

Bronchial Responsiveness and Five-year FEV₁ Decline A Study in Miners and Nonminers

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Increased nonspecific bronchial responsiveness (NSBR) may be a risk factor for the development of chronic airflow obstruction. We evaluated this hypothesis in a cohort of 378 underground coal miners and working nonminers. Methacholine testing was performed at the beginning and end of a 5-yr study period. Spirometry was repeated at 6-mo intervals and individual 5-yr FEV₁ slopes were calculated by linear regression. Relationships between FEV₁ slopes and NSBR were examined using multiple linear regression models, controlling for FEV₁ level, smoking, and mining. Increasing NSBR at the initial survey was associated with a somewhat greater rate of subsequent FEV₁ decline. Methacholine responders at the final survey had a considerably increased rate of decline during the previous years. Responsiveness status changed over the 5 yr in 22% of the subjects. Both the development and persistence of increased NSBR were strongly associated with higher rates of FEV₁ decline. In contrast, FEV₁ declines were not accelerated among workers with increased NSBR that reverted to normal. Smoking and mining were both independently associated with FEV₁ declines, but did not substantially modify the effect of NSBR. Due to its variability over time, NSBR testing predicts lung function decline only in some individuals, and its value as a prognostic test for chronic airway disorders is limited. Because improvement in bronchial hyperresponsiveness was associated with a reduction in the rate of FEV₁ loss, interventions directed at preventing or reducing nonspecific airway hyperresponsiveness should be investigated. Hodgins P, Henneberger PK, Wang M-L, Petsonk EL. Bronchial responsiveness and five-year FEV₁ decline: a study in miners and nonminers.

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Increased nonspecific bronchial responsiveness (NSBR) has been associated with airflow obstruction in studies in working populations (1-3). Several longitudinal studies have investigated NSBR and noted an association between increased NSBR and subsequent declines in FEV₁ (1-7), suggesting that increased NSBR might be a useful predictor of subsequent declines in ventilatory function. However, it is recognized that over time, bronchial responsiveness may increase, or if increased can revert to normal in up to 48% of individuals (2, 8-10). It is unclear if a change in NSBR status is associated with a change in the rate of decline in ventilatory function.

We conducted a 5-yr prospective study of a cohort of underground bituminous coal miners and nonminers from central Appalachia in order to investigate the relationships between NSBR, declines in FEV₁, cigarette smoking, and mining. The questions addressed in this analysis are: (1) Is increased nonspecific bronchial responsiveness predictive of future accelerated declines in FEV₁? (2) Is a change in NSBR status as-

sociated with a change in the rate of FEV₁ decline? and (3) Is the relationship between mean annual change in FEV₁ and NSBR modified by mining or smoking history?

METHODS

Subject selection and methods have been described in detail (11), and are reviewed briefly below. The protocol was reviewed and approved by the institutional review board, and all volunteers gave written informed consent prior to participating.

Subject Selection

Miners were recruited from three large Appalachian underground bituminous coal mines. Nonmining control subjects were recruited in the same region from nine public and private employers with no history of adverse respiratory exposures. The recruitment period began in May 1985, and ended in July 1987. Clerical staff were not recruited in order to increase comparability between miners and control subjects. Spirometry was performed at the work site immediately prior to the workshift, at 6-mo intervals for 5 yr. Questionnaires and methacholine tests were completed at the initial and final surveys.

The criteria for inclusion were applied in the following order: (1) completion of at least three spirometry tests; (2) male; (3) white; (4) > 25 yr old at baseline; (5) lifetime self-reported work history available; (6) mean annual change in FEV₁ from baseline to final survey was not an extreme value. The cutoff points for extreme values in FEV₁ change were determined by taking twice the interquartile range and adding it to the value at the 75th percentile, and subtracting it from the value at the 25th percentile (12).

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Questionnaire

A standardized self-administered respiratory symptom questionnaire, modified from the British Medical Research Council (1976) was used. Additional questions on tobacco use, allergic symptoms, medical history, and occupational history were included.

Spirometry

Testing was conducted using an 8L survey spirometer with an attached microprocessor (Eagle II; Warren E. Collins, Braintree, MA). All testing was performed at the worksite, using the standards of the American Thoracic Society 1978 Snowbird workshop (13). Forced exhalation maneuvers were done in the standing position with a nose clip in place. A minimum of three and generally a maximum of five traces were obtained from each subject. Spirometry was similarly performed at 6-mo intervals during the 5 yr of follow-up. Test results were not excluded from the study if the two largest values for FEV₁ or FVC varied by more than 5%, providing that the subject had produced at least three smooth traces without premature termination or excessive back extrapolated volumes.

Methacholine Tests

Subjects whose initial or final FEV₁ or FVC was less than 80% of predicted (14) did not perform methacholine inhalation challenge testing. Methacholine testing was conducted before the workshift and if possible immediately after the initial and final spirometry. Due to time constraints a few subjects did not perform the methacholine testing at the time of initial spirometry testing, but instead returned several weeks after the initial spirometry for repeat spirometry and methacholine testing. The technique used for the methacholine test was modified from Chatham and coworkers (15). A DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA) was filled with 2.5 ml of methacholine solution (J.T. Baker Chemicals, Phillipsburg, NJ, or Spectrum Chemicals, Gardena, CA), and was powered by a DeVilbiss 571 series compressor delivering an air pressure of 20 pounds per square inch. The mean (\pm SD) of measured nebulizer outputs was found to be 0.0072 ± 0.016 ml/s. Methacholine solutions were refrigerated and discarded if not used within 30 d. Inhalation breaths were performed over a 10-s time interval, starting at residual volume and ending at total lung capacity. Subjects took up to five inhalation breaths of methacholine aerosol at each concentration. The initial concentration of the methacholine solution was 25 mg/ml, unless there was a history of asthma in which case the initial concentration was 5 mg/ml. Spirometry was performed after each dose of methacholine. If a smooth trace of apparent maximal effort showed a 15% or greater decline in FEV₁, the FEV₁ maneuver was repeated to confirm the decline, the protocol was ended, and a bronchodilator was administered. Subjects with reproducible FEV₁ declines of 15% or greater at any point in the protocol were classified as methacholine responders. If declines were less than 15% after five inhalations of the highest concentration (25 mg/

ml) of methacholine aerosol, the individual was classified as having normal nonspecific bronchial responsiveness. In addition, each subject was characterized by the percentage decrease in FEV₁ per total dose of methacholine administered (% FEV₁ decline/mg) (7).

Statistical Analysis

The equation of Morris and coworkers (14) was used to arrive at the predicted FEV₁ for each worker based on the gender, age, and height of the individual. The percentage predicted FEV₁ was calculated by dividing the observed FEV₁ by the predicted FEV₁ and then multiplying by 100. The mean annual decline in FEV₁ was determined for each subject by least-squares linear regression using all the available spirometric values from the follow-up period. Height-adjusted FEV₁ was calculated as actual FEV₁ divided by the square of the individual's height in inches and multiplied by the square of the cohort's mean height (4,950 inches²).

The statistical methods used in this study include the Student's *t* test, analysis of variance, and least-squares linear regression (16). The analyses were accomplished with SAS personal computer software (SAS Institute, Cary, NC, 1988).

The following steps were followed to fit linear regression models for mean annual change in FEV₁:

1. The following potential confounders were included in all models: age (years) as a mean of the baseline and final ages, started smoking cigarettes during follow-up (yes/no), stopped smoking cigarettes during follow-up (yes/no), kept smoking cigarettes during follow-up (yes/no), remained an ex-smoker during follow-up (yes/no), cumulative pack-years at initial survey, mean packs per day smoked between baseline and final surveys, and mean of the initial and final height-adjusted FEV₁ values (liters). The values for age and FEV₁ were then centered by subtracting the group mean (i.e., 41 yr and 4.08 L, respectively) from each individual's value.

2. Coal mining tenure was characterized by three types of work: any coal mining (i.e., both surface and underground), underground mining only, and work at the mine face. Underground mining was a subset of any coal mining and work at the mine face was a subset of underground mining. The amount of time employed in each type of work was represented by two variables: the years worked up to the baseline survey and the years worked between the baseline and final surveys. Each of the three pairs of variables was introduced into the model and the pair that provided the most substantial improvement in model fit was retained.

3. Both dichotomous and continuous variables for NSBR findings were devised for the initial and final surveys, and were introduced separately into the regression models. Also, interactions between the initial and final measurements were tested.

4. Additional regression models were fit to test whether the association between mean annual decline in FEV₁ and NSBR status was modified by either cigarette smoking or coal mining tenure.

TABLE 1

DESCRIPTIVE CHARACTERISTICS AT INITIAL SURVEY, FINAL SURVEY, AND BETWEEN SURVEYS FOR ALL PARTICIPANTS AND BY NUMBER OF METHACHOLINE CHALLENGE TESTS COMPLETED

Time Frame	Characteristic	All Subjects (<i>n</i> = 378)	Methacholine Challenge Tests Completed	
			Two (<i>n</i> = 289)	0 or One (<i>n</i> = 89)
Initial survey	Mean age, yr (SEM)	39.3 (0.5)	38.8 (0.5)	40.9 (1.0)
	Smokers, % (n)	29 (108)	30 (86)	25 (22)
	Ex-smokers, % (n)	28 (106)	27 (77)	33 (29)
	Mean pack-years (SEM)	10.9 (0.8)	10.5 (0.9)	12.1 (1.7)
	Mean % pred FEV ₁ (SEM)	104.8 (0.6)	106.8 (0.6)	98.4 (1.5)
Initial to final	Mean yr (SEM)	5.0 (0.04)	5.1 (0.02)	4.4 (0.13)
	Mean packs/d (SEM)	0.5 (0.03)	0.6 (0.04)	0.4 (0.07)
	Mean ml/yr FEV ₁ (SEM)	-59 (2)	-55 (2.4)	-70 (6)
Final survey	Smokers, % (n)	21 (79)	22 (64)	17 (15)
	Ex-smokers, % (n)	38 (142)	36 (105)	42 (37)
	Mean pack-years (SEM)	13.6 (0.9)	13.4 (1.0)	14.0 (1.9)
	Mean % pred FEV ₁ (SEM)	100.7 (0.7)	103.3 (0.7)	92.2 (1.0)

RESULTS

A total of 478 subjects volunteered to participate in the study. From these we excluded 67 subjects who had not completed at least three sets of spirometry testing. We also excluded 12 females, 10 nonwhites, five who were less than 25 yr old at the initial survey, one whose work history was incomplete, and five with extreme values for mean annual change in FEV₁. The remaining 378 workers (194 miners and 184 nonminers) were included in the analyses. Of these, 21 did not undergo the initial methacholine challenge testing, and 85 did not undergo the final methacholine testing.

Descriptive Statistics

Descriptive characteristics are presented in Table 1 for all 378 workers, and separately for the participants who completed both initial and final testing and for those who failed to complete one or both methacholine tests. The mean age for all subjects at the initial survey was 39 yr, and the mean period of follow-up was 5 yr. From the initial to the final survey, the percentage of current smokers declined and the percentage of ex-smokers increased. Overall, both the initial and final mean percent predicted FEV₁ were greater than 100%. A total of 89 individuals did not undergo the initial and/or final methacholine testing. At the initial survey, there were 13 who were not given the test due to either the FEV₁ or FVC < 80% predicted and eight who refused. At the final survey, there were 31 with either FEV₁ or FVC < 80% of predicted, 17 refusals, and 37 who did not keep appointments. For those workers who completed both initial and final methacholine test, the proportion with increased NSBR changed only slightly from 27% (98 of 357) at the initial survey to 30% (87 of 293) at the final survey. The proportion of methacholine responders was similar among the miners (initial 27%, final 29%) and nonminers (initial 28%, final 31%).

FEV₁ Decline and Dichotomous Measures of Responsiveness

Among the 289 subjects who completed both initial and final methacholine tests, 77 (26.6%) were considered methacholine responders at the first survey because their FEV₁ decline was 15% or greater in response to any dose of methacholine (see METHODS for details of protocol). Subsequent crude rates of decline in FEV₁ were slightly greater in workers with increased NSBR (-59 ml/yr), versus those with normal NSBR (-54 ml/yr) at the initial survey, as shown in the right margin of Table 2 ($t = 0.95$, $p = 0.34$). In contrast, the 85 individuals with increased NSBR at the final survey had experienced greater mean annual FEV₁ declines (-68 ml/yr) than those with normal NSBR (-50 ml/yr, $t = 3.55$, $p = 0.0004$) (see *bottom margin*, Table 2).

Annual decline in FEV₁ was modeled using least-squares linear regression, and potential confounders such as age, cigarette smoking, and mean height-adjusted FEV₁ were included. Pairs of variables for years in coal mining, underground mining, and face work were introduced into the model, and the variables for all years of coal mining provided the best fit and were retained in the model (Table 3). When dichotomous variables for initial and final methacholine responsiveness were put in the model, the coefficient for increased NSBR at the initial survey was small and not statistically significant (4.2 ml/yr, $p = 0.49$). In contrast, an accelerated decline in FEV₁ was associated with an increased NSBR at the final survey, with a coefficient of -20.8 ml/yr and $p = 0.0007$. A similar pattern was observed when either the initial or final NSBR variable was introduced into the model without the other (models not shown). Another model (not shown) was fit to test for an interaction between the

TABLE 2

MEAN ANNUAL CHANGE IN FEV₁ BY DICHOTOMOUS MEASURES OF INITIAL AND FINAL METHACHOLINE RESPONSIVENESS*

Initial NSBR Status	Final NSBR Status		Total
	Normal	Responder	
Normal	-50 ml/yr (SEM = 3) n = 176	-72 (6) n = 36	-54 (3) n = 212
Responder	-48 (9) n = 28	-66 (5) n = 49	-59 (5) n = 77
Total	-50 (4) n = 204	-68 (4) n = 85	-55 (2) n = 289

* The protocol for methacholine challenge testing is explained in METHODS. Subjects with $\geq 15\%$ decline in FEV₁ at any point in the testing were considered methacholine responders.

initial and final responsiveness, but none was observed ($p = 0.85$). Thus, both the crude results (Table 2) and the results controlled for potential confounders (Table 3) revealed the same pattern: an accelerated decline in FEV₁ was associated with increased NSBR at the final survey, but only a small and nonsignificant effect of NSBR at the initial survey was noted.

FEV₁ Decline and Continuous Measures of Responsiveness

The results of the methacholine testing were also expressed as continuous measures in units of change (% decrease in FEV₁) per dose of methacholine administered (mg). The responsiveness test results ranged from -0.65%/mg to 112.3%/mg for the initial testing and from -0.65 to 55.1%/mg for the final testing. There was one apparent outlying responsiveness value at both the initial (i.e., 112.3%/mg) and final (i.e., 55.1%/mg) surveys. Because these values were each considerably greater than the next largest value (which was about 22%/mg in each case), these maximal values were both recoded to 23. The distributions were still noted to be skewed toward higher values, and to address this skewing, the base 10 logarithm was taken. To adjust for negative and very small positive responsiveness values before taking the logarithms, all results less than 0.1 were recoded to 0.1 (four values at the initial survey, 12 at the final survey). Initial and final methacholine test results were then divided into 10 groups (deciles) of approximately equal numbers of subjects. For all study participants in each decile,

TABLE 3

LINEAR REGRESSION MODELS FOR MEAN ANNUAL CHANGE IN FEV₁ (ml/yr) DURING FOLLOW-UP, WITH DICHOTOMOUS COVARIATES FOR INITIAL AND FINAL METHACHOLINE RESPONSIVENESS

Covariate	Estimate (SEM)	p Value
Intercept	-47.8 (4.9)	0.0001
Mean age (centered on 41), yr	-0.2 (0.4)	0.51
Start smoking, yes/no	-24.6 (13.6)	0.07
Stop smoking, yes/no	-3.5 (10.1)	0.73
Kept smoking, yes/no	-11.0 (8.5)	0.19
Remained ex-smoker, yes/no	-8.0 (7.9)	0.31
Cumulative pack-years by initial survey	0.2 (0.3)	0.42
Mean packs/d from initial to final survey	4.8 (6.7)	0.47
Mean ht-adj. FEV ₁ (centered on 4.08), L	-4.9 (6.6)	0.46
Cumulative years mining by initial survey	1.4 (0.7)	0.05
Years mining from initial to final survey	-3.6 (1.6)	0.03
Initial methacholine responder, yes/no	4.2 (6.0)	0.49
Final methacholine responder, yes/no	-20.8 (6.0)	0.0007
r ²		0.090

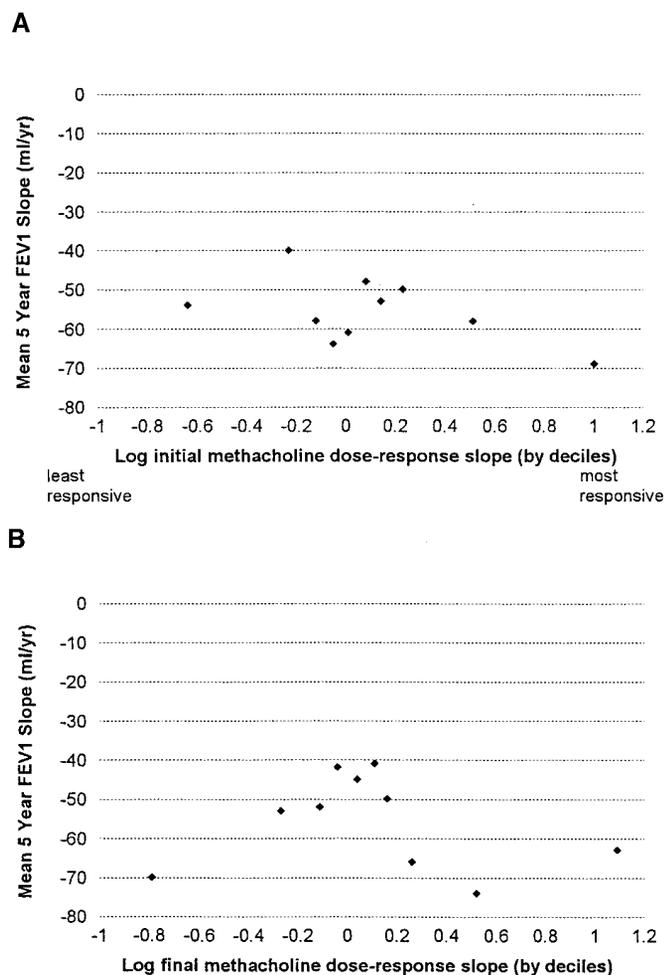


Figure 1. Five-year FEV₁ slopes and initial (A) or final (B) airway responsiveness among 289 coal miners and control workers.

the mean 5-yr FEV₁ slope was computed and plotted against the mean of the log initial (Figure 1A) and final (Figure 1B) methacholine responsiveness. The findings suggest a largely linear relationship between log initial responsiveness and subsequent decline in FEV₁. However, the relationship between log final responsiveness and decline in FEV₁ appears to be more of an inverted U-shape rather than linear, with a particularly large decline in FEV₁ in the lowest decile.

Regression modeling of annual change in FEV₁ during follow-up using the logarithm of the continuous measures of responsiveness revealed that the coefficient for initial responsiveness was negative and of borderline statistical significance (-13.3 ml, $p = 0.053$), while the coefficient for final responsiveness was small and not statistically significant (3.3 ml, $p = 0.59$) (Table 4). This pattern of results persisted when the variable for either initial or final responsiveness was introduced into the model without the other (models not shown). Another model (not shown) was fit to test for an interaction between the initial and final continuous responsiveness covariates, but the interaction term was not statistically significant ($p = 0.18$).

FEV₁ Decline and Change in Responsiveness Status

The association between decline in FEV₁ and longitudinal change in NSBR is seen in Table 2. Among the 289 workers

TABLE 4

LINEAR REGRESSION MODEL FOR MEAN ANNUAL CHANGE IN FEV₁ (ml/yr) WITH CONTINUOUS COVARIATES FOR INITIAL AND FINAL METHACHOLINE DOSE-RESPONSE SLOPE

Covariate	Estimate (SEM)	p Value
Intercept	-52.1 (4.6)	0.0001
Mean age (centered on 41), yr	-0.3 (0.4)	0.44
Start smoking, yes/no	-29.1 (13.7)	0.04
Stop smoking, yes/no	-2.9 (10.2)	0.77
Kept smoking, yes/no	-13.0 (8.6)	0.13
Remained ex-smoker, yes/no	-6.8 (8.0)	0.39
Cumulative pack-years by initial survey	0.2 (0.3)	0.50
Mean packs/d from initial to final survey	5.7 (6.7)	0.40
Mean ht-adj. FEV ₁ (centered on 4.08), L	-3.0 (6.8)	0.66
Cumulative years mining by initial survey	1.5 (0.7)	0.05
Years mining from initial to final survey	-3.6 (1.7)	0.03
Log of the initial methacholine dose-response slope*	-13.3 (6.8)	0.053
Log of the final methacholine dose-response slope*	3.3 (6.1)	0.59
r ²	0.063	

* Logarithm (base 10) of the percent change in FEV₁ per mg methacholine dose.

who completed methacholine testing at both surveys, 64 (22.1%) experienced a change in NSBR status between surveys. Of these, 28 had increased NSBR at the initial survey that reverted to normal by the final survey. In these 28, the rate of FEV₁ decline was approximately equal to that seen in participants who had normal responsiveness at both surveys. In the 36 subjects who developed increased NSBR during the study period, the rate of FEV₁ decline was comparable to that seen in subjects who had increased NSBR at both surveys. A regression model was also fit to include indicator variables for the dual initial/final responsiveness categories, with the normal/normal subjects as the comparison group (Table 5). FEV₁ declines were associated with the initial responder/final responder subjects (-16.2 ml/yr) and the initial normal/final responder subjects (-21.7 ml/yr), but not with the initial responder/final normal subjects (3.1 ml/yr), confirming the crude findings from Table 2. Thus, FEV₁ declines were not increased among subjects whose NSBR was increased at the initial survey but subsequently reverted to normal.

TABLE 5

LINEAR REGRESSION MODEL FOR MEAN ANNUAL CHANGE IN FEV₁ (ml/yr) WITH COVARIATES FOR LONGITUDINAL METHACHOLINE RESPONSIVENESS STATUS

Covariate	Estimate (SEM)	p Value
Intercept	-47.7 (4.9)	0.0001
Mean age (centered on 41), yr	-0.2 (0.4)	0.52
Start smoking, yes/no	-24.5 (13.7)	0.08
Stop smoking, yes/no	-3.6 (10.1)	0.72
Kept smoking, yes/no	-11.0 (8.5)	0.20
Remained ex-smoker, yes/no	-7.9 (7.9)	0.32
Cumulative pack-years by initial survey	0.2 (0.3)	0.43
Mean packs/d from initial to final survey	4.7 (6.7)	0.48
Mean ht-adj. FEV ₁ (centered on 4.08), L	-4.8 (6.6)	0.47
Cumulative years mining by initial survey	1.4 (0.7)	0.05
Years mining from initial to final survey	-3.6 (1.6)	0.03
Initial and final methacholine response*		
Initial normal/final responder	-21.7 (7.5)	0.004
Initial responder/final normal	3.1 (8.2)	0.70
Initial responder/final responder	-16.2 (7.0)	0.02
r ²	0.090	

* Each of three categories is compared with the initial normal/final normal subjects.

Effect of Mining and Smoking on the Relationship between FEV₁ Decline and Responsiveness

The effects of mining and smoking variables were consistent across the different regression models (see Tables 3, 4, and 5). The greatest effect of cigarette use was evident for those who started smoking during follow-up, with annual FEV₁ declines 24.5 to 29.1 ml greater than that experienced by never-smokers. Years of coal mining during follow-up was associated in all models with increased FEV₁ loss. In contrast, cumulative years of mining prior to the initial survey had a consistently positive coefficient for FEV₁ change during follow-up.

From the crude data, the difference in FEV₁ decline between subjects with final increased NSBR and those with normal responsiveness was similar in miners (-20 ml/yr) and nonminers (-18 ml/yr). With respect to smoking, the decline in FEV₁ associated with final increased NSBR was most apparent for those who started smoking (-26 ml/yr), stopped smoking (-26 ml/yr), or continued to smoke (-24 ml/yr) during follow-up. The effect of final NSBR status was somewhat less among never-smokers (-18 ml/yr) and negligible among those who remained ex-smokers during follow-up (-3 ml/yr).

To evaluate further whether mining or smoking status modified the relationship between annual decline in FEV₁ and final NSBR, interaction terms were introduced one at a time into the regression model in Table 3. Similar to the crude data, there was no indication of an interaction between final NSBR status and coal mining tenure variables (models not shown). Among the smoking covariates, only the interaction between remaining an ex-smoker and final NSBR status approached statistical significance (24.0 ml/yr, SEM = 12.8, $p = 0.061$) (model not shown), again suggesting a possibility of effect modification associated with cigarette smoking status.

DISCUSSION

In this study, we examined the relationship between longitudinal FEV₁ change over 5 yr and nonspecific bronchial responsiveness. NSBR was determined at the beginning and the end of the study period, and was characterized in two different ways (i.e., dichotomous and continuous). When a dichotomous measure (responder/normal) was used to characterize methacholine responsiveness, an accelerated decline in FEV₁ was strongly associated with the final but not the initial responsiveness. Using a continuous variable to characterize responsiveness in the linear models, an increased decline in FEV₁ during follow-up was associated ($p = 0.053$) with the initial but not the final methacholine responsiveness (Table 4). Two apparent contradictions are raised by these findings. First: Why is there an association between FEV₁ decline and the dichotomous but not the continuous *final* NSBR measure? This apparent contradiction is explained by the nonlinearity of the relationship between FEV₁ decline and final responsiveness (Figure 1B). The nonlinearity of this relationship is due largely to the high rates of decline among subjects in the lowest decile of responsiveness. The continuous measure gives weight to all levels of responsiveness. In contrast, when final responsiveness is characterized as a dichotomous variable, the high FEV₁ declines found in the least responsive decile are not apparent, because these declines are averaged with all the other "normal" subjects, and a significant effect of final responsiveness is seen (see Tables 2 and 3).

The second apparent contradiction in the findings is: Why is there an association between FEV₁ decline and the continuous but not the dichotomous *initial* NSBR measure? Using the dichotomous measurement of initial responsiveness, the re-

sponders do not consistently have an accelerated FEV₁ loss with respect to the normals. However, a slight negative relationship between FEV₁ slope and initial responsiveness can be seen in Figure 1A, and this relationship is of borderline statistical significance ($p = 0.053$) in the regression model (Table 4). Thus, although results with the two measures are similar in direction, only the continuous measure approaches statistical significance.

The decile of study participants with the lowest final level of responsiveness experienced one of the highest rates of FEV₁ decline. The reason for the high rates of decline in this subgroup is not entirely clear, but may be related in part to self-selection. We have previously shown that individuals with increased NSBR appear to select jobs with lower dust exposure (11). Because responsiveness levels were very low in the subgroup, these workers may have been better able to tolerate the dustier (and higher paying) coal mining jobs, but still experienced the lung function declines associated with underground mine exposures. In this subgroup, 67% of those with high rates of decline were in fact coal miners. Coal face exposures were also significantly greater in the subgroup than among the remaining workers.

An important observation was that 22% of the study participants changed responsiveness status over the 5 yr of follow-up, and changes in responsiveness appeared to be reflected in the rate of FEV₁ loss. Thus, increased NSBR at the initial survey only predicted subsequent accelerated declines in FEV₁ in individuals who also had increased NSBR at the final survey, rendering the initial NSBR measurement a weak predictor of subsequent FEV₁ decline. As expected, cigarette smoking and mine dust exposures during the study interval also affected the FEV₁ slopes (17). There was no evidence of a disproportionate effect of mine dust in relation to methacholine responsiveness, but a suggestion that responsiveness-related FEV₁ declines might be less in long-term ex-smokers.

Overall, the findings of this study are consistent with earlier investigations (18). In several previous studies (6, 19), NSBR measured at the end of the study period was associated with antecedent accelerated declines in FEV₁. These studies could not, however, address the issue of whether NSBR status was a predictor of subsequent decline in lung function. Several prospective studies have measured NSBR at the beginning of the study period (1-7, 20). In general, these studies associated subsequent declines in ventilatory function with increased baseline NSBR. O'Connor and coworkers, using methods similar to ours in an older male population, observed a very similar coefficient associated with log 10 initial methacholine dose-response slope (8 to 13 ml/yr additional FEV₁ decline over 3.3 yr, compared with -13.3 ml/yr in the current study (7). Rijcken and coworkers determined the provocative concentration of histamine causing a 10% decline in FEV₁ (PC₁₀) in a group of 921 young males, and also observed a subsequent additional 12.5 ml/yr FEV₁ decline in association with histamine responsiveness (4). Vedal and coworkers studied 227 western red cedar sawmill workers, and measured responsiveness to methacholine three times during 2 yr of follow-up (2). Of the nine sawmill workers with increased responsiveness that resolved, 7 of 9 showed a small annual increase in FEV₁, whereas among the 24 workers who developed increased responsiveness during the study, 20 of 24 had a decline in FEV₁, over the year, findings similar to the current study.

Previous studies have not evaluated airway responsiveness in relation to coal mine exposures; some investigators have found evidence that NSBR modifies the effect of smoking on FEV₁ decline (3, 6, 21), while others have not (7, 19).

Baseline airway caliber is one of the determinants of air-

way responsiveness (22). In the current study, persons with increased NSBR did have lower mean percent predicted FEV₁ values, at both the initial and final surveys, than subjects with normal bronchial responsiveness (data not shown). However, several of the study results tend to refute the hypothesis that the relationship observed between NSBR and accelerated FEV₁ decline was primarily a function of initial airway caliber. First, even after controlling for FEV₁ level, the relationship persisted. Second, more than a third of subjects who had increased NSBR at the initial survey did not have increased NSBR at the final survey, despite continued declines in FEV₁. Furthermore, the prevalence of increased NSBR was similar at the initial and final surveys even though the mean percent predicted FEV₁ values had dropped substantially during the follow-up. Taken together, these findings suggest that airway caliber was not the major determinant of increased NSBR among the individuals who experienced excess lung function loss.

An unexplained finding in this study is that the nonminers had more marked declines in lung function than the 25 to 30 ml/yr mean annual loss that would be expected in a healthy, nonsmoking population (23–25). Smoking was prevalent in the study workers; but declines were increased even in non-smoking nonminers. Nonminers had been recruited from employment where no significant pulmonary exposures were known to occur, such as telephone linemen and university maintenance workers. A minority of the nonminers had worked in the construction industry, and 15 nonminers had limited prior employment in the mining industry. Thus, it is possible that prior occupations or geographical location contributed to the greater than expected mean annual declines in nonminers. It is also possible that those who volunteered for the study were not entirely representative of the eligible population in these workplaces. However, despite the higher than expected rate of FEV₁ decline, the relative effect of NSBR was evident in both miners and nonminers, and the expected effects of smoking and coal mining were detected. Other factors also tend to reinforce the validity of the study results: Multiple spirometry tests were performed by each subject at 6-mo intervals (mean 9.1, range 3 to 12), reducing the potential for FEV₁ slopes to be affected by outlying results. No survey or technician biases were evident (data not shown). Finally, the observed prevalence of increased NSBR was similar at both surveys (approximately 30%), and within the range of 18 to 42% reported by other investigators (4, 7, 18, 26). For all these reasons, the findings of the study should be valid and generalizable to other similar working populations.

The study has several limitations. First, because of safety concerns in performing challenge studies immediately prior to the mining shift, subjects with FEV₁ values less than 80% of predicted did not receive methacholine testing, and we were unable to determine if those impaired workers had increased NSBR. In the group of subjects who could not undergo challenge testing for this reason, a high mean rate of FEV₁ decline (91 ml/yr) was noted. Second, miners with reduced lung function may self-select out of the mines, and thus not be available for testing. Both of these factors would tend to bias the study toward the null hypothesis (26). Alternatively, it could be argued that workers with health concerns and early respiratory diseases were more likely to volunteer for the study. There is evidence against such an “unhealthy worker” selection bias. The mean FEV₁ values at the initial survey were 104.8% of predicted, and there was a paradoxical small increase in FEV₁ associated with years of underground mining prior to the initial survey, suggesting that miners with reduced lung function after long tenure either were no longer in the mines or did not

volunteer for testing. A third limitation of the study involved the classification of increased NSBR as a decline in FEV₁ of 15% or more following administration of methacholine, rather than the more common 20%. This may have resulted in differential misclassification of normal responsiveness as increased NSBR, and should have resulted in bias toward rather than away from the null hypothesis. Finally, this study used mining tenure as a surrogate measure for coal mine dust exposure, and cannot determine if quantitative dust exposures are potential modifiers of NSBR effects. In summary, study design and plausible selection factors may have resulted in bias toward the null hypothesis in the analysis performed.

Nonspecific bronchial responsiveness to histamine and acetylcholine has been considered as a constitutional or host factor which was associated with chronic bronchitis and asthma since 1961, when the “Dutch Hypothesis” was described by Orié and colleagues (27, 28). This constitutional factor was hypothesized to be the primary determinant of subsequent declines in ventilatory function, with perhaps some contribution from environmental exposures. If airway reactivity closely reflects this constitutional factor, then it would be expected to be consistent in each individual. The findings in this study and others suggest that over time, there is significant intraindividual variation in the degree of NSBR. NSBR has been related to environmental and occupational exposures, respiratory illnesses, and tobacco smoking (28, 29), implying that airway reactivity is not a purely constitutional factor, and also limiting the utility of airway reactivity as a predictor of ventilatory declines. Clearly, both the “host” and the environment should be considered as important factors in the development of increased airway reactivity.

In conclusion, in this 5-yr study of underground coal miners and nonmining workers, increased nonspecific bronchial responsiveness at the first survey was predictive of somewhat increased subsequent rates of decline in FEV₁. However, increased NSBR at the final survey was more strongly associated with accelerated FEV₁ declines over the preceding 5-yr. NSBR status was variable in 22% of subjects, and a change in status to increased responsiveness or to normal responsiveness was associated with a corresponding increased or normal rate of FEV₁ decline. Because of its variability over time, increased NSBR predicts lung function decline only in some individuals, and as a consequence, its use as a prognostic test in chronic airway disorders has limitations. Increased airway responsiveness appears to be a manifestation of a pathophysiological process that results in ventilatory impairment; however, that process may be reversible. Thus, future studies among individuals at risk for chronic airflow limitation should further explore modifiable determinants of NSBR and the potential utility of interventions directed at preventing or reducing nonspecific airway hyperresponsiveness.

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