Diesel Asthma

Reactive Airways Disease following Overexposure to Locomotive Exhaust

John F. Wade III, MD

Lee S. Newman, MD

While some of the gaseous and particulate components of diesel exhaust can cause pulmonary irritation and bronchial hyperreactivity, diesel exhaust ⁎ posure has not been shown to cause asthma. Three railroad workers developed asthma following excessive exposure to locomotive emissions while riding immediately behind the lead engines of caboose-less trains. Asthma diagnosis was based on symptoms, pulmonary function tests, and measurement of airways hyperreactivity to methacholine or exercise. One individual's peak expiratory flow rates fell in a work-related pattern when riding immediately behind the lead diesel engine. None had a previous history of asthma or other respiratory disease and none were current smokers. All three developed persistent asthma. In two cases, physiologic abnormalities suggesting reversible restriction were observed. This is the first report implicating diesel exhaust as a cause of reactive airways disease.

Diesel-powered equipment has long been used in industrial applications, resulting in diesel exhaust exposure for railroad workers, miners, bridge and tunnel workers, truck drivers and bus maintenance garage workers, among others. The National Institute for Occupational Safety and Health (NIOSH) estimated in 1983 that between 1 and 1.5 million workers were exposed to diesel emissions.[1] Mounting concerns about potential health effects of diesel exhaust have led to numerous studies of the carcinogenicity and respiratory consequences of chronic exposure.[2-13] Much less is known about the acute respiratory effects of high level exposure to diesel exhaust.[14,15]

We have identified three railroad workers who developed new asthma from diesel exhaust inhalation. Overexposure to diesel combustion products occurred in these individuals after two railroad companies had discontinued the use of cabooses on freight trains. One of the principle functions of the caboose is to shuttle second railroad crews for future runs, a practice called "deadheading." As a result of caboose-less trains, deadheading crews have to ride in locomotive units trailing immediately behind the lead locomotive. In each of our patients, diesel exhaust from the lead unit entered the second unit, inducing acute or subacute onset of asthma.

Report of Cases

Case 1

A 40-year-old white man developed persistent dyspnea beginning acutely during a 5-hour exposure to diesel locomotive exhaust in April 1987.

The patient, employed for 14 years as a railroad conductor and brakeman, had been riding in the second locomotive unit trailing immediately behind the lead locomotive. The lead engine's diesel exhaust blew almost continually into the cab in which the patient was riding, producing acute symptoms of shortness of breath, burning chest pain with inspiration, and burning eyes. The patient reported no cough, fever, or hemoptysis and had no intercurrent respiratory infection at the time of exposure. He had no prior history of asthma, allergies, bronchitis, pneumonia, or other respiratory illness. He was a former smoker (17 pack-years) having quit in 1982.

The patient reported that he had never experienced work-related respiratory symptoms or previously been overexposed to diesel exhaust until then, noting that deadhead crews did not ride in the second unit of cabooseless trains until approximately 6 months before the onset of his symptoms. He noted that wind direction had contributed to the intensity of his acute exposure.

Upon arrival at the train's destination, the patient was seen at a local emergency room where he was found to be dyspneic, with poor air movement and conjunctival injection. Spirometry was not performed, but arterial blood gas analysis demonstrated profound hypoxemia (pO$_2$ 35 mm Hg, O$_2$ saturation 69%, pCO$_2$ 34 mm Hg, pH 7.45). He was treated as an inpatient with corticosteroids and supplemental oxygen, leading to gradual improvement in symptoms and oxygenation. Because of persistent dyspnea, the patient saw a pulmonologist 3 weeks later. Reactive airways disease was diagnosed based on the demonstration of airflow limitation and exercise-induced bronchospasm. Theophylline and inhaled beta-agonists produced subjective improvement, and the patient returned to work. Despite medication, a second, similar exposure to excessive diesel locomotive exhaust 2 months later precipitated another severe asthma attack. Since that time, the patient's respiratory symptoms have been precipitated by nonspecific triggers such as exercise, cold air, and fumes. .

Fourteen months following the initial accident, the patient was referred to the National Jewish Center for I munology and Respiratory Medici He had continued to experience e sodic aggravation of his respirat symptoms, although they were fa well controlled with oral theophylli an inhaled beta-agonist, and inha triamcinolone. Past medical and cupational history was noncontri tory, except as noted above. The tient's father and brother had reaci airways disease, and his two sons I seasonal rhinitis. He had no aller or atopy.

Physical examination revealed s tered expiratory wheezes and sli prolongation of expiratory phase forced expiration. Chest radiogr: was normal, as were radiographs fr 1987 and 1988. Pulmonary funct tests suggested a mixed restrictive obstructive disorder, with impro ment in airflow limitation follow bronchodilator. Diffusing capa was normal (see Table 1). Pulmon mechanics showed the patient to h normal elastic recoil, suggesting the mildly decreased lung volui were related to the patient's we: rather than to coexisting intersti lung disease.

TABLE 1
Pulmonary Function Tests in Diesel Asthma Cases*

	Case 1		Case 2		Case 3			
					Initial		Follow-up§	
	Pre†	Post‡	Pre	Post	Pre	Post	Pre	Post
FEV$_1$	2.57 (59)	3.81 (91)	1.33 (38)	2.54 (73)	3.16 (79)	3.23 (81)	2.65 (65)	3.19 (81
FVC	3.31 (61)	4.75 (85)	2.17 (45)	3.86 (80)	3.55 (66)	3.62 (67)	3.69 (69)	3.73 (7(
FEV$_1$/FVC (%)	78	80	61	66	89	89	71	85
Total lung capacity	4.87 (67)	6.56 (90)	6.86 (107)	6.61 (103)	6.03 (86)	5.47 (78)	5.39 (77)	5.27 (7£
Thoracic gas volume	2.92 (72)	3.49 (86)	3.98 (109)	3.80 (103)	2.10 (53)	2.05 (52)	2.62 (66)	2.31 (5£
Residual volume	1.78 (84)	2.08 (98)	2.81 (135)	2.47 (118)	1.54 (95)	1.24 (76)	1.65 (99)	1.17 (7(
DL$_{co}$‖	106		104		157		143	
Airways hyperreactivity	Positive#		0.2 mg/dL**		6.2 mg/dL**			

* Expressed in liters, with percent predicted in parentheses, unless otherwise indicated.
† Measured prior to administration of inhaled bronchodilator.
‡ Measured after administration of inhaled bronchodilator.
§ Follow-up 3 years after initial exposure, 1 year after initial tests.
‖ Single breath-diffusing capacity for carbon monoxide (% predicted).
Positive exercise-induced bronchospasm study.
** Provocative concentration of methacholine producing 20% or greater drop in FEV$_1$ (PC$_{20}$ FEV$_1$) (normal > 8 mg/dL).
Note.—FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; DL$_{co}$, diffusing lung capacity for carbon monoxide.

Case 2

A 50-year-old white man non-smoker had been in good health, without prior history of lung disease or lower respiratory tract symptoms until one evening in January 1987. The patient, employed as a railroad conductor and brakeman for 25 years, was riding in a diesel exhaust-filled second locomotive unit for several hours when he noted the acute onset of shortness of breath, dry cough, chest tightness and wheezing. Although he closed the windows of the cab, diesel exhaust emanating from the lead locomotive entered through the seams in the doors and through the electrical panels, filling the cab with the most intense exposure he had ever experienced. He recalled previous more moderate diesel exhaust exposures, beginning when his employer had removed the cabooses from the trains several months earlier.

When the train's run was completed, he was admitted to a local hospital. He was found to have bilateral rhonchi and hypoxemia (pO_2 53 mm Hg, pCO_2 31 mm Hg, pH 7.49). The patient improved with theophylline, inhaled beta-agonists and corti-

costeroids, but subjectively never returned to his pre-January 1987 baseline. Upon returning to work, he repeatedly experienced aggravation of his symptoms when exposed to diesel exhaust, even on shorter trips of less intense diesel exhaust exposure, as illustrated by his peak expiratory flow rates (see Fig. 1). He gradually required a more intensive medical regimen, including two courses of systemic corticosteroids.

Two years after the original incident, the patient was referred to National Jewish Center for evaluation of persistent respiratory symptoms. He continued to have episodic aggravation of respiratory symptoms, despite oral theophylline, inhaled and oral beta-agonists, beclomethasone nasal spray, oral antihistamines, and a recent course of oral corticosteroids. Nonspecific triggers included cooking smoke, cigarette smoke, and exertion. Past medical history was notable for preexisting seasonal rhinitis controlled with antihistamines and prior nasal polypectomy. He had no history of aspirin sensitivity, previous asthma, or other lung disease. Family, occupational, and environmental histories were noncontributory except as noted

above. Medical records indicated peripheral eosinophilia ranging from 6% to 15%, present since 1987.

Physical examination revealed a Cushingoid male in moderate respiratory distress. He had diffuse, wheezing and boggy, erythematous nasal mucosa without polyps. White cell count was 5.3×10^9/L with 9% eosinophils. Serum immunoglobulin E was normal. Chest radiograph demonstrated hyperinflation and peribronchial thickening, the latter finding having been present at the time of initial presentation. Pulmonary function tests showed airflow limitation with significant improvement following bronchodilator and nonspecific airways hyperresponsiveness. Diffusing capacity was normal (see Table 1).

Case 3

A 44-year-old Hispanic man never-smoker developed the subacute onset of episodic dyspnea on exertion, cough, wheezing, and nasal congestion beginning in late 1986. He reported a temporal association of these symptoms with high diesel exhaust exposures, usually within the first few hours of exposure. The patient, employed by the railroad for 23 years, worked for the past 11 years as a brakeman. He had never experienced respiratory problems until he began riding in second locomotive units on deadhead runs where he described being exposed to significantly more diesel exhaust than in previous years.

The patient sought medical attention in early 1987 because of increased frequency of these episodic respiratory symptoms. A graded treadmill test produced bronchospasm and cough. Despite treatment with inhaled beta-agonists, triamcinolone, several courses of oral corticosteroids, and removal from exposure, he remained symptomatic. Two years after symptom onset, he was referred to National Jewish Center with persistent, slowly progressive respiratory symptoms. Past medical history was notable for von Willebrand's disease, rhinoplasty for a nasal bone deformity, and cholecystectomy. He had no allergies or atopy. Except for diesel exhaust, he recalled no significant past occupa-
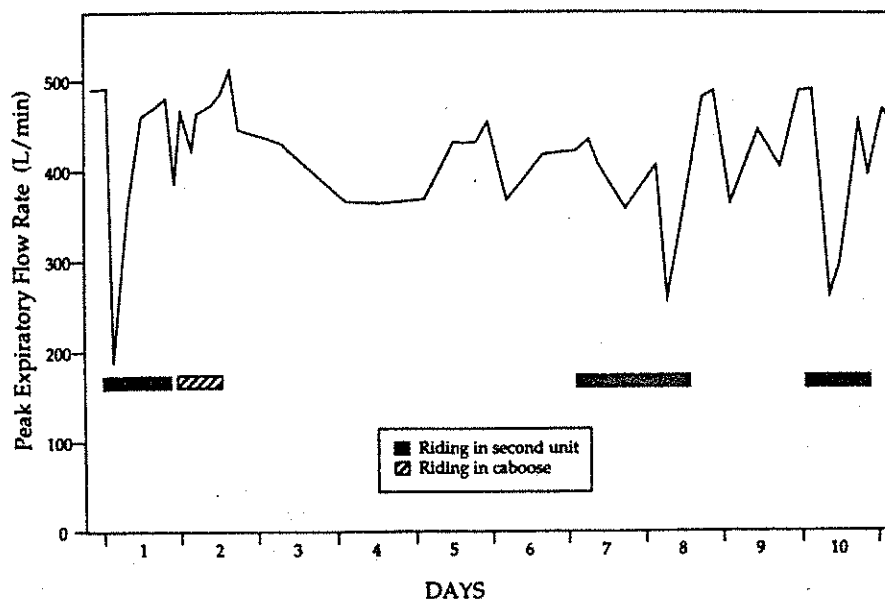

Fig. 1. Recording of peak expiratory flow rates in case 2, performed in January 1990, 2 years after initial onset of asthma. Bars indicate all workshifts. Note the fall in peak flow occurring shortly after the start of three shifts in which he rode in the train's second unit (*solid bars*). The patient's peak flows did not drop during one work period in which he rode in the train's caboose (hatched bar).

tional or environmental exposures.

Physical examination revealed a moderately obese male. The mucosa of the anterior nares was mildly hyperemic. Oropharynx was normal. Lungs were clear without wheezes, rales or rhonchi. Chest radiograph was normal. Initial pulmonary function tests suggested a possible restrictive process without airflow obstruction. Diffusing capacity was elevated (Table 1). Pulmonary mechanics revealed normal elastic recoil of the lungs suggesting that his reduced lung volumes were probably due to obesity. We observed mild airways hyperreactivity to methacholine (Table 1). A graded exercise treadmill test induced bronchospasm and cough, as had occurred in 1987. Accurate post-exercise spirometry was not obtainable due to severe cough. On a follow-up visit, 3 years after onset of symptoms, he remained symptomatic, noting nonspecific triggers such as grasses and exercise in cold or hot weather. Repeat pulmonary function tests showed airflow limitation with a significant bronchodilator response (Table 1).

Comments

Although millions of Americans are occupationally or environmentally exposed to diesel exhaust,[5] this is the first time that diesel exhaust has been reported as a cause of asthma. Several lines of evidence support the conclusion that railroad locomotive diesel exhaust exposure induced asthma in these three individuals (see Tables 1 and 2): 1) all three demonstrated airways hyperreactivity, air flow limitation, and reversibility with bronchodilators, consistent with asthma; 2) none had preexisting asthma or significant respiratory tract disease, based on our review of all past medical records and medical history; 3) each developed symptoms within the first hours of the overexposure to diesel exhaust; 4) in two cases, a single unusually high exposure led to immediate first time hospitalization and treatment for asthma; 5) all three experienced exacerbation of symptoms upon reexposure to locomotive diesel exhaust; and 6) in one individual, a work-related pattern of airflow limitation was documented by peak expiratory flow rate records. These three workers were employed by two different railroads and were unaware of the others or of their shared diagnosis and etiology at the time of presentation.

Asthma resulting from overexposure to diesel exhaust may occur more frequently than is recognized. Kahn and co-workers recently reported 13 cases of acute overexposure to diesel exhaust among railroad workers, two of whom complained of chest tightness and wheezing.[14] The symptoms were suggestive of asthma, however, no other clinical or physiologic data were provided in that report.

While a number of population-based studies have examined the respiratory effects of diesel exhaust, none has tested for the development of asthma. However, data from several of these studies suggest that asthma could be occurring. In a large study of diesel bus garage workers, Gamble and co-workers found a significant increase in eye irritation, labored breathing, chest tightness, and wheezing in a subgroup of "high-exposure" individuals, although these symptoms were not associated with pulmonary function decrements at any measured level of nitrogen dioxide or diesel exhaust particulate concentration.[16] These same investigators showed that bus garage workers with longer job tenure had a higher prevalence of dyspnea, wheezing, cough and phlegm, and accelerated decline in spirometry compared to nonexposed control subjects.[13] In another study, diesel-exposed salt miners experienced a small but significant drop in FEV_1 across the workshift, correlating with increasing nitrogen dioxide levels.[11] In a later study of salt miners, this same group found that phlegm production was associated with increasing diesel exhaust exposure, but cough, dyspnea, and pulmonary function were not significantly different between the exposed and unexposed subjects.[12] In contrast, other researchers have found no effect of diesel exposure on respiratory symptoms or spirometry.[6–8,10,15] Many of the cross-sectional studies may be biased by a healthy-worker effect with asthmatics less likely to stay in the work force. Taken in composite, these epidemiologic studies present contradictory results, probably due in part to the heterogeneity of diesel exhaust,[17] variability in exposure conditions[17] and population and methodologic differences. None has attempted to measure outcome variables pertinent to the recognition of asthma, such as airways hyperreactivity or reversibility of airflow limitation.

We do not know the levels of exposure to combustion products that produced disease in our patients, as is

TABLE 2
Demographics and Clinical Features of Disease in Diesel Asthma Cases

	Case 1	Case 2	Case 3
Age (years)	40	50	44
Smoking history	Former	Never	Never
Prior respiratory tract disease	None	Seasonal rhinitis, nasal polyps	None
Pattern of disease onset	Acute	Acute	Subacute
Chest radiograph	Normal	Hyperinflation, peribronchial thickening	Normal
Subsequent nonspecific triggers*	+	+	+
Airways hyperreactivity testing†	+	+	+
Airflow limitation and bronchodilator response‡	+	+	+
Peak expiratory flow records	Not done	Work-related pattern	Not done
Duration of symptoms since onset (months)	14	24	36

* Development of asthma symptoms resulting from nonspecific exposures, since time of diesel exposure.

† By exercise or methacholine challenge testing (see Table 1).

‡ Based on FEV_1 pre- and post-albuterol (see Table 1).

commonly the case in occupational asthma. Nor can we know, in retrospect, which component parts of diesel emissions may have been causative. Diesel exhaust varies considerably, containing complex, respirable gases and particulates to which a variety of organic compounds adsorb.[18] Due to this complexity and variability, we did not perform specific bonrchoprovocation testing to diesel exhaust in our patients. Many of the component parts of diesel exhaust can cause asthma and/or act as pulmonary irritants. Potentially important constitutents include oxides of nitrogen,[19,20] sulfur oxides,[21-26] aldehydes,[27,28] and carbonaceous particulates.[29-31]

In addition to the potential for these irritants to cause airways hyperreactivity, intense exposures to the oxides of nitrogen and sulfur can result in bronchiolitis obliterans.[26,32-34] Symptoms of dyspnea and cough generally occur several weeks after recovery from exposure. Pulmonary function tests show a restrictive, obstructive, or mixed obstructive/restrictive pattern. Obstructive physiology is typically fixed and unresponsive to bronchodilator, unlike the reversible airways dysfunction in our patients. We can not exclude the possibility of coexistent bronchiolitis obliterans in our cases, as lung biopsy was not performed.

Interestingly, two of our patients exhibited physiology consistent with "reversible restrictive" lung disease.[35,36] Spirometry in cases 1 and 3 revealed a normal FEV_1/FVC ratio with reduced lung volumes characteristic of a classic restrictive defect. Bronchodilator treatment, however, produced a dramatic improvement in flow rates and normalization of lung volumes in case 1 and improved flow rates with reduced air trapping (decreased residual volume) in case 3 on follow-up testing. The pathophysiology of reversible restriction is unknown, but may relate to smooth muscle contraction and constriction of distal respiratory bronchioles and alveolar ducts. Constriction of these small terminal airways may preclude the development of hyperinflation typically seen in asthma. We do not

know whether reversible restriction is common in diesel exhaust overexposure, however as cases 1 and 3 demonstrate, this disorder would be easily overlooked if evaluation were limited to simple spirometry without bronchodilator testing.

These cases share many similarities with the patients described by Brooks and others as having reactive airways dysfunction syndrome (RADS).[37-44] This term has been used to describe a persistent clinical picture of asthma resulting from a single massive exposure to an irritant gas, fume, vapor, or smoke. However, our patients worked for the railroad for many years, and presumably had been chronically exposed to lower levels of diesel exhaust prior to their acute overexposures. One patient had a subacute onset of disease without recognizing a single precipitating exposure; however, recurrent, high exposures resulted in persistent symptoms. Occupational asthma can develop through one of several postulated mechanisms.[45] While the RADS-like presentation in our cases is compatible with an irritant mechanism,[44] it is notable that environmental automotive exhaust exposure has been implicated in the development of allergies,[46] and that diesel exhaust particulate can function as an adjuvant, enhancing antigen-specific immunoglobulin E formation in mice.[47] Future studies may elucidate the mechanism of diesel-induced asthma.

In conclusion, we have described three railroad workers who developed persistent asthma as a result of overexposure to diesel exhaust. This is the first time that any form of diesel exhaust has been associated with asthma. Future studies should be performed that can relate diesel exhaust dose and constitutents to measures of airways hyperreactivity among diesel-exposed workers. Regulations and work practices that may lead railroad workers to be overexposed to diesel exhaust should be reexamined and rectified.

Acknowledgments

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