APPENDIX AVAILABLE ON REQUEST

Research Report 124

Particulate Air Pollution and Nonfatal Cardiac Events
Part II. Association of Air Pollution with Confirmed Arrhythmias Recorded by Implanted Defibrillators

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Appendix D. Air Pollution and Incidence of Cardiac Arrhythmia

This article reports the results from the pilot study referenced in the Investigators' Report:

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh JA, Allen G, Monahan K, Dockery DW. 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11:11–17.

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Air Pollution and Incidence of Cardiac Arrhythmia

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Air pollution episodes have been associated with increased cardiovascular hospital admissions and mortality in time-series studies. We tested the hypothesis that patients with implanted cardioverter defibrillators experience potentially life-threatening arrhythmias after such air pollution episodes. We compared defibrillator discharge interventions among 100 patients with such devices in eastern Massachusetts, according to variations in concentrations of particulate matter, black carbon, and gaseous air pollutants that were measured daily for the years 1995 through 1997. A 26-ppb increase in nitrogen dioxide was associated with increased defibrillator interventions 2 days later (odds ratio = 1.8; 95% confidence interval = 1.1–2.9). Patients with ten or more interventions experienced increased arrhythmias in association with nitrogen dioxide, carbon monoxide, black carbon, and fine particle mass. These results suggest that elevated levels air pollutants are associated with potentially life-threatening arrhythmia leading to therapeutic interventions by an implanted cardioverter defibrillator. (Epidemiology 2000;11:11–17)

Keywords: pollution, cardiovascular diseases, implantable cardioverter defibrillators, arrhythmias, nitrous dioxide, carbon monoxide, black carbon, particulate matter.

Particulate air pollution episodes have been associated with increased hospital admissions for cardiovascular disease[1–4] and increased cardiovascular mortality[5–11] in epidemiologic studies. Persons with underlying heart disease appear to be at increased risk for the adverse health effects of particulate air pollution.[1–11]

Controlled exposure of animals and natural exposures of humans to particulate pollution have shown possible effects of air pollution on the heart. Instillation of 250 micrograms of combustion particles into the lungs of rats with pharmacologically induced pulmonary hypertension produced arrhythmia and doubled their mortality rate.[12] Dogs inhaling concentrated ambient particles showed changes in heart rate variability and electrocardiographic morphology consistent with increased sympathetic nervous system activity.[13,14] Heart rates of elderly subjects in Utah Valley increased in association with elevated concentrations of inhalable particulates (particulate matter less than 10 micrometers in aerodynamic diameter; PM_{10}).[15] In a subset of these subjects, heart rate variability decreased with increasing PM_{10} concentrations.[15] Increased heart rate and decreased heart rate variability are indicators of altered autonomic control, specifically increased sympathetic stress. Raised sympathetic activity increases the risk of ventricular fibrillation, a severe form of arrhythmia that, without intervention, leads to sudden death.[16]

We tested the hypothesis that patients with a history of serious arrhythmia requiring implanted cardioverter defibrillators (ICDs) would experience potentially life-threatening arrhythmia associated with air pollution episodes. Traditionally, ventricular arrhythmia is treated with drug therapies.[17] Implantable cardioverter defibrillators monitor electrocardiographic abnormalities and initiate therapeutic interventions. On detection of ventricular fibrillation or ventricular tachycardia, the ICD device will initiate pacing and/or shock therapy to restore a normal cardiac rhythm. Several recent clinical trials have suggested that ICD devices are more effective at preventing death from heart rhythm abnormalities than medications alone.[18,19] The ICD devices provide objective and accurate records of the occurrence and timing of arrhythmic events. We report the results of a pilot study to assess the feasibility of linking cardiac

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Editors' note: See related editorial on page 2 of this issue.

TABLE 1. Distribution of Events in the Sample of 100 Patients with Implanted Cardioverter Defibrillators, According to Age and Gender

Number of Events	No. of Persons	Total No. of Events	Person-Days	Median Follow-Up	Age		Male Patients
					Mean	Range	
0	67	0	40,248	574	61.9	22–85	75%
1–4	20	39	12,459	592	64.9	30–81	90%
5–9	7	48	5,583	798	59.0	30–78	86%
10 and more	6	136	5,338	961	60.5	37–77	83%
Total	100	223	63,628	644	62.2	22–85	79%

arrhythmias detected by ICD devices with air pollution exposures.

Subjects and Methods

Events of Cardiac Arrhythmia and Patient Follow-Up

We abstracted records of cardiac device clinic patients who had a device implanted before September 1997, survived until December 1997, had more than 30 days of follow-up, and lived in eastern Massachusetts (zip code areas 01800–02799). The 2 months after surgical implantation of the device were excluded to avoid effects of implantation and initial adjustment of programmable device settings. One hundred of the 120 patients seen at the clinic met the inclusion criteria.

Patients return to the clinic approximately every 3 to 6 months for follow-up. Records of detected arrhythmias and therapeutic interventions are downloaded from the implanted defibrillators, printed, and reviewed by the nurse managers. We copied the Episode Summary Report listing the date, time, type, and intervention for each detected arrhythmia. We restricted the analysis to defibrillator discharges precipitated by ventricular tachycardias or fibrillation and tabulated the subject- and day-specific arrhythmic interventions.

Air Pollution Measurements

We measured particulate air pollution concentrations in South Boston starting in January 1995. We measured $PM_{2.5}$ (mass of particles with an aerodynamic diameter below 2.5 μm) and PM_{10} (mass of particles with an aerodynamic diameter below 10 μm) concentrations with a tapered element oscillating microbalance (Rupprecht and Patashnick, model 1400A, Albany, NY). Elemental carbon was measured by the attenuation of light (effective center wavelength, 820 nm) of particles collected on a prefired quartz fiber filter (Aethalometer, Magee Scientific Inc, Berkeley, CA). Ozone (O_3) concentration was measured using an ultraviolet photometer analyzer (model 49, Thermal Environmental Co, Franklin, MA). Carbon monoxide (CO) concentration was measured by a continuous nondispersive infrared analyzer (Bendix model 8501-5CA, Lewisburg, WV). Relative humidity and temperature were measured continuously using an in-line probe (Vaisala model MP113Y, Woburn, MA). Sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) were measured hourly in Chelsea (approximately 7.5 kilometers north of South Boston) by the Massachusetts Department of Environmental Protection.

We calculated 24-hour means (midnight to midnight) for days with 16 or more valid hourly measurements. We calculated 5-day running means of the air pollutants when at least three 24-hour means were available.

Statistical Analyses

Defibrillator discharge interventions were analyzed by logistic regression models using fixed effect models with individual intercepts for each patient. We used multivariate analysis to evaluate confounding by trend, season, meteorologic conditions and day of the week. The final model included a linear trend; sine and cosine terms with periods of one, one-half, one-third, and one-quarter year; quadratic functions of minimum temperature and humidity; and indicators for day of the week. We selected this model without considering air pollutants on the basis of a comparison of the log likelihood of nested models. We conducted sensitivity analyses for the subgroup of patients who had more than ten events using robust logistic regression in a generalized linear model.[4] We also assessed the potential nonlinear dependence of defibrillator discharges on season or weather using nonparametric smooth functions.

We considered mean air pollution concentrations on the same day and lags of 1, 2, and 3 days. We evaluated possible cumulative effects of the air pollutants on the basis of the 5-day mean concentration. The linearity of the air pollution defibrillator discharge associations were assessed through categorical analysis, in which residuals of a linear regression analyses of the pollutant concentrations were divided into quintiles after adjusting for season, trend, meteorology, and day of the week as in the logistic regression model.

We present odds ratios (ORs) and 95% confidence intervals (CIs) based on an increase in each air pollution concentration from the 5th to the 95th percentile. The magnitude of estimates for different pollutants is therefore based on comparable increments of exposure for the study period.

Results

The study population was predominantly male (79%), with a mean age of 62.2 years. During 63,628 person-days of follow-up over 3 years in 100 patients, we observed 223 defibrillator discharges (Table 1). No discharges were recorded in 67 persons followed for a mean

TABLE 2. Distribution of the Air Pollutants Measured at Two Sites in Boston between January 1995 and December 1997

	Unit	Time Period	N	Mean	Percentiles					Maximum
					5%	25%	50%	75%	95%	
PM_{10}	$\mu g/m^3$	1/95–12/97	1,066	19.3	7.8	12.6	17.2	24.2	37.0	62.5
$PM_{2.5}$	$\mu g/m^3$	1/95–12/97	1,052	12.7	4.6	7.6	10.8	16.1	26.6	53.2
BC	$\mu g/m^3$	1/95–03/97	769	1.38	0.49	0.86	1.21	1.74	2.84	4.92
CO	ppm	1/95–03/97	789	0.58	0.32	0.43	0.53	0.66	0.97	1.66
O_3	ppm	1/95–03/97	746	0.0186	0.004	0.011	0.017	0.025	0.036	0.059
SO_2	ppm	1/95–12/97	1,072	0.007	0.001	0.003	0.005	0.009	0.019	0.087
NO_2	ppm	1/95–12/97	1,043	0.023	0.011	0.017	0.022	0.028	0.037	0.065
Minimum temperature	°C	1/95–12/97	1,075	7.03	−7.8	0.6	7.2	15.0	20.6	24.4
Relative humidity	%	1/95–12/97	1,068	66.61	38.8	53.8	67.1	80.0	93.0	101.8

PM_{10} ($PM_{2.5}$) = particulate matter less than 10 (2.5) micrometers in aerodynamic diameter; BC = black carbon.

of 601 days (40,248 person-days). Ten or more events per follow-up occurred in 6 patients (18% of 33 patients with any discharge), accounting for a total of 136 events (61% of all interventions). Patients with 10 or more events were slightly younger on average and predominantly male (Table 1). Separate analyses were conducted for this group.

Particle concentrations were modest, with mean concentrations of 19.3 $\mu g/m^3$ for PM_{10} and 12.7 $\mu g/m^3$ for $PM_{2.5}$ at the South Boston site (Table 2). Black carbon contributed on average 11% of $PM_{2.5}$. The concentrations of the gaseous pollutants—CO, O_3, and NO_2—were moderate, whereas sulfur dioxide concentrations were low. The concentrations of $PM_{2.5}$ and PM_{10} were highly correlated (Table 3). Black carbon was strongly correlated with $PM_{2.5}$, PM_{10}, CO, and NO_2. CO and NO_2, however, were only moderately correlated with PM_{10} and $PM_{2.5}$. In contrast, both SO_2 and O_3 were weakly correlated with the other pollutants, suggesting different seasonal patterns and sources. The highest $PM_{2.5}$, PM_{10}, O_3, and SO_2 concentrations were recorded during the summer, whereas black carbon, CO, and NO_2 had elevated peak concentrations throughout the year (Figure 1).

The rate of defibrillator discharge per person-day decreased over time in both the whole sample and a subgroup of persons with repeated events. Season was a strong predictor of the defibrillator discharges, with the highest frequency during the summer months and a second peak during the second half of the winter. In contrast, daily minimum temperature and daily relative humidity were only weak predictors of defibrillator discharges. No clear day-of-the-week pattern was observed.

We found no consistent evidence of increased defibrillator discharges associated with the concentration of the air pollutants on the same day for the sample of patients with any discharges (Table 4). A positive association was observed between the defibrillator discharges and the NO_2 concentrations on the previous day as well as with a 5-day mean. All other pollutants showed weaker and less consistent effects than NO_2.

Among the six patients who experienced ten or more discharges, defibrillator discharges were associated with exposures to PM_{10} as well as $PM_{2.5}$ lagged by 2 days (Table 4). Consistent positive association was observed with black carbon and CO. The strongest associations were observed for NO_2 (Table 4). Elevated concentrations of NO_2 1 and 2 days before and the mean over the previous 5 days were associated with defibrillator discharges. No association was observed between the defibrillator discharges and SO_2. The odds of defibrillator discharge increased monotonically with quintile of $PM_{2.5}$ and NO_2 lagged by 2 days (Figure 2). Including both pollutants into one model reduced the effect estimate of $PM_{2.5}$ effectively to 0, whereas the effect estimate of NO_2 was unchanged. Black carbon lagged by 2 days showed a linear increase in the odds ratio below 1.5 $\mu g/m^3$ with a potential plateau above 1.5 $\mu g/m^3$. There was weaker evidence for a linear association between the 5-day means of CO or black carbon and the defibrillator discharges. Discharge was as strongly associated with NO_2 2 days before as it was with the 5-day mean. Two-pollutant models including 5-day means of NO_2 and CO or black carbon found a consistent effect estimate for NO_2 but not for CO or black carbon.

TABLE 3. Day-to-Day Correlation between Air Pollution and Meteorologic Measures

	$PM_{2.5}$	BC	CO	O_3	NO_2	SO_2	Minimum Temperature	Humidity
PM_{10}	0.90	0.69	0.51	0.13	0.60	0.35	0.16	−0.01
$PM_{2.5}$		0.74	0.56	0.06	0.57	0.37	0.13	0.13
BC			0.75	−0.28	0.75	0.37	0.08	0.13
CO				−0.40	0.71	0.41	−0.13	0.22
O_3					−0.33	−0.26	0.46	−0.12
NO_2						0.51	−0.15	−0.03
SO_2							−0.31	−0.05
Minimum temperature								0.28

PM_{10} ($PM_{2.5}$) = particulate matter less than 10 (2.5) micrometers in aerodynamic diameter; BC = black carbon.

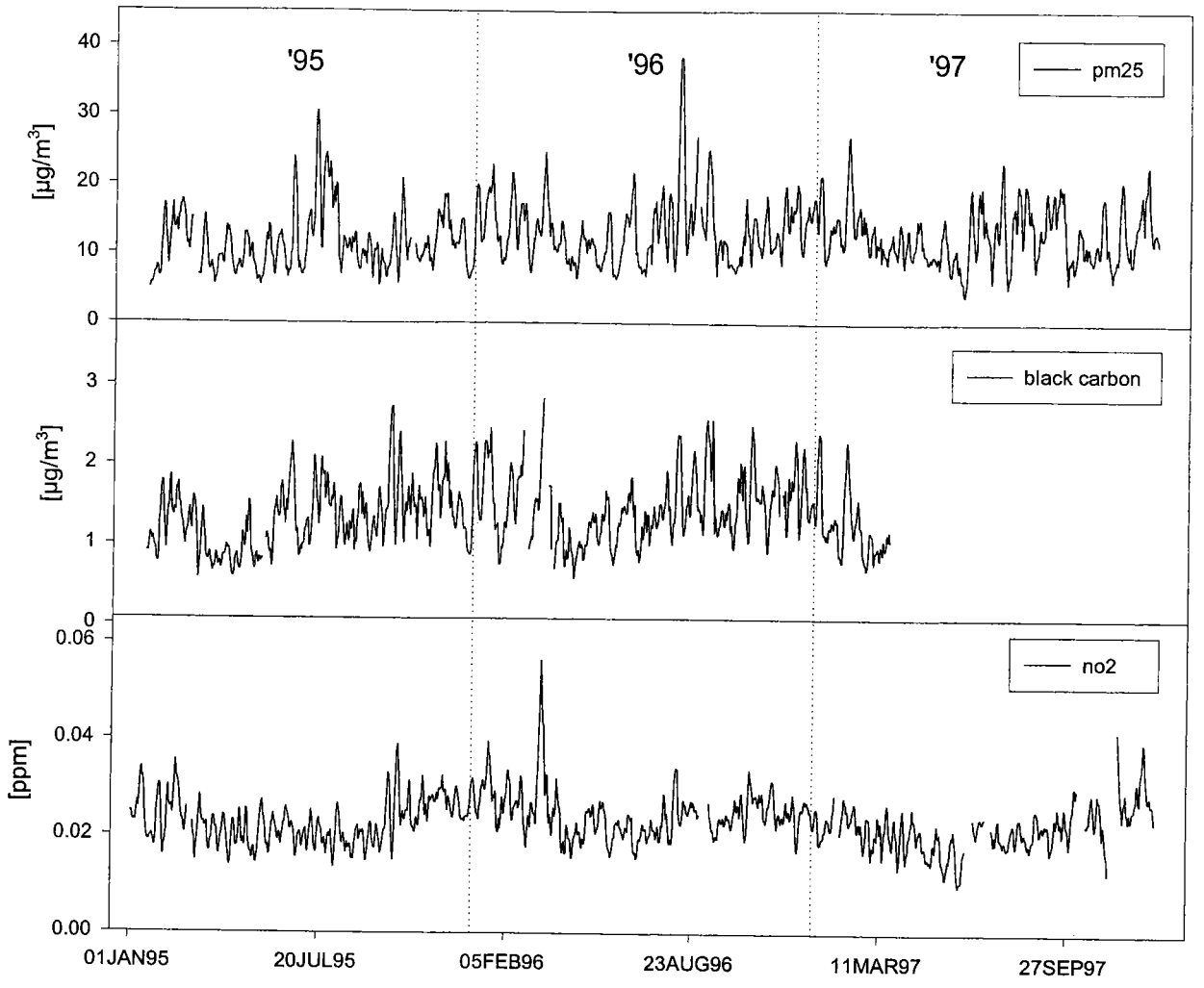

FIGURE 1. Daily concentrations of the 5-day means of $PM_{2.5}$, black carbon (BC), and NO_2 for the time period January 1, 1995, through December 31, 1997.

Additional analyses, including nonparametric functions for season (9.9 degrees of freedom) and meteorologic variables (2.3 degrees of freedom for minimum temperature and 2.7 degrees of freedom for relative humidity) improved the model fit. The effect estimates of NO_2 were reduced (OR = 2.03; 95% CI = 0.66–6.20) for 26 ppb NO_2 (lagged 2 days) whereas the effect estimate for $PM_{2.5}$ increased (OR = 1.87; 95% CI = 0.77–4.55) for 22 $\mu g/m^3$ $PM_{2.5}$ (lagged 2 days).

Analyses of only those days with $PM_{2.5}$ less than 30 $\mu g/m^3$ gave an effect estimate of 1.90 (95% CI = 0.99–3.68) for 22 $\mu g/m^3$ $PM_{2.5}$ (lagged 2 days).

Discussion

We observed increased risk of a cardiac arrhythmia in association with elevated concentrations of air pollutants in patients with ICDs. The odds of a therapeutic intervention to treat ventricular fibrillation or tachycardia in patients with at least 10 discharges nearly tripled in association with an increase of 26 ppb NO_2 and increased 60% in association with an increase in $PM_{2.5}$ concentrations of 22 $\mu g/m^3$. These associations were monotonic and close to linear. Defibrillator discharges did not follow exposures immediately but required an induction time of 1 or 2 days.

The subgroup of patients with repeated potentially life-threatening arrhythmias was most susceptible to exposure to ambient air pollution. Repeated discharges indicate that these patients belong to a subgroup of patients who experience acute arrhythmia in response to triggers.[20] This subgroup might be especially sensitive to air pollution. This group also provides most of the power for the analyses, because other potent triggers, such as transient ischemia,[20] add noise to the association of interest. Therefore, we would be more likely to detect an air pollution association in patients with repeated events than in patients who only experienced one or two events during the 3-year follow-up.

There was an induction period of 1–2 days between the exposure to air pollution and the observed defibrillator discharges. This is consistent with a hypothesized mechanism in which the deposition of particles in the

TABLE 4. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Defibrillator Discharges in Association with an Increase of the Air Pollutant from the 5th to 95th Percentile Adjusted for Season, Trend, and Minimum Temperature, Humidity, and Day of the Week

	Unit Change	At Least 1 Event: 33 Patients		At Least 10 Events: 6 Patients	
		OR	95% CI	OR	95% CI
PM_{10} ($\mu g/m^3$)					
Same day	29	0.95	0.59–1.54	0.91	0.48–1.70
Previous day	29	1.01	0.63–1.64	1.26	0.69–2.30
2 days ago	29	1.04	0.67–1.61	1.68	0.98–2.86
3 days ago	29	0.85	0.54–1.32	1.06	0.61–1.84
5-day mean	18	0.87	0.53–1.41	1.26	0.70–2.27
$PM_{2.5}$ ($\mu g/m^3$)					
Same day	22	0.87	0.55–1.37	0.82	0.45–1.49
Previous day	22	0.99	0.64–1.53	1.10	0.63–1.93
2 days ago	22	1.12	0.75–1.66	1.64	1.03–2.62
3 days ago	22	0.86	0.57–1.30	1.11	0.67–1.82
5-day mean	13	0.88	0.57–1.35	1.22	0.73–2.01
Black carbon ($\mu g/m^3$)					
Same day	2.4	0.95	0.51–1.78	1.27	0.57–2.81
Previous day	2.4	1.02	0.55–1.90	1.11	0.49–2.50
2 days ago	2.4	1.33	0.75–2.38	1.90	0.91–3.96
3 days ago	2.4	1.08	0.60–1.94	1.83	0.88–3.83
5-day mean	1.4	1.26	0.66–2.39	2.16	0.96–4.86
Carbon monoxide (ppm)					
Same day	0.65	1.07	0.62–1.86	1.12	0.54–2.32
Previous day	0.65	1.06	0.61–1.85	1.13	0.54–2.33
2 days ago	0.65	1.05	0.62–1.77	1.62	0.85–3.09
3 days ago	0.65	1.09	0.65–1.83	1.98	1.05–3.72
5-day mean	0.42	1.23	0.71–2.12	1.94	1.01–3.75
Ozone (ppm)					
Same day	0.032	0.96	0.47–1.98	1.23	0.53–2.87
Previous day	0.032	1.09	0.55–2.15	1.22	0.55–2.72
2 days ago	0.032	1.53	0.80–2.92	1.51	0.71–3.21
3 days ago	0.032	0.66	0.33–1.30	0.55	0.25–1.24
5-day mean	0.014	0.88	0.53–1.45	0.89	0.49–1.60
Nitrogen dioxide (ppm)					
Same day	0.026	1.24	0.75–2.06	1.70	0.91–3.18
Previous day	0.026	1.77	1.06–2.93	2.45	1.30–4.61
2 days ago	0.026	1.48	0.91–2.40	2.79	1.53–5.10
3 days ago	0.026	1.19	0.73–1.94	1.83	0.99–3.37
5-day mean	0.016	1.66	1.01–2.72	3.13	1.76–5.56
Sulfur dioxide (ppm)					
Same day	0.018	0.76	0.48–1.21	0.72	0.40–1.31
Previous day	0.018	0.91	0.60–1.37	0.77	0.44–1.37
2 days ago	0.018	0.89	0.59–1.34	1.01	0.63–1.61
3 days ago	0.018	1.09	0.78–1.52	1.08	0.72–1.62
5-day mean	0.015	0.85	0.50–1.43	0.75	0.38–1.47

lung elicit inflammatory responses resulting in a systemic signal.[21,22]

Possible Pathophysiologic Mechanisms

Most sudden cardiac deaths are caused by acute fatal arrhythmias—ventricular tachycardia/fibrillation.[17] Clinical trials that have evaluated the implantation of cardioverter defibrillator devices have shown that persons with known malignant arrhythmias benefit from the ICD devices compared with traditional drug therapy.[18,19]

Time series analyses have shown an association between mortality and hospital admissions for coronary disease with episodes of elevated levels of air pollution.[1–4,23] Stratification by diagnosis showed specific associations between air pollution and ischemic heart diseases[2,3,5] and congestive heart diseases.[2,3,23] Both ischemic and congestive heart disease are chronic diseases that are risk factors for acute tachycardia and ventricular fibrillation.[20] Arrhythmias might have been the acute event leading to the hospitalization. Admissions for dysrhythmia were positively associated with particulate air pollution concentrations, but the CIs were broad.[2,3] In London, Fairley[5] found an association between hospital admissions for dysrhythmia and NO_2 exposure. Hospital admission for arrhythmia increased 50% during a 1985 air pollution episode in Germany compared with a nonepisode period.[24]

Increased plasma viscosity also was observed during this 1985 European air pollution episode,[25] which suggests a systemic response in association with exposure to air pollution. Increased plasma viscosity might lead to transient ischemic events in persons with severe coronary artery disease. Ischemic events are responsible for approximately 80% of sudden deaths.[20] Direct activation of the autonomic nervous system and the altered excitability of the heart cells caused by air pollution exposures may lead to fibrillation. Therefore, an altered sympathetic or diminished parasympathetic tone of the heart in response to particle exposures might result in life-threatening tachycardias, as observed in this study.

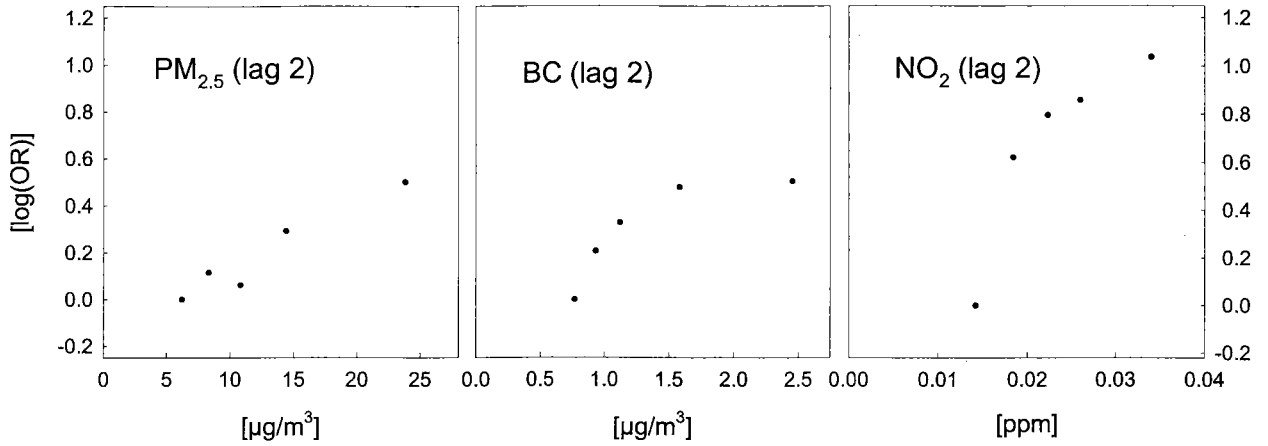

FIGURE 2. Associations between defibrillator discharges and quintiles of 2-day-lagged values of $PM_{2.5}$, black carbon, and NO_2, adjusted for season, trend, minimum temperature, humidity, and day of the week.

Whereas concentrations of individual air pollutants are correlated day to day, differences by season suggest different sources of particulate air pollution. The highest concentrations of $PM_{2.5}$ were recorded in Boston during the summer months. Measurements throughout the east coast region indicate that these summer particulate air pollution episodes are caused by regional transport.[26] In contrast, NO_2 was higher during the winter. Black carbon and CO were highly variable throughout the year. In the colder months local emissions are the dominant source of particulate air pollution. The primary hypothesis of the study was that $PM_{2.5}$ would be associated with the incidence of defibrillator discharges. We found support for this hypothesis; however, a stronger association was found for NO_2 and black carbon than for $PM_{2.5}$. NO_2 and black carbon might be markers for local traffic-related pollution, whereas $PM_{2.5}$ is influenced both by local and by regional transported particulate matter.[27]

Strengths and Limitations

One major advantage of these data is the complete, passive monitoring of cardiac arrhythmias. On the other hand, discharges might be initiated in cases of normal rather than life-threatening events, because screening of cardiac arrhythmias is optimized to avoid underdetection of ventricular tachyarrhythmias.[28] For this pilot study, clinical review of detected arrhythmias was not included in the abstraction of the data. If misclassification of defibrillator discharges is independent of air pollution exposure, we would expect a loss of power (that is, wider CIs) but not any bias in the estimated association.

ICD discharges were rare events in this follow-up of 100 patients. The small number of subjects with multiple defibrillator discharges is a limitation. In particular, the power to adequately adjust for confounding might be limited in multivariate analyses. These patients clearly represent a highly selected cohort, and these results would not be generalizable to the entire population. On the other hand, this cohort is of special interest, because their previous history of cardiovascular disease might make them particularly sensitive to the effects of air pollution episodes. Indeed, effects were seen most strongly among the six subjects with repeated arrhythmias. Data on baseline clinical characteristics and prescribed antiarrhythmic medications were not available in this pilot study to determine the characteristics associated with increased (or decreased) responsiveness.

Misclassification of air pollution exposure is another potential source of bias in this study. Whereas patients were living in eastern Massachusetts, air pollution exposure was estimated based on a single monitor in Boston. The day-to-day correlations of fine-particle concentrations between sites is high across large regions in the eastern United States. Suh *et al.*[27] reported correlations of more than 0.90 between fine-particle monitoring stations across the Washington, DC, metropolitan area and a correlation of 0.76 between monitors in Washington and Philadelphia. For the gaseous pollutants, there might be only weak correlation between monitoring sites within a region.[27] We would expect any exposure misclassification to be nondifferential with respect to ICD discharges and to bias the estimates toward the null.

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