Asbestos and Airflow Limitation

Z. Mohsenifar, MD; A. J. Jasper, MD; T. Mahrer, MD; and S. K. Koerner, MD

To assess the effect of asbestos on the airways, researchers studied 45 shipyard workers who were lifelong nonsmokers and had asbestos-related abnormalities seen on their chest roentgenograms. Patients with interstitial lung disease, bronchial asthma prior to asbestos exposure, recurrent pneumonias, or significant cardiovascular disease were excluded from the study. In addition to chest films, they had spirometry performed before and after bronchodilator inhalation, lung volumes, diffusing capacity, and arterial blood gases. Forced vital capacity and forced expired volume in one second were normal in all patients. Maximum midexpiratory flow rates (MMFR) were abnormal (MMFR less than 75% of predicted) in 13 patients (29%). Therefore, 29% of lifetime nonsmokers with asbestos exposure exhibited evidence of small airways dysfunction. An abnormal MMFR in these workers may be due, in part, to asbestos exposure and could conceivably indicate a population at risk for pulmonary fibrosis and/or obstructive airways disease.

Pulmonary function studies in asbestos workers without parenchymal abnormalities are usually normal. When abnormal they are characterized by a restrictive pattern and a reduced diffusing capacity.[1] A few investigators have suggested that airways obstruction, particularly in small airways, is associated with exposure to asbestos.[2-5] However, past or current smokers were not excluded, so the specificity of the abnormal physiologic findings is unclear. A recent study reported that seven of 17 lifetime nonsmoking asbestos workers had spirometric evidence of airflow limitation. However, this abnormality was associated with a restrictive ventilatory defect, while workers without restrictive ventilatory defects had pulmonary function comparable to control subjects.[6] From 1980 until 1984, we evaluated approximately 400 shipyard workers, of whom 45 were lifetime nonsmokers. This allowed us the opportunity to assess the effect of asbestos on the airways without the compounding influence of cigarette smoke.

Division of Pulmonary Medicine, Cedars-Sinai Medical Center, UCLA School of Medicine, Box 48570, 8700 Beverly Blvd, Los Angeles, CA 90048 (address correspondence to Dr Mohsenifar).

0096-1736/86/2809-817$02.00/0

Subjects and Methods

Patients were referred to us by the Department of Labor. Most were exposed primarily to chrysotile asbestos while working in the shipyards of Long Beach, California. The following evaluations were done: (1) a complete history and physical examination, including a detailed occupational history; (2) posteroanterior, lateral, and bilateral oblique chest roentgenograms; (3) a 12-lead ECG; and (4) resting pulmonary function studies.

The occupational history included a complete job history and industrial toxin exposure history. Asbestos exposure was classified according to (1) duration of exposure; (2) qualitative nature of exposure, which was either primary (worked directly with asbestos-containing materials) or secondary (worked in same area, but not directly with asbestos); (3) quantitative nature of exposure, which was either heavy (asbestos dust visible in air), moderate (asbestos dust visible on floor and work surface), or light (no dust visible).

Radiographic findings on the chest roentgenograms were categorized according to the International Labor Organization/UC classification.[7] The degree of pleural thickening was classified into three grades. Grade 1 was pleural thickening up to 5 mL in thickness which, alone or combined with similar shadows, did not exceed one half of the projection of one lateral chest wall. Grade 2 was pleural thickening more than 5 mL in thickness and up to one half of the lateral chest wall or less than 5 mL in thickness if it extends over more than one half of the lateral chest wall. Grade 3 was pleural thickening more than 5 mL in thickness and extending over more than one half of a lateral chest wall.

The resting pulmonary function study included measurement of lung volumes, forced expiratory flow rates, single-breath diffusing capacity for carbon monoxide, and arterial blood gases. Slow vital capacity (SVC),

forced vital capacity (FVC), and forced expired volume in one second (FEV_1) were measured in duplicate using a 12-L dry rolling seal spirometer (Cardiopulmonary Instruments, Model 220). Flow rates were repeated after the inhalation of four puffs of isoetharine. We considered FVC or FEV_1/FVC abnormal if either was more than one SD below the predicted value.[8] Lung volumes were measured by helium dilution,[9] and predicted values were calculated using the data of Goldman and Becklake[10] and Boren et al.[11] Arterial blood gases were measured using a blood gas analyzer (Corning Model 175), and the alveolar-arterial oxygen difference (A-a)PO_2 was calculated. The single-breath diffusion capacity (DL_{CO}) was measured in the sitting position in duplicate by the single-breath method described by Ogilvie et al.[12] Breath-holding times during DL_{CO} determinations were 10 seconds and were measured by the method of Jones and Mead.[13] Predicted values for DL_{CO} were calculated using the data of McGrath and Thomson.[14] When FEV_1/FVC was normal, maximum midexpiratory flow rate (MMFR) was used to detect small airways obstruction. We expressed MMFR as a percent of predicted. Values of less than 75% of predicted were considered abnormal.[15] Patients with interstitial lung disease, history of prior bronchial asthma, prior pneumonias or cardiac disease were excluded from the study. Patients with any history of smoking tobacco or any history of exposure to other toxins or fumes were excluded from the study.

Statistical Analysis

All data are presented as mean ± one SD of the mean. We compared patients with abnormal MMFR to those with normal MMFR by means of the Kruskal-Wallis test and the Mann-Whitney U test, which are nonparametric tests similar to the analysis of variance and Student's *t* test. We considered *P* values of less than .05 to be significant.

Results

All patients were make with a mean age of 53 ± 11 years. All had been occupationally exposed to asbestos for a mean of 17 ± 8 years. Nineteen gave a history of heavy exposure and 26 of moderate exposure. In nine patients, the exposure was primary and in 36, secondary. None of the workers had ever smoked tobacco in any form, and none were exposed to any other known fumes or toxins. All patients had a normal 12-lead ECG. All patients had pleural plaques, but none had interstitial changes seen on their chest roentgenograms. Thirty-two patients had grade 1, ten patients had grade 2, and the remaining three had grade 3 pleural changes. Thirty patients complained of dyspnea with moderate exertion, whereas 22 complained of cough and sputum production.

All patients had a normal FVC with a mean FVC of 98 ± 14% of predicted. FEV_1/FVC ratios were normal in all patients with a mean ratio of 80 ± 4%. DL_{CO} was normal in all patients with a mean value of 106 ± 18% of predicted. Mean PaO_2 and P(A-a)O_2 were 82 ± 7 and 15 ± 9 mm Hg, respectively. Fourteen subjects had mild hypoxemia on room air and 12 had a slightly elevated P(A-a)O_2 difference (Table 1a).

The MMFR was less than 75% of predicted in 13 patients (29%) of total (Tables 1b and 2). Three of these 13 patients had heavy primary exposure. The remaining ten were exposed to asbestos on a moderate, secondary basis. Two of these 13 patients had a normal MMFR after inhaling two puffs of isoetharine. However, only one of the two had a significant change in isovolume MMFR.[16] When we compared the two groups by age, symptoms, degree of pleural thickening, duration of exposure, qualitative nature of exposure, total lung capacity, FVC, FEV_1/FVC, PaO_2, P(A-a)O_2 and DL_{CO}, patients with abnormal MMFR had significantly lower FVC and FEV_1/FVC ($P < .01$). The two groups did not, however, differ with respect to any other parameters. The meaned data for the abnormal MMFR group and the normal MMFR group may be found in Tables 1b and 1c, respectively.

Discussion

We found evidence of small airways dysfunction in a group of nonsmoking asbestos workers. This was not readily explained by or correlated with exposure history or other clinical, roentgenographic, or physiologic variables. Review of pathologic data led us to suspect a priori that asbestos exposure may be associated with small airways dysfunction. The evolution of pathologic changes from initial asbestos exposure to fibrosing parenchymal asbestosis is unknown. The process must be inferred from the study of animals exposed to asbestos.[17] Asbestos fibers seem to be deposited first in respiratory bronchioles and alveolar ducts. A polymorphonuclear response is provoked, followed by a macrophagic peribronchiolar alveolitis. Somewhat later, discrete foci of fibrosis develop in the walls of respiratory bronchioles.[18] The foci are associated with accumulation of asbestos bodies. Recent pathologic evidence in man has described lesions of the small airways in asbestos workers which are different from lesions found in smokers, but which are similar to lesions seen in animals. The human asbestos lesions are characterized by fibrosis in and around the respiratory bronchioles and alveolar ducts, often accompanied by ferruginous bodies.[19] These lesions are similar to those described by Churg et al[20] in workers exposed to a variety of nonasbestos mineral dusts, and thus may not be specific to asbestos.

There has been a reluctance to accept that asbestos exposure may cause an obstructive ventilatory defect because the workers are commonly also cigarette smokers, and they may be exposed to other toxins as well. Founier-Massey and Becklake[21] reported that FEV_1/FVC was reduced in workers exposed to asbestos, but some also had a reduced lung volume, suggesting interstitial lung disease. Begin et al[6] studied 17 lifelong

TABLE 1
Mean Pulmonary Function Data for All Patients, for Group With Abnormal Maximum Midexpiratory Flow Rate (MMFR) and for Group With Normal MMFR*

		Age (Yr)	Exposure (Yr)	TLC (% Predicted)	FVC (% Predicted)	$FEV_1/FVC \times 100$ (%)	MMFR (% Predicted)	DL_{CO} (% Predicted)	PaO_2 mm Hg
a) All patients	Mean	52	17	109	98	80	91	106	82
	±	±	±	±	±	±	±	±	±
	SD	13	8	12	14	4	29	18	7
N = 45									
(b) Patients with abnormal MMFR	Mean	53	15	108	91†	76†	61†	104	82
	±	±	±	±	±	±	±	±	±
	SD	12	8	11	12	3	10	16	6
N = 13									
(c) Patients with normal MMFR	Mean	52	17	110	106	81	103	107	81
	±	±	±	±	±	±	±	±	±
	SD	12	8	12	15	4	26	20	13
N = 32									

* Abbreviations used are: TLC, total lung capacity; FVC, forced vital capacity; FEV_1, forced expired volume in one second; DL_{CO}, diffusing capacity; PaO_2, arterial oxygen tension.
† Different from group C, $P < .01$.

TABLE 2
Pulmonary Function Data for Patients With Abnormal Maximum Midexpiratory Flow Rates (MMFR)*

Patients	Age (Yr)	Exposure (Yr)	FVC (% Predicted)	$FEV_1/FVC \times 100$ (%)	MMFR (% Predicted)	DL_{CO} (% Predicted)	PaO_2 mm Hg
1	63	19	86	78	74	109	76
2	55	2	80	81	73	99	84
3	51	28	97	74	54	103	83
4	48	8	109	76	66	139	79
5	60	22	84	72	46	104	82
6	40	11	109	71	48	125	86
7	77	20	77	76	64	105	85
8	54	11	98	73	54	89	90
9	39	19	93	80	73	82	83
10	33	7	92	77	54	108	76
11	61	17	112	76	74	120	94
12	46	6	83	79	64	86	72
13	65	22	75	79	61	90	78

* Abbreviations used are: FVC, forced vital capacity; FEV_1, forced expired volume in one second; DL_{CO}, diffusing capacity; PaO_2, arterial oxygen tension.

nonsmoking asbestos workers. Seven had parenchymal asbestosis and ten did not. The workers with asbestosis had a restrictive ventilatory defect and also had increased upstream resistance at low lung volumes. In the ten workers without asbestosis, MMFR did not differ significantly from control subjects; however, they had higher values for the helium iso-flow volume curves. Lung biopsies in three of the workers with asbestosis demonstrated that the airways were narrowed and distorted, and that their walls were thickened. These two studies, therefore, suggest that airways pathology and airflow limitation occur in asbestosis. Hedenstierna et al[2] found small airways dysfunction in workers exposed to asbestos, even in the absence of parenchymal disease. However, because many patients were ex-smokers, Hedenstierna's evidence of airway obstruction specifically related to asbestos was weak.

MMFR has been cited as a sensitive test for early pulmonary disease.[22] McFadden et al[23] used MMFR to determine improvement of small airways defects after cessation of cigarette smoking. A recent study has correlated MMFR with pathologic abnormalities of small airways, ie, intraluminal inflammation and fibrosis of respiratory bronchioles.[24] The definition of an "abnormal" result is not perfectly clear; some authors compare observed values with predicted values,[15] and others compare observed MMFR with observed FVC.[25] Kuperman and Riker[25] showed that the lower limit of normal for MMFR (twice the SE of estimate below the mean) was 65% of vital capacity. Even if we use this less sensitive criterion for abnormality, we found that nine of our 45 patients had evidence of small airways dysfunction. Furthermore, the mean FVC and FEV_1/FVC were significantly lower in patients with an abnormal MMFR, even though these patients had normal FVC and FEV_1/FVC. This difference in FEV_1/FVC supports our suggestion that some asbestos workers have an early obstructive ventilatory defect unrelated to smoking.

Airflow limitation in these patients may be due to asbestos. The deposition of inhaled particles and fibers depends on their velocity, diffusion coefficient, and fiber length. The site of initial deposition may be a nidus for a slowly progressive reaction or may merely be a way station, as the fibers migrate distally. The response to bronchodilators in one of our patients raises the possibility that the inhaled agents may cause reactive bron-

choconstriction, though of course the finding could be due to de novo development of "garden variety" bronchial hyperreactivity,[26] independent of asbestos exposure. Follow-up studies may determine whether these early abnormalities progress toward more severe lung involvement.

All of our patients worked in the shipyards of Long Beach, so it is appropriate to compare our results to the general population data accumulated by Rokaw et al[15] for residents of Burbank, which has a similar pollution level to Long Beach and is without any asbestos particles in the air. The prevalence of MMFR less than 75% predicted in the nonsmoking, asymptomatic subset of Rokaw's population is about 15%, less than our value of 29%.

We found a high prevalence of mild airflow limitation in a group of 45 lifetime nonsmoking asbestos workers. We were careful to include only patients who had never smoked in their lifetime and who did not have histories of other pulmonary disease. Furthermore, they were not known to be exposed to industrial dusts other than chrysotile. It is possible that small airways dysfunction in asbestos workers is, at least in part, independent of smoking. Furthermore, it may indicate an increased risk for future parenchymal asbestosis and/or obstructive ventilatory defects.

Acknowledgment

The authors acknowledge the secretarial assistance of Ms Debra Craig.

References

1. Murphy RL, Gaensler EA, Fenis BG, et al: Diagnosis of asbestosis: Observation from a longitudinal survey of ship-yard pipe coverers. *Am J Med* 1978;65:488–498.

2. Hedenstierna G, Alexanderson R, Kolmodin-Hedman B, et al: Pleural plaques and lung function in construction workers exposed to asbestos. *Eur J Respir Dis* 1981;62:111–112.

3. Rodriquez-Roison R, Cochrane GM, Clark TJH: Asbestos exposure and small airways disease. *Scand J Respir Dis* 1976;57(6):318.

4. Menza LD, Ruff F, Bignon J, et al: Small airway obstruction with professional exposure to asbestos. *Ann Anat Pathol* 1976;21:261–268.

5. Jodoin G, Gibbs GW, Macklem PT, et al: Early effects of asbestos on lung function. *Am Rev Respir Dis* 1971;104:525–535.

6. Begin R, Cantin A, Berthiaume Y, et al: Airway function in lifetime nonsmoking older asbestos workers. *Am J Med* 1983;75:631–638.

7. *ILO/UC International Classification of Radiographs of Pneumoconiosis*, 1971 (No. 22 revised). Geneva, Occupational Safety and Health Services, International Labour Office, 1972.

8. Schmidt CD, Dickman ML, Gardner RM, et al: Spirometric standards for healthy elderly men and women. *Am Rev Respir Dis* 1973;108–933–939.

9. McMichael J: A rapid method of determining lung capacity. *Clin Sci* 1939;4:167–173.

10. Goldman, HL, Becklake MR: Respiratory function test: Normal values at median altitude and the prediction of normal results. *Am Rev Tuberc Pulm Dis* 1959;79:457–467.

11. Boren HG, Kory RC, Syner JC: The Veterans' Administration-Army Cooperative study of pulmonary function: II. The lung volume and its subdivisions in normal man. *Am J Med* 1966;41:96–114.

12. Ogilvie CM, Forster RE, Blackmore WS, et al: A standardized breath-holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *J Clin Invest* 1957;36:1–7.

13. Jones RS, Mead F: A theoretical and experimental analysis of anomalies in the estimation of pulmonary diffusing capacity by the single-breath method. *Q J Exp Physiol* 1961;46:131–43.

14. McGrath MW, Thomson ML: The effect of age, body size and lung volume change on alveolar-capillary permeability and diffusing capacity in man. *J Physiol* 1959;146:572–582.

15. Rokaw SN, Detels R, Coulson AH, et al: The UCLA population studies of chronic obstructive respiratory disease: III. Comparison of pulmonary function in three communities exposed to photochemical oxidants, multiple pollutants or minimal pollutants. *Chest* 1980;78:252–262.

16. Sherter CB, Connolly JJ, Schilder DP: The significance of volume adjusting the maximal mid-expiratory flow in assessing the response to bronchodilator. *Chest* 1978;73:568–571.

17. Vorwald AJ, Durkan TM, Pratt PC: Experimental studies of asbestosis. *Arch Ind Hyg Occup Med* 1951;3:1–43.

18. Begin R, Masse S, Bureau MA: Morphologic features and function of the airways in early asbestosis in sheep model. *Am Rev Respir Dis* 1982;126:870–876.

19. Craighead JE, Abraham JL, Churg A, et al: The pathology of asbestos-associated disease of the lungs and pleural cavities: Diagnostic criteria and proposed grading schema. *Arch Pathol Lab Med* 1982;106:544–596.

20. Churg A, Wright JL, Wiggs B, et al: Small airways disease and mineral dust exposure. *Am Rev Respir Dis* 1985;131:139–143.

21. Fournier-Massey G, Becklake MR: Pulmonary function profiles in Quebec asbestos workers. *Bull Physiopathol Respir* 1975;11:429–445.

22. Leuallen EC, Fowler WS: Maximal mid-expiratory flow. *Am Rev Tuberc Pulm Dis* 1955;72:783.

23. McFadden ER, Linden DA: A reduction in maximum mid-expiratory flow rate. *Am J Med* 1972;52:725.

24. Wright VL, Lawson LM, Pare PD, et al: The detection of small airways disease. *Am Rev Respir Dis* 1984;129:989–994.

25. Kuperman AS, Riker JB: The predicted normal maximal mid-expiratory flow. *Am Rev Respir Dis* 1973;107:231–238.

26. Boushey HA, Holtzman MJ, Sheller JR, et al: Bronchial hyperreactivity (state of the art). *Am Rev Respir Dis* 1980;121:389–413.