Relationship between extent of emphysema by HRCT and lung elastic recoil in patients with COPD.

Relationship between Extent of Pulmonary Emphysema by High-resolution Computed Tomography and Lung Elastic Recoil in Patients with Chronic Obstructive Pulmonary Disease

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We investigated the relationship between the extent of pulmonary emphysema, assessed by quantitative high-resolution computed tomography (HRCT), and lung mechanics in 24 patients with chronic obstructive pulmonary disease (COPD). The extent of emphysema was quantified as the relative lung area with CT numbers < -950 Hounsfield Units (HU). Patients with COPD had severe airflow obstruction (FEV_1 35 $\pm$ 15% pred) and severe reduction of CO diffusion constant (D_{CO}/V_A 37 $\pm$ 19% pred). Maximal static elastic recoil pressure (Pst_{max}) averaged 54 $\pm$ 24% predicted, and the exponential constant K of pressure–volume curves was 258 $\pm$ 116% predicted. Relative lung area with CT numbers < -950 HU averaged 21 $\pm$ 11% (range 1 to 38%). It showed a highly significant negative correlation with D_{CO}/V_A ($r = -0.84$, $p < 0.0001$), a weak correlation with FEV_1% predicted, and no correlation with either Pst_{max} or constant K. A significant relationship was found between the natural logarithm of K and the full width at half maximum of the frequency distribution of CT numbers, taken as an index of the heterogeneity of lung density ($r = 0.68$, $p < 0.0005$). We conclude that currently used methods of assessing the extent of emphysema by HRCT closely reflect the reduction of CO diffusion constant, but cannot predict the elastic properties of the lung tissue.

Keywords: Pressure–volume curve; elastic recoil pressure; HRCT quantitative analysis; emphysema heterogeneity

The contribution of emphysema to loss of lung elastic recoil in patients with expiratory flow limitation remains controversial, in spite of various attempts to relate structure and function in this condition (1). Measurements of CO diffusing capacity and maximal static elastic recoil pressure are the best predictors of emphysema, when correlated with postmortem morphological measurements (2, 3). Since the original description by Christie (4), loss of lung elastic recoil has been regarded as the functional hallmark of pulmonary emphysema, and it has been extensively documented in patients with airflow obstruction ranging from mild to severe (5–7). However, there is considerable variation in maximal static elastic recoil pressure, hyperinflation, and leftward shift of the pressure–volume curves *in vivo* compared with pathological scores of emphysema on resected lung specimens or on excised lungs obtained at postmortem (5–7).

Reportedly, high-resolution computed tomography (HRCT) is the most accurate imaging technique to detect pulmonary emphysema *in vivo* (8). Both qualitative (subjective) and quantitative (objective) methods have been described to assess emphysema by CT scanning. Qualitative evaluation is based on visual scoring of the size and extent of lung areas with low attenuation values (9–11). Objective quantitation of emphysema can be obtained by measuring the relative lung area occupied by pixels with attenuation coefficients (CT numbers) below a predetermined threshold (12–14). Objective methods are preferable over those based on visual scoring because they reflect more precisely the extent of macroscopic emphysema and are operator independent (15).

The present study was aimed at investigating the relationship between pulmonary emphysema, as assessed by HRCT quantitative analysis, and physiological abnormalities of lung parenchyma in patients with chronic airflow obstruction.

METHODS

Pulmonary Function Studies

We studied 24 patients (18 males and six females), aged 61 $\pm$ 11 yr (mean $\pm$ SD), who had chronic obstructive pulmonary disease (COPD) and airflow obstruction ranging from mild to very severe, according to American Thoracic Society (ATS) criteria (16). Twelve patients were current smokers and 12 were ex-smokers, with an average smoking history of 46 $\pm$ 26 pack-years. Symptoms of chronic bronchitis (17) were present in 15 of 24 clinically stable patients. After obtaining informed consent, we measured lung function, including maximum inspiratory and expiratory flow rates, single breath CO diffusing capacity (D_{CO}) (18), thoracic gas volume, partial tension of oxygen (Pa_{O_2}), and carbon dioxide (Pa_{CO_2}) of arterial blood. Thoracic gas volume at end-tidal expiration was measured in a constant volume body plethysmograph (2800 Transmural Body Box; Sensor Medics, Anaheim, CA) by panting at slow frequency against a closed shutter. Patients were considered to have fixed expiratory flow limitation if FEV_1 values, measured after two inhalations of salbutamol (400 μg) from a metered-dose inhaler, increased by less than 12% (or < 200 ml) of the baseline value (16). All the above parameters were expressed as percentage of the predicted values according to the respective reference equations (19, 20) (*see* online data supplement).

Static expiratory pressure–volume curves were obtained with the patient seated in the body plethysmograph, using conventional techniques with a thin walled esophageal balloon (Volgens E.G.K.S.-NORM) *in situ* (21) (*see* online data supplement). At least three maneuvers were obtained in each patient. The values were considered acceptable if maximal static elastic recoil pressure was reproduced within 1 cm H_2O in at least two separate maneuvers.

A best-fit exponential function was fitted to the pressure–volume data. It was obtained by an iterative least-squares method according to Colebatch and colleagues (22). The exponential constant K was expressed as natural logarithm (ln K) (23). Maximal elastic recoil pressure, elastic recoil pressure at 90% of total lung capacity (TLC), and constant K were expressed as percentage of their predicted values according to the formula derived by Colebatch and colleagues (24) (*see* online data supplement).

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TABLE 1. PULMONARY FUNCTION DATA IN 24 PATIENTS WITH COPD

	Mean	SD	Range
VC, % pred	83	25	(49–151)
FVC, % pred	78	22	(33–116)
FEV_1, % pred	35	15	(17–72)
FEV_1/VC, %	32	12	(16–62)
TLC,* % pred	138	20	(95–172)
FRC,* % pred	190	41	(129–274)
RV,* % pred	213	72	(117–335)
D_{CO}, % pred	40	22	(11–109)
Pa_{O_2}, mm Hg	72	10	(54–99)
Pa_{CO_2}, mm Hg	38	5	(29–50)
K, % pred	258	116	(77–513)
Pst_{max},% pred	54	24	(20–128)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; D_{CO} = single-breath diffusing capacity of carbon monoxide; K = constant derived from exponential fitting of pressure–volume data, in percentage of predicted according to Colebutch and coworkers (24); Pst_{max} = maximal static elastic recoil pressure in percentage of predicted according to Colebatch and coworkers (24); RV = residual volume; TLC = total lung capacity; VC = vital capacity.

Computed Tomography

Conventional CT scans were performed at suspended full inspiration on a GE SYTEC 3000 scanner (General Electric, Milwaukee, WI). No contrast medium was infused. Technical parameters were 1 mm collimation, 120 kVp, 160 mA, and 3 s scanning time. The lungs were scanned from the apex through the base at 2 cm intervals and were reconstructed with bone algorithm (HRCT). All CT scan images were processed off-line using a semiautomated image-processing program developed at the Research Service Branch (RSB) of National Institutes of Health (NIH *Image* V1.62), which (*1*) extracts boundaries of the lungs (25), (*2*) calculates lung cross-sectional areas and histograms of attenuation values (CT numbers) of individual highlighted sections, and (*3*) summarizes data to obtain the frequency distribution of attenuation values for both lungs.

From the frequency distribution of CT numbers, we derived (*1*) mean CT number, in Hounsfield Units (HU); (*2*) full width at half maximum, that is, the width of the frequency distribution of attenuation values at 50% of the mode (26); and (*3*) percentage of the whole lung area with attenuation values lower than −950 HU (27, 28) (*see* online data supplement).

Statistical Analysis

Correlation of HRCT scan quantitative analysis with physiological variables was tested by linear regression analysis; p values lower than 0.05 were accepted as indicating significance. Unless stated otherwise, data in the text are given as means ± SD.

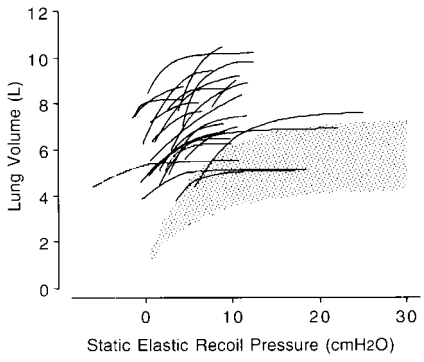

Figure 1. Static lung elastic recoil pressure–volume curves in 24 patients with COPD. Individual pressure–volume curves are obtained by exponential fitting of experimental data points measured in the volume interval from TLC to 70% of TLC. *Shaded area* is the confidence interval at 95% of pressure–volume data predicted according to Colebatch and coworkers (24).

RESULTS

Lung function data in the 24 patients with COPD are summarized in Table 1. Physiological abnormalities known to be associated with pulmonary emphysema, such as loss of elastic recoil pressure, severe hyperinflation, and reduction of CO diffusing capacity, were present in most patients. Chronic airflow obstruction ranged from mild to very severe. In all but four patients, changes in postbronchodilator FEV_1 were less than 200 ml or < 12% over the prebronchodilator value.

The HRCT quantitative analysis was successfully performed in all patients. The mean CT number averaged −877 ± 21 HU (range −904 to −809 HU). The full width at half maximum averaged 99 ± 11 HU (range 73 to 115 HU). The extent of emphysema, expressed as relative lung area with CT number < −950 HU, was 21 ± 11% of total lung cross-sectional area (range 1 to 38%).

To describe the static pressure–volume curve, a single exponential function was used. This function provides a satisfactory fit to the pressure–volume data from TLC to a lower volume limit of about 70% of TLC, which represents the end-expiratory lung volume in most of our patients. In each patient, approximately 12 points were used for the exponential fitting. The residual variance percentage of the measured points in the volume interval from TLC to 70% TLC was 3.5 ± 1.5% (range 1.2 to 6.4%).

Figure 1 shows the results of exponential analysis of the pressure–volume curves. In all but one patient, the curves fell above the range predicted by the equations of Colebatch and colleagues (24) (*stippled area* in Figure 1).

From the exponential analysis of pressure–volume curves, we calculated the constant K, an index of lung distensibility that relates changes in size of lung units to changes in distending pressure, independently of lung volume. On the average, the constant K was markedly increased (Table 1). However, the value of K was within 2 standard deviations of the mean predicted value for age in five patients of whom one had mild extent of emphysema (5%) and the other four had moderate or moderately severe extent of emphysema (17, 19, and 35%, respectively).

As shown in Table 2, there was a fair correlation between FEV_1 % predicted and mean CT number, and a weaker correlation between FEV_1 % predicted and relative lung area with CT number < −950 HU. No correlation was found between FEV_1 % predicted and full width at half maximum. Similarly,

TABLE 2. COMPARISON OF FEV_1 WITH LUNG MECHANICS AND HRCT DATA

	FEV_1 (*% pred*) (*r*)	p Value
Pst_{max}, % pred	0.31	NS
P_{90}, % pred	0.34	NS
K constant	0.10	NS
ln K	0.27	NS
Mean CT no., HU	0.62	< 0.001
FWHM	0.12	NS
RA_{950}%	−0.50	< 0.01

Definition of abbreviations: FWHM = full width at half maximum of the frequency distribution of CT numbers, that is, width of frequency distribution of CT numbers at 50% of the mode; HRCT = high-resolution computed tomography; K = constant derived from exponential fitting of pressure-volume data, in percentage of predicted according to Colebatch and coworkers (24); Pst_{max} = maximal static elastic recoil pressure, in percentage of predicted according to Colebatch and cowrokers (24); P_{90} = static elastic recoil pressure calculated at 90% TLC from the exponential function, in percentage of predicted according to Colebatch and coworkers (24); ln K = natural logarithm of constant K; mean CT no. = mean value of the frequency distribution of CT numbers; RA_{950}% = relative lung area with CT numbers < −950 HU.

TABLE 3. COMPARISON OF MEAN CT NUMBER WITH LUNG MECHANICS AND CO DIFFUSING CAPACITY

	FEV_1 (*% pred*) (*r*)	p Value
Pst_{max}, % pred	0.55	< 0.005
Pst_{max}/TLC, %	0.56	< 0.005
D_{CO}, % pred	0.78	< 0.0001
D_{CO}/V_A, % pred	0.70	< 0.0005

Definition of abbreviations: CT = computed tomography; D_{CO} = single-breath diffusing capacity of carbon monoxide; Pst_{max} = maximal static elastic recoil pressure, in percentage of predicted according to Colebatch and coworkers (24); Pst_{max}/TLC = coefficient of retraction, in percentage of predicted according to Colebatch and coworkers (24); V_A = alveolar volume.

there was no significant correlation of FEV_1 % predicted with indices derived from the pressure–volume curves.

Table 3 summarizes the comparison of the mean CT number with both CO diffusing capacity and lung mechanics, which were all significant.

Figure 2A shows the relationship between relative lung area with CT number < -950 HU and Pst_{max}. There was a wide scatter of data about the regression line, and the correlation coefficient did not attain significance ($r = -0.27$). Abnormally low values of Pst_{max} were equally found in patients with mild emphysema on HRCT and in those with moderately severe or severe emphysema. The relationship did not improve when the coefficient of retraction (Pst_{max}/TLC) was plotted against relative lung area with CT number < -950 HU (Figure 2B). There was one patient (identified by an arrow in Figure 2) who had a nearly normal value of Pst_{max} in spite of significant emphysema on HRCT. This patient, a 38-year-old female, had very severe airflow obstruction (FEV_1 17% of predicted), severe impairment of D_{CO} (18% of predicted), and severe hyperinflation (RV 288% of predicted). The exponential constant K was 132% of predicted, and P_{90} 32% of predicted. In this patient, emphysematous lesions had a peculiar distribution in that they were predominantly located in the peripheral lung regions with a relative sparing of the lung parenchyma around the heart and the lower mediastinum. Such a peculiar distribution of emphysema may have had some bearing on the measurement of Pst_{max}. By excluding this patient, the correlation between of Pst_{max} and relative lung area with CT number < -950 HU becomes significant ($r = 0.42$, $p < 0.05$), but the coefficient of variance ($r^2 = 0.18$) remains low. No correlation was found between relative lung area with CT number < -950 HU and P_{90}, that is, elastic recoil pressure measured at 90% of TLC ($r = -0.24$). Similarly, there was no correlation between relative lung area with CT number < -950 HU and the natural logarithm of the constant K (ln K), which describes the shape of the pressure–volume curve (Figure 3).

As opposed to the previous comparisons, a highly significant negative correlation was found between relative lung area with CT number < -950 HU and both D_{CO}% predicted ($r = -0.77$, $p < 0.0001$) and D_{CO}/V_A% predicted ($r = -0.84$, $p < 0.0001$) (Figure 4).

A significant correlation ($r = 0.68$, $p < 0.0005$) was also found between full width at half maximum, which provides an index of the heterogeneity of lung density, and ln K (Figure 5).

DISCUSSION

A number of radiological–pathological studies (8, 9, 29) have demonstrated that HRCT scanning is a reliable, noninvasive method to assess the severity and quantify the extent of macroscopic emphysema *in vivo*. However, CT scanning is relatively insensitive in detecting emphysematous lesions of less than 0.5 mm in diameter (30). In our investigation, we used a quantitative CT index of extent of emphysema: the relative lung area occupied by pixels with attenuation values lower than – 950 HU. This index has been previously validated against macroscopic and microscopic assessment of emphysema (27, 28). The threshold value of -950 HU is the only level for which no significant difference was found between HRCT and morphometric data (27).

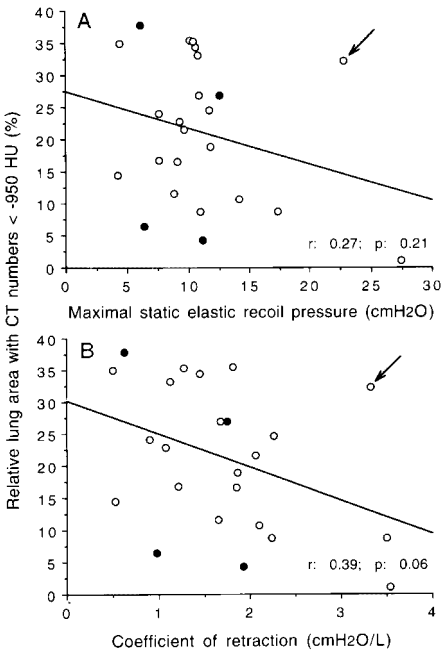

Figure 2. Extent of emphysema as assessed by HRCT quantitative analysis plotted against Pst_{max}, cm H_2O (*A*) and, respectively, coefficient of retraction, that is, Pst_{max}/TLC (*B*). *Closed circles* identify patients with change in postbronchodilator $FEV_1 > 200$ ml or 12% over the prebronchodilator value. The *arrow* refers to a 38-year-old female with a nonuniform, peculiar distribution of emphysema (*see* text).

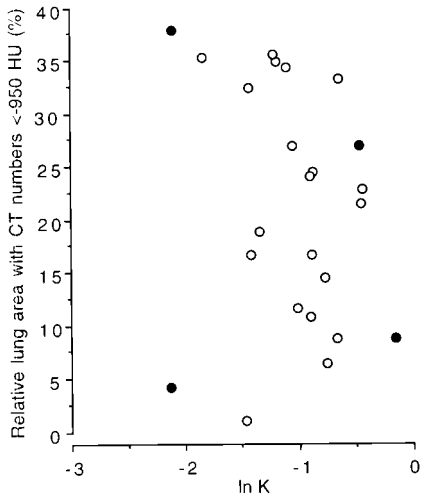

Figure 3. Extent of emphysema as assessed by HRCT quantitative analysis is plotted against the natural logarithm of shape constant K (ln K). No relationship exists between the two variables. *Closed circles* identify patients with change in postbronchodilator $FEV_1 > 200$ ml or 12% over the prebronchodilator value.

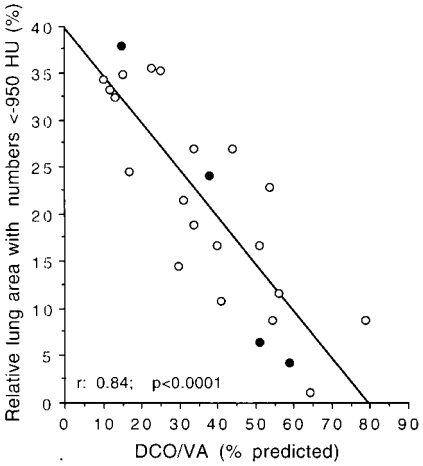

Figure 4. Extent of emphysema as assessed by HRCT quantitative analysis plotted against D_{CO}/V_A, % pred. *Closed circles* identify patients with change in postbronchodilator $FEV_1 > 200$ ml or 12% over the prebronchodilator value.

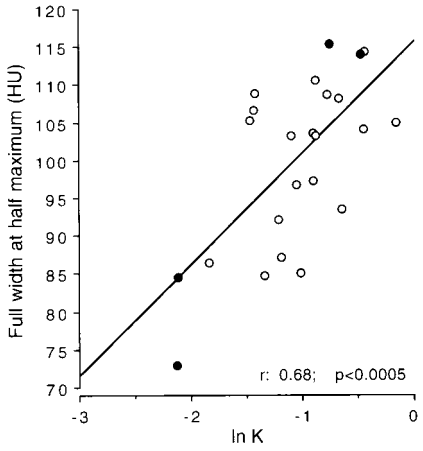

Figure 5. Full width at half maximum, that is, width of frequency distribution of CT numbers at 50% of the mode, plotted against the natural logarithm of shape constant K (ln K). *Closed circles* identify patients with change in postbronchodilator $FEV_1 > 200$ ml or 12% over the prebronchodilator value.

In the present study, we found a fair correlation between mean CT number, as an index of physical density of the lung tissue, and both elastic recoil pressure and CO diffusing capacity. This is in agreement with previous reports (31). Also, we found that reduction of CO diffusing capacity is strongly correlated with the extent of emphysema as assessed by HRCT quantitative analysis.

Other investigators suggested that the prevalence of CT-scored significant emphysema is low in patients with COPD, and that CO diffusing capacity may yield spuriously low values in patients without evidence of emphysema when FEV_1 is less than 1 L (32, 33). We also documented spuriously low D_{CO}/V_A (51%, 56%, and 65% of predicted) in three patients in whom relative lung area with CT number < -950 HU was within the upper 95% limit of the predicted normal value measured in a group of subjects whose lungs were considered normal histologically (28). Thus, CO diffusing capacity is a test that reflects the reduction of alveolar–capillary surface, although in the presence of very severe airflow limitation, it does not, in itself, predict significant emphysema in any individual.

In the patients reported on in the present study, we found a good relationship between FEV_1 % predicted and mean CT number, and a weaker relationship between FEV_1 % predicted and extent of emphysema. The latter finding is in agreement with the data reported by Gelb and colleagues (32–34), and suggests that expiratory flow limitation in advanced COPD is not entirely accounted for by the extent of emphysema.

Recently, it has been reported that competition for space of enlarged alveoli may result in stenosis of intraseptal bronchioles (35). This lends support to the hypothesis that noninflammatory stenosis, related to compression by enlarged air spaces, may contribute to the severity of airflow limitation in COPD besides the inflammatory airway disfunctioning described in smokers and in pulmonary emphysema.

Because loss of lung elastic recoil is a distinctive feature of emphysema, we compared *in vivo* measurements of the extent of emphysema by HRCT with the maximal static elastic recoil pressure (Pst_{max}) and the exponential constant K (1, 36).

As shown in Figure 2, there was no relationship between extent of emphysema and Pst_{max}. One point is influential to the correlation that attains significance if this point is excluded. The nonuniform, peculiar distribution of emphysema observed in this case might have affected the measurement of Pst_{max}. Alternatively, the influence of effort could be responsible for the observed high value of Pst_{max}. However, even by excluding this influential point, the coefficient of variance (r^2) was only 0.18, indicating that no more than 20% of the variability of Pst_{max} is accounted for by the extent of macroscopic emphysema.

Morrison and colleagues (37) found only a weak relationship between maximal static elastic recoil pressure and both pathological grade of emphysema ($r^2 = 0.18$) and CT visual score of emphysema ($r^2 = 0.10$). A closer correlation has been documented by Gugger and colleagues (31), who compared ln K and elastic recoil pressure measured at 90% of TLC with the mean and the lowest fifth percentile of the CT lung density histogram from both lungs in 24 patients with COPD. The discrepancy between Gugger's results and ours may reflect differences in the study population. In our patients, both FEV_1 and D_{CO}% predicted were more severely reduced than those of the patients studied by Gugger and colleagues. Moreover, they included comparison with four normal subjects.

The exponential constant K is recognized as a reliable index of alveolar distensibility. Greaves and Colebatch (36) measured pressure–volume curves *ex vivo* in lungs or lobes obtained from 14 normal subjects and 7 patients with severe emphysema. They reported a highly significant correlation between K and mean linear intercept (Lm), and a weaker relationship between K and the pathology grade of emphysema. They concluded that both K and Lm weigh the contribution of less severely diseased lung regions, whereas the pathology score of emphysema mainly reflects the grossly diseased lung parenchyma.

This issue has been further addressed by Osborne and colleagues (6), who found no significant relationship between the exponential constant K and the pathological grade of emphysema in resected lung specimens from 173 patients who had preoperative measurements of pressure–volume curves. They concluded that K reflects airspace size unless airway closure "subtracts" the contribution of the most abnormal lung areas of emphysema from the deflation pressure–volume curve (6).

We also documented a value of K within the age-predicted normal range in five patients who had mild to moderately severe emphysema on HRCT. In most of our patients, however, the constant K was markedly increased independently of the extent of emphysema. It appears, therefore, that the elastic

properties of lung tissue cannot be predicted by CT quantitation of emphysema.

We observed a significant positive correlation between the exponential constant K and the width of the frequency distribution of attenuation values at 50% of the mode, taken as an index of the heterogeneity of lung density (Figure 5). Gierada and colleagues (26), who analyzed pixel-attenuation statistics in order to define relevant CT parameters of emphysema, found that full width at half maximum is a useful predictor of outcome in patients undergoing lung volume reduction surgery, and a potential means of assessing the heterogeneity of emphysema. Unfortunately, no CT-pathological correlation has so far been reported to validate full width at half maximum as an index of emphysema heterogeneity. Thus, the interpretation of the observed relationship between full width at half maximum and exponential constant K remains largely speculative.

In conclusion, our study suggests that currently used methods to assess the extent of emphysema by HRCT closely reflect the volume-corrected CO diffusing capacity in emphysema, but cannot predict the elastic properties of the lung tissue.

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