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Quantitative evaluation by high resolution computed tomography (HRCT) of patients with asthma and emphysema

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Abstract : Background: Assessment of low attenuation areas and lung densitometry on high resolution computed tomography (HRCT) have been reported in studies of patients with chronic obstructive pulmonary disease.

Objective : The purpose of this study was to examine if HRCT could separate asthmatic patients from normal control subjects and patients with emphysema.

Methods : Subjects were divided into three groups : 24 patients with bronchial asthma, 23 patients with pulmonary emphysema and 15 normal controls. HRCT scans of the lung were performed at three different levels at both end inspiration and expiration in all patients and control subjects.

Results : The mean CT number of three slices was significantly lower in asthmatic subjects compared with normal individuals at both end inspiration ($p < 0.05$) and expiration ($p < 0.01$). The relative area of the lung with an attenuation value lower than -950 HU (%LAA) for three slices was significantly higher in asthmatic subjects than in normal individuals at end inspiration ($p < 0.05$), but there was no significant difference at end expiration. The mean CT number and %LAA obtained from studies that were performed at three cm above the top of the diaphragm provided the best separation among three anatomic levels. In comparison between asthmatic and emphysema patients, both parameters were significantly different in asthmatic subjects than in those with emphysema at both end inspiration and expiration on each scan and in the total scans ($p < 0.001$).

Conclusions : HRCT is a useful method to separate asthmatic subjects from patients with emphysema and normal subjects.

Key words : HRCT, asthma, emphysema

Introduction

It has been suggested that the diagnosis of emphysema by pathologic examination is correlated with high resolution computed tomography (HRCT) scan findings¹⁻³. The relative area of the lung with attenuation values lower than -950 Hounsfield Units (HU) (LAA, low attenuation area) on HRCT scans at full inspiration is an objective measure of the extent of pulmonary emphysema^{4,5}.

In asthmatic patients, HRCT is also useful for visualization of acute airway responses to bronchoconstrictor and bronchodilator stimuli as well as airway and parenchymal changes in chronic asthma⁶. In other words, changes such as bronchial wall thickening, bronchiectasis, emphysema and mosaic patterns of lung attenuation, which indicate airway and parenchymal reconstruction, have been observed by HRCT^{7,8}. It has been shown that patients with nonallergic asthma have more extensive emphysematous changes than those with allergic asthma⁹, and that asthmatics with abnormal HRCT findings demonstrate poorer lung function and less hyperresponsive bronchi than those with normal HRCT findings¹⁰. In a recent study, air trapping on expiratory HRCT scans in patients with normal findings on inspiratory scans was found to be most often associated with bronchiolitis obliterans and asthma¹¹.

A previous study suggested that the percent of pixels below -900 HU on expiratory HRCT scans was significantly correlated with pulmonary function, reflecting air trapping in asthmatic patients¹². However, the significance of HRCT findings at the end inspiration and expiration has not been determined in distinguishing asthmatic individuals from normal subjects and patients with emphy-

sema. The present study attempted to clarify whether a %LAA of the lung lower than -950 HU and the mean CT number on HRCT could separate asthmatic patients from normal control subjects and patients with emphysema at full inspiration and expiration.

Subjects and Methods

Subjects

The subjects in this study were 24 asthmatics (21 females and 3 males) who were 39 to 80 years of age (mean, 62.1 years). None were current or previous smokers. Asthma was diagnosed according to the criteria of the International Consensus on Diagnosis and Management of Asthma¹³. All subjects with asthma had episodic symptoms of wheezing and coughing and experienced symptomatic relief and reversible airway response with increases in values for forced expiratory volume in one second (FEV1) exceeding 15% upon treatment with beta-adrenergic agonists. Their ages at onset ranged from 16 to 66 years (average, 46.4 years), and the mean duration of asthma was from 2 to 40 years (average, 15.9 years). The onset and duration of asthma were estimated by the patients' history, followed by a careful examination.

Other subjects in this study were 23 patients with pulmonary emphysema with fixed airflow limitation diagnosed using the criteria of Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease¹⁴. They had FEV1 of less than 70% of the predicted value and a difference between prebronchodilator and postbronchodilator values of FEV1 not exceeding 15%. They were 54 to 82 years of age (mean, 69.3 years). All patients with emphysema were long-time cigarette smokers with an average

smoking history of 42.4 ± 14.4 pack-years (mean \pm SD).

We also studied 15 adult control subjects who had no history of wheezing or asthma and normal spirometric data. They were from 44 to 81 years old (mean, 66.2 years) and had never smoked.

A signed informed consent form agreeing to participation in the study protocol was obtained from all subjects. The study protocol was approved by the ethics committee of our institution. All patients were well at the time of evaluation without evidence of exacerbation or respiratory tract infection. Pulmonary function tests

All pulmonary function tests were performed by a CHESTAC 33 (Chest Co., Tokyo, Japan) linked to a computer. The FEV1 was derived from a forced vital capacity maneuver. The functional residual capacity (FRC) was measured by the helium dilution method and expressed as the percent of the predicted value¹⁵. Computed tomography

CT scans were performed on a TOSHIBA Xpeed scanner (TOSHIBA, Tokyo, Japan) (2.7s, 200 mAs, 120 kVp) without infusion of contrast medium, using 2-mm collimation (HRCT) with patients breath holding at full inspiration and full expiration and were reconstructed with a bone algorithm. The lungs were scanned at three preselected anatomic levels: (1) top of the aortic arch, (2) origin of the lower lobe bronchus, and (3) three cm above the top of the diaphragm, as reported by Miniati et al.¹⁶. Each HRCT scan was analyzed with the density mask program and evaluated quantitatively by measuring the percentage of lung area with a CT number < -950 HU (%LAA) and the mean CT number in HU. These were expressed as the value of each slice and an

average value of three anatomical lung levels. CT scan studies were obtained on the same day as the lung function measurement.

Statistical Analysis

Results were expressed as means \pm SD. Differences between the means were tested with analysis of variance (ANOVA). Correlations between any two variables were determined by the least squares linear regression analysis. A p value of <0.05 was considered as significant.

Results

Table 1 provides information on the characteristics, lung function and medication in the normal subjects and those with emphysema and asthma. Patients with emphysema were significantly older than those with asthma (mean: 69.3 and 62.1 years, respectively; $p<0.01$). The mean FEV1 as a percentage of the predicted value was significantly lower in patients with emphysema than in those with asthma and in the normal subjects ($p<0.001$). There was also a significant difference in FEV1 between asthmatic patients and normal subjects ($p<0.001$).

Table 1. Patient characteristics, lung function and medication in normal subjects, asthmatic subjects and subjects with emphysema.

	Normal Subjects (n=15)	Asthmatic Subjects (n=24)	Subjects with Emphysema (n=23)
M/F	0/15	3/21	23/0
Age (Mean \pm SD) (years) *	66.2 \pm 10.9	62.1 \pm 9.9	69.3 \pm 7.2
Inhaled steroids	NA	13	NA
Theophylline	NA	23	19
Systemic steroids	NA	19	9
FEV1, %predicted (Mean \pm SD) [†]	119.8 \pm 7.2	79.2 \pm 22.2	48.6 \pm 12.1
FRC, %predicted (Mean \pm SD)	ND	106.4 \pm 23.3	119.5 \pm 20.9

Definition of abbreviations: FEV1 = forced expiratory volume in one second; FRC = functional residual capacity; NA = not available; ND = not done.

* Subjects with emphysema were significantly older than asthmatic subjects ($p<0.01$).

[†] There was a significant difference among the three groups ($p<0.001$).

The quantitative data derived from the analysis of both the inspiratory and expiratory scans were used for comparison among normal subjects, asthmatic patients and patients with emphysema. The results of HRCT scan measurements at individual levels are presented in Table 2. On all individual scans, the mean CT number and %LAA of the lungs in patients with emphysema were significantly different from those in asthmatics and normal subjects at both full inspiration and expiration. When considering the

measurements obtained at full inspiration, there was a significant difference between asthmatics and normal subjects in the mean CT number ($p < 0.01$) and in %LAA on the inferior level ($p < 0.01$). When the same measurements were repeated at full expiration, there was a significant difference between asthmatics and normal subjects in the mean CT number on both intermediate ($p < 0.01$) and inferior levels ($p < 0.001$) but no difference in %LAA.

Table 2. Mean CT number and low attenuation area of individual slices in subjects studied

	Normal Subjects (n=15)	Asthmatic Subjects (n=24)	Subjects with Emphysema (n=23)
Mean CT number (HU)			
Inspiratory scans			
superior *	-872.1 ± 27.7	-886.7 ± 26.0	-935.8 ± 24.2
intermediate *	-880.3 ± 22.2	-896.2 ± 24.4	-933.8 ± 13.0
inferior †	-873.5 ± 19.9	-895.8 ± 26.6	-944.6 ± 15.0
expiratory scans			
superior *	-815.7 ± 24.0	-834.9 ± 32.3	-906.5 ± 34.3
intermediate †	-833.8 ± 24.0	-859.9 ± 33.1	-912.4 ± 19.5
inferior ‡	-830.8 ± 16.2	-863.4 ± 31.4	-920.5 ± 20.9
%LAA < -950HU			
Inspiratory scans			
superior *	3.7 ± 7.4	8.2 ± 9.3	45.6 ± 20.5
intermediate *	7.5 ± 7.0	16.1 ± 13.0	43.6 ± 11.3
inferior †	6.5 ± 6.0	18.2 ± 12.5	53.3 ± 12.0
expiratory scans			
superior *	0.1 ± 0.1	1.0 ± 2.0	28.4 ± 21.2
intermediate *	1.0 ± 1.7	5.4 ± 5.7	43.6 ± 11.3
inferior *	1.1 ± 1.3	7.9 ± 8.4	53.3 ± 12.0

Definition of abbreviations: CT = computed tomography; %LAA < -950HU = %low attenuation area of the lung; NS = not significant; superior = at the top of the aortic arch; intermediate = at the origin of the lower lobe bronchus; inferior = at 3 cm above the top of the diaphragm.

* There was no significant difference between normal and asthmatic subjects, but in both groups values were significantly different from those in patients with emphysema ($p < 0.001$).

† There was a significant difference between normal and asthmatic subjects ($p < 0.01$), but values in both were significantly higher than in subjects with emphysema ($p < 0.001$).

‡ There was a significant difference among the three groups ($p < 0.001$).

As shown in Figure 1, %LAA values were significantly greater in subjects with emphysema than in asthmatic and normal subjects at full inspiration (Figure 1a) and expiration (Figure 1b). Although there was no significant difference in %LAA between asthmatics and controls at full expiration, %LAA was significantly greater in asthmatics than in controls at full inspiration ($p < 0.05$). The mean CT numbers of all three slices are shown in Figure 2. The mean CT numbers were significantly lower in subjects with emphysema than in asthmatic and normal subjects at full inspiration and expiration. There was a significant difference between asthmatics and controls on both full inspiratory ($p < 0.05$) and expiratory ($p < 0.01$) scans. It is also evident that the difference of mean CT number between full inspiration and expiration is greater in controls than in asthmatics, and, as the value of the mean expiratory CT number decreases, the difference between the inspiratory and expiratory values of the mean CT number decreases.

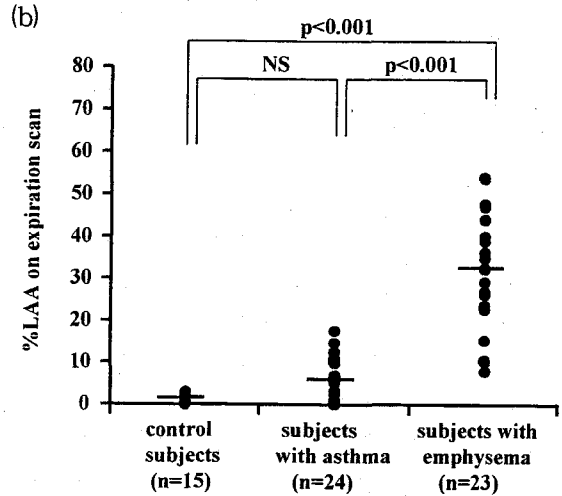
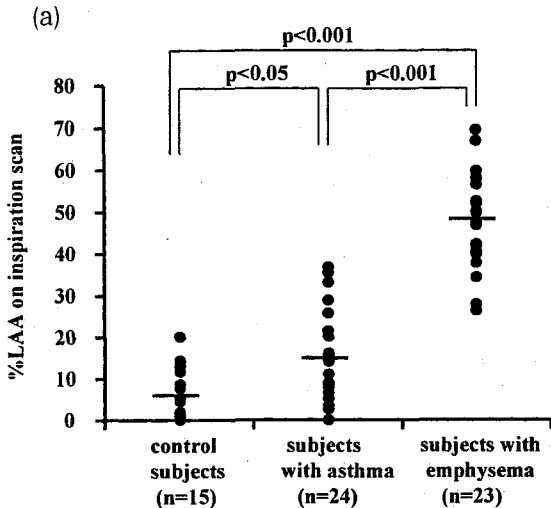


Fig. 1. Comparison of % lung area with attenuation values less than -950 HU (%LAA) of 15 control subjects, 24 patients with asthma and 23 patients with pulmonary emphysema on maximal inspiratory (a) and expiratory (b) scan. Data shown were calculated from mean % lung area with attenuation values of three anatomical slices. Solid horizontal lines refer to the average value of mean % lung area with attenuation values of each group.

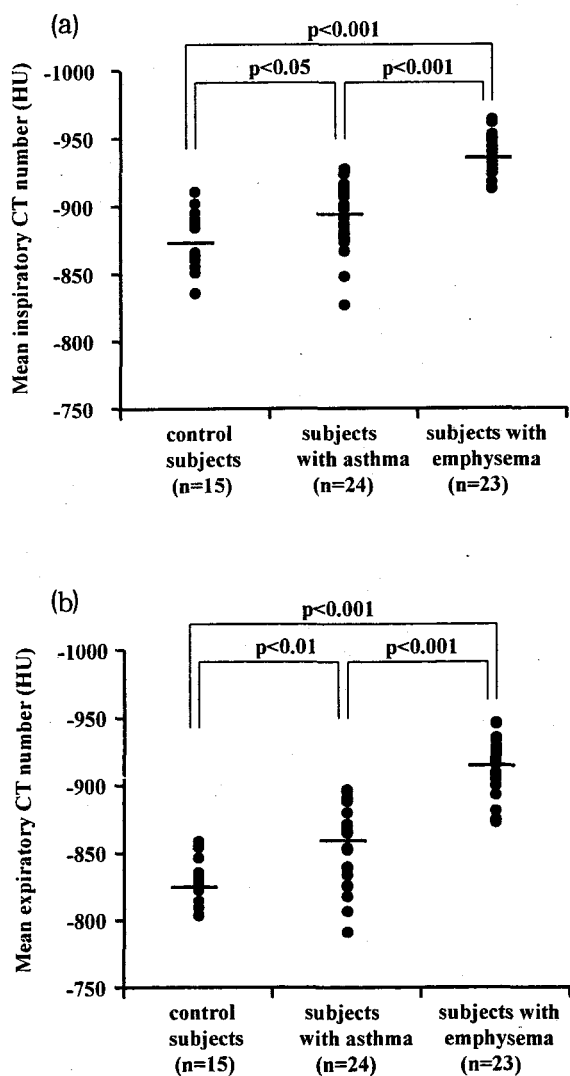
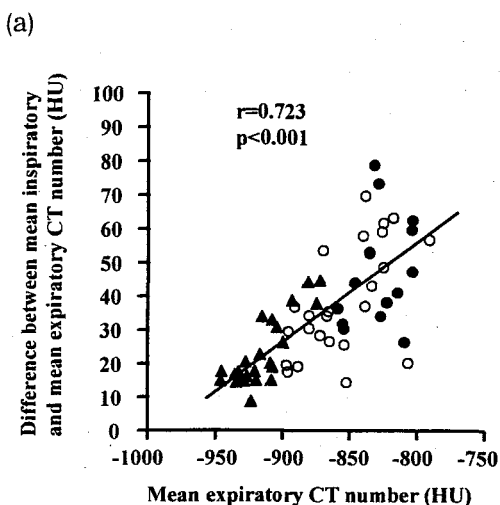


Fig. 2. Comparison of mean CT number in Hounsfield Units (HU) of 15 control subjects, 24 patients with asthma and 23 patients with pulmonary emphysema at full inspiration (a) and full expiration (b). Data shown were calculated from three anatomical slices. Solid horizontal lines refer to the average value of the mean CT number of each group.

As shown in Figure 3a, there was a highly significant correlation ($r=0.723$; $p<0.001$) between the mean expiratory CT number and the inspiratory-expiratory variation in the mean CT number. When the difference between the mean expiratory CT number and mean inspiratory CT number was plotted against the mean inspiratory CT number, the correlation was still significant but not as great as with data for the mean expiratory CT number ($r=0.428$, $p<0.001$) (Figure 3b). In Figure 4, the inspiratory-expiratory variation in the mean CT number was significantly lower in subjects with emphysema than in asthmatic ($p<0.01$) and normal subjects ($p<0.001$). In contrast, there was no significant difference between asthmatics and controls.



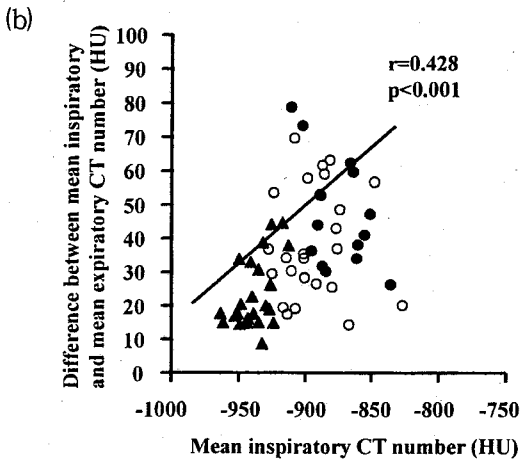


Fig. 3. Comparison of expiratory (a) and inspiratory CT number (b) in Hounsfield Units (HU) and inspiratory-expiratory CT number difference in 15 control subjects (closed circles), 24 subjects with asthma (open circles) and 23 subjects (closed triangles) with pulmonary emphysema.

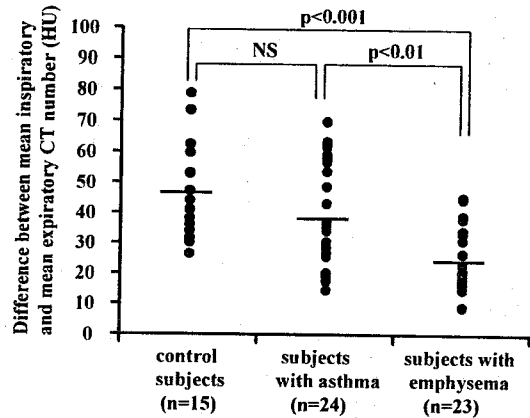


Fig. 4. Comparison of differences between mean inspiratory and mean expiratory CT number in Hounsfield Units (HU) of 15 control subjects, 24 patients with asthma and 23 patients with pulmonary emphysema. Data shown are for mean CT number of three anatomical slices. Solid horizontal lines refer to the average value of inspiratory-expiratory difference in the mean CT number of each group.

Discussion

It is generally agreed that CT scanning is a sensitive technique for detecting emphysematous lesions¹⁷; however, the possible influences of hyperinflation and of nonemphysematous expiratory airflow limitation on the CT quantification of pulmonary emphysema have not been investigated¹⁸. HRCT values (mean CT values and %lung area < -900 HU) have been shown to differ more greatly between control subjects and patients with emphysema at full expiration than at full inspiration¹⁶. It has been observed in HRCT that patients with asthma show more abnormalities related to airway remodeling

than do normal subjects^{7, 8}. Previously Paganin et al. reported that the severity and duration of asthma was related to remodeling of the airways, and patients with nonallergic asthma had more extensive remodeling of the airways than those with allergic asthma⁹. Patients with more severe asthma have been observed to have greater airway thickening than those with mild asthma¹⁹. The significance of measuring the LAA of the lungs on HRCT has been controversial in asthma. Gevenois et al. did not find any significant change in CT lung density parameters by measuring the LAA of the lungs < -950 HU during allergic challenge tests. They concluded that hyperinflation

and airflow obstruction without emphysematous lung destruction would not influence densitometric measurements obtained from inspiratory scans²⁰. Newman et al. found no significant difference between asthmatic patients and control subjects for the inspiratory HRCT scans obtained in the lower areas (level of diaphragm. $LAA < -900$ HU); however, the difference was significant for the upper area (level of transverse aorta, $LAA < -900$ HU)¹².

In the present study, on the analysis of individual scans, we found a greater difference in the mean CT number and %LAA between asthmatic patients and control subjects in the lower areas than in the upper area; however, there was no significant difference in %LAA for expiratory scans. At full expiration, differences between asthmatics and control subjects were more evident in the mean CT number than in %LAA, but not at full inspiration. Therefore, the best separation was obtained in the lower area (3 cm above the top of the diaphragm) among the three anatomic levels on expiratory mean CT number.

When using the single slice for HRCT analysis, the difference in the level between inspiration and expiration might be critical to determine the values. Accordingly, we calculated the mean CT number and %LAA derived from three anatomical lung levels in each subject. It was observed that the mean CT values on full expiration can clearly distinguish asthmatic patients from normal subjects. It is considered that the differences of LAA between asthmatic and control subjects are less at full expiration than at full inspiration, since the value of %LAA is not expressed below zero. In this study, it is also suggested that patients with emphysema are

definitely distinguishable from asthmatics and control subjects at both inspiration and expiration on any of the three anatomical levels. The mean CT number is linearly related to the fraction of air in the lungs, showing the ratio between the volume of air and the volume of air plus the volume of tissue²¹. In patients with chronic obstructive pulmonary disease, Miniati et al. suggested that as the value of the mean expiratory CT number decreases, i.e., as the fraction of air in the lungs increases, the difference between the inspiratory and expiratory values of the mean CT number progressively decreases, thus indicating that less air is moved in and out of the lungs¹⁶. We observed that inspiratory-expiratory variations in the mean CT number were significantly increased in asthmatic and normal subjects compared to subjects with emphysema, and those in controls were greater than those in asthmatics. These results suggest that inspiratory-expiratory variations in the mean CT number can express the difference in air movement between patients with air flow limitation and normal subjects. Our results reveal that the measurement of both the mean CT number and the percent of lung area with attenuation values < -950 HU at full inspiration and expiration can be applied to distinguish patients with asthma from patients with emphysema and normal subjects. It is still unclear whether the high %LAA in asthma is due to hyperinflation and nonemphysematous inspiratory airflow limitation or to emphysematous lesions. Further studies are necessary to clarify the influences of hyperinflation and airflow limitation in the CT quantification of asthma.

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胸部高分解能CT(HRCT)による肺野
low attenuation area (LAA)の定量的評価
—気管支喘息および肺気腫症例の比較検討—

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【目的】肺野low attenuation area (LAA)は、慢性閉塞性肺疾患(COPD)における肺気腫の存在ならびに程度を反映することが知られている。そこで喘息患者におけるLAAの意義を明らかにすることを目的として、COPD患者、コントロールとの比較検討を行った。

【対象と方法】喘息症例24例、COPD症例23例、コントロール15例を対象として、上・中・下肺野の3スライスで深吸気、深呼気時において胸部高分解能CT(HRCT)を施行し3群間で比較検討を行った。CTパラメーターとしては、平均CT値、肺野面積に対する-950HU以下のLAAの割合(%LAA)を採用した。

【結果】1. 3スライスの平均CT値は、吸気および呼気とも3群間での有意の差が認められた。2. 3スライスの%LAAは、吸気では3群間での有意の差が認められたが、呼気では喘息とコントロール間での有意の差は認められなかった。3. COPD症例では、吸気、呼気ともに平均CT値は他の2群より有意に低値を示し、%LAAは他の2群より有意に高値を示した。4. 3群間の平均CT値と%LAAの相違は下肺野のスライスで最も顕著であった。

【考案】平均CT値および%LAAは、喘息、COPD、コントロールにおいて有意に異なっており、喘息およびCOPDの病態を反映する可能性が示唆された。