Asbestos-induced Pleural Fibrosis and Impaired Exercise Physiology*

Jen-Fu Shih, M.D., M.S., F.C.C.P.; Jeffery S. Wilson, M.D.; Ann Broderick, M.D., M.S.; Janet L. Watt, B.A., R.R.T.; Jeffery R. Galvin, M.D.; James A. Merchant, M.D., Dr.P.H.; and David A. Schwartz, M.D., M.P.H., F.C.C.P.

To further assess the clinical significance of asbestos-induced pleural fibrosis, we performed cardiopulmonary exercise testing in 90 subjects who were exposed to asbestos. Of the 82 subjects without an abnormal resperate exercise, 35 had normal pleura, 33 had circumscribed pleural plaques, and 14 had diffuse pleural thickening. Interstitial fibrosis (International Labor Organization [ILO].≥1/0) was present in 14 of 35 subjects with normal pleura, 13 of 33 subjects with circumscribed pleural plaques, and 2 of 14 subjects with diffuse pleural thickening. Although pleural fibrosis did not appear to be related to impaired respiratory function with exercise in our entire cohort, this finding was confounded by a higher proportion of interstitial fibrosis in subjects with normal pleura. In fact, among study subjects without asbestosis, significant decreases in gas exchange (higher VD/VT and increased alveolar-arterial oxygen pressure difference) were observed at maximal exercise among subjects with pleural fibrosis. Interestingly, neither a higher respiratory rate nor a lower VT/FVC ratio was observed among those with pleural fibrosis, suggesting that the mechanical effects of pleural fibrosis on the chest wall do not explain the increased VD/VT. Using multivariate analyses to control for potential confounders, regression models showed that pleural plaques (p=0.04) and diffuse pleural thickening (p=0.03) were independently associated with significant increases in dead space ventilation (VD/VT) with maximal exercise. These findings indicate that asbestos-induced pleural fibrosis is independently associated with decrements in gas exchange with maximal exercise and suggest that interstitial lung disease, not detected on the routine chest x-ray film, may be responsible for this abnormal response to exercise.

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AT=anaerobic threshold; BF=breath frequency; Dco=diffusing capacity for carbon monoxide; FEV_1= forced expiratory volume in one second; FVC=forced vital capacity; HR=heart rate; ILO=International Labor Organization; MVV=maximal voluntary ventilation; $P(A\text{-}a)O_2$=alveolar-arterial oxygen pressure difference; $P(a\text{-}ET)CO_2$=arterial-end tidal P_{CO_2} difference; TLC=total lung capacity; VD=physiologic dead-space volume; VT=tidal volume

Circumscribed plaques and diffuse pleural thickening are the most common manifestations of asbestos exposure.[1] Circumscribed plaques occur as discrete elevated, gray-white lesions on the parietal pleura of the thoracic wall and diaphragm. Pleural plaques usually appear about 20 years after first exposure to asbestos. On posteroanterior chest x-ray film, plaques tend to show increasing density with a distinct medial border and a dense lateral shadow. The radiographic features of pleural plaques are even more evident when the plaques are calcified. Diffuse pleural thickening that may be unilateral or bilateral, is the result of fibrosis and thickening of the visceral pleura. In diffuse pleural thickening, the fibrotic process may involve the parietal pleural and extend into the interlobar fissures and costophrenic angles. Although a pre-existent asbestos-related pleural effusion is postulated to be the cause of diffuse pleural thickening,[2] the exact pathogenesis remains unclear.

For editorial comment see page 1312

Collectively termed pleural fibrosis, circumscribed pleural plaques and diffuse pleural thickening are important for several reasons. Not only are they reliable radiographic markers of past asbestos exposure, but pleural fibrosis has been found to be independently associated with an increased risk for development of asbestosis.[3] Once pleural fibrosis exists, these chest wall lesions are likely to progress throughout life.[4] Importantly, previous investigations have shown that both circumscribed pleural plaques and diffuse pleural fibrosis are independently associated with restrictive ventilatory impairment[5-13] and excess dyspnea.[6,12,14] As cumulative occupational exposure to asbestos decreases, the prevalence and extent of parenchymal abnormalities will also decrease[15] and

*From the Pulmonary Disease Division, Department of Internal Medicine, Department of Preventive Medicine, Department of Veterans Affairs, The University of Iowa, Iowa City, Iowa; and Department of Chest Medicine, Veterans General Hospital, Taipei, Taiwan, Republic of China.

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Reprint requests: Dr. Schwartz, Department of Medicine C33-GH, University of Iowa, Iowa City 52242

pleural abnormalities may become more frequently the sole manifestation of asbestos exposure. Accordingly, it is important to further understand the physiologic significance of these abnormalities.

Although asbestos-induced pleural fibrosis is the most common roentgenographic abnormality among asbestos-exposed workers and has recently been shown to contribute to the development of restrictive lung function,[5-13] only a few investigations have examined the effect of pleural fibrosis on maximal exercise.[16-18] Pleural fibrosis may either limit lung expansion and increase the work of breathing or lead to altered proprioceptive information resulting in an abnormal ventilatory pattern.[19] Alternatively, pleural fibrosis may simply be an indicator of prior asbestos exposure, placing an individual at higher risk of parenchymal fibrosis that is not appreciated on the routine chest radiogram.[9,20] Since pleural plaques arise from the parietal pleural and diffuse pleural thickening primarily involves the visceral pleura, it is very likely that more than one of these mechanisms account for the development of restrictive lung function.

The purpose of this investigation was to clarify the relationship between asbestos-induced pleural fibrosis and abnormal lung function by examining the effect of pleural fibrosis on maximal exercise. Since exercise requires not only lung and heart function but also an intact systemic and pulmonary circulation for gas transport and exchange, cardiopulmonary exercise testing is considered to be useful in reflecting pulmonary physiology,[16-18,21-25] evaluating unexplained dyspnea[26-27] and determining the overall extent of pulmonary impairment.[22] Previous studies[16-18] have shown that diminished gas exchange (V_D/V_T or alveolar-arterial oxygen pressure [$P(A\text{-}a)O_2$] difference) are associated with the presence of pleural fibrosis during exercise. It is reasonable to hypothesize that if radiographically undetected parenchymal disease is responsible for the restrictive lung function among individuals with asbestos-induced pleural fibrosis, certain gas-exchange indices (dead space ventilation, alveolar-arterial PO_2 difference, and arterial-end tidal P_{CO_2} difference) during maximal exercise would be independently associated with pleural fibrosis.

Methods

Study Population

The subjects were selected as part of our NHLBI-supported SCOR program in interstitial and occupational lung disease. The subjects were occupationally exposed to asbestos and were identified through either the Sheet Metal Worker's 1986 screening program[5] or from the Occupational Medicine Clinic at the University of Iowa. All study subjects had been occupationally exposed to asbestos for at least 1 year in a high-exposure setting and had a minimum of 20 years between the first exposure to asbestos and entry into the study.

Chest Radiographs

Posteroanterior chest radiographs were interpreted independently by three experienced readers, according to the International Labor Organization (ILO) 1980 classification system of radiographs of pneumoconioses.[28] Each reader was blinded to all other clinical information. Agreement between at least two of three readers was required to identify either a parenchymal or pleural abnormality. There was only one case that all three readers differed on the degree of parenchymal profusion; the median reading was chosen for this case. For the purpose of this study, we defined asbestosis as an ILO profusion of 1/0 or greater. The ILO classification system was used to identify the presence of pleural fibrosis and differentiate circumscribed plaque from diffuse pleural thickening. We defined diffuse pleural thickening as requiring obliteration of the costophrenic angle on the involved side. This distinction has been shown to be helpful in decreasing intra- and interreader variability[29] in distinguishing circumscribed pleural plaques from diffuse pleural thickening.

Pulmonary Function Testing

The resting pulmonary function tests included spirometry that were determined by using a Medical Graphics 1070 system (St. Paul, Minn), lung volumes were determined by body plethysmography (Medical Graphics 1085 system), a single breath diffusing capacity was measured using a Medical Graphics 1070 system, and arterial blood gases were measured using a standard blood gas analyzer. The measurements were performed according to the standard protocols set forth by the American Thoracic Society guidelines.[30] The predicted normal values of Morris et al[31] were used for spirometry, Goldman and Becklake[32] for lung volumes, and Van Ganse et al[33] for diffusing capacity. Standard calculations were used to determine the $P(A\text{-}a)O_2$ difference. None of the study subjects were using supplemental oxygen.

Exercise Testing

The subjects were exercised on a cycle ergometer. Care was taken to adjust the saddle and valve mouthpiece in a comfortable position. Resistance was increased in a constant fashion between 20 and 25 W/min. A 12-lead electrocardiogram was performed on each patient. A percutaneous arterial blood gas was performed immediately pre- and postexercise to assess ventilation perfusion relationships. Subjects inspired through a low resistance, high velocity Hans Rudolph valve. Expired gas was sampled and analyzed for oxygen and carbon dioxide using a Medical Graphics CPX/Max metabolic cart (St. Paul, Minn). Patients were exercised to a symptom-limited maximal effort. The following variables were measured: min ventilation ($\dot{V}_E$), O_2 uptake ($\dot{V}_O$), CO_2 output ($\dot{V}_{CO_2}$), respiratory exchange ratio (R), oxygen pulse (O_2-pulse), tidal volume (V_T), breath frequency (BF), end-tidal P_{O_2} and P_{CO_2} ($P_{ET}O_2$ and $P_{ET}CO_2$), ventilatory equivalents for O_2 and CO_2 ($\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$), and heart rate. Physiologic dead space (V_D was calculated using the Bohr equation [$V_D/V_T=(PaCO_2-P_ECO_2)/PaCO_2$], where P_ECO_2 is partial pressure of mixed expired CO_2.[34] The ratio of dead space to tidal volume (V_D/V_T), arterial-end-tidal P_{CO_2} difference [$P(a\text{-}ET)CO_2$], and alveolar-arterial P_{O_2} difference [$P(A\text{-}a)O_2$] were determined immediately before and immediately after exercise. The maximal $\dot{V}_{O_2}$ ($\dot{V}_{O_2}$ max) was chosen as the highest $\dot{V}_{O_2}$ recorded for any 30-s exercise. Maximal heart rate (HR) was similarly determined. The maximal O_2-pulse was measured as $\dot{V}_{O_2}$max/HR measured at the time of $\dot{V}_{O_2}$max. We estimated the anaerobic threshold (AT) as $\dot{V}_{O_2}$ during incremental exercise at which the $P_{ET}O_2$ increased while the $P_{ET}CO_2$ remained constant and the $\dot{V}_E/\dot{V}_{O_2}$ increased while the $\dot{V}_E/\dot{V}_{O_2}$ remained unchanged. Two variables were used to determine potential cardiac and pulmonary limitation to

exercise capacity. The HR reserve was calculated as predicted maximal HR minus the maximal exercise HR/predicted maximal HR, where predicted maximal HR was calculated as 220-age.[35] The breathing reserve was determined using a standard equation (1-[$\dot{V}_E$max/MVV]). Maximal work capacity was defined as $\dot{V}_{O_2}$max/pred $\dot{V}_{O_2}$max. Work capacity at anaerobic threshold was defined as $\dot{V}_{O_2}$ at AT/pred $\dot{V}_{O_2}$max. The predicted maximal oxygen uptake was calculated using Hanson et al's modified values for cycle exercise of Bruce et al's treadmill calculation.[36,37] A physician interpreted the gas exchange and other data collected during exercise and assessed the primary limiting factor to exercise. A fall in systolic BP more than 15 to 20 mm Hg, a rise in systolic BP in excess of 240 mm Hg, or a rise in diastolic BP in excess of 130 was considered as unstable BP. In addition, a progressive ST-segment depression with horizontal or downslope of ST segment, T wave inversion or the appearance of Q waves was considered an ischemic change on electrocardiogram. Exercise was performed until either the subject indicated that he could no longer continue or the physician thought that further exercise was potentially hazardous. In total, 8 exercise tests were stopped by the physician and 26 subjects stopped because of dyspnea, 1 subject stopped because of chest pain, 49 subjects stopped because of muscle pain, and 3 subjects stopped because of joint pain (Table 1).

Statistical Methods

Univariate comparisons were made to determine whether demographic or clinical variables were associated with the presence and type of pleural fibrosis. The difference of prevalence of categorical variables between asbestos-exposed workers with normal pleura and those with either circumscribed pleural plaques or diffuse pleural thickening were compared by either the chi-square test of Fisher's Exact Test of probability. The Fisher's Exact Test was used when the expected cells contained five or fewer subjects. Analysis of variance and Student's *t* test were used to examine differences of means for normally distributed continuous variables, such as physiologic results from pulmonary exercise testing. Whereas Kruskal-Wallis test and the Mann-Whitney *U* test were used for those continuous variables that were not distributed normally.

Linear multivariate analysis was performed to identify whether the presence of either circumscribed plaques or diffuse pleural thickening was independently associated with physiologic results obtained from exercise testing after controlling for all potential confounders. Dummy variables were established for smoking history and for ILO roentgenographic profusion category. This approach enabled us to determine the relative strength of the relationship between specific physiologic changes with maximal exercise and pleural fibrosis after controlling for age, height, weight, the degree of interstitial fibrosis (ILO profusion), and the subject's smoking history.

Table 1—*Demographic Characteristics* of Study Subjects (n=82)*

Age, yr	62.1 ± 8.4
Male, %	100
White, %	97.6
Smoking history	
Never	17 (20.7%)
Former	51 (62.2%)
Current	14 (17.1%)
Reason for stopping exercise	
Chest pain	1 (1.2%)
Leg pain	49 (59.8%)
Dyspnea	26 (31.7%)
Joint pain	3 (3.7%)
Other	3 (3.7%)

*Values are expressed as the mean ± SD for continuous variables and % for categorical variables.

RESULTS

In total, 90 subjects participated in this study and had a full exercise test performed. Eight of these subjects were found to have an abnormal cardiac response to exercise (six unstable BP and two ischemic electrocardiogram) and these individuals were excluded from further analysis. The remaining subjects consisted of 82 men, having a mean age of 62 years (Table 1). Almost all of our subjects were white (97.6 percent) and most had a history of cigarette smoking (79.3 percent were either former or current smokers).

Among the 82 study subjects, 35 were classified as having normal pleura, 33 were classified as having circumscribed pleural plaques, and 14 subjects were classified as having diffuse pleural thickening. Interstitial fibrosis (ILO≥1/0) was present in 40 percent of those with normal pleura, 39 percent of those with circumscribed pleural plaques, and 14 percent of those with diffuse pleural thickening (Table 2). Although the prevalence of interstitial fibrosis in subjects with normal pleura was higher than those with diffuse pleural thickening, this finding was quite different from the usual observation that subjects with diffuse pleural thickening are more likely to have asbestosis than those of normal pleura.[7] The explanation for this difference is that our study subjects were selected from an asbestos-exposed cohort on the basis of specific radiographic abnormalities that we have been particularly interested in studying.

When compared with those with normal pleura, asbestos-exposed workers with pleural plaques tended to be older and have a lower maximum voluntary ventilation and FVC (Table 3). Similarly, in subjects with diffuse pleural thickening, both measures of air flow and lung volume were significantly reduced when compared with those with normal pleura. In addition, large mean differences in the diffusing capacity of carbon monoxide were observed between subjects with diffuse pleural thickening and those with normal pleura. These differences, however,

Table 2—*Comparison of Roentgenographic Fibrosis by Presence and Type of Pleural Fibrosis**

	Normal Pleura (n=35)	Pleural Plaque (n-33)	Diffuse Pleural Thickening (n=14)
Asbestosis ≥1/0	14 (40.0%)	13 (39.4%)	2 (14.3%)
ILO Profusion			
<1/0	21 (60%)	20 (60.6%)	12 (85.7%)
≥1/0, <2/1	11 (31.4%)	13 (39.4%)	2 (14.3%)
≥2/1	3 (8.6%)	0 (0%)	0 (0%)

*Data in table represent subjects (%).

Table 3—*Demographic and Clinical Characteristics by Presence and Type of Pleural Fibrosis*

	Normal Pleura (n=35)	Pleural Plaque (n=33)	Diffuse Pleural Thickening (n=14)
Age, yr	59.6±8.1	64.1±7.7*	63.4±9.3
Smoking history			
Never	6 (17.1%)	7 (21.2%)	4 (28.6%)
Former	22 (62.9%)	21 (63.6%)	8 (57.1%)
Current	7 (20.0%)	5 (15.2%)	2 (14.3%)
Pack-years of smoking	33.1±26.8	31.6±27.2	23.7±24.7
White, %	100	93.9	100
Height, cm	173.9±5.6	172.8±5.5	174.8±5.6
Weight, kg	90.3±16.3	92.3±13.4	90.8±18.4
Yr in trade	31.5±12.2	33.5±10.5	36.1±10.0
Yr from first asbestos exposure	40.0±9.0	44.2±7.7	41.8±9.9
MVV, L	125.7±29.9	100.1±30.0*	107.3±25.5*
FEV_1, % pred	95.7±22.2	88.0±22.7	79.9±12.9*
FVC, % pred	95.7±19.3	86.0±17.4*	84.6±9.4*
FEV_1/FVC, %	71.1±8.9	71.2±10.8	66.1±10.7
TLC, % pred	113.2±18.3	110.9±15.6	99.7±17.5*
Dco, % pred	108.7±25.7	109.3±20.9	100.0±13.0

*p value <0.05 compare with workers with normal pleura.

were not statistically significant. Importantly, workers with either pleural plaques or diffuse pleural thickening had similar asbestos exposure history and smoking status when compared with those with normal pleura.

Interestingly, neither circumscribed plaques nor diffuse pleural thickening appeared to be related to impaired respiratory function or gas exchange with exercise (Table 4). Subjects with asbestosis, however, were found to have evidence for $\dot{V}/Q$ mismatch (a higher P[A-a]O_2 difference, V_D/V_T ratio, and P[a-ET]CO_2 difference) with maximal exercise (data not presented). Since asbestosis was more prevalent among those with normal pleura, the relationship between pleural fibrosis and the pulmonary response to exercise was confounded by the excess presence of interstitial fibrosis among those with normal pleura. Stratifying by the presence of asbestosis, we found that among study subjects without asbestosis, significant decreases in gas exchange (higher V_D/V_T ratio and increased P[A-a]O_2 difference) were observed at maximal exercise among subjects with diffuse pleural thickening (Table 5). Interestingly, for measures of gas exchange with maximal exercise, subjects with pleural plaques fell in-between those with normal pleura and those with diffuse pleural thickening. Importantly, neither a higher respiratory rate nor a lower V_T/FVC ratio accompanied the decrement in gas exchange among those with pleural fibrosis. This finding suggests that decreased chest wall compliance alone does not explain the increased V_D/V_T among those with pleural fibrosis (Table 5). Similar differences of gas exchange among subjects with asbestos-induced pleural fibrosis, however, were not observed when we limited our analysis to study subjects with asbestosis (Table 6).

Table 4—*Exercise Testing Results* by Presence and Type of Pleural Fibrosis*

	Normal Pleura (n=35)	Pleural Plaque (n=33)	Diffuse Pleural Thickening (n=14)
Maximal work capacity, %	88.5±18.7	89.2±20.6	84.4±21.1
Work capacity at AT, %	53.8±13.9	56.3±14.0	50.0±13.2
Breathing reserve, %	36.7±18.6	29.3±19.3	33.5±17.4
P(A-a)O_2 (rest), mm Hg	23.7±15.1	23.7±9.2	18.8±7.3
P(A-a)O_2 (max), mm Hg	17.9±15.3	19.2±11.6	19.7±10.4
V_D/V_T (rest), %	39.2±9.0	39.7±5.7	39.6±6.4
V_D/V_T (max), %	20.6±12.6	23.6±9.0	25.6±8.2
P(a-ET)CO_2 (rest), mm Hg	4.09±6.08	3.29±3.64	1.77±3.37
P(a-ET)CO_2 (max), mm Hg	−0.88±5.36	0.52±3.98	0.23±2.68
Heart rate reserve, %	14.6±10.2	16.9±13.3	11.4±9.9

*Values in table are expressed as the mean±standard deviation.

To further examine the relationship between pleural fibrosis and gas exchange with maximal exercise, we used multivariate analysis to evaluate this rela-

Table 5—*Exercise Testing Results* by Presence and Type of Pleural Fibrosis in Subjects without Asbestosis (ILO <1/0)*

	Normal Pleura (n=21)	Pleural Plaque (n=20)	Diffuse Pleural Thickening (n=12)
Maximal work capacity, %	93.3±15.0	91.4±20.7	82.7±21.6
Work capacity at AT, %	57.2±14.2	54.1±11.8	50.6±14.2
Breathing reserve, %	36.7±17.1	29.7±17.9	33.9±18.2
P(A-a)O_2 (rest), mm Hg	18.8±8.8	22.5±9.4	19.2±7.8
P(A-a)O_2 (max), mm Hg	12.7±8.7	15.4±8.7	21.3±10.5†
V_D/V_T (rest), %	38.7±8.7	38.7±4.6	39.7±6.9
V_D/V_T (max), %	17.6±10.8	20.2±7.9	25.6±8.9†
P(a-ET)CO_2 (rest), mm Hg	3.43±3.12	3.05±3.63	1.91±3.67
P(a-ET)CO_2 (max), mm Hg	−1.85±5.30	−0.53±3.47	0.09±2.91
Heart rate reserve, %	11.6±9.8	16.9±13.5	12.5±10.1
Respiratory rate (max)	36.2±7.4	41.0±12.5	36.5±9.5
V_T/FVC (max), %	52.7±9.8	51.8±10.1	52.6±10.1

*Values in table represent the mean±standard deviation.
†p value <0.05 compare with workers with normal pleura.

Table 6—*Exercise Testing Results* by the Presence of Pleural Fibrosis in Subjects with Asbestosis (ILO ≥1/0)*

	Normal Pleura (n=14)	Pleural Fibrosis (n=15)
Maximal work capacity, %	81.2±21.7	87.0±20.2
Work capacity at AT, %	48.8±12.2	57.8±16.3
Breathing reserve, %	36.7±21.4	29.0±20.9
P(A-a)O_2 (rest), mm Hg	31.0±19.5	24.4±8.8
P(A-a)O_2 (max), mm Hg	25.2±19.7	23.1±13.4
V_D/V_T (rest), %	40.0±9.7	40.9±6.6
V_D/V_T (max), %	24.8±14.1	28.5±7.7
P(a-ET)CO_2 (rest), mm Hg	5.07±8.95	3.29±3.63
P(a-ET)CO_2 (max), mm Hg	0.50±5.32	2.00±4.00
HR reserve, %	19.1±9.4	15.3±13.5

*Values in table represent the mean±standard deviation.

tionship in all study subjects. In these analyses, we controlled for potential confounders (age, height, weight, smoking history, pack-years of smoking, and ILO profusion category) and examined the relationship between asbestos-induced pleural disease and specific measures of gas exchange with maximal exercise. Regression models showed that pleural plaques and diffuse pleural thickening were independently associated with significant increases in dead space ventilation (V_D/V_T ratio) with maximal exercise (Table 7). The regression coefficients indicated that after controlling for age, height, weight, smoking history, pack-years of smoking, and ILO profusion category, compared with subjects with normal pleura, asbestos-exposed workers with diffuse pleural thickening had on average a 8.1 percent increase in V_D/V_T ratio and workers with circumscribed plaques had on average a 4.8 percent increase in V_D/V_T ratio with maximal exercise.

Discussion

Our results indicate that significant decreases in gas exchange in response to maximal exercise are observed among those with asbestos-induced pleural fibrosis. Although these findings were most apparent when we limited our analysis to those with normal parenchyma on the chest x-ray film, we also observed these findings in all of our study subjects using multivariate modeling. Interestingly, neither a higher respiratory rate nor a lower V_T/FVC ratio was observed among those with pleural fibrosis, suggesting that the mechanical effects of pleural fibrosis on the chest wall do not explain the abnormal trends in dead space ventilation with maximal exercise. In aggregate, these results suggest that interstitial lung disease, not detected on the routine chest x-ray film, may be responsible for this abnormal response to exercise in patients with asbestos-induced pleural fibrosis.

Previous studies[16-18] support our findings that asbestos-induced pleural fibrosis is associated with diminished gas exchange during exercise. Howard et al[16] evaluated pulmonary function tests at rest and exercise in 90 asbestos-exposed subjects who were dyspneic and had pleural plaques radiographically. Interestingly, an elevated dead space ventilation fraction and associated increase in $\dot{V}_E/\dot{V}_{O_2}$ were observed among many of those with an isolated reduction in the diffusing capacity. Picado et al[17] reported exercise physiology in six dyspneic patients with asbestos-related pleural fibrosis. Significant interstitial fibrosis was excluded by gallium scan and CT. Most subjects showed increases in minute ventilation, higher respiratory rate, decreased tidal volume, and elevated V_D/V_T ratio during submaximal exercise. Diaphragmatic fatigue assessed by electromyographic techniques did not appear to contribute to the abnormal exercise pattern. Since Picado et al selected patients with normal lung compliance, the abnormal response to exercise was attributed to

Table 7—*Multivariate Linear Regression for Relationship between Type of Pleural Fibrosis and V_D/V_T Ratio at Maximal Exercise*

	Pleural Plaques vs Normal Pleura			Diffuse Thickening vs Normal Pleura		
	Coefficient	(SE)	p Value	Coefficient	(SE)	p Value
Pleural fibrosis	0.048	(0.023)	0.04	0.081	(0.035)	0.03
Age, yr	0.005	(0.001)	0.001	0.002	(0.002)	0.24
Weight, kg	−0.002	(0.001)	0.05	−0.003	(0.001)	0.04
Height, cm	0.003	(0.002)	0.16	0.004	(0.004)	0.26
ILO profusion						
1	0.050	(0.023)	0.04	0.031	(0.036)	0.40
2	0.173	(0.059)	0.01	0.182	(0.069)	0.01
Current smoker	0.063	(0.047)	0.18	0.121	(0.073)	0.10
Former smoker	0.039	(0.033)	0.25	0.075	(0.046)	0.11
Pack-years	$5.0\cdot10^{-4}$	($5.5\cdot10^{-4}$)	0.37	$-0.1\cdot10^{-4}$	($8.5\cdot10^{-4}$)	0.99
Constant	−0.549	(0.377)	0.15	−0.496	(0.547)	0.37
Model R^2	0.43			0.42		
F (df)	5.21 (9,61)			2.90 (9, 36)		

reduced compliance of the visceral pleura. This, in turn, could be accounted for by increases in chest wall impedance due to reduced compliance of the pleural surface. A recent study involved 23 dyspneic workers with asbestos-induced pleural fibrosis and no evidence of asbestosis on chest x-ray film. Among these subjects, pleural fibrosis was reported to be associated with excess dead space ventilation with exercise.[18] Importantly, increased V_D/V_T ratio with exercise is characteristic of interstitial fibrosis rather than chest wall deficits.[38] Thus, although some investigators[17,39-40] have concluded that compliance of the chest wall/pleura contributed to the development of restrictive lung function in those with pleural fibrosis, the exact determinants of this functional deficit are not at all clear. Moreover, since individuals with circumscribed pleural plaques (usually with very little chest wall involvement) also develop restrictive lung function,[8-13] abnormal diffusing capacity of carbon monoxide,[8,10,13] and abnormal gas exchange with exercise, it remains difficult to accept chest wall compliance as the sole mechanism accounting for this functional abnormality.

The cause of an elevated V_D/V_T associated with asbestos-induced pleural disease can be explained in two ways. First, the increased V_D/V_T ratio is an indicator of ventilation-perfusion mismatching and suggests subclinical interstitial fibrosis. With V/Q mismatching present, the ventilation of these poorly perfused lung units contributes little to gas exchange, hence causing wasted ventilation or increased V_D/V_T. The widening of $P(A\text{-}a)O_2$ during exercise that was observed in our study may further support the existence of V/Q mismatching. Second, decreased tidal volume may be caused by asbestos-related pleural fibrosis due to decreased chest wall compliance. Increased frequency of breathing and decreased tidal volume may accompany these conditions; however, this was not observed in our study (Table 5). Widening of $P(A\text{-}a)O_2$ without a concomitant increase in respiratory rate and decreased V_T/FVC at maximal exercise were observed among our study subjects with pleural fibrosis. These results suggest that interstitial lung disease not detected on the routine chest x-ray film may be responsible for this abnormal response to exercise.

Fridriksson et al suggested "since the asbestos fiber must pass through the lungs to reach the pleural space, it is conceivable that persons with pleural plaques also may have lung parenchymal changes that are not detectable on the chest radiogram."[11] Several pieces of evidence suggest that parenchymal inflammation, fibrosis, or both are the principal determinants of abnormal gas exchange in workers with asbestos-induced pleural fibrosis. First, the conventional chest radiograph is not a very sensitive tool for diagnosing early pulmonary fibrosis. Recent data indicate that the high-resolution CT scan is more sensitive than the chest x-ray for detection of asbestosis.[41,42] It is able to identify the presence of asbestos-induced interstitial change not yet apparent on conventional radiographs. Second, among subjects with pleural fibrosis, an autopsy study revealed that 5 of 29 individuals with radiologically normal lung parenchymal proved to have interstitial fibrosis pathologically.[43] Third, bronchoalveolar lavage showed a higher percentage of lymphocyte in persons with asbestos-induced pleural fibrosis and no evidence of asbestosis on the chest radiogram.[13,44] Fourth, pulmonary function tests revealed decreased diffusing capacity for carbon monoxide[8,10,13] and decreased lung compliance[11] in conjunction with reduced lung volume in workers with pleural fibrosis.

In conclusion, our findings indicated that asbestos-induced pleural fibrosis is independently associated with decrements in gas exchange with maximal exercise and suggest that interstitial lung disease, not detected on the routine chest x-ray film, may be responsible for this abnormal response to exercise.

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