Mechanism of mosaic attenuation of the lungs on computed tomography in induced bronchospasm

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The timing of the CT examinations and their relationship to the metacholine challenge, $FEV_1$ measurements, and oxygen administration are summarized in Fig. 1.

Bronchial challenge. A standard bronchial challenge was performed with methacholine (Sigma Chemical, Poole, Dorset, UK) administered via a nebulizer (Dosimeter MB3, Mefar, Bovezzo, Italy) in increasing doubling concentrations, starting at 0.0625 mg/ml. The subjects were asked to avoid physical exercise and bronchodilator drugs for 24 h before the challenge. A first baseline assessment of $FEV_1$ was performed with a spirometer (Vitalograph, Buckingham, UK) before and after the subject had inhaled five breaths of saline-control. The decrease in $FEV_1$ during the methacholine was monitored after each dose of methacholine until a $40\%$ fall in $FEV_1$ from the postsaline baseline value was achieved. In one patient in group C, the challenge had to be limited to a fall in $FEV_1$ of only $30\%$ because of a low prechallenge $FEV_1$. The log concentration of methacholine, measured in mg/ml, needed to cause a $20\%$ decrease in $FEV_1$ was calculated by linear interpolation of the log dose-response curve. Before the subjects left the department after the second CT examination, their $FEV_1$ had to have returned to within $5\%$ of the presaline baseline. A short acting $\beta$-agonist was administered by a metered dose inhaler if necessary.

CT. Images were obtained with an electron-beam CT (Imatron, San Francisco, CA) with a scan-acquisition time of 200 ms. Scanning and reconstruction parameters were 130 kV, 630 mA, 30-cm field-of-view, 1.5-mm section thickness, $512 \times 512$ matrix size, and high-spatial-frequency reconstruction algorithm. The first CT was performed immediately after the bronchial challenge and consisted of three adjacent sections obtained at the level of the carina (upper zone) and 4 cm above the dome of the right hemidiaphragm (lower zone). The images were obtained at suspended full inspiration, with a 5-mm gap between the three sections obtained at each level. The second CT followed 20 min later (Fig. 1). To obtain comparable sections for the second examination, volume acquisitions centered around the central section of the initial scan in each of the two zones were performed ($n = 7$ slices; covered volume 10.5 mm) at suspended full inspiration. Each CT examination was performed within $\sim$10 min.

Image analysis. Matching sections of the first and the second CT scans were obtained by comparing anatomic landmarks, and each lung was considered separately. The selected image sets were transferred to a workstation (Sun Microsystems, Mountain View, CA). Postprocessing was applied to outline the lungs and remove pulmonary vessels and bronchial walls. This was achieved by thresholding the vessels and bronchi at a value of $-400$ Hounsfield units (HU). To minimize the effects of partial volume averaging, mathematical morphology tools were applied to remove pixels immediately adjacent to thresholded areas (Fig. 2). The lungs were divided into anterior, middle, and posterior regions, each comprising a third of the anterior-posterior diameter of the lung. In both the upper and the lower zones, a set of six density measurements was obtained for each lung and each region by using a circular region of interest (ROI) with a diameter of 10 pixels (6 mm). The ROIs were placed on the images of the first CT in areas judged to be of decreased attenuation (ROI$_{hypodense}$) and areas of increased attenuation (ROI$_{dense}$) of the mosaic pattern (Fig. 2). For the measurements on the second CT images, the ROIs were placed at near-identical sites according to anatomic landmarks. The window setting for selecting the ROIs was $-800/1,000$ (window level/width). The percent density differences [(ROI$_{CT2}$ - ROI$_{CT1}$)/ROI$_{CT1}$] were calculated for ROI$_{hypodense}$ and ROI$_{dense}$.

As a global measurement of density alterations between the first and the second CT, histograms were obtained from the postprocessed images for both lungs in each zone. The

![Fig. 2. Example of CT through lower lung zones of a subject in group B (oxygen via nasal prongs). After postprocessing, both lungs are outlined, and black pixels represent major pulmonary vessels that have been extracted and not taken into account for region of interest (ROI) measurements. ROIs are located in hypoattenuating (1) and dense (2) areas of posterior part of left lung. Mean density values in ROI 1 and ROI 2 were $-910$ and $-856$ Hounsfield units (HU), respectively. On 2nd CT, there was a density increase in ROI 1 and ROI 2 of $+20$ and $+4$ HU, respectively.](http://jap.physiology.org/Downloadedfrom)
The increase in mean density in ROIhypodense on serial scans. Postprocessed images were used to assess the cross-sectional area of the lung tissue excluding pulmonary vessels. The validity of the assumptions of linear regression were confirmed by testing for omitted variables (none identified, P > 0.20 for all analyses) and heteroscedasticity (P > 0.20). P < 0.05 was considered statistically significant. All analyses used percent change from baseline.

RESULTS

The median fall in FEV₁ from the postsaline baseline was 48.1, 45.02, and 49.42% in groups A, B, and C, respectively (Table 1). In all subjects, FEV₁ spontaneously recovered after the challenge. The median percentage of FEV₁ recovery was comparable in all groups (Table 1). The recovery of FEV₁ was not related to density changes in ROIhypodense (P = 0.07). As shown in Figs. 3 and 4, these trends were almost entirely due to increases between groups A and B, with little further increase in group C; on the basis of this finding, data from groups B and C were combined in subsequent bivariate analyses. In the lower zone, histogrammean increased most in group C and more in group B than in group A, with the difference between groups A and C reaching statistical significance (P = 0.03) (Table 3). Correspondingly, histograms of the frequency distribution of lung attenuation in the lower zone were shifted to the right for groups B and C, but there was no overt density increase in group A (Fig. 5, A–C).

When the density change peculiar to ROIhypodense was calculated (ROIhypodense-corrected), it was higher in group B than in group A (P < 0.002), and in group C than in group A (P < 0.02). In the lower zone, density increased in group C and more in group B than in group A (P < 0.005); upper zone changes were not statistically significant. By contrast, density change in ROIdense did not differ significantly among the three groups.

Table 1. Alterations in FEV₁ after methacholine challenge

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Group A Median, %</th>
<th>Range, %</th>
<th>Group B Median, %</th>
<th>Range, %</th>
<th>Group C Median, %</th>
<th>Range, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prechallenge</td>
<td></td>
<td>Postchallenge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>90.25</td>
<td>71.55–97.00</td>
<td>96.03</td>
<td>78.52–127.2</td>
<td>85.85</td>
<td>55.85–100.3</td>
</tr>
<tr>
<td>10</td>
<td>51.90</td>
<td>46.70–58.40</td>
<td>54.98</td>
<td>40.00–60.10</td>
<td>50.58</td>
<td>43.94–63.75</td>
</tr>
<tr>
<td>30</td>
<td>54.14</td>
<td>48.90–72.20</td>
<td>56.20</td>
<td>40.81–82.10</td>
<td>60.01</td>
<td>41.40–68.92</td>
</tr>
<tr>
<td>40</td>
<td>68.34</td>
<td>62.61–77.00</td>
<td>64.95</td>
<td>49.31–90.60</td>
<td>67.00</td>
<td>43.63–77.52</td>
</tr>
</tbody>
</table>

Table 2) but not in upper zone ROIhypodense (P = 0.29). As shown in Figs. 3 and 4, these trends were almost entirely due to increases between groups A and B, with little further increase in group C; on the basis of this finding, data from groups B and C were combined in subsequent bivariate analyses. In the lower zone, histogrammean increased most in group C and more in group B than in group A, with the difference between groups A and C reaching statistical significance (P = 0.03) (Table 3). Correspondingly, histograms of the frequency distribution of lung attenuation in the lower zone were shifted to the right for groups B and C, but there was no overt density increase in group A (Fig. 5, A–C).

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RESULTS

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The increase in mean density in ROIhypodense on serial CT was greatest in group C and greater in group B than in group A (P = 0.04) (Fig. 3); this finding remained significant in lower zone ROIhypodense (P = 0.03) (Fig. 4,
The cross-sectional area of the lung decreased most in group C (upper zone: median −13%; range −15.40 to −0.89%; lower zone: median −13.4%; range −16.66 to −1.95%), and more in group B (upper zone: median −4.2%; range −13.28 to 3.36%; lower zone: median −1.8%; range −20.66 to 40.93%) than in group A (upper zone: 2.2%; range −23.94 to 13.88%; lower zone: median 2.7%; range −19.25 to 35.08%). Change in cross-sectional area correlated strongly with change in density in ROI hypodense (combined zones R5 = −0.71, P < 0.0005) (Fig. 6) (upper zone R5 = −0.61, P < 0.005; lower zone R5 = −0.77, P < 0.00085) (Fig. 7), with change in histogram mean (combined zones R5 = −0.70, P < 0.0005; upper zone R5 = −0.58, P < 0.005; lower zone R5 = −0.89, P < 0.00005) and with change in density in ROI dense (lower zone R5 = −0.76, P = 0.0005).

On bivariate analysis, density increase in ROI hypodense, if both upper and lower zone were taken together, was positively related to decrease in cross-sectional area (P < 0.0005) and to increasing inspired oxygen dosage (P = 0.01), equation R² = 0.71. Density increase in lower zone ROI hypodense was also positively and independently related to both decrease in cross-sectional area (P < 0.005) and increasing inspired oxygen dosage (P < 0.005), equation R² = 0.77. Furthermore, increasing oxygen concentration was the sole determinant of density increase in ROI hypodense-corrected both in upper and lower zone taken together (P = 0.02) and in lower zone regarded separately (P < 0.001).

**DISCUSSION**

High-resolution CT has recently been used to elucidate several pathophysiological phenomena in the lungs (4, 17, 18, 24, 42), particularly the response of the macroscopic airways to various bronchoactive stimuli (12, 12a, 29). The striking heterogeneity of the constrictive airway reaction has been attributed to local mechanisms in the airways and is largely independent of the route of administration of histamine (5). The lung density alterations visible on CT images after experimentally induced bronchoconstriction correspond to the mosaic pattern of lung attenuation observable in other airway diseases, such as acute spontaneous asthma, constrictive bronchitis, bronchiectasis, and hypersensitivity pneumonitis (14–16, 26). There appears to be a good correlation between recovery of FEV1 and regression of the mosaic pattern on expiratory CT images after drug-induced bronchodilation; the underlying cause of the decreased attenuation on expiratory CT images has been ascribed to air trapping (10), implying that an increased residual volume at end expiration causes compression of alveolar capillaries and thus a reduction in perfusion, as well as an increased proportion of gas within each voxel. However, it has not been clear whether the same mosaic pattern on inspiratory CT images is due to hypoxic pulmonary vasoconstriction (41) or air trapping, causing mechanical pressure on blood vessels (36). The latter has been regarded as the predominant mechanism of the hypertransradiant lung caused by central airways obstruction (13).

We have shown that for all regional and global measurements, with the exception of ROI dense, a significant density increase occurs in subjects breathing oxygen. Confirmation of the effect of oxygen was provided by bivariate analysis, which showed an independent relationship to the density measurements in ROI hypodense. Furthermore, oxygen concentration was the sole determinant for ROI hypodense-corrected. Thus hypoxic pulmonary vasoconstriction contributes to the regional hypodense areas of the mosaic pattern of lung attenuation on inspiratory CT images.

**Table 2. Density differences within hypattenuating areas (2nd CT value minus 1st CT value)**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median, HU</td>
<td>Range, HU</td>
<td>Median, HU</td>
</tr>
<tr>
<td>Upper zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>1.25</td>
<td>−3.0−19.5</td>
<td>12.8</td>
</tr>
<tr>
<td>Middle</td>
<td>0.75</td>
<td>−13.5−19.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Posterior</td>
<td>3.50</td>
<td>−9.0−24.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Average</td>
<td>0.75</td>
<td>−5.6−20.6</td>
<td>10.0</td>
</tr>
<tr>
<td>Lower zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>−1.00</td>
<td>−12.0−22.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Middle</td>
<td>−2.30</td>
<td>−12.5−17.0</td>
<td>16.0†</td>
</tr>
<tr>
<td>Posterior</td>
<td>−2.30</td>
<td>−29.0−10.5</td>
<td>14.7†</td>
</tr>
<tr>
<td>Average</td>
<td>−3.60</td>
<td>−18.0−16.5</td>
<td>14.3</td>
</tr>
</tbody>
</table>

CT, computed tomography; HU, Hounsfield units; average, mean of measurements in anterior, middle, and posterior regions. Different from group A: *P < 0.05; †P < 0.02.
In long-standing, irreversible airway disease, hypoxic vasoconstriction is likely to be fixed due to vascular remodeling (35); thus a model of induced acute airway obstruction is best suited to investigate the influence of hypoxic pulmonary vasoconstriction on the mosaic attenuation pattern because of its reversibility. Furthermore, in irreversible small airway disease caused by constrictive obliterative bronchiolitis, increased total lung capacity can cause a global decrease in lung density (16).

The effect of oxygen administration on hypoxic pulmonary vasoconstriction was most pronounced in the dependent parts of the lungs. This is in accordance with previous functional CT studies that have shown that, after a methacholine challenge, the attenuation shift toward lower density values is most marked in the dependent lung regions (12, 24, 27). The same applies to the attenuation decrease after a hypoxic challenge, which has been reported to be significant only in the middle and posterior parts of the lungs (18). In addition to this gradient effect, there was a greater density increase in the lower zones compared with the upper zones. It seems probable that this phenomenon also reflects the gravity-dependent increased perfusion of the more dependent lung: the greater vertical distance in the lower zones (in the recumbent position) results in relatively more perfusion and a potentially greater vasoconstrictor response to the methacholine-induced bronchoconstriction.

Because respiratory gating was not used in our study, a possible influence of different degrees of inspiration on the density measurements has to be considered, even with cooperative volunteers (19). Cross-sectional area of the lungs decreased during the second CT examination in subjects breathing oxygen via nasal cannulas; this was even more pronounced in subjects who were administered oxygen via face masks. This phenomenon was also reflected by the curves representing the frequency distribution of lung attenuation and affected predominantly the lower zone of the lungs (Fig. 5, A-C). The changes in cross-sectional area correlated with regional (ROI\textsubscript{hypodense} and ROI\textsubscript{dense}) and global (histogram mean) density alterations. However, because the density increase within hypoattenuating areas of the mosaic pattern was more pronounced than the overall shift of the histograms toward higher-density values, there was no correlation between the decrease in the cross-sectional area of the lungs and ROI\textsubscript{hypodense}-corrected. Therefore, the decrease in cross-sectional area had an independent effect on the global lung density measurements and on the hypoattenuating and dense areas of the mosaic pattern and was distinct from the effect of the oxygen administration.

Table 3. Mean values of histogram curves and their differences (2nd CT value minus 1st CT value)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st CT</td>
<td>-883.53 ± 7.64</td>
<td>-891.69 ± 15.13</td>
<td>-891.05 ± 6.71</td>
</tr>
<tr>
<td>2nd CT</td>
<td>-879.51 ± 9.85</td>
<td>-886.38 ± 15.85</td>
<td>-879.64 ± 12.87</td>
</tr>
<tr>
<td>Change</td>
<td>+4.02 ± 10.2</td>
<td>+5.31 ± 7.23</td>
<td>+11.41 ± 7.94</td>
</tr>
<tr>
<td>Lower zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st CT</td>
<td>-883.70 ± 11.59</td>
<td>-897.25 ± 17.99</td>
<td>-891.98 ± 10.94</td>
</tr>
<tr>
<td>2nd CT</td>
<td>-884.84 ± 16.81</td>
<td>-892.16 ± 12.10</td>
<td>-882.94 ± 16.33</td>
</tr>
<tr>
<td>Change</td>
<td>-1.14 ± 11.2</td>
<td>+5.09 ± 10.1</td>
<td>+9.04 ± 7.02*</td>
</tr>
</tbody>
</table>

Values are means ± SD in HU. Different from group A, *P < 0.03.

Fig. 5: A: average frequency distributions of lung attenuation (1st and 2nd CT; solid and dashed lines, respectively) in lower lung zones of subjects breathing room air after methacholine challenge. B: average frequency distribution of lung attenuation (1st and 2nd CT) in lower lung zones of subjects supplied with oxygen via nasal prongs after methacholine challenge. C: average frequency distributions of lung attenuation (1st and 2nd CT) in lower lung zones of subjects supplied with oxygen via face masks after methacholine challenge.
The predominance of this effect in the lower lung zones is in keeping with the previously reported observation that changes in lung volume affect the density of the lung in dependent regions more than in nondependent parts of the lungs (38).

In our study, the mode of administration of oxygen seemed to be related to the degree of decrease in cross-sectional area of the lungs. This might be explainable by the method of oxygen delivery causing an alteration in the breathing pattern or total lung capacity of the subjects. Although a significant increase in total lung capacity has been reported in acute spontaneous asthma, this does not occur in induced asthma attacks (3, 22, 30). Similar effects of oxygen have been described (6, 9, 37). These changes have been attributed to a decrease in the hypoxic drive, resulting in a decrease in minute ventilation, thus causing a delay of ventilatory muscle fatigue and an altered respiratory muscle recruitment pattern (6, 9, 37). Interactions between changes in the breathing pattern and the degree of inspiration might therefore be a further explanation.

A potential source of measurement error relates to the positioning of the ROIs on the images of the first and second CTs. Exactly comparable positioning was not possible because the ROIs could not be automatically maintained between scans. The influence of major pulmonary vessels on the density measurement within ROIs was minimized by applying a threshold postprocessing, which eliminated pixels with density values less than -400 HU and pixels immediately next to them. Thus the image postprocessing allowed a greater choice for the positioning of ROI measurements. The usefulness of an automatic ROI maintenance program on nonpostprocessed images is limited because larger anatomic landmarks (pulmonary vessels) are relatively fixed, whereas smaller vessels are more liable to appear inconsistently in ROIs on serial CT images (18, 24).

Oxygen administration is a potent method of reversing hypoxia in acute asthmatic attacks. The intra-alveolar concentration of oxygen achieved by the methods of oxygen administration used in this study is unknown because there is no noninvasive technique for assessing the regional alveolar oxygen concentration. The oxygen concentration supplied by low-flow devices, such as nasal prongs, is variable and depends mainly on minute ventilation. By applying an oxygen flow rate of 5 l/min through nasal prongs, a 10–15% increase in the oxygen concentration in the inhaled air is usually assumed (25). With simple oxygen masks without rebreathing bags or entrainment ports, oxygen concentrations as high as 55–65% can be achieved at a flow rate of 12 l/min (25). Hypoventilated areas distal to severely constricted bronchi or bronchioles are usually supplied by collateral ventilation. An increase in the end-expiratory volume has been shown to reduce the resistance of the collateral ventilatory system in normal humans (8). After methacholine challenge, a reverse effect has been described in dogs: methacholine causes constriction of the collateral pathways, but the time constant for the collateral ventilation does not change (34). The lack of a significant intrapulmonary shunt is a further indication of the efficacy of the collateral ventilatory system, but the time constant for the collateral ventilation does not change (32, 40). Given the duration and flow rates of the oxygen supply in the present study, and the effectiveness of the collateral ventilatory system, it seems reasonable to assume that sufficient intra-alveolar oxygen concentration was achieved even in severely bronchoconstricted regions of the lungs.

The basic mechanism of hypoxic pulmonary vasoconstriction has been studied in cats, and it is thought to be the key physiological mechanism for maintaining ventilation-perfusion homogeneity in underventilated parts of the lung to minimize arterial hypoxia (11). The hypoxic vasoconstrictive response occurs within 1–2 min and is reversible in <1 min after alveolar hypoxia has been relieved (28). Therefore, if a sufficient intra-alveolar oxygen concentration is achieved, the vascular response should be detectable almost immediately in induced acute airway obstruction.
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In an earlier study, after an initial drop in FEV₁ after methacholine, there was a plateau with a mean duration of 74.6 ± 53.7 (SD) min and a consecutive recovery phase of 56.7 ± 38.3 min (7). In our study, a plateau phase was not as obvious, possibly because of the relatively long intervals between FEV₁ measurements. However, severe airflow obstruction was present at the end of the study protocol and, equally importantly, there was no significant difference in the recovery rate among the three groups. In addition, the recovery of FEV₁ showed no correlation with the measurable density increase. This is in agreement with previous studies, in which discrepancies between FEV₁ measurements and parameters of gas exchange and peripheral resistance in asthmatic subjects have been demonstrated (31, 39, 40). In these studies, recovery of gas exchange did not parallel recovery of FEV₁. Furthermore, the peripheral resistance remained elevated despite a return to normal FEV₁ values after an acute asthmatic attack (31, 39). Thus the mosaic pattern of lung attenuation most likely reflects abnormalities of the smaller peripheral airways.

In summary, we have shown that hypoxic pulmonary vasoconstriction is a major determinant of the hypodense areas of the mosaic pattern of lung attenuation on CT in acute airway obstruction.

We are grateful to Professor Neil B. Pride for advice; to Jennifer McGrath and Sarah Aikman of the Clinical Studies Unit, National Heart and Lung Institute, Imperial College, who performed the methacholine challenges, for assistance; and to Wendy Jordan for help with CT in acute airway obstruction.

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