*	NS	-0.41*	-0.22$	NS
FVC (129)	-0.51*	-0.57*	NS	-0.49*	-0.23^	0.21$
FEV1/FVC	0.34*	0.36*	NS	0.38*	NS	-0.33*
RV (117)	-0.26^	-0.50*	NS	-0.37*	NS	NS
TLC (117)	-0.48*	-0.66*	NS	-0.55*	NS	0.24$
RV/TLC (117)	0.19$	NS	NS	NS	0.30^	NS
DLco (124)	-0.48*	-0.61*	NS	-0.54*	-0.18$	NS
Kco (124)	-0.23$	-0.21$	NS	-0.25^	NS	-0.23^
CPI (123)	0.55*	0.66*	NS	0.58*	0.21$	NS

Linear regression analysis demonstrating relationships (R values) significant to a level of <0.05($), <0.01 (^) and <0.0001 (*) between interstitial parenchymal patterns (light grey) and gas trapping parenchymal patterns (light blue) characterized by visual CT scoring and pulmonary function tests in patients with hypersensitivity pneumonitis. FEV1=forced expiratory volume in one second, FVC=forced vital capacity, DLco=diffusing capacity for carbon monoxide, Kco=carbon monoxide transfer coefficient, RV=residual volume, TLC=total lung capacity, CPI=composite physiologic index, ILD=interstitial lung disease, Fibrosis=sum of reticular pattern and honeycombing, GGO=ground glass opacity, Mosaic=mosaic attenuation (decreased attenuation component), Emph=emphysema, TxBx=traction bronchiectasis, NS=not significant.

Table 3. Linear regression analyses demonstrating relationships between functional indices and CALIPER CT scores

PFT (patient numbers)	Interstitial disease				Gas Trapping
	ILD	Fibrosis	GGO	PVV	LAA
FEV1 (129)	-0.65*	-0.47*	-0.61*	-0.67*	0.51*
FVC (129)	-0.73*	-0.54*	-0.69*	-0.75*	0.64*
FEV1/FVC	0.38*	0.36*	0.34*	0.40*	-0.38*
RV (117)	-0.53*	-0.49*	-0.47*	-0.52*	0.37*
TLC (117)	-0.75*	-0.62*	-0.69*	-0.79*	0.64*
RV/TLC (117)	NS	NS	NS	0.24^	-0.28$
DLco (124)	-0.61*	-0.51*	-0.55*	-0.68*	0.60*
Kco (124)	NS	NS	NS	NS	0.19$
CPI (123)	0.70*	0.57*	0.64*	0.76*	-0.69*

Linear regression analysis demonstrating relationships (R values) significant to a level of <0.05($), <0.01(^) and <0.0001(*) between interstitial parenchymal patterns (light grey) and gas trapping parenchymal patterns (light blue) characterized by CALIPER CT scoring and pulmonary function tests in patients with hypersensitivity pneumonitis. FEV1=forced expiratory volume in one second, FVC=forced vital capacity, DLco=diffusing capacity for carbon monoxide, Kco=carbon monoxide transfer coefficient, RV=residual volume, TLC=total lung capacity, CPI=composite physiologic index, ILD=interstitial lung disease, Fibrosis=sum of reticular pattern and honeycombing, GGO=ground glass opacity, LAA=low attenuation area, PVV=pulmonary vessel volume, NS=not significant.

Figure Legend

Figure 1. CT image of the lung bases in a 66-year-old never smoker diagnosed with hypersensitivity pneumonitis. Fibrosis is evident in the lower lobes with reticulation, traction bronchiectasis and volume loss, identified by the position of the right oblique fissure. Areas of decreased attenuation lung are visible bilaterally, suggesting a CT pattern of hypersensitivity pneumonitis. On the CALIPER colour-overlay image, areas of grade 1 decreased attenuation corresponding to air-trapping are colour-coded light green. Fibrosis (orange), ground glass opacities (yellow) and normal lung (dark green) reflect corresponding regions of the lung on the CT image.