Measurement of CT lung density in patients with chronic asthma

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Abstract: Evidence for the presence of emphysema in patients with asthma is controversial. We have previously shown that decreased lung density, measured by computed tomographic (CT) scanning, preoperatively, correlates with morphometric measurements of microscopic emphysema in subsequently resected lungs. The aim of this study was to compare CT lung density, in 17 patients with chronic asthma (forced expiratory volume in one second (FEV1) 1.98 (SD 0.77) L), 17 patients with chronic bronchitis and emphysema (FEV1 0.97 (0.56) L) and seven normal subjects (FEV1 3.5 (0.34) L).

All subjects underwent CT scanning of the lungs and respiratory function testing within 2 days of each other. In five of the asthmatic patients a CT scan was performed on two occasions before and after treatment with nebulized bronchodilator. In a different group of five asthmatics these measurements were performed at the end of and 6 weeks after an exacerbation.

The mean value of the lowest fifth percentile of the CT lung density in the patients with chronic obstructive pulmonary disease (COPD) was -942 (SD 36) Hounsfield units (HU), in the 17 asthmatic patients was -912 (34) HU, and in normal subjects was -880 (13). Despite a significant increase in peak expiratory flow rate from 266 (SD 102) to 406 (83) L·s⁻¹ (p<0.02) following nebulized β₂-agonist in five patients with chronic asthma, there was no significant change in CT lung density (p>0.05).

Our study indicates that at least some patients with chronic, stable asthma develop a reduction in computed tomography lung density, similar to that in patients with emphysema.


Subjects and methods

Subjects

Three groups of patients/subjects were studied: seven healthy volunteers (forced expiratory volume in one second (FEV1) 3.5 (SD 0.34) L), 17 patients with chronic asthma (FEV1 1.98 (0.77) L); and 17 patients with chronic bronchitis and chronic airflow limitation (FEV1 0.97 (0.56) L).
The healthy volunteers, who were recruited from hospital workers were all lifelong nonsmokers, had no historical or clinical evidence of lung disease, and had a normal chest radiograph, and normal values for spirometry, lung volumes and transfer factor of the lung for carbon monoxide (TLC). All patients were recruited consecutively from out-patients clinics, with the exception of five asthmatics who required admission to hospital with an exacerbation of their condition.

All of the asthmatic patients had a history of nonallergic asthma and none had clinical features of bronchopulmonary aspergillosis. All of the asthmatics were lifelong nonsmokers and had a >20% increase in baseline FEV1 in response to nebulized β2-agonist shown within 2 yrs prior to admission. However, when clinically stable, these patients had a degree of chronic irreversible airflow limitation.

The 17 patients with chronic bronchitis were all current or exsmokers with no clinical evidence or family history of asthma. They had all experienced chronic cough and hypersecretion of mucus for 3 months·yr⁻¹, history of asthma. They had all experienced chronic airflow limitation (mean FEV1 32 (SD 13) % pred) for at least two consecutive years. They had a wide range of airways obstruction as measured by FEV1/forced vital capacity (FVC) (table 1) and had less than a 15% improvement in their baseline FEV1 in response to nebulized β2-agonist. Some of these patients had plain chest radiographic evidence of emphysema. However, the degree of emphysema was not assessed on plain radiography, since this relates poorly to the pathological assessment of the disease [12]. None of these patients had evidence of bullous emphysema (intrapulmonary airspaces >1 cm) on visual inspection of their CT scans. Respiratory function was measured within 2 days of the CT scan.

All patients, except those with acute asthma, were studied when they were clinically stable, without an exacerbation of their condition in the preceding month. Five patients with an exacerbation of asthma, who required admission to hospital, had a CT scan and lung function analysis performed prior to discharge. These patients were receiving inhaled bronchodilators and were on oral corticosteroids at this time. Their usual medication, which consisted of inhaled β2-agonists, ipratropium bromide and inhaled steroids, was continued unchanged.

In a different group of five asthmatic patients, CT scan and lung function were measured at the end of an exacerbation, which was severe enough to require hospital admission, and again 6 weeks later when their condition was considered to be clinically stable.

Lung function. FEV1 and vital capacity (VC) were measured using a 7 L dry spirometer (Vitagold Ltd, Maids Morton, Bucks, UK) and lung volumes were measured using the helium dilution technique (P.K. Morgan, UK). Single-breath diffusing capacity was measured by the method of Ogilvie et al. [13] (Automatic Transfer Test, Model A System; P.K. Morgan, Gillingham, UK) with the breathholding time calculated by the modified Jones and Meade [14] technique. In males, normal predicted values were taken from Crapo et al. [15] for FEV1 and VC, Crapo et al. [16] for total lung capacity (TLC) and residual volume (RV), and Cotes et al. [17] for TLC. In females normal predicted values were taken from Hall et al. [18] for FEV1, VC, TLC and RV, and Billiet et al. [19] for TLC.

CT scanning. CT scans were performed on a GE 9000 scanner with a 4 s scan time, at 3 cm intervals from the apex of the lung to the diaphragm using 10 mm collimation. On average, seven slices were obtained from each lung. During the scan, the patient held his/her breath at full inspiration close to TLC. A custom-written computer program was used to outline the lung fields excluding the hilar region, as described previously [11]. A cumulative frequency histogram of CT density numbers in Hounsfield units (HU) was obtained for each percentile within all CT scan cuts. On the Hounsfield scale -1,000 = air; 0 = water; and +1,000 = bone density. Lung density was characterized as the mean or the lowest fifth percentile (L5P) of these cumulative frequency histograms from both lung fields, which had previously been evaluated against measurements of distal airspace size [11]. The system was calibrated daily with a water phantom and any scans containing artifacts were excluded from the analysis.

Statistical analysis

All values are given as mean±sd. Significant differences were calculated using Mann-Whitney U-test for two independent samples or by analysis of variance (ANOVA) when multiple comparisons were made.

Results

The patients with asthma had a wide range of airflow limitation as measured by an FEV1 of 33–105% predicted (table 1). Similarly, a wide range of airflow limitation, FEV1 15–68% pred., was present in the patients with COPD. The patients with COPD had a more severe airflow limitation (mean FEV1 32 (SD 13) % pred) than the patients with asthma (65 (20) % pred; p<0.005).

TLC/alveolar volume (VA) was significantly lower in the patients with COPD (58 (20) % pred) compared with asthmatic subjects (90 (20) % pred; p<0.005). Seven of the 17 patients with asthma had a TLC/VA <80% pred.

The mean value of the L5P of the CT lung density from the cumulative frequency histograms, from all
lung slices (mean L5P) in the 17 asthmatic subjects was -905 (34) HU (range -822 to -956 HU). The patients with COPD had a lower CT density than asthmatic subjects (mean L5P -942 (36) HU, range -906 to -905; p<0.05). However, both asthmatics and patients with COPD had a lower lung CT density than normal subjects (mean L5P -880 (12) HU, range -862 to -898 HU; p<0.02). There was a considerable overlap between the CT lung density in patients with asthma and COPD (fig. 1).

There was no significant correlation between CT lung density (measured as the L5P or mean of the cumulative frequency histograms of CT lung density) and FEV1 and FVC, Tlco/VA and RV/TLC, either when the individual groups were analysed separately or when the data were combined. However, both asthmatics and patients with COPD had a lower CT lung density than normal subjects (mean L5P -880 (12) HU, range -862 to -898 HU; p<0.02). There was a considerable overlap between the CT lung density in patients with asthma and COPD (fig. 1).

The results of CT lung density before and after nebulized β2-agonist are shown in table 2. Although nebulized β2-agonist increased PEFR, CT lung density (L5P) did not change significantly.

In the group of five patients with asthma studied at the end of an exacerbation and 6 weeks thereafter when clinically stable, FEV1 improved significantly (table 3). However, there was no significant change in TLC, RV/TLC ratio, or CT lung density (table 3).

Discussion

This study indicates that some patients with stable asthma, particularly those with a degree of irreversible airflow limitation have values of CT lung density which are similar to patients with historical and functional evidence of chronic bronchitis and emphysema. Since we have previously shown that measurements of CT lung density correlate with morphometric measurements of the size of distal airspaces [11], this may indicate that these patients with chronic asthma have emphysema. Some support for this comes from the fact that a proportion of the asthmatics in this study had a low Tlco/VA, the lung function parameter which correlates best in previous structure/function studies with emphysema [20, 21], and which we have previously shown correlates best with CT lung density in patients with COPD [22].

Table 1. – Characteristics of patients studied

<table>
<thead>
<tr>
<th>Group</th>
<th>Age yrs</th>
<th>FEV1 % pred</th>
<th>TLC % pred</th>
<th>Tlco/VA % pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=7)</td>
<td>42 (32–54)</td>
<td>103 (90–110)</td>
<td>104 (102–106)</td>
<td>96 (92–104)</td>
</tr>
<tr>
<td>COPD (n=17)</td>
<td>63 (55–74)</td>
<td>32 (15–68)</td>
<td>139 (100–211)</td>
<td>58 (36–111)</td>
</tr>
<tr>
<td>Asthma (n=17)</td>
<td>52 (27–74)</td>
<td>65 (33–105)</td>
<td>115 (82–149)</td>
<td>90 (51–118)</td>
</tr>
</tbody>
</table>

Values are presented as mean, and range in parenthesis. FEV1: forced expiratory volume in one second; TLC: total lung capacity; Tlco: transfer factor of the lung for carbon monoxide; VA: alveolar volume; COPD: chronic obstructive pulmonary disease; % pred: percentage of predicted value.

Table 2. – PEFR and CT lung density (L5P) before and after nebulized terbutaline (5 mg) in five patients with stable asthma

<table>
<thead>
<tr>
<th>Time</th>
<th>PEFR L·s⁻¹</th>
<th>CT lung density HU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>266 (102)</td>
<td>-888 (46)</td>
</tr>
<tr>
<td>Post-bronchodilation</td>
<td>406 (83)</td>
<td>-888 (56)</td>
</tr>
</tbody>
</table>

Values are presented as mean, and SD in parenthesis. PEFR: peak expiratory flow rate; CT: computed tomography; HU: Hounsfield units; L5P: lowest fifth percentile.

Table 3. – Respiratory function and CT lung density (L5P) at the end of an exacerbation (T0) and 6 weeks later (T6) in five patients with asthma

<table>
<thead>
<tr>
<th>Time</th>
<th>FEV1 % pred</th>
<th>TLC % pred</th>
<th>RV/TLC %</th>
<th>CT lung density HU</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>70 (22)</td>
<td>125 (36)</td>
<td>42 (4)</td>
<td>-898 (24)</td>
</tr>
<tr>
<td>T6</td>
<td>81 (17)</td>
<td>120 (17)</td>
<td>41 (7)</td>
<td>-896 (260)</td>
</tr>
</tbody>
</table>

Values are presented as mean, and SD in parenthesis. RV: residual volume. For further definitions see legends to tables 1 and 2.

Discussion

This study indicates that some patients with stable asthma, particularly those with a degree of irreversible airflow limitation have values of CT lung density which are similar to patients with historical and functional evidence of chronic bronchitis and emphysema. Since we have previously shown that measurements of CT lung density correlate with morphometric measurements of the size of distal airspaces [11], this may indicate that these patients with chronic asthma have emphysema. Some support for this comes from the fact that a proportion of the asthmatics in this study had a low Tlco/VA, the lung function parameter which correlates best in previous structure/function studies with emphysema [20, 21], and which we have previously shown correlates best with CT lung density in patients with COPD [22].
However, a low CT lung density could result from chronic overinflation, which is difficult to differentiate pathologically from early microscopic emphysema (D. Lamb, personal communication). Some of the present patients with clinically stable asthma had CT lung density values similar to patients who have previously been shown to have macroscopic emphysema pathologically [11]. This may result from the fact that 10 of the 17 asthmatic patients who were studied had a degree of chronic airflow limitation (FEV1 <65% pred) and over-inflation even when clinically stable. Patients with asthma, particularly acute asthma, develop overinflation [23], which may account for the low CT lung density in these patients. Support for this comes from the significant but weak relationship between CT lung density and TLC in the asthmatic patients. However, the weak correlation suggests that overinflation is not the only factor influencing low CT lung density in asthmatic subjects.

In the present study all CT scans were performed in full inspiration, since we have shown that this correlates best with morphometric assessment of emphysema [11]. However, there have been studies suggesting that CT scans performed in full expiration can be advantageous in assessing emphysema more accurately [24, 25]. Furthermore, Newman et al. [26] suggested that a CT scan taken at full expiration can be useful in assessing air-trapping. However, none of these studies compared CT data with pathological assessments of emphysema. Very recently, Gervenois et al. [27] studied 89 patients with COPD and found that expiratory quantitative CT was not as accurate as inspiratory CT scans to quantify pulmonary emphysema.

We have previously shown that CT lung density correlates best with TLC/VA in patients with COPD [22]. However, we were unable to demonstrate a similar significant relationship (r=0.35; p>0.05) in this group of patients with COPD, presumably due to the smaller number of patients studied.

In a previous paper, Kinsella et al. [28] showed that asthmatic patients with a TLC greater than 120% pred showed no evidence of macroscopic emphysema as assessed by CT scanning. Using a visual scoring system, Kodoh et al. [29] found CT evidence of emphysema, but only in smoking asthmatics. Lynch et al. [30] also found mild emphysema in some asthmatic patients, but again most were smokers. However, Paganin et al. [31] showed the presence of emphysema in CT scans in nonsmoking patients with severe asthma. They speculated that the presence of emphysema was not due to parenchymal-destruction disease, but may be related to cicatrical emphysema and to airway remodelling. In a more recent paper, the same group [32] found more irreversible changes, including bronchiectasis, emphysema and peribronchial wall thickening in patients with non-allergic asthma compared with a group of patients with allergic asthma. In the present study the majority of the asthmatic patients had a reduced CT lung density similar to the patients with chronic bronchitis and emphysema. Most of the irreversible changes described by Paganin and co-workers [31, 32] could increase the CT density. In addition, visual inspection of the CT scans in the present patients did not reveal significant bronchiectatic or fibrotic changes. Furthermore, our technique uses CT lung density as a measure of microscopic emphysema or chronic overinflation, which may be indistinguishable by CT scanning.

In order to determine whether an improvement in airflow limitation, which may decrease overinflation, alters CT lung density, we measured CT lung densities in five patients with stable asthma before and after nebulized β2-agonist was administered. Despite the significant improvement in PEFR, CT lung density did not change. Similarly, Gervenois et al. [27] found no significant changes in CT density measurements in a group of asthmatics who underwent allergen provocation testing, with a subsequent decrease in FEV1 of 0.9 L. However, as in our patients, they did not observe any significant changes in TLC following this inhalation. In the present study, we were not able to measure lung volumes accurately by determining the cumulative area × slice thickness for each CT slice, since we undertook scans which were not contiguous and thus measurements of TLC would have been inaccurate.

To test the hypothesis that low CT lung density in asthmatic patients is due to chronic overinflation, CT lung density was studied in five patients at the end of an exacerbation of their asthma and again when the patients were clinically stable 6 weeks later. In spite of an increase in FEV1, CT lung density did not change. However, these patients also showed no change in TLC or RV/TLC, indicating that there was no significant change in lung volumes, at least, as measured by helium dilution, between the end of the exacerbation and clinical stability. Paganin et al. [32] also found, in 10 patients with asthma who underwent CT scan during an exacerbation and 1–2 weeks thereafter, that there was no improvement in visual assessment of emphysema, bronchial wall-thickening or bronchiectasis, although this assessment was quantitative. However, the changes of mucoid impaction, acinar patterns and segmental collapse disappeared. Unfortunately, they did not measure lung volumes in these patients. Measurements in patients with more acute asthma, with repetition when their condition had stabilized, could have shown a change in lung volumes that may have been reflected as a change in CT lung density. However, such a study would be limited by the inability to undertake CT scanning in acutely ill, breathless patients. Moreover, measurement of lung volumes, both by helium dilution and by body plethysmography are potentially erroneous in patients with severe airflow limitation [33]. Radiographic planimetry [34] or contiguous CT slices [35] could have been used to avoid such errors in the measurement of lung volume but would have involved a greater radiation burden for the patients.

This study also shows that, in addition to low lung CT density, patients with chronic asthma develop functional abnormalities similar to those in patients with COPD, such as a reduction in TLC/VA. One other study has also suggested that longstanding chronic asthma results in functional changes which mimic those seen in patients with chronic bronchitis and emphysema [36].

The debate in the literature over the presence of emphysema in patients with chronic asthma [5, 6] remains unresolved. This may relate to differences in techniques for measuring both macroscopic and microscopic emphysema. This question can only be answered when modern
morphometric techniques used to measure the size of distal airspaces produce a normal range of these values, which can then be applied to the lungs of patients dying with chronic asthma.

In summary, our study confirms that low lung computed tomography density, with values similar to those in patients with chronic bronchitis and emphysema, occurs in chronic asthma. This low lung computed tomography density represents microscopic emphysema or chronic overinflation. It is not altered by bronchodilator therapy and is similar when measured at the end of an exacerbation of asthma or at a time of clinical stability.

References