# Physiological associations of computerized tomography lung density: a factor analysis

Suzanne Marsh[1]
Sarah Aldington[1]
Mathew V Williams[1]
Michael Nowitz[2]
Andrew Kingzett-Taylor[2]
Mark Weatherall[3]
Phillipa Shirtcliffe[1]
Alison Pritchard[1]
Richard Beasley[1,4]

[1]Medical Research Institute of New Zealand, Wellington, New Zealand; [2]Pacific Radiology Limited, Wellington, New Zealand; [3]Wellington School of Medicine & Health Sciences, Wellington, New Zealand; [4]University of Southampton, United Kingdom

Correspondence: Richard Beasley
Medical Research Institute of New Zealand, PO Box 10055, Wellington, New Zealand
Tel + 64 4472 9199
Fax + 64 4472 9224
Email Richard.Beasley@mrinz.ac.nz

**Background:** Objective quantification of emphysema using computerized tomography (CT) density measurements is rapidly gaining wide acceptance as an in vivo measurement tool. However, some studies have suggested that abnormal lung function in the absence of emphysema can affect lung density, and the role of such measurements in identifying and monitoring the progression of emphysema is not clear.

**Objective:** To clarify the relationship between lung density measurements and pulmonary function.

**Methods:** CT measurements of the proportion of lung occupied by low density tissue (as percentage of lung area below predetermined Hounsfield unit [HU] thresholds) were obtained in a large random population (n = 739) and the association with detailed pulmonary function tests studied using factor analysis.

**Results:** Density measurements showed a greater association with measures of hyperinflation and airflow obstruction than measures of gas transfer (correlation coefficient, high resolution scan, −950 HU threshold vs $FEV_1/FVC$, RV, and DLCO/VA of −0.39, 0.22, and −0.15 respectively). The strongest lung density factor coefficients of 0.51 (standard resolution scan, −950 HU threshold) and 0.46 (high resolution scan, −910 HU threshold) were seen with factors predominantly consisting of measures of airflow obstruction and hyperinflation. Most variation in lung density was not accounted for by lung function measurements (communality 0.21–0.34).

**Conclusion:** Lung density measurements associate most strongly with measures of airway disease that are not specific to emphysema.

**Keywords:** emphysema, CT lung density, COPD, lung function tests

## Introduction

The application of computerized tomography (CT) scanning in the detection and assessment of emphysema has evolved since the 1980s when it was first demonstrated that objective CT measurements could be used to detect the presence of emphysema (Hayhurst et al 1984). Through the use of a density threshold, an objective method of CT quantification was developed whereby the proportion of lung with attenuation below a predetermined value, expressed relative to the total area of that particular lung slice, was calculated (Muller et al 1988). Several thresholds have been proposed to quantify the extent of emphysema (Cosio et al 2001), with the relative area of lung with attenuation values below −910 and −950 Hounsfield units (HU) being shown to correlate closely with macro- and microscopic pathological features of emphysema (Muller et al 1988; Genenois et al 1995; Gevenois, De Vuyst, de Maertelaer, et al 1996). Lung density measurements have also been shown to correlate with measurements of the degree of abnormal lung function in emphysema, including $FEV_1$ and diffusing capacity (Kinsella et al 1990; Gould et al 1991). However, other authors have reported an increase in areas of low attenuation in asthma (Newman et

al 1994; Biernacki et al 1997; Mitsunobu et al 2001), suggesting that this feature may not be specific to emphysema.

In this study we set out to clarify the relationship of RA% lung density measurements (the relative area of lung tissue below the threshold density expressed as a percentage of the total area of that lung slice) to detailed pulmonary function tests using a large population sample. By exploring these associations at different thresholds, using different CT reconstruction algorithms we aimed to investigate the likely influence of changes in lung function on density measurements and therefore explore the relationship between these measurements and the presence of obstructive airways disease.

## Methods

### Study participants

Study participants were recruited from a postal screening survey sent to 3500 people aged 25–75 years, randomly selected from the electoral register. Subjects completing the screening survey were invited to attend the research centre to complete an interviewer-administered, written questionnaire followed by visits to undertake detailed respiratory function testing and a CT scan of the chest.

### Written questionnaire

All participants completed a detailed written questionnaire compiled from a series of validated questionnaires (Pistelli et al 2001) administered by a trained interviewer in a standardized manner. The Wellington Ethics Committee approved the study and written informed consent was obtained from each subject.

### Pulmonary function testing

Pulmonary function tests were carried out on 1 site by 1 of 3 trained operators (SA, SM, MVW), using two Jaegar Master Screen Body volume constant plethysmography units with pneumotachograph and diffusion unit for spirometry and measurement of gas transfer (Masterlab 4.5 and 4.6 Erich-Jaegar, Wurzburg, Germany). Equipment was calibrated daily prior to testing.

Subjects were requested to avoid carbonated drinks and caffeine for 6 hours and refrain from smoking for 2 hours prior to testing. Subjects that had been prescribed inhaled medication were instructed not to use short-acting bronchodilators for 6 hours and to avoid long-acting bronchodilators (long-acting beta agonists or anticholinergic

agents) for 36 hours prior to testing. Inhaled corticosteroids or other medication was not altered. Testing did not occur within 3 weeks of an upper or lower respiratory tract infection (new or increased cough, sputum production, sore throat or nasal congestion). Subjects over 125 kg in weight were excluded due to the weight restriction of the CT scanner.

All pulmonary function tests were carried out in accordance with American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria (ATS 1995a; 1995b; Coates et al 1997) and a nose clip was worn for all tests. Airway resistance was measured during relaxed breathing at a rate of approximately 0.5 Hz. Following a minimum of 10 measurements of airway resistance ($R_{tot}$) and attainment of a stable baseline representing functional residual capacity (FRC), the plethysmography shutter was closed, occluding breathing for 2–3 seconds. During this time the subject was instructed to pant gently, without glottis closure, and thoracic gas volume at FRC was calculated. Immediately following FRC measurement the subject was instructed to breath out comfortably, maximally inspire and slowly expire to completely empty for measurement of slow vital capacity (SVC). Expiratory reserve capacity (ERV) was measured from FRC to the point of maximum expiration and residual volume (RV) was calculated from FRC−ERV. The total lung capacity (TLC) was calculated as SVC (measured)+RV. Specific conductance (sGaw) and resistance (sRaw) were calculated from measurements of airway resistance and FRC. A minimum of 3 and usually 5 measurements of FRC were carried out and maximum values from individual maneuvers for ERV and SVC were used in the above calculations.

Following measurement of static lung volumes a minimum of 3 acceptable spirometry maneuvers were carried out with the best $FEV_1$ and FVC selected for analysis. Maximal mid expiratory flow rate ($FEF_{25-75}$) was taken from the maneuver with the best combination of $FEV_1$ and FVC. For gas transfer measurement, washout and sample volumes of 750 ml were used except in subjects with COPD or asthma who were unable to manage this when a decrease was made to a minimum of 500 ml. Gas transfer measurements were expressed as raw values (DLCO) and corrected for alveolar volume (DLCO/VA). All results were corrected for body temperature, atmospheric pressure, and water saturation (BTPS) and expressed as a percentage of predicted based on the formulae of the ERS (Cotes et al 1993; Quanjer et al 1993) except for $FEV_1$/FVC which was expressed as an

absolute ratio, and sGaw which was expressed as a percentage of the lower limit of normal (Quanjer et al 1983).

## CT scanning

Subjects were scanned using a single machine (GE Prospeed, General Electric Medical Systems, YMS, Japan) by radiographers specifically trained in the study protocol. The scanner was calibrated at weekly intervals using the manufacturers' standard phantom. Scans were obtained at full inspiration with a breath hold time of 4.5 seconds and no intravenous contrast was used. Three images were obtained at levels of 1 cm above the aortic arch, 1 cm below the carina, and 3 cm above the top of the right hemidiaphragm (Mishima et al 1999) with a 1 mm collimation and a voltage of 120 kVp. Images were reconstructed using high (GE bone) and low spatial frequency (GE standard) algorithms and the manufacturer's "density mask" program was used to measure tissue density. The trachea and main stem bronchi were excluded from measurements of lung area and the total area of lung tissue per slice was calculated using a density of $-300$ to $-1200$ HU to separate lung tissue from the chest wall. The areas of tissue below the thresholds of $-950$ HU and $-910$ HU were expressed as a percentage of the total lung area for that slice as the RA950 and RA910 respectively (Gevenois et al 1995).

## Statistical analysis

Simple descriptive statistics were used to describe the subject characteristics and lung density estimates both for individual slices and the average of the 3 slices for each measurement technique. Product moment correlation coefficients were calculated for lung function and lung density measurements. Factor analysis by an initial principal components method followed by a varimax rotation with Kaiser normalization was used to determine which measures of lung function were associated with lung density measurements. The measures of lung function entered into the factor analysis were: $FEV_1$ percent predicted, $FEV_1/FVC$ ratio, $FEF_{25-75}$ percent predicted, and sGaw percent of lower limit of normal (measures of airflow obstruction); RV and TLC percent predicted (measures of hyperinflation); DLCO and DLCO/VA percent predicted (measures of gas transfer). This method of analysis finds coefficients for each variable that associates them with a particular underlying factor. In this case 3 underlying factors were expected to be present: airflow obstruction, lung hyperinflation, and gas transfer. The coefficients vary from $-1$ to 1 and if variables have high

absolute values of coefficients then they load highly, are highly correlated, on to a particular factor. Communality, or the proportion of variation in the original variables that is explained by the new factors, was calculated for the factor analysis. A proportion close to 1 means that most of the variation in the original variables is explained by the underlying factors while a communality close to zero means little variation in the original variable is explained by the underlying factors. SAS version 8.2 was used for all analyses.

## Results

The initial recruitment resulted in 2319 responses from 3500 screening questionnaires. With the exclusion of the 508 subjects unable to be traced from the address on the electoral register and 13 subjects who had died, this represented a response rate of 2319/2979 (78%). Of those subjects who completed the screening questionnaire, 758 completed the detailed questionnaire and undertook pulmonary function tests. 739 of these (97%) had CT scans. Of these, 549 had scans that were reconstructed using both algorithms and assessed at both thresholds. 175 subjects had scans that were reconstructed with a high resolution algorithm and assessed for RA950 only, and the remaining 15 had images with a high reconstruction algorithm assessed for both thresholds. Most subjects were able to complete all 3 modalities of pulmonary function testing (airway resistance and static lung volumes, dynamic lung volumes, and gas transfer measurements); however 19 subjects were unable to satisfactorily complete plethysmography measurements and 7 subjects were not able to complete flow volume loops. Gas transfer measurements were completed by all but 26 subjects.

Table 1 shows the epidemiological characteristics and results of pulmonary function tests of the subjects. There was a slight excess of male subjects (n = 405, 54.8%), 74 subjects (10%) were current smokers, 295 were past smokers (40%) (pack years, all smokers, mean [SD], 15 [18.0] range 0.03–171).

The lung density measurements for the individual slices and the mean of all 3 slices are shown in Table 2. The apical RA% values were smaller than those at the other 2 standardized sites. Higher RA% values were observed with the high (compared with standard) resolution algorithm and with the $-910$ HU (compared with the $-950$ HU) threshold. As the correlation between RA% values for individual slices was strong (data not shown) further analyses were carried out using data presented as the mean of all 3 slices.

**Table 1** Subject characteristics including pulmonary function tests

| Characteristic of population (n = 739) | Mean (SD) | Range |
|---|---|---|
| Age (years) | 53.6 (12.8) | 26–75 |
| FEV$_1$/FVC % predicted | 74.2 (8.9) | 31–95 |
| FEV$_1$ % predicted | 106.5 (21) | 24–161 |
| FEF$_{25-75}$ % predicted | 74.2 (28.9) | 6–181 |
| sGaw % lower limit of normal | 132.9 (48.6) | 15–345 |
| RV % predicted | 107 (25.9) | 39–303 |
| TLC% predicted | 110.3 (12.6) | 61–155 |
| DLCO % predicted | 94.3 (14.8) | 28–138 |
| DLCO/VA % predicted | 96.5 (14.4) | 42–145 |
| Smokers (current n = 74, past n = 295) | | |
| Cigarette pack years (all smokers) | 15 (18.0) | 0.03–171 |

**Abbreviations:** DLCO, transfer factor for carbon monoxide; FEF$_{25-75}$, maximum forced expiratory flow rate; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; sGaw, airway conductance; RV, residual volume; TLC, total lung capacity; VA, alveolar volume.

The correlation matrix for lung function tests and lung density for the high resolution algorithm and threshold of −950 HU (Table 3) shows that RA950 was poorly correlated with most lung function variables, with the highest correlation coefficient of −0.39 seen with FEV$_1$/FVC. Similar results (not shown) were seen with the other reconstruction algorithms and thresholds.

The results for the factor analysis are shown in Tables 4 and 5. In high resolution scans (Table 4a and b) lung density measurements predominantly clustered on to measurements associated with hyperinflation (RV and TLC). The strongest

association for lung density measurements, obtained with the standard resolution algorithm and −950 HU threshold (Table 5a), was with measurements of airflow obstruction with a component of hyperinflation (RV). Standard resolution scans with −910 HU threshold (Table 5b) showed a weaker and more inconsistent result, with slightly greater loading on to factors with predominant components of hyperinflation and airflow obstruction. Weak clustering with gas transfer variables was seen only for the standard resolution scans and −950 HU threshold (Table 5b).

Communality of the lung density measurements for each of the 4 combinations of algorithm and threshold values is low (0.21–0.34) (Tables 4 and 5). This means that most variation in lung density is not accounted for by the lung function tests included in the factors (1, 2, and 3) identified in the factor analysis. In contrast the communality for individual lung function measurements, except for sGaw, is high (0.72–0.97) (Tables 4 and 5), meaning variation within individual lung function measurements (except sGaw) is largely explained by the underlying factors (1, 2, and 3) identified. As a result, sGaw is likely to be measuring a component of airway physiology not accounted for by the other parameters.

## Discussion

This study has shown that measurements of lung density have, as their most dominant relationship, a consistent

**Table 2** Descriptive statistics for lung density measurements

| Reconstruction algorithm and threshold | Level[b] | Number of subjects | Mean (SD)[a] | Median (inter-quartile range)[a] | Range[a] |
|---|---|---|---|---|---|
| High resolution − 950 HU | Level 1 | 739 | 13.1 (8.0) | 11.9 (7.3–17.5) | 0.02–68.3 |
| | Level 2 | 739 | 15.4 (7.3) | 15.2 (10.1–20.7) | 0.39–57.3 |
| | Level 3 | 739 | 15.5 (7.4) | 15.0 (9.9–20.5) | 0.07–38.5 |
| | Mean | 739 | 14.7 (7.1) | 14.4 (9.2–19.9) | 0.52–50.7 |
| High resolution − 910 HU | Level 1 | 549 | 31.3 (12.4) | 31.2 (22.0–39.3) | 2.4–79.4 |
| | Level 2 | 548[c] | 35.8 (12.2) | 37.0 (27.4–45.0) | 3.0–70.2 |
| | Level 3 | 549 | 34.6 (12.3) | 35.6 (25.5–43.9) | 0.43–60.2 |
| | Mean | 549 | 33.9 (11.8) | 34.8 (25.3–43.2) | 4.0–68.2 |
| Standard resolution − 950 HU | Level 1 | 564 | 1.28 (5.1) | 0.14 (0.03–0.65) | 0–68.2 |
| | Level 2 | 564 | 2.33 (3.5) | 1.4 (0.58–2.78) | 0–54.4 |
| | Level 3 | 564 | 3.63 (3.7) | 2.5 (1.2–4.70) | 0–31.5 |
| | Mean | 564 | 2.41 (3.5) | 1.4 (0.67–2.80) | 0–45.9 |
| Standard resolution − 910 HU | Level 1 | 549 | 16.4 (16.7) | 10.4 (2.8–25.1) | 0–81.3 |
| | Level 2 | 549 | 24.6 (16.8) | 22.7 (10.1–37.5) | 0.1–72.7 |
| | Level 3 | 549 | 24.5 (15.7) | 23.2 (10.8–36.0) | 0.01–63.5 |
| | Mean | 549 | 21.8 (15.5) | 19.4 (8.2–33.9) | 0.15–64.2 |

[a]Results are presented as RA% values, the proportion of lung tissue below the threshold density expressed relative to the total area of that lung slice.
[b]Level 1: 1 cm above the aortic arch, Level 2: 1 cm below the carina, and Level 3: 3 cm above the top of the right hemi-diaphragm.
[c]Due to a technical problem it was not possible to analyse data for 1 subject.

**Table 3** Correlation matrix for lung function tests and lung density for high resolution scan and − 950 HU threshold

|  | HR950 mean[a] | DLCO | DLCO/VA | FEV$_1$ | FEV$_1$/FVC | MMEF | RV | sGaw | TLC |
|---|---|---|---|---|---|---|---|---|---|
| HR950 mean[a] | 1.00 | −0.10 | −0.15 | −0.13 | −0.39 | −0.19 | 0.22 | −0.03 | 0.17 |
| DLCO | −0.10 | 1.00 | 0.71 | 0.42 | 0.22 | 0.29 | −0.19 | 0.22 | 0.18 |
| DLCO/VA | −0.15 | 0.71 | 1.00 | −0.01 | 0.67 | 0.15 | −0.37 | 0.23 | −0.47 |
| FEV$_1$ | −0.13 | 0.42 | −0.01 | 1.00 | 0.21 | 0.76 | −0.42 | 0.44 | 0.36 |
| FEV$_1$/FVC | −0.39 | 0.22 | 0.21 | 0.67 | 1.00 | 0.85 | −0.56 | 0.45 | −0.22 |
| MMEF | −0.19 | 0.29 | 0.15 | 0.76 | 0.85 | 1.00 | −0.45 | 0.51 | 0.01 |
| RV | 0.22 | −0.19 | −0.37 | −0.42 | −0.56 | −0.45 | 1.00 | −0.46 | 0.57 |
| sGaw | −0.03 | 0.22 | 0.23 | 0.44 | 0.45 | 0.51 | −0.46 | 1.00 | −0.18 |
| TLC | 0.17 | 0.18 | −0.47 | 0.36 | −0.22 | 0.01 | 0.57 | −0.18 | 1.00 |

[a]Lung density measurements for high resolution scan, − 950 HU threshold as a mean of all 3 slices
See Table 1 for abbreviations.

**Table 4** Factor analysis for mean lung density measurements for high resolution CT scans for a) − 950 HU threshold and b) − 950 HU threshold

**Table 4a**

| Original variable | Factor 1 loading[a] | Factor 2 loading | Factor 3 loading | Communality[b] |
|---|---|---|---|---|
| HR950 mean[c] | −0.25 | 0.39 | −0.02 | 0.21 |
| DLCO | 0.28 | 0.17 | 0.93 | 0.97 |
| DLCO/VA | −0.01 | −0.42 | 0.87 | 0.96 |
| FEV$_1$ | 0.91 | 0.25 | 0.14 | 0.91 |
| FEV$_1$/FVC | 0.84 | −0.34 | 0.06 | 0.83 |
| MMEF | 0.92 | −0.09 | 0.09 | 0.86 |
| RV | −0.48 | 0.69 | −0.15 | 0.73 |
| sGaw | 0.58 | 0.27 | 0.15 | 0.43 |
| TLC | 0.18 | 0.95 | −0.06 | 0.94 |

**Table 4b**

| Original variable | Factor 1 loading | Factor 2 loading | Factor 3 loading | Communality |
|---|---|---|---|---|
| HR910 mean[d] | −0.12 | 0.46 | 0.01 | 0.22 |
| DLCO | 0.27 | 0.19 | 0.93 | 0.97 |
| DLCO/VA | 0.03 | −0.39 | 0.90 | 0.97 |
| FEV$_1$ | 0.90 | 0.29 | 0.13 | 0.90 |
| FEV$_1$/FVC | 0.85 | −0.31 | 0.08 | 0.83 |
| MMEF | 0.92 | −0.06 | 0.10 | 0.86 |
| RV | −0.52 | 0.64 | −0.17 | 0.72 |
| sGaw | 0.60 | −0.24 | 0.13 | 0.43 |
| TLC | 0.13 | 0.95 | −0.09 | 0.93 |

[a]Factor analysis finds coefficients (−1 to 1) for each variable associating them with a particular underlying factor (in this case factors 1 to 3). If variables have high absolute coefficient values then they are highly correlated onto a particular factor.
[b]Communality expresses the proportion of variation in the original variables explained by the new factors. A proportion close to 1 means most of the variation in the original variables is explained by the underlying factors.
[c]Lung density measurements for high resolution scan, − 950 HU threshold, as a mean of all 3 slices.
[d]Lung density measurements for high resolution scan, − 950 HU threshold, as a mean of all 3 slices.
See Table 1 for abbreviations.

association with hyperinflation in all 4 reconstruction algorithm and threshold models. Weaker associations are seen with airflow obstruction and essentially no association is seen with gas transfer variables.

## Methodological issues

We chose a limited 3-scan CT protocol based on a need to reduce radiation exposure in a research setting and evidence that a 3-slice protocol gives information closely comparable with that of more detailed 10-slice assessments (Mishima et al 1999). Although it has been suggested that expiratory scans are more closely correlated with physiological variables consistent with a diagnosis of emphysema (Knudson et al 1991), Gevenois, De Vuyst, Sy, et al (1996) found inspiratory scans to be superior when compared with pathological measurements. Scans taken as close to TLC as

**Table 5** Factor analysis for mean lung density measurements for standard resolution CT scans for a) − 950 HU threshold and b) − 950 HU threshold

**Table 5a**

| Original variable | Factor 1 loading | Factor 2 loading | Factor 3 loading | Communality |
|---|---|---|---|---|
| STD950 mean[a] | 0.51 | 0.23 | −0.16 | 0.34 |
| DLCO | 0.55 | 0.00 | 0.80 | 0.95 |
| DLCO/VA | 0.53 | −0.58 | 0.55 | 0.92 |
| FEV$_1$ | 0.71 | 0.63 | 0.03 | 0.91 |
| FEV$_1$/FVC | 0.86 | 0.13 | −0.24 | 0.82 |
| MMEF | 0.83 | 0.37 | −0.17 | 0.85 |
| RV | 0.72 | 0.34 | 0.31 | 0.74 |
| sGaw | 0.62 | 0.03 | −0.26 | 0.46 |
| TLC | −0.24 | 0.88 | 0.37 | 0.96 |

**Table 5b**

| Original variable | Factor 1 loading | Factor 2 loading | Factor 3 loading | Communality |
|---|---|---|---|---|
| STD910 mean[a] | −0.28 | 0.32 | 0.21 | 0.23 |
| DLCO | 0.54 | 0.06 | 0.82 | 0.97 |
| DLCO/VA | 0.51 | −0.54 | 0.64 | 0.97 |
| FEV$_1$ | 0.73 | 0.61 | −0.01 | 0.91 |
| FEV$_1$/FVC | 0.87 | 0.09 | −0.27 | 0.83 |
| MMEF | 0.85 | 0.33 | –0.17 | 0.80 |
| RV | −0.72 | 0.37 | 0.24 | 0.72 |
| sGaw | 0.64 | 0.03 | −0.13 | 0.42 |
| TLC | 0.24 | 0.90 | 0.26 | 0.93 |

[a]Lung density measurements for standard resolution scan, − 950 HU threshold, as a mean of all 3 slices.
See Table 1 and Table 4 for abbreviations and explanation of terms.

possible are recommended for longitudinal follow up of emphysema (Newell et al 2004). Two density thresholds (−910 and −950 HU) were used based on previous correlations with pathological measures and pulmonary function tests (Muller et al 1988; Kinsella et al 1990; Gevenois et al 1995; Gevenois, De Vuyst, Maertelaer, et al 1996). A 1 mm collimation was used as this has been employed in studies showing a close macro- and microscopic association between lung density measurements and emphysema (Gevenois et al 1995; Gevenois, De Vuyst, Maertelaer, et al 1996).

## Relationship between physiological measurements and lung density

The finding that lung density measurements associate most closely with measures of airflow obstruction and hyperinflation are consistent with those of Mitsunobu et al (2001) who, in subjects with asthma, found a strong correlation between RA950 levels and FEV$_1$, FEV$_1$/FVC, and RV but no correlation with measures of gas transfer. Similarly Kinsella et al (1990) found that a "density mask"

threshold of −910 HU correlated most strongly with FEV$_1$/FVC and more weakly with measures of gas transfer. Conversely Gould et al (1991), using the lowest 5th percentile derived from CT density histograms, found the correlation with gas transfer to be greater than that with FEV$_1$/FVC and showed weaker, but significant relationships with measurements of lung volume (RV and TLC). Different correlations between density measurements and pulmonary function parameters between studies may be due, in part, to the size and nature of the population groups being studied. Two of the previous studies (Kinsella et al 1990; Gould et al 1991) had relatively small samples of around 80 subjects and included few "normal" subjects in respect of respiratory health and smoking status. By using factor analysis and a large number of randomly selected subjects to explore the relationship of lung density measurements to pulmonary function tests in a diverse population, this problem is overcome and we were able to address the question of which lung function parameters are reflected by lung density.

Prior to CT scanning, pulmonary function tests have represented the best noninvasive method to indicate the

presence of emphysema. Although not a gold standard compared with anatomical diagnosis, assessment of gas transfer, through the measurement of diffusing capacity, is often considered to be one of the best predictors of emphysema (Heremans et al 1992) and is the best single physiological discriminator between subjects with asthma and COPD (Sciurba 2004). In addition gas transfer measurements correlate more closely with microscopic pathological measurements of emphysematous change than do measures of airflow obstruction and hyperinflation (Gould et al 1988; Gevenois, De Vuyst, Maertelaer, et al 1996). By showing that RA% values cluster most strongly with physiological measurements that are not specific to emphysema the validity of a measurement of RA% as an index of emphysema is called into doubt.

Our findings suggest that the use of lung density measurements in the longitudinal assessment of emphysema may be confounded by short-term variations in airflow obstruction and hyperinflation. Such variations could cause significant changes in lung density unrelated to the progression of emphysema.

## Conclusion

We conclude that lung density measurements correlate more strongly with measures of hyperinflation and airflow obstruction than with measures of gas transfer. Such measurements should be used with caution in the long-term assessment of the progression of emphysema. The ability of lung density measurements to diagnose emphysema and discriminate it from other forms of obstructive airway disease awaits further study.

## Acknowledgments

## References

[ATS] American Thoracic Society. 1995a. Single-breath carbon monoxide diffusing capacity (transfer factor): Recommendations for a standard technique. *Am J Respir Crit Care Med*, 152:2185–98.

[ATS] American Thoracic Society. 1995b Standardization of Spirometry, 1994 Update. *Am J Respir Crit Care Med,* 152:1107–36.

Biernacki W, Redpath A, Best J, et al. 1997. Measurement of CT lung density in patients with chronic asthma. *Eur Resp J*, 10:2455–9.

Coates AL, Peslin R, Rodenstein D, *et al.* 1997. ERS/ATS workshop report series: Measurement of lung volumes by plethysmography. *Eur Respir J,* 10:1415–27.

Cosio M, Snider G. 2001. Chest computed tomography: is it ready for major studies of chronic obstructive pulmonary disease? *Eur Resp J*, 17:1062–4.

Cotes JE, Chinn DJ, Quanjer PH, et al. 1993. Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Resp J*, 6(Suppl 16):41–52.

Gevenois PA, De Maertelaer V, De Vuyst P, et al. 1995. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med*, 152:653–7.

Gevenois PA, De Vuyst P, de Maertelaer V, et al. 1996. Comparison of computed density and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med*, 154:187–92.

Gevenois PA, De Vuyst P, Sy M, et al. 1996. Pulmonary emphysema: quantitative CT during expiration. *Radiology*, 199:825–9.

Gould G, MacNee W, McClean A, et al. 1988. CT measurements of lung density in life can quantitate distal airspace enlargement - an essential defining feature of human emphysema. *Am Rev Resp Dis*, 137:380–92.

Gould GA, Redpath AT, Ryan M, et al. 1991. Lung CT density correlates with measurements of airflow limitation and the diffusing capacity. *Eur Resp J*, 4:141–6.

Hayhurst M, MacNee W, Flenley D, McLean A, et al. 1984. Diagnosis of pulmonary emphysema by computerized tomography. *Lancet*, 2:320–2.

Heremans A, Verschakelen J, Van fraeyenhoven L, et al. 1992. Measurement of lung density by means of quantitative CT scanning; a study of correlations with pulmonary function tests. *Chest*, 102:805–11.

Kinsella M, Muller NL, Abboud RT, et al. 1990. Quantitation of emphysema by computed tomography using a "density mask" program and correlation with pulmonary function tests. *Chest*, 97:315–21.

Knudson R, Standen R, Kalternborn W, et al. 1991. Expiratory computed tomography for assessment of suspected pulmonary emphysema. *Chest*, 99:1357–66.

Mishima M, Itoh H, Sakai H, et al. 1999. Optimized scanning conditions of high resolution CT in the follow up of pulmonary emphysema. *J Comput Assist Tomogr*, 23:380–4.

Mitsunobu F, Mifune T, Ashida K, et al. 2001. Influence of age and disease severity on high resolution CT lung densitometry in asthma. *Thorax*, 56:851–56.

Muller NL, Staples CA, Miller RR, et al. 1988. "Density Mask" An objective method to quantitate emphysema using computerized tomography. *Chest*, 94:782–7.

Newell JD, Hogg JC, Snider GL. 2004. Report of a workshop: quantitative computed tomography scanning in longitudinal studies of emphysema. *Eur Respir J*, 23:769–75.

Newman K, Lynch D, Newman L, et al. 1994. Quantitative computed tomography detects air trapping due to asthma. *Chest*, 106:105–9.

Pistelli F, Viegi G, Carrozzi L, et al. 2001. Compendium of respiratory standard questionnaires for adults (CORSQ). *European Respiratory Review*, 11:118–43.

Quanjer P, Dalhuijsen A, Van Zoramen B. 1983. Standardised Lung Function Testing. Report of the working party for the European Community for Coal and Steel. *Bull Eur Physiopathol Respir*, 19:(Suppl. 5):1–95.

Quanjer P, Trammeling G, Cotes J, et al. 1993. Lung volumes and forced ventilatory flows. Report of the working party for standardization of lung function tests. European Community for Steel and Coal. Official statement of the European Respiratory Society. *Eur Resp J*, 6 (Suppl 16):S5–40.

Sciurba FC. 2004. Physiologic Similarities and Differences Between COPD and Asthma. *Chest*, 126 (Suppl 1):S117–24.