The High Resolution Computed Tomography in Assessment of Patients with Emphysema Following Smoking Cessation

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Abstract

The purpose of our study was to evaluate the short-term effect of changes in smoking cessation on subjects with chest high resolution computed tomography (HRCT)-diagnosed emphysema, both cross-sectionally and longitudinally. All patients participated in 3 months smoking cessation program. A detailed clinical history was taken and physical examination performed. We performed serum study, lung function testing and HRCT scanning to assess emphysema. After participation in the program, there was a significant increment in body mass index (0.88 kg/m², p < 0.001). There was a significant decline in forced expiratory volume in one second (3.0 % (33 ml), p < 0.001), but smaller than decline in smokers. There was also a significant decline in C-reactive protein (0.40 mg/L, p < 0.001) & St. George's Respiratory Questionnaire (21, p < 0.001). In CT image, there were significant decreases in mean lung density and the attenuation value separating the least 15% pixels (7.7 HU, p < 0.001), but a significant increase in the percentage of the relative area of the lungs with attenuation values < -950 Hounsfield unit (1.9%, p < 0.001). There were significant declines in smoking, modified Medical Research Council scale, Age-Dyspnea-Obstruction (ADO) index, Dyspnea-Obstruction-Smoking-Exacerbation (DOSE) index (all p < 0.001), and exacerbation (p < 0.01), but a significant increase in emphysema severity (p < 0.05). This study shows the possible important change of HRCT in patients with emphysema following smoking cessation. (J Intern Med Taiwan 2015; 26: 107-114)

Key Words: Emphysema; High resolution computed tomography; Mean lung density; Percentile; Relative area; Smoking cessation

Introduction

The major advantage of high resolution computed tomography (HRCT) in pulmonary emphysema is that in addition to providing data concerning overall lung destruction, it also identifies the specific locations in the lung where the alveolar surface has been destroyed. Accurate diagnosis and quantification of pulmonary emphysema during life is important to understand the natural history of the disease, to assess the extent of the disease, and to evaluate and follow-up therapeutic interventions.
Our & other studies have addressed the capability of CT to accurately quantify the extent and severity of pulmonary emphysema. However, the effect of smoking cessation on lung density has not yet been fully investigated, and this may play a role in the evaluation of the severity and progression of lung diseases such as emphysema.

Chronic obstructive pulmonary disease (COPD) is characterized by increased inflammatory cells in the airway and parenchyma, increased expression of lung cytokines, and increased extracellular matrix components. Tobacco smoking is the most important risk factor for developing COPD. Cessation of tobacco smoking is the only intervention in COPD that slows the accelerated decline in FEV₁. The effect of smoking cessation on the underlying inflammation present in COPD patients has been reported a clear reduction in inflammatory biomarkers in both blood and bronchial fluids. Most studies to date have focused on pulmonary function tests, blood samples and bronchial fluids, and little is known about the short-term changes in morphology that occur in relation to changes in smoking cessation. The purpose of our study was to evaluate the short-term effect of changes in smoking cessation on subjects with chest CT scan-diagnosed emphysema, both cross-sectionally and longitudinally, using repeated CT scans.

Methods

Subjects

We recruited patients, who had stable symptoms (without dyspnea or dyspnea under control) of COPD at outpatient department. Patients were excluded if they had a history of chronic bronchitis, bronchiolitis, asthma, bronchiectasis, tuberculosis, or other concomitant respiratory diseases. All smokers had an FEV₁/FVC of less than 70%, and HRCT revealed emphysematous change (low attenuation subjectively or HU < -950 objectively). The study was approved by the Hospital Ethics Review Board. Patients were prospectively recruited for the purpose of the study and gave their written informed consent prior to participation.

Clinical variables

A detailed clinical history was taken and physical examination performed. Lung function testing consisted of spirometry by spirometer (CHEST-GRAPH HI – 101; Chest MI Inc, Tokyo, Japan), carried out according to the ATS guidelines. The degree of dyspnea was checked with the use of the modified Medical Research Council (MMRC) dyspnea scale, and the scores on the MMRC dyspnea scale were classified as 0-1, 2, 3 and 4. The ADO index includes Age, Dyspnea, and airflow Obstruction and does not require 6-minute walk distance (6MWD), which may facilitate its use in primary care settings. The DOSE index, another attempt to create a multicomponent assessment index of COPD severity, includes symptoms (MMRC Dyspnea scale), airflow Obstruction (FEV₁), Smoking status (current vs. former) and, importantly, previous Exacerbation frequency per year. The serum C-reactive protein (CRP) was measured using nephelometry in accordance with recommendations from Centers for Disease Control and Prevention and the American Heart Association. Health-related quality of life was assessed using the validated Chinese version of the St. George's Respiratory Questionnaire (SGRQ). The SGRQ is a self-administered, disease-specific questionnaire. Scores range from 100 (worst possible health status) to 0 (best possible health status). Based on clinical assessment, all subjects were enrolled according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. None of the patients was atopic and none showed significant bronchodilator reversibility (≥12% of baseline FEV₁ and > 200 ml).

Imaging variables

HRCT scanning was used for the evaluation
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of emphysema and scans (Somatom Sensation 16 scanner, Siemens, Erlangen, Germany) were performed on full inspiration at 6 mm intervals with a collimation (slice thickness) of 1 mm. The scanner was subject to a weekly quality assessment with a phantom check including uniformity, linearity, and noise. In addition there was a 3 monthly engineering check of spatial and contrast resolution and an annual medical physics check. Scanning voltage was 120 kV and current was 120 mA. Hard copy images were photographed at a window level of –600 Hounsfield units (HU) and a window width of 1600 HU, as appropriate for viewing lung parenchyma. The scans were evaluated for the presence of emphysema both qualitatively by the radiologists independently of the remaining research and quantitatively by a computerized portable and expandable software (Osiris 4.19, University Hospital of Geneva, Geneva, Switzerland) for interactive display and manipulation of medical images from different imaging modalities. After data is processed through Microsoft® Office Excel 2007, three major lung density parameters were measured. Both lungs were divided into six areas comprising the upper, middle, and lower lung fields; an upper section was obtained 1 cm above the superior margin of the aortic arch, a middle section was taken at 1 cm below the carina, and a lower section was taken approximately 3 cm above the top of the diaphragm19. The severity of emphysema was scored as 0 points, no emphysematous lesions; 1 point, occupying less than 25% of the entire lung field; 2 points, occupying 25% to less than 50% of the entire lung field; 3 points, occupying 50% to less than 75% of the entire lung field; 4 points, occupying more than 75% of the entire lung field20. Mild emphysema was defined as a total score less than 8 points, moderate emphysema was defined as a total score 8-16 points, and severe emphysema was defined as a total score more than 16 points. Mean lung density (MLD) is the mean attenuation value of all pixels excluding the mediastinum and trachea. The 15th percentile (PERC15) is defined as the threshold value for which 15 percent of all pixels have a lower density. The relative area 950 (RA950) of low attenuation has been defined as the percentage of pixels within the lungs with a density lower than a predefined threshold (-950 HU). Histogram analysis was calculated from computerized data also.

Smoking cessation program

The smoking cessation program consisted of an intensive group-orientated course for 3 months, followed by 9 meetings throughout the rest of the one year. If necessary, nicotine replacements were administered during the first 3 months. A quitter was defined as someone who refrained from smoking for a minimum of 1 year, monitored by questionnaire.

Statistical analysis

Analysis of the data was done using Microsoft® Office Excel 2007 (Microsoft, Santa Rosa, CA, 2007) and a Statistical Package SPSS18 (SPSS, Chicago, IL, 2009) using a personal computer. The Student t test was applied to assess differences in continuous variables, and the Chi-Square test was performed to assess differences in categorical variables. A p value <0.05 was considered to be statistically significant. Continuous variables were expressed as mean ± SD unless otherwise specified.

Results

Cross-sectional analysis of baseline scans

The final analysis was based on data from 45 patients. The average age was 67 ± 9 years, and 71% (n = 32) were men. Mean height was 162 ± 7 cm, and weight was 56 ± 8 kg. The characteristics of the 45 patients were summarized in Table 1, and we measure the HRCT from emphysema patients subjectively and objectively by the mentioned variables. They were moderate impaired health-related quality of life (SGRQ was 52 ± 13), moderate obstructive ventilatory impaired (FEV1
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was 56 ± 15% predicted (1090 ± 292 ml), FVC was 64 ± 15% predicted (1879 ± 440 ml), FEV₁/FVC was 58 ± 10%, normal weighted (BMI was 21.3 ± 2.3 kg/m²), mild inflamed (CRP was 4.1 ± 1.2 mg/L), heavy smoked (55 ± 17 pack-year), moderate emphysematous (MLD was -879 ± 23 HU, PERC15 was -956 ± 24 HU, and RA950 was 17 ± 6%), moderate COPD severity, few exacerbated, mild to moderate dyspneic, mild to moderate risky for poor prognosis, and moderate emphysematous imaged.

Table 1. The characteristics of the 45 patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67 ± 9 (50 - 84)</td>
</tr>
<tr>
<td>FEV₁, %</td>
<td>56 ± 15 (26 - 87)</td>
</tr>
<tr>
<td>FEV₁, ml</td>
<td>1090 ± 292 (506 - 1694)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.3 ± 2.3 (15.6 - 25.5)</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>4.1 ± 1.2 (2.1 - 6.8)</td>
</tr>
<tr>
<td>SGRQ</td>
<td>52 ± 13 (27 - 80)</td>
</tr>
<tr>
<td>MLD, HU</td>
<td>-879 ± 23 (-920 - -840)</td>
</tr>
<tr>
<td>PERC15, HU</td>
<td>-956 ± 24 (-999 - -912)</td>
</tr>
<tr>
<td>RA950, %</td>
<td>17 ± 6 (6 - 27)</td>
</tr>
<tr>
<td>Smoking, pack-year</td>
<td>55 ± 17 (30 - 100)</td>
</tr>
<tr>
<td>Exacerbation, 0/1/2</td>
<td>9(20)/24(53)/12(27)</td>
</tr>
<tr>
<td>MMRC scale, 0/1/2/3</td>
<td>4(9)/13(29)/13(29)/15(33)</td>
</tr>
<tr>
<td>ADO index, 1/2/3/4/5/6/7</td>
<td>1(2)/11(24)/8(18)/9(20)/5(11)/9(20)/2(4)</td>
</tr>
<tr>
<td>DOSE index, 1/2/3/4/5</td>
<td>16(35)/10(22)/6(13)/4(9)/9(20)</td>
</tr>
<tr>
<td>COPD severity, mild/moderate/severe/very severe</td>
<td>5(11)/26(58)/14(31)/0(0)</td>
</tr>
<tr>
<td>Emphysema severity, mild/moderate/severe</td>
<td>11(24)/19(42)/15(33)</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in one second; BMI = body mass index; CRP = C-reactive protein; SGRQ = St. George’s Respiratory Questionnaire; MLD = mean lung density; HU = Hounsfield unit; PERC15 = the 15th percentile; RA950 = the relative area 950; MMRC = Modified Medical Research Council; ADO index including age, dyspnea, and airflow obstruction (from 0 to 10 points); DOSE index including dyspnea, airflow obstruction, smoking status, and previous exacerbation frequency per year (from 0 to 8 points); COPD = chronic obstructive pulmonary disease. Continuous variables were shown as mean ± SD (range). Categorical variables were shown as number (percentage).

Table 2. The change of continuous variables of the patients following smoking cessation for one year

<table>
<thead>
<tr>
<th>Variables</th>
<th>change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, % (ml)</td>
<td>-3.0 ± 0.8 (-33 ± 9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.88 ± 0.15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>-0.40 ± 0.07</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SGRQ</td>
<td>-21 ± 6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MLD, HU</td>
<td>-7.7 ± 2.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PERC15, HU</td>
<td>-7.7 ± 2.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RA950, %</td>
<td>1.9 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in one second; BMI = body mass index; CRP = C-reactive protein; SGRQ = St. George’s Respiratory Questionnaire; MLD = mean lung density; HU = Hounsfield unit; PERC15 = the 15th percentile; RA950 = the relative area 950. Continuous variables were shown as mean ± SD.
Longitudinal analysis of baseline and follow-up scans

Table 2 showed the change of continuous variables of the patients following smoking cessation for one year. After participation in the program, there was a significant increment in BMI (0.88 kg/m², p < 0.001). There was a significant decline in FEV₁ (3.0% (33 ml), p < 0.001), but smaller than decline in smokers. There was also a significant decline in CRP (0.40 mg/L, p < 0.001) & SGRQ (21, p < 0.001). For image, there were significant decreases in MLD and PER15 (7.7 HU, p < 0.001), but a significant increase in RA950 (1.9%, p < 0.001). Table 3 showed the change of categorical variables of the patients following rehabilitation for one year. There were significant declines in smoking, MMRC scale, ADO index, DOES index (all p < 0.001), and exacerbation (p < 0.01), but a significant increase in emphysema severity (p < 0.05).

Discussion

This is the clinical study to assess whether the HRCT variables are as good as other known clinical variables in grading emphysema patients following smoking cessation. The present results showed that our emphysema patients was moderate emphysematous and MLD was -879 ± 23 HU, PERC15 was -956 ± 24 HU, & RA950 was 17 ± 6%, as shown in Table 1. Besides, all imaging variables in emphysema patients following smoking cessation were potentially useful like other known clinical variables, as shown in Table 2 and Table 3. There were significant decreases in MLD and PER15 (7.7 HU, p < 0.001), but a significant increase in RA950 (1.9%, p < 0.001) and emphysema severity (p < 0.05).

The ultimate goal of smoking cessation programs is to assist smokers in quitting smoking and remaining smoke free. Smoking cessation is the only convincing intervention that has reduced the rate of decline of FEV₁ in patients with COPD, and smoking cessation needs to be undertaken early for maximal benefit. Smoking cessation is followed by changes in food preferences and increased caloric intake, possibly mediated by dopaminergic mechanisms, and this might contribute to weight gain with increased BMI. Some studies have showed a

<table>
<thead>
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<th>Variables</th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no/yes</td>
<td>0/45</td>
<td>45/0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1/2</td>
<td>9/24/12</td>
<td>20/15/10</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>MMRC scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1/2/3</td>
<td>4/13/13/15</td>
<td>15/8/10/12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ADO index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1/2/3/4/5/6/7</td>
<td>0/1/11/8/9/5/9/2</td>
<td>1/11/8/9/5/9/1/1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DOES index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1/2/3/4/5</td>
<td>0/16/10/6/4/9</td>
<td>12/11/5/5/4/8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Emphysema severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild/moderate/severe</td>
<td>11/19/15</td>
<td>5/22/18</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

MMRC = Modified Medical Research Council; ADO index including age, dyspnea, and airflow obstruction (from 0 to 10 points); DOES index including dyspnea, airflow obstruction, smoking status, and previous exacerbation frequency per year (from 0 to 8 points); COPD = chronic obstructive pulmonary disease. Categorical variables are shown as number.
decline in inflammatory biomarker levels after quitting smoking\textsuperscript{25-26}. Our study showed a significant reduction in serum CRP levels following quitting smoking. Smoking cessation was associated with statistical and clinically relevant improvements in SGRQ in our and other studies\textsuperscript{27}. This finding could be used as a motivational tool for smokers with COPD, and may persuade more reluctant smokers to quit, as they should expect a noticeable improvement in quality of life. Our and other studies showed smoking cessation resulted in fewer symptoms including dyspnea such as MMRC\textsuperscript{28}, and it was associated with less hyperreponsiveness and a greater increase in bronchodilator response\textsuperscript{29}. Smoking cessation may be accompanied by other healthy behaviors, such as improved adherence to medical therapy or curtailing bad habit that may reduce the risk of exacerbations.

The accumulation of soot and tar in the lungs (anthracosis) due to smoking may explain the higher lung density among current smokers\textsuperscript{30}. The accumulation of foreign material provokes inflammation, and the presence of inflammatory cells in the lung contributes to the higher density. Previous studies have shown that inflammation is present in active smokers\textsuperscript{31-32}. Smoking cessation reduces PERC15 resulting in an increasing number of RA\textsuperscript{950}. A study has shown that after smoking cessation the lung probably undergoes a cleansing process that inflammation gradually diminish\textsuperscript{33}. Previous study has shown decreased inflammatory response after smoking cessation\textsuperscript{34}. Besides, the other factors (such as irreversible emphysematous change, insufficient smoking cessation period, insufficient study period) should be considered also. So CT like FEV\textsubscript{1} could show decreased inflammatory response after smoking cessation. Smoking induces emphysema and alveolar destruction with loss of lung density, so long-term smoking is associated with decreasing lung density\textsuperscript{35}. These opposite short and long-term effects of smoking should be taken into consideration when using CT lung density as an outcome measure, where the presence of areas of low lung density, referred to as RA\textsuperscript{950}, is the main CT characteristic of emphysema, and is commonly used as a marker for emphysema\textsuperscript{36-37}.

Our study has some other limitations. First, there was no control group. Second, it took time and introduced errors to perform automatic lung parenchyma segmentation manually on a slice-by-slice basis as well as to calculate the variables related to the severity of the pulmonary emphysema component. Third, we did not have any biological confirmation of smoking status such as with cotinine or carbon monoxide measurements. Fourth, we did not consider the influence of comorbidities or medication. Fifth, our sample size was small. Finally, the study lacked histopathologic corroboration. For these reasons, our findings may not be applicable to all patients with COPD, and larger scale studies that adjust for these limits are needed to investigate the effects.

In the future, further follow-up of our patients could be of interest, but these data are not yet available. However, follow up studies are planned, and these may provide further insight into the effect of smoking cessation on lung density assessed by CT. This study shows the possible important change of HRCT in patients with emphysema following smoking cessation.

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References

肺气肿患者戒菸後的高解析度電腦斷層掃描評估

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摘 要

本研究的目的是評估胸部高解析度電腦斷層掃描 (HRCT)-診斷肺氣腫受試者戒菸後的
短期效應變化，無論是橫斷面和縱斷面，重複使用HRCT掃描，進行詳細臨床病史和體格検
查。我們進行血清研究，肺功能測試和HRCT掃描，以評估肺氣腫。所有患者參加為期3月
戒菸計畫。參與戒菸之後，身體質量指數顯著增加 (0.88 千克/平方米，P <0.001)。第一秒用
力呼氣容積顯著下降 (3.0% (33ml)，P <0.001)，但小於抽菸者的下降。還有C反應蛋白顯著
下降 (0.40 毫克/ L，P<0.001)及肺炎呼吸困難顯著下降 (21，P <0.001)。影像方面，平均肺
密度和衰減值分開至少15%的像素顯著下降 (7.7 HU，P <0.001)，但衰減值百分比<= -950 HU
單位的肺部的相對面積顯著增加 (1.9%，P <0.001)。吸煙，modified Medical Research Council
scale，ADO指標，DOSE指標 (P 均 <0.001)，和急性發作顯著下降 (P <0.01)，但肺氣腫的嚴重
程度顯著增加 (P <0.05)。本研究顯示肺氣腫患者戒菸後的高解析度電腦斷層掃描評估的可能
重要的變化。