Restrictive Lung Function and Asbestos-induced Pleural Fibrosis

A Quantitative Approach

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Abstract

To assess further the clinical significance of asbestos-induced pleural fibrosis, we used a computer algorithm to reconstruct images three dimensionally from the high-resolution computerized tomography (HRCT) scan of the chest in 60 asbestos-exposed subjects. Pulmonary function tests, chest radiographs, and HRCT scans were performed on all study subjects. The volume of asbestos-induced pleural fibrosis was computed from the three-dimensional reconstruction of the HRCT scan. Among those with pleural fibrosis identified on the HRCT scan (n = 29), the volume of the pleural lesion varied from 0.01% (0.5 ml) and 7.11% (260.4 ml) of the total chest cavity. To investigate the relationship between asbestos-induced pleural fibrosis and restrictive lung function, we compared the computer-derived estimate of pleural fibrosis to the total lung capacity and found that these measures were inversely related (r = −0.40; P = 0.002). After controlling for age, height, pack-years of cigarette smoking, and the presence of interstitial fibrosis on the chest radiograph, the volume of pleural fibrosis identified on the three-dimensional reconstructed image from the HRCT scan was inversely associated with the total lung capacity (P = 0.03) and independently accounted for 9.5% of the variance of this measure of lung volume. These findings further extend the scientific data supporting an independent association between pleural fibrosis and restrictive lung function. (*J. Clin. Invest.* 1993. 91:2685–2692.) Key words: asbestos • image analysis • pleural fibrosis

Introduction

Asbestos-induced pleural fibrosis (circumscribed plaques and diffuse pleural thickening) is the most common radiographic abnormality among asbestos-exposed persons (1–5) and has been shown to be consistently associated with the presence of restrictive lung function (6–20). Findings from our center (21) suggest that although parenchymal inflammation and fibrosis contribute to the loss of lung function in persons with asbestos-induced pleural fibrosis, the pleural lesions themselves appear to independently contribute to the impaired lung function. Interestingly, the type (circumscribed vs. diffuse) and size (length and width) of the pleural lesion have recently been shown to be critical elements influencing the extent of lung function impairment (9, 10, 22). Thus, the size or volume of the pleural lesion may be particularly important in determining the extent of restrictive lung function that has been found to be associated with asbestos-induced pleural fibrosis.

The computerized analysis of a radiographic image is a multistage process that uses sophisticated, relatively inexpensive digital computing devices to reliably quantify and characterize the underlying process (23). Although originally designed for industrial and engineering applications (24), these techniques can be readily applied to biomedical images in that they permit visualization of an object without a need for a specific geometric or physical model. In fact, three-dimensional image processing methodology has been applied to biomedical images and has proved useful in planning maxilofacial surgery (25) and orthopedic procedures (26), identifying central nervous system pathology (27), and assessing several aspects of cardiac function (28). Although these computer-assisted approaches are only beginning to be applied to the lung (29–32), these methods may help to diminish bias, improve reliability, and enhance the quantitative assessment of specific types of lung disease.

To assess further the clinical significance of asbestos-induced pleural fibrosis, we reconstructed images from the high-resolution computerized tomography (HRCT)[1] scan and quantified the three-dimensional characteristics of the pleural lesions. Our findings indicate that the pleural lesions identified on the three-dimensional reconstructed image were found to be inversely and independently related to the total lung capacity.

Methods

Study population. The subjects for this investigation were identified as part of our ongoing SCOR Program in interstitial and occupational lung disease at our institution. Subjects for this study were primarily identified through the Sheet Metal Workers' 1986 National Screening Program (9). However, several subjects were also enrolled through the Occupational Medicine Clinic at the University of Iowa. All study subjects had been occupationally exposed to asbestos for at least 1 yr in a high exposure setting (i.e., direct contact with asbestos) and a minimum of 20 yr was required between first exposure to asbestos and entry into the study. Although subjects with asbestos-induced parenchymal fibrosis (i.e., asbestosis) and asbestos-induced pleural disease were preferentially invited to participate in this study, asbestos-exposed individuals without obvious lung disease were also included in this study population.

Pulmonary function testing. The pulmonary function tests consisted of standard spirometry that was obtained with the use of a 1070 System (Medical Graphics, St. Paul, MN) and lung volume via body

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1. *Abbreviations used in this paper:* HRCT, high-resolution computerized tomography; ILO, International Labor Organization.

plethysmography Medical Graphics 1085 System. A single-breath diffusing capacity was measured by using the Medical Graphics 1070 System. The measurements of lung function were performed with standard protocols, and the American Thoracic Society guidelines (33) were used to determine acceptability. The predicted normal values used were those of Morris and co-workers (34) for spirometry, Goldman and Becklake (35) for lung volumes, and Van Ganse and associates (36) for diffusing capacity.

Chest radiographs. Chest radiographs were performed in the posteroanterior projection on all study subjects and individually interpreted by three experienced readers (Drs. Schwartz, Galvin, and Merchant) who used the International Labor Organization (ILO) 1980 classification of radiographs of pneumoconioses (37). Each reader was blinded to the exposure history, clinical data, and the opinions of the other readers when interpreting the radiographs. At least two of the three readers agreed on the category of parenchymal profusion (0, 1, 2, and 3) on 100% of the films. Agreement between at least two of the three readers was required to identify a parenchymal or pleural abnormality. For the purposes of this study, we defined asbestosis as an ILO profusion of 1/0 or greater (37).

Chest HRCT. HRCT scans of the lung parenchyma were obtained on all study subjects by using an ultrafast scanner (model C-100, Imatron Corp., San Francisco, CA). Images were obtained at full inspiration with the subjects prone. A high spatial frequency algorithm was used to reconstruct the image data, and the smallest possible scanning circle was employed to maximize the resolution. The scanning time was 0.6 s. Three mm images were obtained every 2 cm from the apex of the lungs to the diaphragms.

Computer-derived volumetric measurements. The steps that are needed to construct a three-dimensional image of the lung include (*a*) identification of tomographic images which encompass the entire lung, (*b*) identification of the spatial position and orientation of each tomographic image, (*c*) identification of the actual region of interest (mediastinum, lung, pleura, etc.), (*d*) reconstruction and display of the three-dimensional image; and (*e*) extraction of quantitative data. Data generated from the HRCT scan were directly transferred to a 4D Iris Workstation (Silicon Graphics, Mountain View, CA) and digitized in a 512 × 512 pixel matrix with 16-bit gray-level resolution. Anatomic features (lung parenchyma and pleural lesions) of each HRCT image were independently traced by two of the investigators (Dr. Schwartz and Mr. Yagla) who were blind to all clinical data when performing the traces. The lung parenchyma and pleural lesions were then defined by a program (SGITRACE) specifically developed for this purpose (Fig. 1). Once outlined, a series of traced contours were used to define the three-dimensional surface of the lung and the pleural lesions (Fig. 2). Using a specific program (SOLIDS), we were able to triangulate (tessellate) a surface between the contours and calculate the volume and surface area of either the lungs or the pleural lesions (Fig. 3). These structures were then displayed as polygonal objects (Fig. 4) using a program (GRUMPS) specifically designed for this purpose. Once displayed in this form, we calculated the volume occupied by each of the individual objects (lungs and pleural abnormalities). The specific computer programs (SGITRACE, SOLIDS, and GRUMPS) used to identify the regions of interest and reconstruct the three-dimensional aspects of the lung and pleural have all been developed by the Image Analysis Facility at the University of Iowa.

Statistical analysis. Although our primary interest was to assess the clinical significance of asbestos-induced pleural fibrosis, we were also interested in identifying the validity of computer-assisted methods to assess the extent of asbestos-induced pleural fibrosis. To accomplish these aims, we first compared the lung volumes derived from the HRCT scan images (estimated by our computer-assisted methods) to the total lung capacity which was independently measured by body plethysmography. Next, we compared the computer-derived volumetric estimate of the pleural lesion to the absolute total lung capacity and other relevant measures of lung function. Univariate parametric and nonparametric statistics were appropriately used to examine these initial comparisons (38).

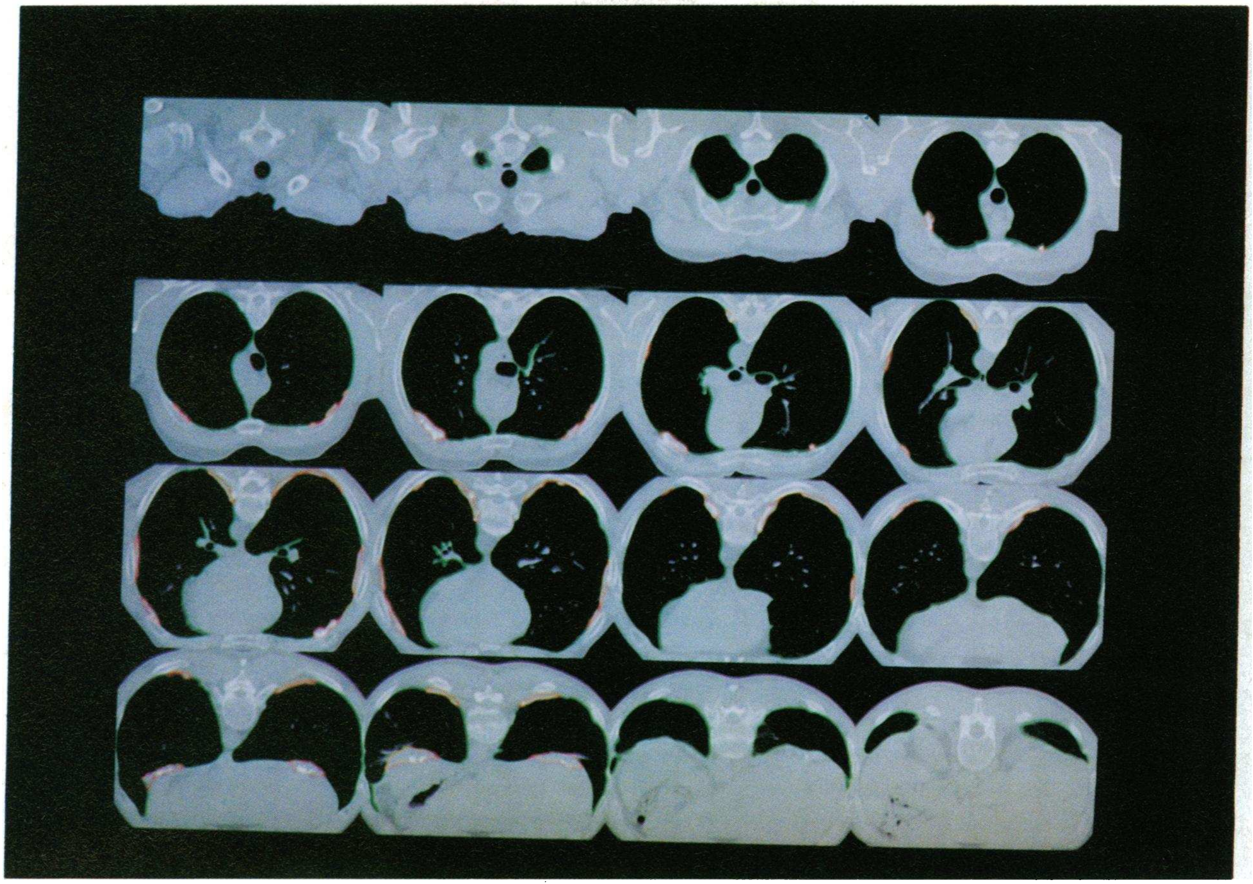
To test whether the computer-derived volumetric estimate of pleural fibrosis was independently associated with the total lung capacity, we used linear multivariate modeling (39). In addition to factors which are known to effect the total lung capacity (age and height) (35), we also controlled for cigarette smoking (pack-years), and the presence of asbestosis (ILO profusion ≥ 1/0) on the chest radiograph. To assess whether the underlying distribution of computer-derived estimates of pleural fibrosis was affecting the multivariate models, logarithmic transformations (base 10) were performed and our model was retested.

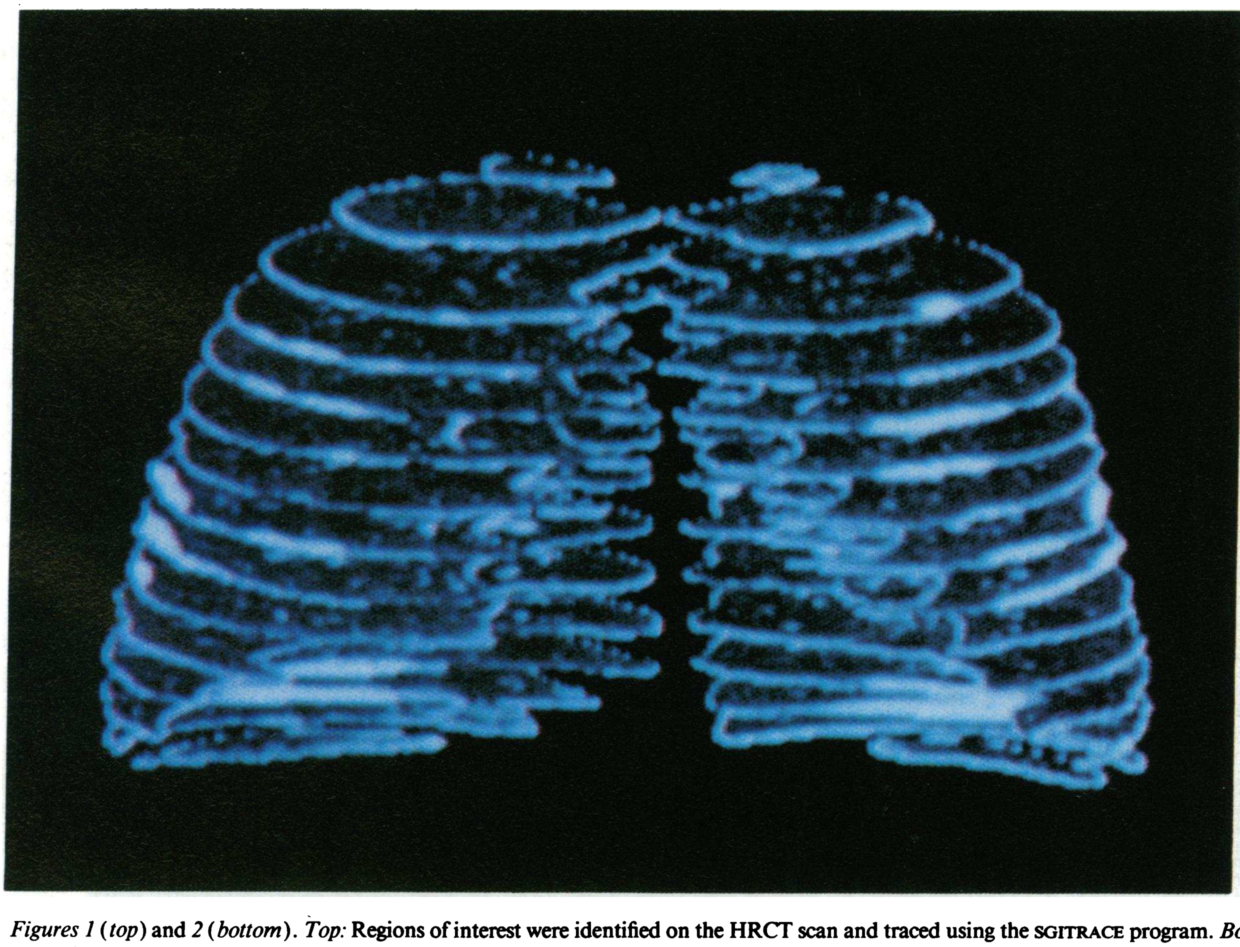
Results

In total, 60 subjects were included in this study. The study population consisted of an older population of primarily white men (Table I). A large percentage of the subjects were either former or current cigarette smokers. Our study population consisted of a high proportion of individuals with radiographic evidence of asbestos-induced lung disease (Table II). In fact, 13.3% had asbestosis, 40.0% had pleural fibrosis, and 18.3% had both asbestosis and pleural fibrosis identified on the chest radiograph. The aggregate pulmonary function results indicate that a wide range of obstructive, restrictive, and gas exchange abnormalities are present in this study population (Table II). Importantly, the total lung capacity and forced vital capacity tended to be lower among those with pleural disease, otherwise, chest x-ray changes were not associated with either obstructive physiology or gas exchange abnormalities.

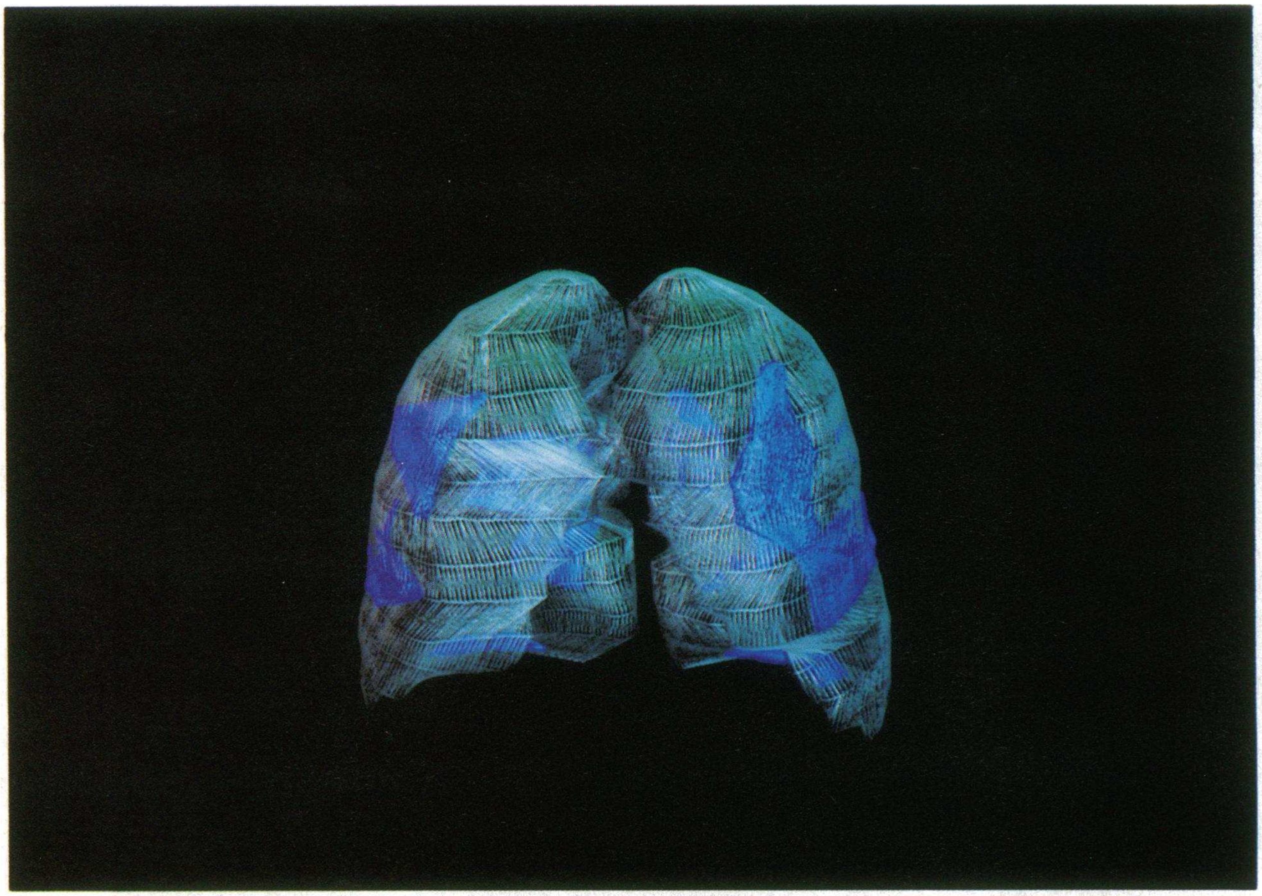
In Table III, we directly compare both the computer-derived estimates of the lung volume and the volume of asbestos-induced pleural fibrosis to the routine chest x-ray and standard measures of lung volume and gas exchange as assessed by pulmonary function tests. Although the computer-derived estimate of lung volume is not significantly related to either radiographic findings or the residual volume, this estimate of lung volume is significantly associated with the total lung capacity and the diffusing capacity of carbon monoxide. In fact, the direct relationship between the computer-derived estimate of lung volume and both the total lung capacity (Table III and Fig. 5) and diffusing capacity of carbon monoxide (Table III) strongly suggests that our computer algorithms that assess volume are a valid representation of the actual lung volume. Since the computer-derived estimates of lung parenchymal volume do not include the "dead space" of the upper and central airways these measures of lung volume are consistently less than the measures of total lung capacity as assessed by body plethysmography (Fig. 5). The HRCT scan identified 29 subjects with pleural fibrosis and the computer algorithms estimated that the volume occupied by the pleural lesions varied from 0.5 to 260.4 ml. Importantly, the volume of the pleural lesion was strongly associated with the presence of pleural fibrosis noted on the chest radiograph and an inverse relationship was observed between the computer-derived estimate of pleural fibrosis and the absolute total lung capacity (Table III and Fig. 6). No clear relationship was identified between the computer-derived estimates of pleural fibrosis and either the residual volume or the diffusing capacity of carbon monoxide.

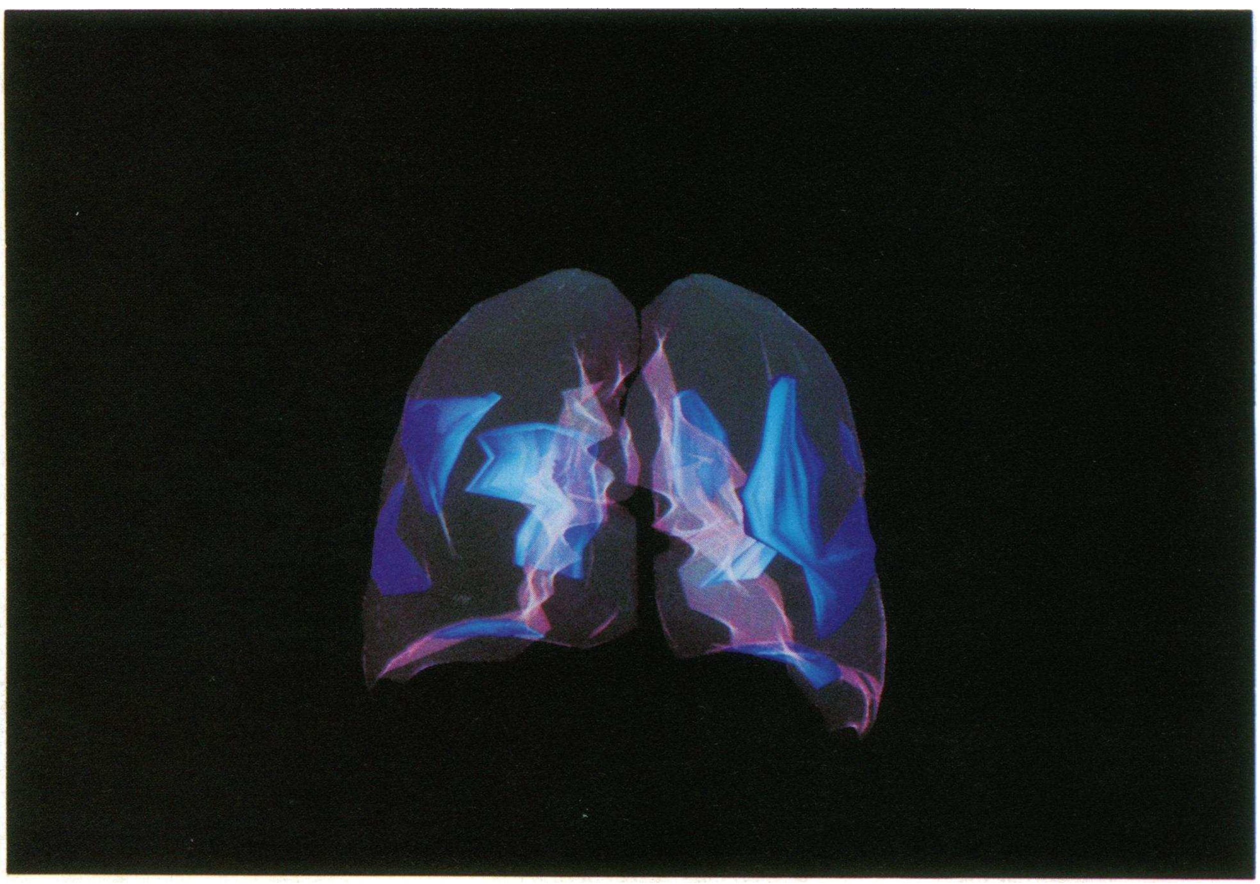
To assess the independent nature of the relationship between the computer-derived volumetric estimate of pleural fibrosis and total lung capacity, we used multivariate modeling. Our initial multivariate model, with only the computer-derived volume of the pleural lesion as our independent variable, demonstrated that pleural fibrosis was significantly (regression





Figures 1 (*top*) and *2* (*bottom*). *Top:* Regions of interest were identified on the HRCT scan and traced using the SGITRACE program. *Bottom:* The traced images were three-dimensionalized by stacking the two-dimensional contours using the actual spacing of the CT slices to separate each traced contour.





Figures 3 (*top*) and *4* (*bottom*). *Top:* The SOLIDS program triangulated (tessellated) the surface between each contour. *Bottom:* The GRUMPS program displayed the triangulated, solid, three-dimensional figure as several polygonal objects.

*Table I. Demographic Characteristics of Study Subjects**

Age (*yr*)	60.0±8.9
Male (%)	100
White (%)	98
Smoking history (%)	
Never	22
Former	65
Current	13
Pack-years of smoking	28.2±23.0

* Values are expressed as the mean±SD for continuous variables and as a percentge of all study subjects for categorical variables.

coefficient = −5.30; $P = 0.017$) associated with the total lung capacity and accounted for 9.5% of the variance of this measure of lung function. After controlling for age, height, the presence of interstitial fibrosis on the chest radiograph, and pack-years of cigarette smoking, the volume of the pleural lesion derived from the HRCT scan remained significantly and inversely related to the total lung capacity (Table IV). Importantly, the regression coefficient between pleural fibrosis and total lung capacity was virtually unaffected by the addition of the potential confounders. Moreover, our results indicate that each ml of pleural fibrosis is independently associated with a 5-ml decrease in the total lung capacity. Very similar results were observed when we used the logarithmic transformation of the computer-derived volumetric estimate of the pleural fibrosis as an independent variable.

Table III. Relationship between the Computer-derived Estimates of Both Lung Volume and Pleural Fibrosis and Both Findings from the Routine Chest X-Ray and Standard Measures of Lung Function

	Computer-derived volumetric estimates	
	Lung volume	Pleural fibrosis
	liters	*ml*
Chest radiograph		
Normal ($n = 17$)	4.4±0.9	9.0±30.2
Asbestosis ($n = 8$)	4.8±0.6	12.9±36.6
Pleural fibrosis ($n = 24$)	4.4±0.7	42.0±51.3*
Asbestosis and pleural fibrosis ($n = 11$)	4.2±0.5	77.5±112.8*
Lung function		
Residual volume	0.18	−0.22
Total lung capacity	0.46‡	−0.40*
Diffusing capacity of carbon monoxide	0.41*	−0.15

The absolute measures of lung function were used in each of these comparisons. For the chest x-ray, computer-derived estimates of lung volume and pleural fibrosis were compared between those with normal chest radiographs and each specific abnormality. Correlation coefficients are presented for the comparison between computer-derived estimates of both lung volume and pleural fibrosis and standard measures of lung function.
* $P \leq 0.001$.
‡ $P \leq 0.0001$.

Discussion

Our results indicate that the volume of the asbestos-induced pleural lesion is independently associated with reduced lung volume. Our results further indicate that computer-derived estimates of lung volume appear to be valid representations of the actual lung volume. In aggregate, these findings indicate that analytic approaches to the CT scan may provide reliable and valid quantitative data that are currently not available in the traditional tools that are used to assess the extent of asbestos-induced lung disease.

Our results further extend the scientific evidence that supports an independent relationship between asbestos-induced pleural fibrosis and lower lung volumes. In fact, our results are supportive of a dose–response relationship between the extent of asbestos-induced pleural fibrosis and the decrement in lung function. We have previously shown that diffuse pleural thickening results in a greater decline in forced vital capacity than

Table II. Pulmonary Function by Type of Chest X-Ray Abnormality for All Study Subjects*

	Chest radiographs			
Pulmonary function	Normal ($n = 17$)	Asbestosis ($n = 8$)	Pleural fibrosis ($n = 24$)	Asbestosis and pleural fibrosis ($n = 11$)
FEV_1	98.3±21.2	95.0±6.6	82.0±20.3‡	86.0±17.2
FVC	95.9±17.9	91.4±9.8	84.8±12.8‡	83.5±10.8‡
FEV_1/FVC ratio	73.2±7.8	75.5±5.0	68.0±11.2	71.6±11.3
TLC	117.0±17.1	111.0±11.8	106.2±16.4‡	106.1±17.8
RV	128.4±36.4	129.3±28.4	116.8±42.0	119.3±42.7
DL_{CO}	108.4±14.7	114.1±11.6	99.9±20.8	105.3±19.4
A-a O_2 difference	20.2±8.3	26.8±6.7	24.8±8.4	26.1±11.3

* Pulmonary function is expressed as the mean±standard deviation. All values represent the percentage predicted except for the FEV_1/FVC ratio and the A-a O_2 difference, which are expressed in absolute terms.
‡ $P < 0.05$ when compared to pulmonary function in those with normal chest x-rays.
Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DL_{CO}, diffusing capacity of carbon monoxide; A-a O_2 difference,

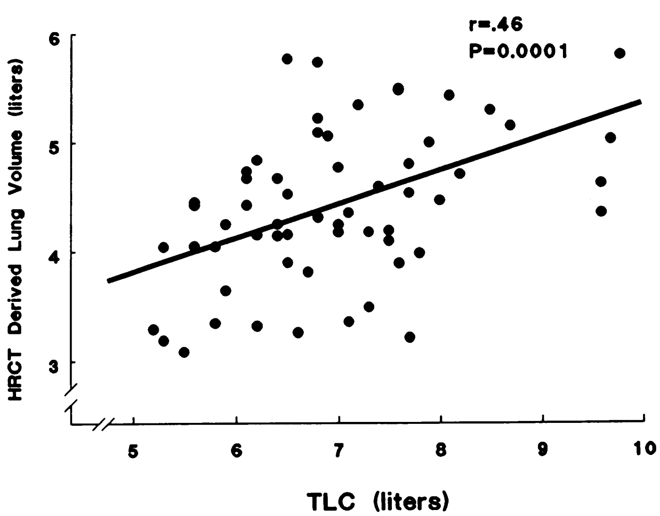


Figure 5. Comparison between the computer-derived estimate of lung parenchymal volume and the total lung capacity, as assessed by body plethysmography.

Table IV. Linear Multivariate Model Assessing the Relationship between the Computer-derived Volumetric Estimate of the Pleural Fibrosis and Total Lung Capacity

	Coefficient (SE)	*P* value
Pleural fibrosis (*liters*)	−5.09 (2.16)	0.02
Age (*yr*)	−0.008 (0.016)	0.63
Height (*cm*)	0.062 (0.027)	0.03
ILO profusion ≥ 1/0	0.029 (0.298)	0.92
Pack-years of smoking	0.007 (0.006)	0.27
Constant	−3.33 (4.70)	0.48
Model R^2	0.18	
F (df)	2.42 (5, 54)	

circumscribed pleural plaques (9). In addition, we (22) and other investigators (10) have found that the length and width of the pleural abnormality and the composite pleural fibrosis index (40) are inversely related to lung function. These observations indicate that lung volumes significantly decline as the amount of asbestos-induced pleural fibrosis increases. Moreover, results from the present investigation demonstrate that each ml of pleural fibrosis is independently associated with a 5-ml decrease in the total lung capacity. Although these findings provide information regarding the cause of restrictive lung function in a cohort of asbestos exposed workers, some caution should be used in the application of these findings to individual patients.

Although compelling evidence (6–20, 40, 41, this investigation) supports an independent association between pleural fibrosis and impaired lung function, the mechanisms accounting for this association are poorly understood. The most logical explanation for this restrictive impairment is that asbestos-induced pleural fibrosis either decreases the compliance of the chest wall or is associated with parenchymal injury that is not evident on the chest radiograph. Although Sison et al. (42) have found that pleural plaques are not associated with pathological evidence of asbestosis, we (21) and others (43) have found that pleural fibrosis is associated with objective evidence of parenchymal injury—either by bronchoalveolar lavage or HRCT scan. Moreover, the chest x-ray is a relatively insensitive indicator of asbestos-induced interstitial changes. Autopsy (44, 45) and pathology (46, 47) studies indicate that 10–15% of individuals with histologic evidence of asbestosis will have normal appearing parenchyma on the chest x-ray. However, findings from our center (21) suggest that although parenchymal inflammation and fibrosis contribute to the loss of lung function in those with asbestos-induced pleural fibrosis, other mechanisms, such as limited expansion of the chest wall may, in part, be responsible for the impaired lung function. In aggregate, these findings suggest that both diminished compliance of the chest wall and asbestos-induced parenchymal injury that is not fully appreciated on the chest x-ray both contribute to the restrictive physiology that has been repeatedly observed in those with asbestos-induced pleural fibrosis.

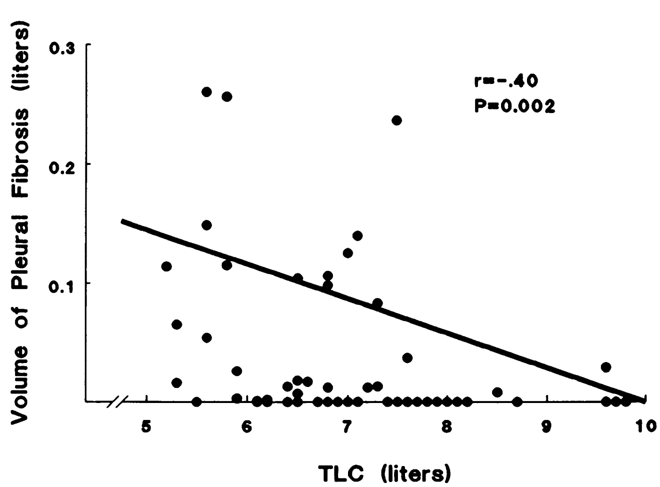


Figure 6. Comparison between the computer-derived volumetric estimate of pleural fibrosis and the total lung capacity, as assessed by body plethysmography.

Although we (21) and others (7, 13, 19) have reported an association between pleural fibrosis and abnormal gas exchange, in the present investigation, we only observed a marginal relationship that was not statistically significant between the computer-derived volumetric estimate of pleural fibrosis and the diffusing capacity of carbon monoxide. The explanation for this inconsistency remains unclear. However, the methodology used to assess pleural disease differed in these studies and may account for the apparent discrepancy. While the previous studies (7, 13, 19, 21) used the standard chest x-ray and the ILO classification system to identify and classify pleural disease, the current investigation used the CT scan and computer modeling to determine the presence and extent of asbestos-induced pleural fibrosis. Importantly, autopsy studies (44, 45) and studies using CT scans (48–51) indicate that the chest radiograph is neither a sensitive nor specific method for identifying asbestos-induced pleural disease. These studies (44, 45, 48–51) indicate that the standard chest x-ray is able to identify between 50% and 80% of the pleural lesions that are actually present. In comparison to the conventional CT scan, the specificity of the chest x-ray for the diagnosis of asbestos-induced pleural fibrosis is only 71% (48). Because images obtained by computer tomography appear to provide more accurate information regarding pleural fibrosis than those obtained by the conventional chest x-ray, one could conclude that the relationship between pleural disease and abnormal gas exchange has probably resulted from misclassification of asbestos-induced lung disease on the chest x-ray. However, further studies are needed to clarify this supposition.

In summary, this investigation identifies a potential role for computer-assisted methods to quantify asbestos-induced pleural lesions. Nonbiased, quantitative approaches to pleural fibrosis may have additional scientific applications. Further studies are needed to clarify the specific determinants of restrictive lung function in asbestos-induced pleural fibrosis and to further explore the relationship between pleural fibrosis and abnormal gas exchange. These techniques will also clearly have important medical applications in assessing the severity and extent of pleural fibrosis, as well as the potential for physiologic consequences, in asbestos exposed workers. Importantly, results from this study clearly demonstrate a dose–response relationship between the amount of pleural fibrosis and the associated decrement in lung volume.

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