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Small Airway Dysfunction and Abnormal Exercise Responses:

A Study in Coal Miners

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Abstract

Rationale—Coal mine dust exposure can cause symptoms and loss of lung function from multiple mechanisms, but the roles of each disease process are not fully understood.

Objectives—We investigated the implications of small airway dysfunction for exercise physiology among a group of workers exposed to coal mine dust.

Methods—Twenty coal miners performed spirometry, first breathing air and then helium-oxygen, single-breath diffusing capacity, and computerized chest tomography, and then completed cardiopulmonary exercise testing.

Measurements and Main Results—Six participants meeting criteria for small airway dysfunction were compared with 14 coal miners who did not. At submaximal workload, miners with small airway dysfunction used a higher proportion of their maximum voluntary ventilation and had higher ventilatory equivalents for both O_2 and CO_2. Regression modeling indicated that inefficient ventilation was significantly related to small airway dysfunction but not to FEV_1 or diffusing capacity. At the end of exercise, miners with small airway dysfunction had 27% lower O_2 consumption.

Conclusions—Small airway abnormalities may be associated with important inefficiency of exercise ventilation. In dust-exposed individuals with only mild abnormalities on resting lung function tests or chest radiographs, cardiopulmonary exercise testing may be important in defining causes of exercise intolerance.

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Keywords

respirable dust; cardiopulmonary exercise test; pneumoconiosis; small airways

Abnormalities in small lung airways, resulting from tobacco smoking and other inhaled agents, may contribute to chronic airflow limitation (1–6). Coal miners who inhale excessive dust develop a characteristic lung pathology in the walls of the terminal and respiratory bronchioles, comprising pigmentation, cellular infiltrate, and collagen deposition, with associated emphysema. This change, labeled the coal macule, may not be apparent on routine radiography (7–10). Physiologic abnormalities attributed to dysfunction in small airways have been observed in coal miners (11); however, the clinical implications of these lesions remain a topic of investigation (12).

Among miners with mild to moderate radiographic evidence of pneumoconiosis, symptoms of breathlessness during cardiopulmonary testing appear to correlate most closely with inefficient ventilation, reflected by an increase in the expired minute ventilation per liter of oxygen consumed (13). Important reductions in exercise performance have been associated with small airway dysfunction among former cigarette smokers (14).

To further assess mechanisms of functional limitation in dust-exposed individuals, we analyzed cardiopulmonary responses to exercise in a group of coal miners with and without physiologic evidence of small airway dysfunction.

Methods

Participants

Research participants were recruited from the longitudinal cohort of underground coal miners of the field-based U.S. National Study of Coal Workers' Pneumoconiosis (15). Twenty-six miners, who had worked an average 25 years underground, volunteered for a more comprehensive laboratory-based evaluation of resting and exercise pulmonary physiology. Six miners could not be included in this study: five did not complete the treadmill exercise, and for one, the exercise equipment malfunctioned. The study was reviewed and approved by the National Institute for Occupational Safety and Health Human Subjects Review Board, and all subjects gave informed consent to participate according to their level of engagement.

Methods for clinical characterizations, resting pulmonary function tests, and scoring of high-resolution computed tomographic images of the chest have been reported (5). Six miners were identified with small airway dysfunction when they demonstrated little or no increase (<20%) in maximal flows at 50% vital capacity when breathing a mixture of 80% helium and 20% oxygen, compared with air ($\Delta \dot{V}_{\max 50}$heliox). For five of the six, forced expiratory flow between 25 and 75% of FVC ($FEF_{25–75\%}$) was below the lower limit of normal, breathing air (16–18).

The 14 other coal miners did not meet either helium spirometry or $FEF_{25–75\%}$ criteria for small airway disease and were classified as referents.

Cardiopulmonary Exercise Testing

Exercise testing was conducted in accordance with the American College of Sports Medicine guidelines (19). Electrocardiograms and pulse oximetry were monitored continuously during the test. Heart rate and blood pressure were recorded during the final 30 seconds of each stage. Expired air was analyzed breath-by-breath for O_2 and CO_2 using either a mass spectrometer (Model 1100; Perkin-Elmer Corp., Waltham, MA; n = 7) or an automated metabolic cart (Cardio2; MGC, St. Paul, MN; n = 17). The following variables were calculated and averaged sequentially every 15 seconds during the exercise: expired ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), heart rate, and Sa_{O_2}. All instruments were calibrated before each test.

Subjects walked on a motorized treadmill at a comfortable pace (range, 1.3–3.5 mph) on the level during a 2- to 4-minute warm-up phase. Subsequently, treadmill speed remained constant while grade increased 2% every 2 minutes until the subject requested that the test be stopped (symptom limited) or test termination criteria were met. Tests were terminated for: (1) heart rate greater than or equal to 90% of age-predicted maximum, (2) a $\dot{V}_{O_2}$ of 25 ml/kg/min, or (3) any of the standard clinical safety end points.

Data Analysis

Statistical analysis was performed using the SAS software version 9.0. Group comparisons were used to analyze differences between miners with evidence of small airway dysfunction and referents. Student t test was used for continuous variables; Fisher exact test was used for dichotomous variables. Probability levels of $P \leq 0.05$ were considered significant; a trend is mentioned for differences in which $0.05 < P < 0.10$.

Multiple regression analysis was performed using data from all 20 study miners to further assess factors affecting ventilation efficiency during exercise. The dependent variable was the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) during exercise at an oxygen consumption of 17 ml/kg/min. We chose to model $\dot{V}_E/\dot{V}_{CO_2}$ rather than $\dot{V}_E/\dot{V}_{O_2}$ because ventilation is closely coupled with CO_2 production, and diffusing impairment should have little impact on CO_2 transfer (20).

Both stepwise and forward multiple linear regression techniques were used to further examine the independent variables that had shown group differences between miners with and without small airway dysfunction (21).

Results

Table 1 shows results of age, height, weight, smoking status, clinical categories, and radiographic patterns for the 20 study participants. When grouped by the presence or absence of small airway dysfunction, there were no significant differences in age, height, or clinical categorizations for chronic obstructive pulmonary disease, emphysema, coal workers' pneumoconiosis, or interstitial lung disease; the group with dysfunction tended to have more bronchospasm ($P = 0.06$) (Table 1). No participant took β-blockers; use of other

medications was similar by small airway group (data not shown). High-resolution computed tomography images tended to show greater emphysema scores in the group with small airway dysfunction ($P = 0.08$), but fibrosis scores were similar ($P = 0.36$). No pleural disease was identified. Grade 3 dyspnea was reported by two of the miners with small airway dysfunction and none without ($P = 0.08$). There were no significant group differences in smoking status, cigarette pack-years, or the presence of cough, phlegm production, or wheezing.

Results of resting pulmonary function tests and cardiopulmonary exercise are summarized in Table 2. Miners with small airway dysfunction had a significantly lower percent predicted FEV_1 and $FEV_1/FVC\%$ as well as a greater residual volume divided by total lung capacity, consistent with air trapping. Both percent predicted diffusing capacity of carbon monoxide $(D_{L_{CO}})$, and percent predicted lung diffusing capacity divided by alveolar volume (D_L/V_A) trended lower with dysfunction; total lung capacity did not differ. Exercise measurements are shown for a submaximal workload (17 ml/kg/min) that was achieved by all 20 participants and also for the end of test. Ventilatory efficiency at the submaximal workload was lower in the group with small airway dysfunction, as evidenced by significant elevations in ventilatory equivalent for O_2 $(\dot{V}_E/\dot{V}_{O_2})$ and ventilatory equivalent for CO_2 $(\dot{V}_E/\dot{V}_{CO_2})$ Miners with dysfunction also used, on average, a higher proportion of their estimated maximum voluntary ventilation (35 times FEV_1; 49.2 vs. 34.7%); end-tidal CO_2 was also significantly lower and end-tidal O_2 higher. Importantly, at the end of the exercise test, although heart rates were similar, total oxygen consumption was 27% lower in the group of miners with small airway dysfunction.

The stepwise selection model for $\dot{V}_E/\dot{V}_{CO_2}$ indicated that small airway dysfunction was the only variable to enter the model at $P < 0.10$ level. A forward selection model (Table 3) showed that the presence of small airway dysfunction explained 35% of the variance and was the only input variable to enter the model with statistical significance.

The relationship between expired ventilation $(\dot{V}_E)$ and carbon dioxide production $(\dot{V}_{CO_2})$ during exercise was further assessed. Participant responses were separated at the midpoint in time of the treadmill exercise and the $\dot{V}_E/\dot{V}_{CO_2}$ slope determined for both the first half (lower workloads) and also the entire exercise. The y-intercept was calculated as the predicted ventilation when $\dot{V}_{CO_2} = 0$, using the slope from the first half of the exercise. Compared with referents, miners with small airway dysfunction had 26% higher mean $\dot{V}_E - \dot{V}_{CO_2}$ slope (31.8 vs. 25.3, $P = 0.002$); the slope at lower workloads was also higher ($P = 0.03$), whereas the y-intercept did not differ between the groups ($P = 0.36$).

Discussion

Small airway disease has been associated with important respiratory abnormalities in some smokers and dust-exposed workers (1, 2, 5, 6, 11, 14, 22, 23). To further address this issue, we compared exercise responses between miners who did and did not meet criteria for dysfunction in small airways. Study participants with evidence of small airway dysfunction

showed inefficient ventilation, as reflected by elevations in $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$, and $\dot{V}_E - \dot{V}_{CO_2}$ slope, and used a greater proportion of their maximal voluntary ventilation at a similar workload compared with referents.

Multivariate models were used to assess if any of the group differences (the presence of small airway dysfunction, $D_{L_{CO}}$, percent predicted FEV_1, or body weight) contributed to the inefficient ventilation. $D_{L_{CO}}$, percent predicted FEV_1, and body weight did not contribute significantly to $\dot{V}_E/\dot{V}_{CO_2}$ in the models ($P = 0.26–0.32$, $R^2 = 4–5\%$); thus, important effects from either generalized emphysema or large airway obstruction seem unlikely to explain the abnormal exercise ventilation. In contrast, small airway dysfunction explained 35% of the variance in the model and was the only input variable of statistical significance, a finding that tends to implicate the pathologic findings that have been observed in the region of the small airways (often associated with focal emphysema) (1, 7–10) as important contributors to the observed ventilatory inefficiency.

The current findings can be compared with previous studies of exercise physiology in relation to $FEF_{25–75\%}$ among nonsmoking bituminous coal miners (22, 23). Nemery and colleagues compared 32 asymptomatic nonsmoking Belgian coal miners (mean, 17.8 yr underground) to 34 nonsmoking steelworkers (22). The miners' mean $D_{L_{CO}}$ was similar to the steelworkers', but FEV_1 and mid-flows were significantly lower and residual volume/total lung capacity higher, findings associated with small airway dysfunction in our current study. On exercise, the Belgian miners' mean $P_{a_{O_2}}$ was lower, and the difference between alveolar and arterial oxygen ($A–aDO_2$) higher, versus the steelworkers. Rasmussen studied 162 lifelong nonsmoking miners and found abnormal gas exchange on exercise (elevations in $A\text{-}aDO_2$) was associated with both increased ventilatory equivalent for oxygen $(\dot{V}_E/\dot{V}_{O_2})$ and reduced $FEF_{25–75\%}$, although the latter was not statistically significant. Arterial P_{CO_2} tended to be lower in the miners with elevated $A\text{-}aDO_2$, particularly those without obstruction on spirometry. In our current study, arterial blood gases were not measured; however, the miners with small airway dysfunction showed elevations of both $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ and a lower end-tidal CO_2 $(P_{ET_{CO_2}})$ than the referents, findings that are similar to Rasmussen (23). Neither Nemery and colleagues nor Rasmussen used statistical modeling to assess associations between exercise responses and small airways variables (22, 23).

Ofir and colleagues reported exercise responses in 21 dyspneic former smokers with mild chronic obstructive pulmonary disease (post-bronchodilator FEV_1 averaged 91% predicted), and 21 healthy comparison subjects (14). Resting lung physiology showed that the former smokers had significant evidence of small airway dysfunction, with prominent elevations in closing capacity and reductions in $FEF_{25–75\%}$. On submaximal exercise, the patient group showed significantly elevated $\dot{V}_E/\dot{V}_{CO_2}$, $\dot{V}_E/\dot{V}_{O_2}$, and percentage maximal voluntary ventilation, and a reduced $P_{ET_{CO_2}}$, results that are all quite similar to our study findings. Ofir and colleagues documented that exertional dyspnea scores were highly correlated with percentage maximal voluntary ventilation (14). They hypothesized that localized areas of

emphysema may affect small airway function even in the absence of diffusion impairments sufficient to cause hypoxemia. These authors concluded that individuals with only mild obstruction on spirometry may have extensive small airway dysfunction, which can result in clinically important dyspnea and exercise intolerance due to excessive ventilatory demand and abnormal dynamic ventilatory mechanics (14). Our results are consistent with the findings of Ofir and colleagues and support their hypothesis that abnormalities in time constants in small airways can lead to inefficient ventilation on exertion and resultant dyspnea (14).

Strengths and Limitations

Our study has both strengths and weaknesses. Testing was performed in a research laboratory setting, according to established calibration and quality assurance protocols, and was supervised by an experienced team including technicians, physicians, and an exercise physiologist. By using novel statistical models, the current study expands previous findings by relating small airway dysfunction to important decrements in the efficiency of ventilation during exercise, while accounting for variation in FEV_1 and diffusing capacity. Although only 20 miners were studied, multiple outcomes demonstrated statistically significant differences, and the results seem unlikely to be due to chance. Participants had long tenures working underground in U.S. coal mines; however, the study cannot determine the overall proportion of miners with small airway dysfunction or the relative contribution of various factors, such as dust and tobacco smoking, on small airway function.

Conclusions

This report demonstrates that dust-exposed workers with abnormalities in small airway function may exhibit an important reduction in the efficiency of ventilation during exertion that is not primarily attributable to abnormalities in FEV_1 or diffusing capacity. The current report provides additional evidence that abnormalities in the region of small lung airways can lead to excessive ventilation during exertion and associated exercise intolerance. Particularly among dust-exposed individuals with only mild abnormalities on resting lung function tests or chest radiographs, cardiopulmonary exercise testing may be important in defining causes of exercise intolerance.

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Table 1

Comparison of coal miners with and without small airway dysfunction: age, height, smoking, questionnaire-based symptoms, and clinical categories

	Small Airway Dysfunction		*P* Value
	Yes (*n* = *6*)	No (*n* = *14*)	
Age, mean (SD), yr	58.8 (9.3)	53.9 (7.7)	0.23
Current smoker, n (%)	5 (83%)	8 (57%)	0.28
Pack-years at follow up, mean (SD)	19.2 (10.1)	12.3 (8.5)	0.13
Height, mean (SD), cm	173.8 (3.4)	176.5 (8.4)	0.33
Weight, mean (SD), kg	166.8 (18.7)	203.3 (25.8)	0.006
Clinical categories, n (%)			
Bronchospasm	3 (50)	1 (7)	0.058
Interstitial lung disease	1 (17)	1 (7)	0.44
Emphysema	1 (17)	0 (0)	0.30
Coal workers' pneumoconiosis	3 (50)	3 (21)	0.19
COPD	0 (0)	0 (0)	NA
Symptoms, n (%)			
Cough	3 (50)	4 (29)	0.34
Phlegm	2 (33)	3 (21)	0.48
Dyspnea grade 3	2 (33)	0 (0)	0.08
Wheeze	4 (67)	9 (64)	0.66
HRCT score, mean (SD)			
Emphysema	11.5 (10.0)	2.4 (3.9)	0.08
Fibrosis	4.7 (5.5)	2.4 (4.9)	0.36

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; HRCT = high-resolution computed tomography.

For categorical variables, *P* values from Fisher exact test. For continuous variables, *P* values from Student *t* test.

Table 2

Comparison of coal miners with and without small airway dysfunction: resting lung physiology test results, and treadmill exercise responses at a submaximal workload and at end-of-test

	Small Airway Dysfunction		*P* value
	Yes (*n* = 6)	No (*n* = 14)	
Resting			
pp FEV_1, %	75.4 (8.7)	95.1 (15.3)	0.009
pp FVC, %	94.4 (11.4)	98.2 (15.5)	0.60
FEV_1/FVC, %	61.7 (10.0)	74.8 (6.0)	0.0017
$FEF_{25–75\%}$, L/s	1.2 (0.5)	2.9 (0.9)	0.0005
$\Delta\dot{V}\,\max 50$ heliox, %	11.2 (5.6)	39.6 (13.5)	0.0008
TLC, L	7.2 (1.3)	6.8 (1.5)	0.59
RV, L	2.8 (0.8)	2.0 (0.8)	0.07
RV/TLC, %	38.3 (4.6)	29.8 (5.6)	0.004
$D_{L_{CO}}$, ml/min/mm Hg	22.3 (5.3)	28.2 (3.5)	0.0097
pp $D_{L_{CO}}$	90.5 (16.6)	105.2 (16.5)	0.088
D_L/V_A, L/min/mm Hg	3.7 (1.0)	4.7 (0.7)	0.04
pp D_L/V_A, %	98.8 (26.3)	119.7 (17.5)	0.0540
Exercise			
Submaximal workload			
$\dot{V}_E$, L/min	42.0 (8.1)	41.9 (7.2)	0.98
$\dot{V}_{O_2}\,\mathrm{rel}$, ml/kg/min	17.0 (0.3)	17.2 (0.3)	0.16
$\dot{V}_E/\dot{V}_{O_2}$	32.3 (4.5)	25.7 (2.3)	0.0004
$\dot{V}_E/\dot{V}_{CO_2}$	32.7 (4.7)	27.1 (3.5)	0.008
% Maximal voluntary ventilation	49.2 (14.9)	34.7 (8.7)	0.013
Sa_{O_2}, %	96.8 (1.5)	95.3 (2.0)	0.10
PET_{O_2}	114.2 (5.0)	105.2 (3.3)	0.001
PET_{CO_2}	37.6 (4.3)	43.3 (3.5)	0.015
End of test			
Breath frequency	29.3 (6.4)	27.9 (6.6)	0.65
Tidal volume	1.8 (0.3)	2.1 (0.4)	0.07
Heart rate, bpm	128 (16.5)	131 (12.0)	0.65
$\dot{V}_{O_2}$, L/min	1.6 (0.3)	2.2 (0.3)	0.003

	Small Airway Dysfunction		*P* value
	Yes (*n* = *6*)	No (*n* = *14*)	
$\dot{V}_{O_2}rel$, ml/kg/min	21.5 (3.6)	23.5 (2.4)	0.17

Definition of abbreviations: $D_{L_{CO}}$ = single-breath diffusing capacity of the lung for carbon monoxide; D_L/V_A = single-breath diffusing capacity for carbon monoxide divided by alveolar volume; $FEF_{25–75\%}$ = forced expiratory flow between 25% and 75% of FVC; $P_{ET_{CO_2}}$ = carbon dioxide partial pressure of end-tidal gas; $P_{ET_{O_2}}$ = oxygen partial pressure of end-tidal gas; pp = percent predicted; RV = residual volume; TLC = total lung capacity; ΔVmax50 heliox = % change in maximal flows at 50% vital capacity when breathing a mixture of 80% helium and 20% oxygen, compared to air (n = 12 with valid tests); $\dot{V}_{O_2}rel$ = oxygen consumption relative to body weight.

Table 3

Forward selection linear regression model of $\dot{V}_E/\dot{V}_{CO_2}$, N = 20 coal miners

Step	Variable Entered	Partial R^2	Model R^2	C(p)	*F* Value	Pr > F
1	Small airway dysfunction, yes/no	0.348	0.348	2.686	9.06	0.0079
2	Weight	0.044	0.392	3.4835	1.17	0.2960
3	FEV_1 % predicted	0.041	0.433	4.0000	1.06	0.3164
4	$D_{L_{CO}}$	0.051	0.484	3.1190	0.83	0.2594

Definition of abbreviations: C(p) = Mallows statistic; $D_{L_{CO}}$ = single breath diffusing capacity of the lung for carbon monoxide; Pr = probability associated with F value for variable.

Small airway dysfunction was considered present when the percentage change in maximal flows at 50% vital capacity when breathing a mixture of 80% helium and 20% oxygen, compared to air, was <20% and/or forced expiratory flow between 25% and 75% of FVC was below the lower limit of normal, and absent when neither of these criteria was met.