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Validation of computed tomographic lung densitometry for monitoring emphysema in α_1-antitrypsin deficiency

David G. Parr MRCP[1], Berend C. Stoel PhD[2], Jan Stolk MD[3], and Robert A. Stockley DSc[1].

[1]Lung Investigation Unit, First Floor, Nuffield House,
Queen Elizabeth Hospital, Birmingham, UK. B15 2TH
[2]Division of Image Processing, Department of Radiology, Leiden University Medical Centre, Leiden 2300-RC, The Netherlands.
[3]Department of Pulmonology, Leiden University Medical Centre, Leiden 2300-RC, The Netherlands.

Correspondence and requests for reprints should be addressed to;
Prof R. A. Stockley, DSc, Lung Investigation Unit, First Floor, Nuffield House,
Queen Elizabeth Hospital, Birmingham, B15 2TH. UK.
Telephone 04 121 472 1311; Fax 04 121 627 2012; r.a.stockley@bham.ac.uk

Key Words; lung densitometry; computed tomography; emphysema; alpha1-antitrypsin deficiency.

ABSTRACT

Background: **Lung densitometry derived from computed tomographic images offers an opportunity to quantify emphysema non-invasively, but a pathological standard cannot be applied to validate its use in longitudinal monitoring studies. Consequently, forced expiratory volume in 1 second (FEV_1) remains the standard against which new methods must be judged. We related progression of densitometry (15^{th} percentile point and voxel index, threshold –950 Hounsfield Units) to disease stage and FEV_1 decline in two studies of subjects with α_1-antitrypsin deficiency (PiZ).**

Methods: **Consistency of progression, measured using densitometry and FEV_1, was assessed in relation to disease stage in a 2-year study of 74 subjects grouped according to the FEV_1 criteria employed in the GOLD guidelines. In the second study of a sub-group of subjects with extended data (n=34), summary statistics were applied to measurements performed annually over 3 years, and the rate of progression of densitometry was related to FEV_1 decline.**

Results: **The progression of percentile point was consistent across a wide spectrum of disease severity, but voxel index progression varied in association with disease stage (p=0.004). In the second study, FEV_1 decline correlated with progression of lung densitometry (percentile point-rs = 0.527, p=0.001; voxel index-rs = -0.398, p = 0.012).**

Conclusions: 15^{th} percentile point is a more consistent measure of lung density loss across a wide range of physiological impairment than voxel index. However, both methods are valid for use in longitudinal and interventional studies in which emphysema is the major outcome target.

Word count 242

INTRODUCTION

The natural history of chronic obstructive pulmonary disease (COPD) is one of accelerated decline in lung function in susceptible individuals, and this progression has been assessed traditionally by measurement of the forced expiratory volume in one second (FEV_1) [1 2]. The FEV_1 is also used as a surrogate measure of emphysema and its progression [3], although the cause of airway obstruction in general COPD is heterogeneous [4 5] and the FEV_1 is recognised as a non-specific parameter. This creates logistical problems in assessing treatment effect in therapeutic trials of disease (particularly emphysema) modifying drugs and, consequently, there is a pressing need for the development of more specific outcome measures.

Emphysema, although defined in morbid anatomical terms [6 7], can now be diagnosed and quantified non-invasively with computed tomography (CT). Various parameters derived from the frequency distribution histogram of lung voxel densities have been proposed as accurate measures[8-13] but in longitudinal studies of emphysema in α_1-antitrypsin deficiency (AATD), the most widely applied parameters are the percentile point and voxel index (V.I.) methods [14-17]. The percentile point is defined as the cut-off value in Hounsfield Units (H.U.) below which a specified percentage of all voxels are distributed and the V.I. is defined as the proportion of lung voxels of low density below a specified threshold (Figure 1). These two parameters may be regarded as having an inverse mathematical relationship but there may be important differences between the methods. The sensitivity of the percentile point method is claimed to be relatively threshold-independent and give almost identical results within a broad range of percentiles from the 10^{th} to the 30^{th} [14] whereas the voxel index method has been shown to be threshold-dependent [14 18]. As a consequence, the progression of the percentile point should be a consistent measure of lung density reduction across a wide spectrum of disease severity whereas, theoretically, the voxel index will vary with disease stage. However, there are no data that directly support either this hypothesis or the superiority of either method.

Cross-sectional pathological studies using a high-resolution protocol have demonstrated that the voxel index at a threshold of –950 H.U. (V.I.-950) relates directly to emphysema [19 20] and it is also likely that this is the optimal threshold for longitudinal studies [18]. In the only study to validate the percentile point method against a pathological standard, comparison between AWUV (airway wall surface area per unit volume) and CT densitometry was restricted to the 5^{th} percentile point [8]. Notwithstanding the above published evidence, a recent peer-reviewed workshop report on the use of CT in longitudinal studies of emphysema advised that the method of choice is the 15^{th} percentile point (Perc 15) measured from inspiratory images without the incorporation of volume control or correction to adjust for inspiratory level [21].

Widespread acceptance of CT densitometry as an outcome measure for trials of emphysema modifying therapy requires validation against a recognised standard [22]. The 'traditional measure' in longitudinal studies of COPD and emphysema is FEV_1 [1 23-27] and, consequently, improved understanding is needed of the relationship between the progression of CT parameters and progression of FEV_1. The present study was therefore undertaken to explore the relationship between emphysema progression and disease stage in AATD, comparing these two principal quantitative CT methods and, in addition, to establish the validity of CT for monitoring emphysema by evaluating whether the progression of CT lung densitometry was related to the rate of decline of FEV_1.

METHODS

Subjects

Patients attending our centre between November 1996 and February 2002 were selected to include all PiZ subjects with complete datasets at baseline and two years later (n=75) and a subset of PiZ subjects with four consecutive complete annual assessments (n=34). Annual attendance on the programme includes full pulmonary function testing, assessment of health status, medical examination and thoracic CT as described previously [28]. Confirmation of α_1-antitrypsin level and phenotype was by immunoassay and isoelectric focusing, respectively, in a central U.S. laboratory (Heredilab, Salt Lake City, UT) using a dried finger-prick blood spot.

The programme was approved by the University of Birmingham Hospital NHS Trust Research Ethics Committee and all subjects gave written informed consent.

Lung Function Testing

Lung function testing was performed according to the British Thoracic Society / Association of Respiratory Technicians and Physiologists (BTS/ARTP) guidelines [29] as described previously [28]. For annual change in FEV_1, only post-bronchodilator (2.5mg salbutamol and 250µg ipratropium bromide, nebulised) results were used.

Computed Tomography

Patients were instructed to take their usual medication prior to scanning. Images were acquired on a Prospeed Scanner (General Electric Medical Systems, Milwaukee, Wis.) at full inspiration in the supine position (120kVp, 200mAs, reconstructed using a high-resolution 'bone' algorithm [28]). Incremental one millimetre axial slices were taken at ten millimetre intervals throughout the thorax for baseline scans and limited imaging at the level of the aortic arch and inferior pulmonary veins for subsequent scans.

CT Densitometry

The 15th percentile point (Perc15) and voxel index at a threshold of –950 HU (V.I.–950) were measured for single images selected from each series representing the upper (through the middle of the aortic arch) and lower (at the junction of inferior pulmonary veins and left atrium) zones using the Pulmo-CMS software (MEDIS Medical Imaging Systems BV, Leiden, Nl.). An internal air calibration process was incorporated as described previously [18].

Trends in Progression Rate - a Comparison of Densitometric Parameters

The relationship between CT densitometic parameters was initially assessed in a cross-sectional analysis of the baseline images ([upper zone parameter + lower zone parameter]/2) in 74 subjects with two-year data. The group was then sub-divided into four using the FEV_1 criteria incorporated into the GOLD classification of disease stage [30] (namely, FEV_1>80% predicted [Group 1]; FEV_1=50-79% predicted [Group 2]; FEV_1=30-49% predicted [Group 3]; FEV_1<30% predicted [Group 4]). In each group, the median rate of progression (and interquartile range-I.Q.R.) was calculated for FEV_1 and for each densitometric parameter derived from the upper and lower zone scans individually and averaged as above.

CT lung density progression and its relationship with FEV_1 decline

The rate of progression in FEV_1 (post-bronchodilator), Perc15 and V.I.-950 was measured in 34 subjects with annual data over three years using Excel (Microsoft Inc., US) to calculate the derived slope between each of the above measures and the date of measurement.

Statistical Analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 11.5, (SPSS Inc., Chicago, US). Demographic data and clinical and radiographic parameters were summarised as median and I.Q.R. Relationships between continuous variables were assessed with Spearman's correlation coefficient and the Jonckheere-Terpstra test used to identify trends associated with disease severity.

RESULTS

Trends in Progression Rate

The baseline characteristics of the 74 patients in the initial group are shown in Table 1.

Table 1 Clinical characteristics of the 74 PiZ subjects cohort at baseline.

	Median	**Interquartile Range**	**Median % predicted.**
Age	51	46 to 56	N/A
Pack Years	15	0 to 28	N/A
FEV_1 (L)*	0.98	1.5 to 2.4	48
VC (L)*	4.0	3.2 to 4.8	101
RV (L) *	2.6	2.1 to 3.4	130
TLC (L) *	7.5	6.2 to 8.4	119
K_{CO}*	1.0	0.8 to 1.4	67
U.Z. Perc15	-944.6	-966.0 to –922.3	N/A
L.Z. Perc15	-967.4	-977.8 to –938.8	N/A
Combined Perc15	-955.6	-971.0 to -931.6	N/A
U.Z. V.I.-950	12.7	5.3 to 23.8	N/A
L.Z. V.I.-950	26.6	10.7 to 34.8	N/A
Combined V.I.-950	20.2	8.1 to 28.7	N/A

*All lung function measurements were performed after dual bronchodilation with inhaled nebulised salbutamol (2.5mg) and ipratropium bromide (250 micrograms).

FEV_1 = forced expiratory volume in 1 second; VC = vital capacity; RV = residual volume; TLC = total lung capacity (helium dilution); K_{CO} = diffusing capacity of the lung for carbon monoxide (mmol/min/kPa/L); U.Z. = upper zone scans; L.Z. = lower zone scans; Combined = average of upper and lower zone scans; Perc15 = 15^{th} percentile point; V.I.-950 = voxel index at a threshold of –950HU.

There was close agreement between both densitometric parameters at baseline, with a curvilinear relationship between Perc15 and V.I.-950 ($r_s = 0.994$, $p<0.001$) as shown in Figure 2.

The characteristics of the four GOLD sub-groups are shown in Table 2 and the results of the Jonckheere-Terpstra test are shown in Table 3.

Table 2 Clinical characteristics of the GOLD sub-groups expressed as the median and interquartile range.

	Group 1	Group 2	Group 3	Group 4
Age	47 (37 to 57)	54 (47 to 61)	51 (47 to 57)	51 (47 to 52)
Number	18	18	20	18
Index cases	7	15	17	15
Pack years	0 (0 to 5)	20 (1 to 29)	20 (15 to 36)	20 (2 to 28)
Sex (male)	12	16	10	13
FEV_1 (L) *	3.8 (2.8 to 4.4)	2.1 (1.8 to 2.3)	1.1 (1.0 to 1.3)	0.8 (0.6 to 1.0)
FEV_1(% predicted)	111.3 (94.1 to 123.0)	61.8 (56.4 to 65.1)	39.1 (35.7 to 42.5)	25.9 (23.2 to 26.9)
K_{CO}*	1.4 (1.2 to 1.6)	1.1 (0.9 to 1.5)	1.0 (0.8 to 1.1)	0.7 (0.5 to 1.0)
K_{CO} (% predicted)	93.3 (79.2 to 104.8)	71.7 (60.2 to 94.8)	63.5 (47.5 to 72.2)	45.6 (35.6 to 62.3)
Upper Zone Perc15	-917.9 (-935.9 to –906.2)	-942.4 (-960.1 to –920.5)	-944.3 (-969.7 to –934.4)	-961.7 (-979.6 to –947.7)
Lower Zone Perc15	-920.1 (-938.6 to –903.0)	-968.1 (-978.7 to –944.1)	-975.7 (-979.1 to –965.5)	-976.7 (-985.6 to –967.4)
Combined Perc15	-919.3 (-937.2 to –900.2)	-955.1 (-969.2 to –932.4)	-958.8 (-972.2 to –952.3)	-969.9 (-983.7 to –957.6)
Upper Zone V.I.-950	3.8 (2.6 to 8.8)	11.5 (4.7 to 20.5)	12.5 (9.0 to 27.8)	21.3 (14.0 to 34.6)
Lower Zone V.I.-950	5.7 (3.4 to 9.9)	26.0 (11.6 to 38.2)	32.6 (24.6 to 39.2)	33.3 (26.6 to 44.2)
Combined V.I.-950	5.2 (3.0 to 9.4)	20.3 (9.5 to 29.2)	24.5 (17.9 to 30.8)	27.7 (20.3 to 44.5)

*All lung function measurements were performed after dual bronchodilation with inhaled nebulised salbutamol (2.5mg) and ipratropium bromide (250 micrograms).
Group 1-FEV1>80% predicted; Group 2-FEV_1=50-79% predicted; Group 3-FEV_1=30-49% predicted; Group 4-FEV_1<30% predicted. FEV_1 = forced expiratory volume in 1 second; K_{CO} = diffusing capacity of the lung for carbon monoxide (mmol/min/kPa/L); U.Z. = upper zone scans; L.Z. = lower zone scans; Combined = average of upper and lower zone scans; Perc15 = 15th percentile point; V.I.-950 = voxel index at a threshold of –950HU.

Table 3 Annual rate of disease progression related to disease severity with the data expressed as the median and interquartile range. The number in each sub-group is as shown in Table 2.

	Group 1	Group 2	Group 3	Group 4	JT test (p)
FEV_1 Rate (ml)	-83.0 (-190.8 to –32.8)	-108.9 (-234.4 to –73.5)	-54.8 (-82.4 to –17.8)	-30.6 (-45.9 to 4.9)	3.56 (p<0.001)
Upper Zone Perc15 Rate (HU)	0.8 (-4.9 to 3.3)	-3.8 (-4.7 to –1.4)	-2.9 (-4.9 to 0.1)	-3.1 (-4.5 to –0.1)	-0.5 (p=0.65)
Lower Zone Perc15 Rate (HU)	-2.1 (-5.6 to 1.5)	-1.9 (-2.8 to 1.4)	-2.4 (-4.1 to –0.2)	-0.9 -3.6 to 1.4)	0.29 (p=0.76)
Combined Perc15 Rate (HU)	-1.2 (-4.5 to 2.8)	-2.5 (-4.1 to –0.2)	-1.9 (-4.2 to –0.5)	-1.9 (-4.7 to 0.8)	-0.5 (p=0.595)
Upper Zone V.I.-950 Rate (%)	-0.1 (-0.5 to 0.9)	1.4 (0.5 to 2.4)	1.2 (0.2 to 2.4)	2.3 (-0.1 to 3.5)	2.85 (p=0.004)
Lower Zone V.I.-950 Rate (%)	0.2 (-0.5 to 0.8)	0.6 (-1.8 to 1.8)	1.3 (0.1 to 3.6)	2.2 (-0.7 to 3.4)	2.56 (p=0.018)
Combined V.I.-950 Rate (%)	0.1 (-0.4 to 0.7)	1.1 (-0.3 to 1.9)	1.3 (0.5 to 2.7)	2.0 (0.1 to 3.9)	2.87 (p=0.004)

Group 1-FEV1>80% predicted; Group 2-FEV_1=50-79% predicted; Group 3-FEV_1=30-49% predicted; Group 4-FEV_1<30% predicted. FEV_1 = forced expiratory volume in 1 second; V.I.-950 = voxel index at a threshold of –950HU; Perc15 = 15th percentile point; Rate = annual progression rate over 2 years; Combined = average of upper and lower zone scans.

The rate of progression in FEV_1 was significantly associated with disease stage (p = 0.001), with the highest decline observed in Group 2 and the lowest in Group 4 (Table 3 and Figure 3A). There was no significant trend in the rate of progression of Perc15 in association with disease stage but the rate of progression V.I.-950 was significantly associated with the disease stage (Table 3). There was a clear trend in progression rate of V.I.-950, with a graded increase in rate in association with worsening disease stage that was observed in both the individual and combined upper and lower zone images (Table 3 and Figure 3C).

CT lung density progression and its relationship with FEV_1 decline

The baseline characteristics of the 34 patients cohort with a complete data set are shown in Table 4.

Table 4 Baseline clinical characteristics of the 34 PiZ subjects cohort studied over 3 years.

	Median	**Interquartile Range**	**Median % predicted.**
Age	51	47 to 56	N/A
Pack Years	16	0 to 26	N/A
FEV_1 (L) *	1.2	0.9 to 1.9	42
VC (L) *	3.9	3.9 to 4.7	100
RV (L) *	2.7	2.2 to 3.4	126
TLC (L) *	6.9	6.2 to 8.3	117
K_{CO}*	1.0	0.8 to 1.3	68
U.Z. Perc15	-942.3	-964.9 to –926.9	N/A
U.Z. V.I.-950	11.8	6.2 to 23.9	N/A
L.Z. Perc15	-969.9	-977.6 to –943.1	N/A
L.Z. V.I.-950	28.3	11.5 to 34.1	N/A

*All lung function measurements were performed after dual bronchodilation with inhaled nebulised salbutamol (2.5mg) and ipratropium bromide (250 micrograms).

FEV_1 = forced expiratory volume in 1 second; K_{CO} = diffusing capacity of the lung for carbon monoxide (mmol/min/kPa/L); U.Z. = upper zone scans; L.Z. = lower zone scans; V.I.-950 = voxel index at a threshold of –950HU; Perc15 = 15^{th} percentile point.

The annual rate of CT progression in the upper zone images correlated with the annual rate of decline in FEV_1 (see Figure 4). The best correlation was seen with Perc15 (rs =0.527, p = 0.001) but a significant correlation was also seen with V.I.-950 (rs = -0.398, p = 0.012). There was no correlation between changes in the lower zone images and changes in FEV_1 (data not shown). However, there was a correlation between the rate of lung density loss in the upper and lower zones (Perc 15 - rs = -0.473, p<0.001 and V.I.-950 - rs = 0.476, p<0.001).

DISCUSSION

We have demonstrated in a cross-sectional study that there is good correlation between the percentile point and voxel index techniques for assessment of lung densitometry across a wide spectrum of disease severity. Of greater importance, is the curvilinear relationship (Figure 2), because differences in the gradient of the curve in mild (V.I.-950 close to 0) and severe disease (V.I.-950 above 30%) suggest that the

relative sensitivity of these parameters to lung density changes is dependent on disease severity. Namely, in early disease when the curve is more vertical, the relative sensitivity of the Perc15 method to change is likely to be greater than the V.I.-950 method, but the reverse would be true in severe disease. The sub-group analysis confirms this, and demonstrates that the above relationship largely reflects the finding of consistent progression of Perc15 across the spectrum of disease severity (Figure 3A) but a trend of increasing V.I.-950 progression in association with worsening disease stage (Table 3 and Figure 3C). Consequently, the sensitivity of the voxel index method to detect progression is not only threshold dependent, as shown previously [14 18], but also varies with disease severity. In contrast, the sensitivity of the percentile point method is threshold–independent [14] and the current study confirms the theoretical concept that it can detect changes in lung density consistently across the spectrum of disease severity. Notwithstanding this, there was wide variability in Perc 15 progression rate in early disease (Group 1). This may be because the subjects in Group 1 were younger, with fewer index cases and lower pack year cigarette exposure (factors known to influence progression) and hence there may not have been significant loss of lung density in some patients. Nevertheless, since there is clear evidence of disease progression indicated by the decline in FEV_1, an alternative explanation is that the limited sampling protocol that was employed in the programme at this time may have failed to detect the initial development of emphysema. Current understanding of the natural history of emphysema in AATD is that in the majority of PiZ subjects, the lung bases are the site of initial change and, as the disease progresses, there is increasing extension of emphysema towards the apical regions. For this reason, the upper and lower zone images were combined in an attempt to overcome the effect that these stage-related changes in emphysema distribution would have on the measurement of densitometry progression using single image analysis. Despite this, similar relationships were also demonstrated in the analysis of the progression measured individually in the upper and lower zones suggesting that this is not a reflection of a temporal process alone.

It is of importance to note that the rate of decline in FEV_1 was shown to vary in association with disease stage, and this has been recognised previously in individuals with AATD [31]. The absolute change in FEV_1 observed in the current study, and the observed trend in decline, are similar to this previous study and indicate that our group of patients is likely to be a representative sample.

The current study demonstrates for the first time that progression of CT densitometry relates to the rate of decline in FEV_1 in patients with AATD. Demonstration of this relationship required the application of summary statistics using linear regression on repeated measures over three years in order to overcome the error arising from the variability that exists in both parameters. The variability in FEV_1 measurements is likely to be minimised by the high level of quality control applied in our physiology laboratory which ensures precision within 50ml, whereas in routine clinical practice, the accepted precision is within 100ml [29]. It is recognised that the variability in CT densitometry due to sampling error and changes in inspiratory level between scans was unavoidable using a limited slice protocol, but the internal consistency of this method has been shown to be high [16] and it allowed repeated measures to be made whilst minimising radiation exposure. Furthermore, we have demonstrated that densitometric indices derived from single image analysis relate well to whole lung analysis (data not shown).

The HRCT protocol utilised for densitometry in the current study has been superceded by the use of volume scanning protocols that allow adjustment of lung density

measurements to a standardised lung volume. In addition, newer 'low dose' scanning protocols have been shown to generate reproducible densitometry [32], and edge-enhancing reconstruction algorithms have been replaced with edge-smoothing algorithms, in order to reduce signal noise. Although our programme now employs a modern volume-scanning protocol, there is an unavoidable interval between the adoption of newer methodology and the generation of longitudinal data. Consequently, the data reported in the current study remain unique, and notwithstanding the limitations of the scanning protocol that was employed, an association between annual change in FEV_1 and CT lung densitometry was identified that was statistically significant. Furthermore, it is anticipated that improvements in scanning methodology will generate data which is even more reproducible than the HRCT protocol employed in our current and previous longitudinal studies [16]. For instance, in the most recent study, which utilised a volume scanning protocol, but limited data collection to just two points spanning the period of observation, an association was found between annual change in CT lung densitometry and health status [17], suggesting that the method is becoming more reliable as an indicator of progression.

The relationship between CT progression and FEV_1 progression was stronger for Perc15 than for V.I.-950. This is not unexpected given the findings of the first part of this study indicating that there is a complimentary trend in progression of FEV_1 and Perc15 (Figures 3A and 3B) across the spectrum of disease severity but a dissimilar trend in progression of V.I.-950 (Figure 3C). In particular, in severe disease (FEV_1 < 30% predicted) when there is a slowing of the decline in FEV_1, V.I.-950 progression is maximal. However, the rationale behind the development of CT densitometry was to overcome rather than reflect the deficiencies of FEV_1 and the differences described above should not necessarily be interpreted as disadvantageous. On the contrary, they may indicate that V.I.-950 is the most appropriate method for monitoring emphysema progression in subjects with severe disease.

It is surprising that the relationship between FEV_1 decline and CT progression was demonstrated in the upper zone rather than the lower zone images, since impairment of FEV_1 relates better to CT indices of severity in the lower lung [33]. However, approximately two thirds of subjects with AATD have predominantly basal disease [33] and the upper zone images may therefore be ideally placed in the majority of patients to monitor extension of emphysema from the lower to the upper lung regions as the disease progresses. Indeed, previous studies that showed CT densitometry to be more sensitive to progression [16] and a better predictor of mortality than FEV_1 in subjects with AATD [34] found that densitometric indices were more informative when derived from the upper rather than the lower lung regions. When taken together, these findings may indicate that selective sampling of the upper lung region is a more sensitive method of detecting progression and treatment effects than whole lung densitometry. Nevertheless, the pattern of distribution of emphysema in subjects with AATD is not uniform [33] and whole lung imaging remains necessary to characterise the distribution of emphysema in individual subjects and the natural history of progression in the different GOLD sub-groups.

In summary, we have demonstrated that, as hypothesised, Perc15 is a more consistent measure of change in lung density than V.I.-950 across a wide spectrum of physiological impairment. In addition, the current study validates the use of CT densitometry in longitudinal studies of emphysema by confirming that progression of change in lung density correlates with decline in the accepted 'gold' standard, namely,

FEV_1. This data should consolidate the role of CT densitometry as a valid outcome measure in studies of emphysema progression and treatment.

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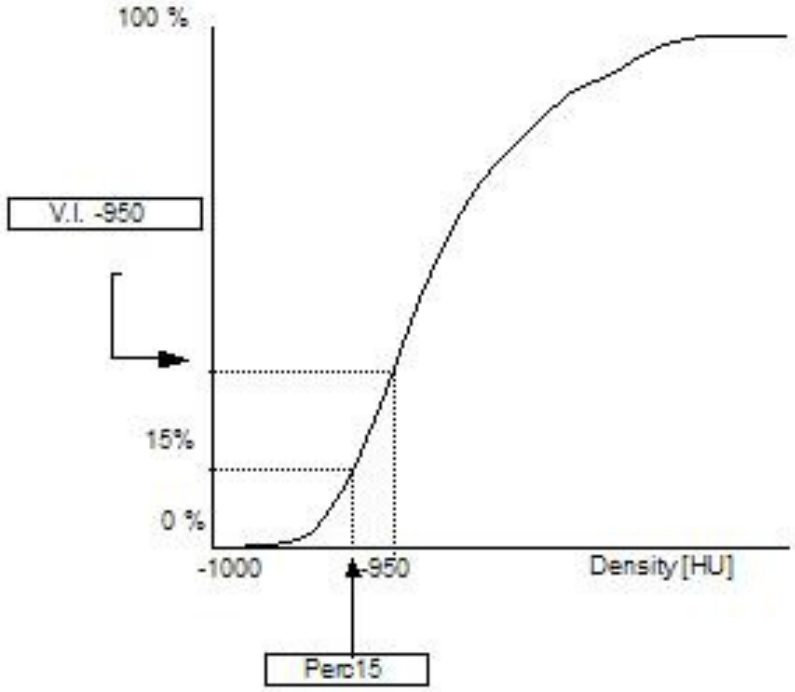
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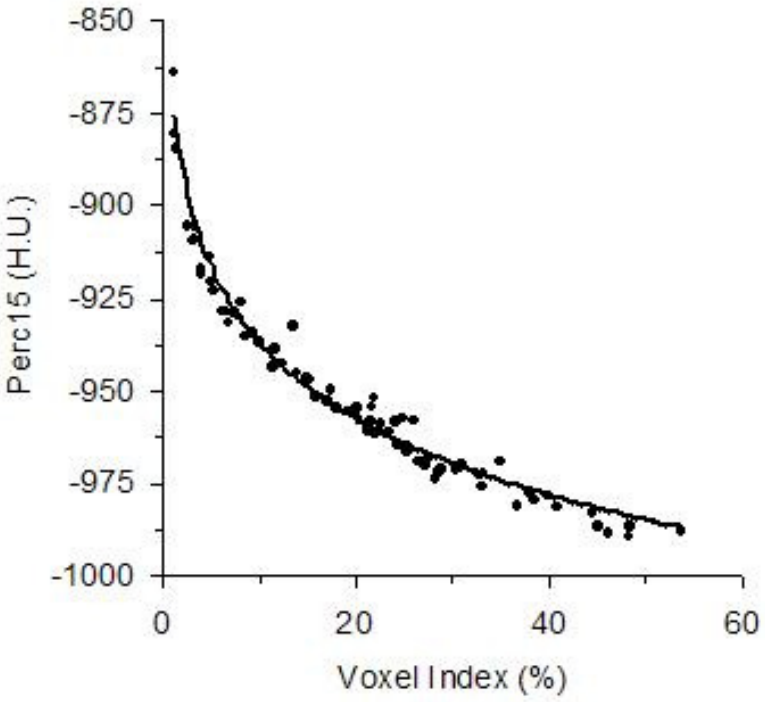
Density [HU]
Perc15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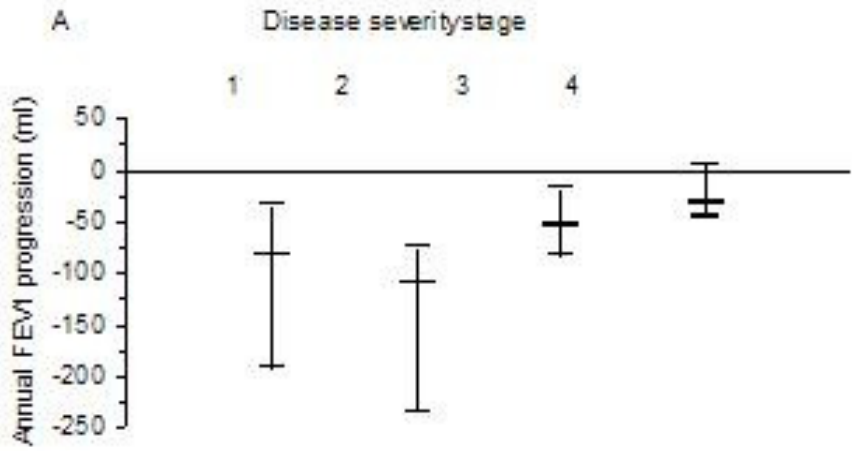
Voxel Index (%)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3
4
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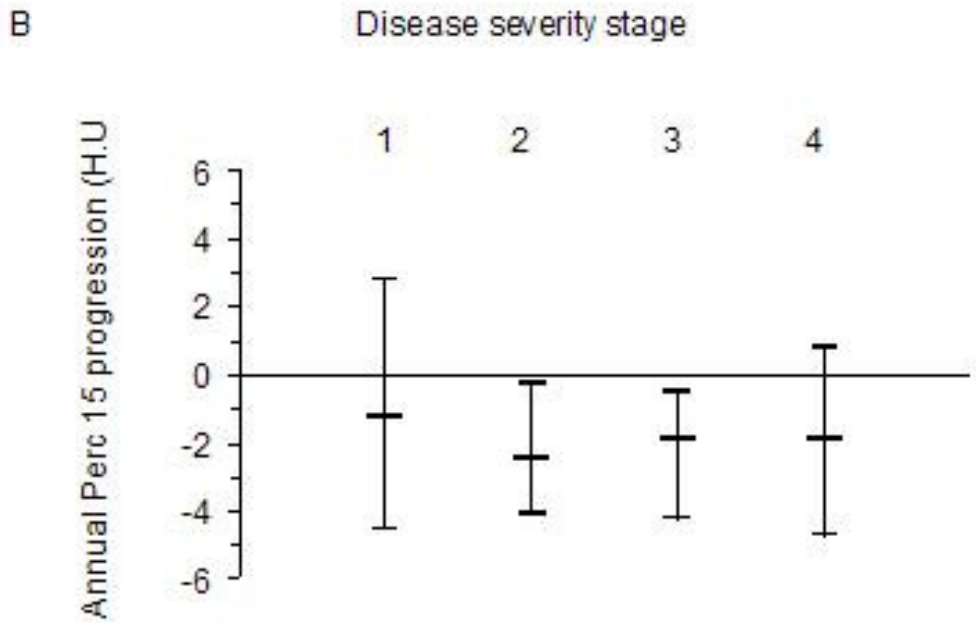
-200
-250


B
Disease severity stage
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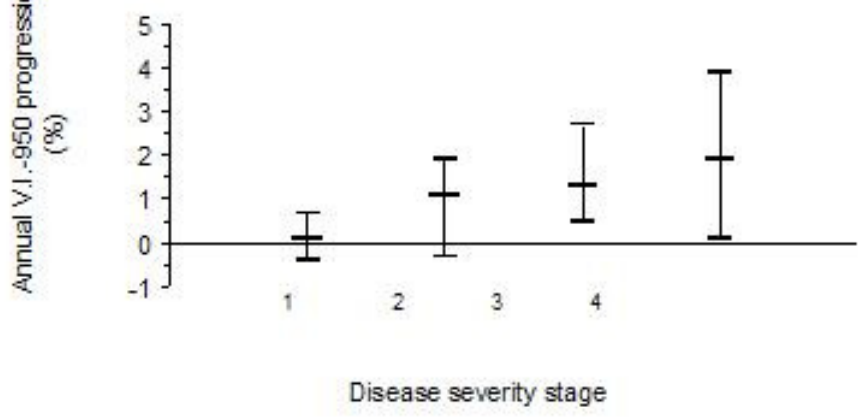
2
3
4
Annual Perc 15 progression (H.U
6
4
2
0
-2
-4
-6

C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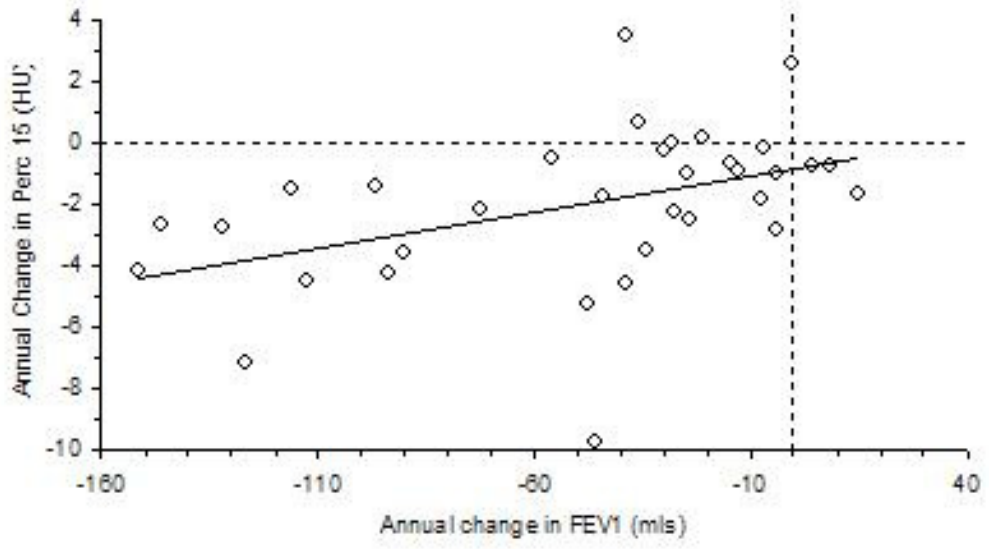
2
1
0
-1
1
2
3
4
Disease severity stage

A


Annual Change in Perc 15 (HU)'
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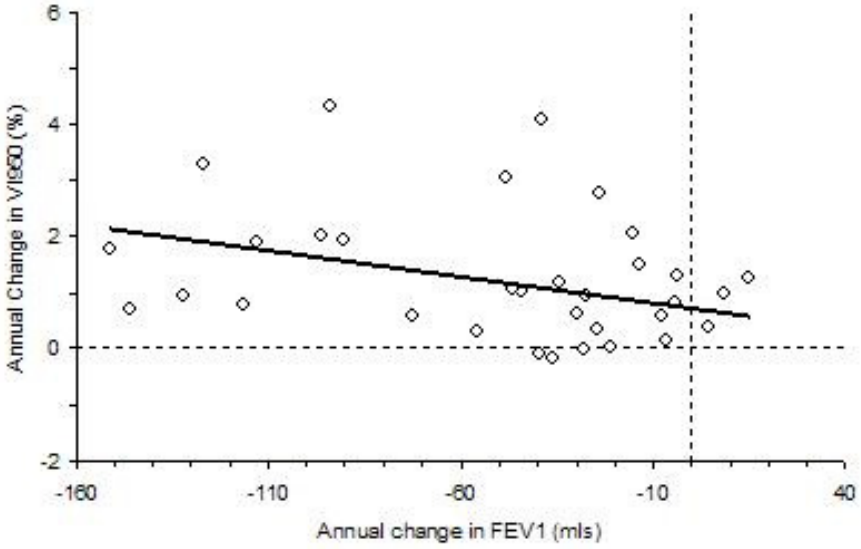
-4
-6
-8
-10
-160
-110
-60
-10
40
Annual change in FEV1 (mls)


6
4
2
0
-2
Annual Change in V̇I3650 (%)
-160
-110
-60
-10
40
Annual change in FEV1 (mls)