Ambient Air Pollution and Cardiac Arrhythmias in Patients With Implantable Defibrillators

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Background: Previous studies of ambient air pollution and ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators have yielded mixed results.

Methods: We examined this relationship in a study of 518 patients with 6287 tachyarrhythmic event-days over a 10-year period in Atlanta, Georgia. The air quality data included daily measurements of PM_{10}, ozone, nitrogen dioxide, carbon monoxide, and sulfur dioxide for the entire study period, as well as speciated measurements of $PM_{2.5}$ mass and oxygenated hydrocarbons for the final 4 years of the study. Our primary analyses utilized generalized estimating equations, controlling for long-term time trends and meteorologic conditions as well as residual correlation within subjects.

Results: Our primary modeling approach found no association; additional sensitivity analyses and alternative analytic approaches supported those findings. The most suggestive positive findings were for coarse particles.

Conclusions: The present study constitutes the largest study to date of ambient air pollution and tachyarrhythmic events in patients with implantable cardioverter defibrillators. Other than the suggestive findings for coarse particles, the study provides little evidence of an association between ambient air quality levels and tachyarrhythmic events.

(*Epidemiology* 2007;18: 585–592)

A consistent link between cardiovascular morbidity and ambient air pollution has been demonstrated in numerous epidemiologic studies.[1–3] The risk of adverse events seems to be increased for certain subpopulations, including those with underlying health conditions such as diabetes, chronic obstructive pulmonary disease, congestive heart failure, previous arrhythmia, and hypertension.[4–8] Several studies suggest that air pollution is associated with adverse changes in cardiac autonomic function such as increased heart rate,[9,10] decreased heart rate variability,[7,11–14] and increased systolic blood pressure.[15] Results from studies of ventricular tachyarrhythmia events in patients with implantable cardioverter defibrillators have been inconsistent.[16–21]

Because patients with implantable defibrillators often have underlying conditions that put them at high risk of ventricular tachycardia and sudden cardiac death,[22] this population could be particularly susceptible to the potential adverse effects of ambient air pollution. The implanted device continuously monitors the heart rate for abnormal heart rhythms. When the implantable defibrillator detects ventricular tachycardia or fibrillation—rapid and potentially fatal heart rhythms—it delivers a high-energy shock (defibrillation) or provides rapid pacing to the ventricles to terminate the malignant tachyarrhythmia and restore normal rhythm. Information regarding the date and time of each tachyarrhythmic event, as well as the type of therapy delivered, is recorded and stored in the device. These recordings can be used retrospectively to identify past tachyarrhythmic events. The devices are routinely interrogated, and the event information is downloaded and stored in clinic records.

The Study of Particles and Health in Atlanta (SOPHIA) was initiated to take advantage of extensive air quality data from an innovative air pollution monitoring station operated by the Aerosol Research and Inhalation Epidemiology Study (ARIES). As one of several epidemiologic studies investigating the short-term relationship between ambient air pollution levels and cardiorespiratory health effects, the present study was developed to examine the association with ventricular tachyarrhythmic events in patients with implantable defibrillators for the time period from 1 January 1993 to 31 December 2002.

METHODS

Patient and Tachyarrhythmic Event Data

Patient information was abstracted from patient medical records at 3 cardiac electrophysiology clinics in Atlanta. Data from 2 clinics were available during the entire study period; data were not available from the third clinic in 2001 and 2002. For all patients, basic demographic information

Submitted 17 November 2005; accepted 16 March 2007.

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Supported by a grant from the Electric Power Research Institute (W03253-07).

Supplemental material for this article is available with the online version of the journal at www.epidem.com; click on "Article Plus."

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ISSN: 1044-3983/07/1805-0585
DOI: 10.1097/EDE.0b013e318124ff0e

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was collected including date of birth, sex, and residential zip code. We included only patients with a residential zip code in the 20-county Atlanta metropolitan area. For patients with at least 1 ventricular tachyarrhythmic event recorded by the device, we collected additional information including the date and time of each event, and the type of electrical therapy delivered, if any. Information from the defibrillator was downloaded by clinic staff at regular intervals. An electrophysiologist or trained technician at each clinic reviewed the intracardiac electrograms for each event at the time the information was downloaded. Detected events that were determined to be not ventricular in origin (eg, supraventricular tachycardia, sinus tachycardia, lead fracture, electromagnetic interference, or oversensing) were excluded from the analysis. This study was approved by the Institutional Review Board of Emory University.

Ambient Air Quality Data

For the period 1 January 1993 to 31 December 2002, we obtained ambient air quality data for 24-hour average PM_{10} (particulate matter with an aerodynamic diameter less than 10 μm) mass, 8-hour maximum ozone, and 1-hour maximum nitrogen dioxide (NO_2), carbon monoxide (CO), and sulfur dioxide (SO_2) from several existing monitoring networks, including the Air Quality System, the Georgia Department of Natural Resources, and the Metro Atlanta Index. Daily measurements of these pollutants from a central monitor located in downtown Atlanta were used in the analyses. For days on which a measurement was not available from the central monitor, we imputed pollution levels using data from at least 1 secondary monitoring site and meteorologic factors. Ozone levels were not monitored during the winter months, when ozone levels in Atlanta are low; the remaining pollutants were measured year-round. Data from the Air Quality System have been described previously.[2,23]

For the period 1 August 1998 through 31 December 2002, an extensive suite of pollutants, including PM components, were measured at the ARIES monitoring station. Included in these analyses were 24-hour averages of $PM_{2.5}$ (particulate matter with an aerodynamic diameter less than 2.5 μm) mass, coarse PM (particulate matter with an aerodynamic diameter between 2.5 and 10 μm), oxygenated hydrocarbons, and the following $PM_{2.5}$ mass components: sulfate, organic carbon, elemental carbon, and an index of water-soluble metals. Although ultrafine particle counts and $PM_{2.5}$ acidity were measured at the ARIES monitoring station for its first 25 months of operation, these analytes were not included in these analyses because missing data led to model instability. The ARIES air quality data have been described previously.[2,23] The spatial variation and correlation between monitors for many of the pollutants studied here [nitric oxides (NO_x), CO, SO_2, 24-hour $PM_{2.5}$, and the following 24-hour $PM_{2.5}$ components: sulfates, organic carbon, and elemental carbon] have been examined.[24] Measurements from the ARIES monitoring station were consistent with those from the Air Quality System and other monitoring stations.[24] As expected, the spatial variability was greater for primary pollutants than for secondary pollutants.[24]

Temperature and dewpoint temperature, as well as additional meteorological data measured at Hartsfield-Atlanta International Airport, were obtained from the National Climatic Data Center network.

Statistical Methods

Analyses were carried out using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC). Our primary analytic approach involved repeated-measures logistic regression utilizing generalized estimating equations (GEE) to account for residual autocorrelation within subjects.[25] A dichotomous outcome variable was defined to distinguish whether a patient experienced at least 1 ventricular tachyarrhythmic event on a given day. Three types of tachyarrhythmic events were considered for the analysis: 1) any ventricular tachyarrhythmic event recorded by the device, 2) any ventricular tachyarrhythmic event that resulted in electrical therapy (cardiac pacing or defibrillation), and 3) any ventricular tachyarrhythmic event that resulted in defibrillation (a subset of the second group, and considered to be the most serious events).

The primary model had the following form:

$$\begin{aligned}\text{logit}(E(Y_{ij})) = {} & \alpha + \beta\, pollutant_{ij} + \sum\nolimits_k \lambda_k\, DOW_{ijk} + \sum\nolimits_p \zeta_p\, holiday_{ijp} \\ & + \delta_1\, temperature_{ij} + \delta_2\, temperature_{ij}^2 + \delta_3\, temperature_{ij}^3 \\ & + \eta_1\, dewpoint_{ij} + \eta_2\, dewpoint_{ij}^2 + \eta_3\, dewpoint_{ij}^3 + g(\gamma_1, \ldots, \gamma_N; time_{ij})\end{aligned}$$

Y_{ij} was an indicator for an event-day or nonevent-day for subject *i* on day *j*. Models included indicator variables for day of week (DOW) and federal holidays (*holiday*). We chose this model based on a priori considerations. Our goal was to control for suspected confounding related to time trends, seasonality, DOW, temperature, and dewpoint. To reduce model assumptions, we controlled for long-term time trends and seasonality (*time*) with cubic splines, $g(\gamma_1,\ldots,\gamma_N; x)$ using seasonal knots. Cubic terms for daily maximum temperature (*temperature*) and mean dewpoint (*dewpoint*) were included in the model (lagged 0 days). The follow-up time for each subject was divided into 6-month intervals by warm (April 15 to October 14) and cold (October 15 to April 14) seasons. To allow for autocorrelation, a stationary 21-dependent correlation structure was specified as the working correlation matrix for each cluster by subject and season. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for an increase of approximately 1 standard deviation (SD) of pollutant levels. We chose to model pollutant levels on the same day as the event day (lagged 0 days) based on results from a previous study of cardiovascular emergency department visits in Atlanta, which reported the strongest associations with ambient air pollution levels on the same day.[2]

We conducted several sensitivity analyses using the GEE framework in order to evaluate the robustness of our primary model. We considered alternative ways of modeling meteorology, such as controlling for daily minimum temperature and using indicator variables for 5-degree increments of daily maximum temperature. We explored models with alternative lag structures, including pollution levels on the previous 6 days (unconstrained distributed lag models) and a

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moving average of pollution lagged 0 and 1 day and of pollution lagged 0, 1, and 2 days. Season-specific analyses were conducted for the warm and cold seasons. As an alternative to modeling pollution as a log-linear variable, we categorized pollutant levels into quintiles. We also considered alternative correlation structures for GEE models. Additionally in some models, we included indicator terms for recent ventricular tachyarrhythmic events and evaluated the potential interaction between the pollutant and occurrence within 3 days of a prior event.

We compared 2 other modeling approaches to the primary GEE model. A case-crossover analysis provided an alternative approach to control for long-term temporal trends.[26–29] In these analyses, we selected comparison days within the same calendar month as the event day (to limit long-term trends), and on the same DOW (to eliminate DOW trends). All strata were assumed independent. This method of defining strata, based on subject and month, avoids bias due to overlapping sampling of controls by selecting from mutually exclusive time windows, and reduces potential autocorrelation by selecting the days at 7-day intervals. Since temperature and dewpoint may vary within a month, we included linear terms for maximum temperature and mean dewpoint, along with product terms with monthly indicator variables, allowing interaction between month and meteorology.

A second sensitivity analysis stratified only on subject. This approach coupled with conditional logistic regression allowed for the control of subject-specific fixed effects. Unlike the case-crossover approach, this method does not inherently match on time, so we included cubic splines in the model for the control of time trends, and indicator variables for DOW and federal holidays, as well as cubic terms for daily maximum temperature and daily mean dewpoint.

RESULTS

Information on 884 patients with implantable defibrillators was collected from 3 clinics during the study period (1 January 1993 to 31 December 2002) (Table 1). The majority of patients were men (78%). The age at the start of follow-up ranged from 15 to 88 years, with a mean of 61 years. The age and sex distribution were similar for those whose ventricular tachyarrhythmias triggered events cardiac pacing or defibrillation and those whose arrhythmias did not. The 518 patients with at least 1 tachyarrhythmia contributed 491,181 days of follow-up time and experienced 13,108 events on 6287 event-days. Three-fourths (72%) of patients with arrhythmia experienced electrical therapy (cardiac pacing or defibrillation); 57% experienced defibrillation. Among those with arrhythmia, the number of days with arrhythmia ranged from 1 to 198, with a mean of 12. One-fourth (24%) of those patients experienced tachyarrhythmia for only 1 day. Among patients who had more than 1 day with arrhythmia, these days appeared to be clustered in time; 21% of event-days were on the day after an arrhythmia, and 50% were within a week of a previous event-day.

The number of patients being monitored and the number of event-days per year generally increased over time; however, the rate of event-days per follow-up time was highest in 1993, decreased through 1995, and then increased again through 2000 (results available with the online version of this article). A slight seasonal pattern in the rate of event-days was observed, with peaks in July and December (results not presented). The weekly pattern indicated a slight peak in the rate of event-days on Monday (results not presented).

Daily concentrations of the air quality analytes are described in Table 2. Measurements of PM_{10}, ozone, NO_2, CO, and SO_2 were available for the entire study period, 1 January 1993 to 31 August 2002, whereas measurements of coarse PM, $PM_{2.5}$, $PM_{2.5}$ components, and oxygenated hydrocarbons were available from 1 August 1998 to 31 December 2002. Correlations among the pollutants are presented in an online supplement.

Our results provided little evidence of associations between ambient air quality measurements and ventricular tachyarrhythmic events (Table 3). The ORs were generally consistent with the null in our primary analyses using GEE models. All of the CIs for the ORs included the null value except for a negative association of $PM_{2.5}$ water-soluble metals and tachyarrhythmic events that resulted in any electrical therapy (pacing or defibrillation). The associations involving pollutants from the ARIES monitoring station, measured for the subperiod 1998–2002, were less precise than those for criteria pollutants, measured from 1993 to 2002. Estimates involving events resulting in defibrillation (a subset of events in the other outcome groups) also had wider CIs due to the lower number of event-days.

Results from additional sensitivity analyses of the primary GEE model were similar, with little or no association

TABLE 1. Demographic Characteristics and Distribution of Ventricular Tachyarrhythmic Event-Days in Patients With Implantable Cardioverter Defibrillators

Type of Patient	No. Patients	Patient Age Mean (Range)	% Male	Event Days		No. Follow-up Days
				No.	Mean/Median (Range)	
All patients	884	61 (15–88)	78	—	—	—
With events (with or without therapy)	518	61 (15–88)	78	6287	12/5 (1–198)	491,181
With events resulting in cardiac pacing or defibrillation	372	61 (15–88)	79	2539	7/3 (1–101)	396,861
With events resulting in defibrillation	296	59 (15–85)	79	821	3/2 (1–16)	331,770

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TABLE 2. Daily Ambient Air Quality Measurements

	Percent of Days Missing	Mean ± SD	Minimum	10%	Median	90%	Maximum
1 January 1993 – 31 December 2002							
24-h PM_{10} ($\mu g/m^3$)	6.1	28.0 ± 12.2	0.5	13.8	26.4	44.7	100
8-h ozone (ppb)*	33.1	53.9 ± 23.0	2.9	26.1	52.1	84	148
1-h NO_2 (ppb)	0.7	44.9 ± 17.7	7	24	43	68	181
1-h CO (ppm)	1.2	1.7 ± 1.1	0.1	0.5	1.4	3.2	7.7
1-h SO_2 (ppb)	0.7	15.5 ± 16.4	1	2	10	36	149
Maximum temperature (°F)	0	72.4 ± 15.3	18	51	74	91	102
Minimum temperature (°F)	0	53.3 ± 15.0	6	32	55	72	80
Dewpoint (°F)	0	50.7 ± 16.2	−2.4	27.5	53.8	69.5	74.7
1 August 1998 – 31 December 2002							
24-h $PM_{2.5}$ ($\mu g/m^3$)	2.7	17.8 ± 8.6	1.7	8.2	16.2	29.5	65.8
24-h coarse PM ($\mu g/m^3$)	8.5	9.6 ± 5.4	0.5	3.9	8.7	16.7	50.3
24-h $PM_{2.5}$ water-soluble metals ($\mu g/m^3$)	11.3	0.029 ± 0.024	0.003	0.009	0.022	0.058	0.202
24-h $PM_{2.5}$ sulfates ($\mu g/m^3$)	11.5	5.0 ± 3.4	0.5	1.7	4.1	9.7	20.9
24-h $PM_{2.5}$ organic carbon ($\mu g/m^3$)	4.7	4.4 ± 2.4	0.4	2	3.9	7.3	25.9
24-h $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	4.8	1.7 ± 1.2	0.1	0.6	1.4	3.2	11.9
24-h oxygenated hydrocarbons (ppb)	25.5	31.1 ± 15.3	0.7	13.3	29.1	51	91.6

*Ozone was measured during the following periods: 3/1/1993–11/30/1993, 3/1/1994–11/30/1994, 3/1/1995–11/30/1995, 3/1/1996–10/31/1996, 4/1/1997–10/31/1997, 4/1/1998–10/31/1998, 4/1/1999–10/31/1999, 3/1/2000–8/31/2000, 3/1/2001–10/31/2001, 3/1/2002–10/31/2002.

TABLE 3. Results of Primary GEE Models for the Associations of Daily Ambient Air Quality Measurements and Tachyarrhythmic Events in Patients With Implantable Cardioverter Defibrillators

Pollutant	Unit*	All Events (n = 6287 Event-Days) OR (95% CI)	Events Resulting in Cardiac Pacing or Defibrillation (n = 2539 Event-Days) OR (95% CI)	Events Resulting in Defibrillation (n = 821 Event-Days) OR (95% CI)
1 January 1993 – 31 December 2002				
24-h PM_{10}	10 $\mu g/m^3$	0.997 (0.970–1.025)	0.972 (0.932–1.014)	0.988 (0.909–1.075)
8-h ozone	25 ppb	0.997 (0.929–1.070)	0.982 (0.886–1.088)	1.081 (0.904–1.294)
1-h NO_2	20 ppb	0.999 (0.965–1.035)	1.009 (0.957–1.063)	1.048 (0.955–1.151)
1-h CO	1 ppm	0.999 (0.970–1.028)	1.008 (0.964–1.054)	1.012 (0.925–1.107)
1-h SO_2	20 ppb	1.002 (0.968–1.037)	0.988 (0.936–1.042)	1.004 (0.911–1.105)
1 August 1998 – 31 December 2002				
24-h $PM_{2.5}$	10 $\mu g/m^3$	0.995 (0.953–1.039)	0.982 (0.920–1.049)	0.969 (0.846–1.110)
24-h coarse PM	5 $\mu g/m^3$	1.031 (0.997–1.066)	1.048 (0.995–1.104)	1.049 (0.943–1.166)
24-h $PM_{2.5}$ water-soluble metals	0.03 $\mu g/m^3$	0.952 (0.904–1.003)	0.897 (0.821–0.979)	0.891 (0.741–1.071)
24-h $PM_{2.5}$ sulfate	5 $\mu g/m^3$	0.994 (0.932–1.061)	0.969 (0.880–1.067)	0.996 (0.805–1.233)
24-h $PM_{2.5}$ organic carbon	2 $\mu g/m^3$	1.005 (0.977–1.034)	0.988 (0.941–1.039)	0.967 (0.883–1.060)
24-h $PM_{2.5}$ elemental carbon	1 $\mu g/m^3$	1.013 (0.982–1.045)	0.984 (0.936–1.035)	0.939 (0.860–1.025)
24-h oxygenated hydrocarbons	15 ppb	0.996 (0.954–1.040)	0.970 (0.912–1.031)	0.905 (0.797–1.028)

*Approximately 1 standard deviation.

between air pollution levels and tachyarrhythmic events. ORs from models that controlled for minimum rather than for maximum temperature were systematically more positive (Table 4). Eleven of the 12 pollutant ORs for any tachyarrhythmic events were greater than 1, but the CIs for all pollutants except coarse PM included the null value. We also examined several alternative lag structures. Results from unconstrained distributed lag models (pollution lagged 0–6 days) were also consistent with the null (Table 4). Models that included pollution lagged 0 and 1 day and models with pollution lagged 0, 1, and 2 days also suggested no association (results not presented).

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TABLE 4. Comparison of Results of the Primary GEE Models and Selected Alternative Analyses for the Associations of Daily Ambient Air Quality Measurements and Tachyarrhythmic Events in Patients With Implantable Cardioverter Defibrillators

Pollutant	Unit*	Primary GEE Model OR (95% CI)	Controlling for Minimum Temperature OR (95% CI)	Using an Unconstrained Distributed Lag (Lags 0–6) OR (95% CI)
1 January 1993 – 31 December 2002				
24-h PM_{10}	10 $\mu g/m^3$	0.997 (0.970–1.025)	1.017 (0.991–1.043)	1.012 (0.956–1.072)
8-h ozone	25 ppb	0.997 (0.929–1.070)	1.020 (0.967–1.077)	1.055 (0.935–1.190)
1-h NO_2	20 ppb	0.999 (0.965–1.035)	1.025 (0.994–1.057)	1.038 (0.962–1.120)
1-h CO	1 ppm	0.999 (0.970–1.028)	1.020 (0.993–1.047)	1.016 (0.912–1.087)
1-h SO_2	20 ppb	1.002 (0.968–1.037)	1.010 (0.976–1.046)	0.996 (0.952–1.083)
1 August 1998 – 31 December 2002				
24-h $PM_{2.5}$	10 $\mu g/m^3$	0.995 (0.953–1.039)	1.008 (0.967–1.050)	0.998 (0.908–1.097)
24-h coarse PM	5 $\mu g/m^3$	1.031 (0.997–1.066)	1.041 (1.010–1.073)	0.974 (0.885–1.072)
24-h $PM_{2.5}$ water-soluble metals	0.03 $\mu g/m^3$	0.952 (0.904–1.003)	0.965 (0.917–1.015)	0.966 (0.847–1.102)
24-h $PM_{2.5}$ sulfate	5 $\mu g/m^3$	0.994 (0.932–1.061)	1.003 (0.941–1.070)	1.059 (0.904–1.241)
24-h $PM_{2.5}$ organic carbon	2 $\mu g/m^3$	1.005 (0.977–1.034)	1.018 (0.992–1.045)	0.962 (0.893–1.036)
24-h $PM_{2.5}$ elemental carbon	1 $\mu g/m^3$	1.013 (0.982–1.045)	1.023 (0.994–1.052)	0.950 (0.884–1.021)
24-h oxygenated hydrocarbons	15 ppb	0.996 (0.954–1.040)	1.001 (0.960–1.043)	0.990 (0.878–1.116)

*Approximately 1 standard deviation.

Results from separate analyses for warm and cold seasons were also largely consistent with the null, with the exception of a positive association for coarse PM in the cold season (Table 5). For PM_{10}, $PM_{2.5}$, sulfate, elemental carbon, and organic carbon, the ORs were more positive during the cold season. For CO, SO_2, and oxygenated hydrocarbons, the estimated ORs were more positive during the warm season. Results from analyses using quintiles of pollutant levels showed no associations, with little evidence of dose-response (results not presented). We found no modification of the pollutant associations by recent tachyarrhythmic events (results not presented). Results from the case-crossover analyses and subject-stratified analyses were also consistent with little or no association (table available in online supplement). The CIs were slightly wider using the case-crossover approach.

DISCUSSION

This study of ventricular tachyarrhythmic events in patients with implanted defibrillators provided little evidence of associations with daily ambient air quality measurements. This pattern was supported by results of alternative analyses using case-crossover and subject-stratified methods. In certain sensitivity analyses of our primary GEE model (eg, controlling for minimum rather than maximum temperature), associations were somewhat more positive; however, CIs still included the null value for almost all analyses. Although we found consistently positive associations between ventricular tachyarrhythmic events and coarse PM, this positive result must be considered in light of the large number of associations assessed. We also observed consistently negative associations with $PM_{2.5}$ water-soluble metals.

Coarse particles, which like fine particles can penetrate into the thoracic region, may have health effects independent of fine particles. Particles in this size tend to have chemical composition and source contributions that are different from those of fine particles. Fine particles are predominantly by-products of combustion processes, whereas coarse particles include relatively more crustal material, resuspended road dust containing tire and brake residues, metals, and plant and animal matter.[30] Recent studies have attempted to assess the relative contributions of the 2 size fractions in health studies. A review of health effects of coarse particles by Brunekreef and Forsberg[31] finds support for an association of coarse PM and cardiovascular admissions in studies that included information on both size fractions. Gong et al[32] reported increased heart rate and decreased heart-rate variability in volunteers exposed to concentrated ambient coarse particles. Additional evidence of reduced heart-rate variability comes from a study by Lipsett et al[33] in relation to coarse particles with a high content of wind-blown sand. In addition, laboratory studies are beginning to provide some insights regarding biological responses to coarse particles. For example, in an in vitro study of normal human bronchial epithelial cells and ambient particles, Becker et al[34] reported that coarse particles were more potent in inducing cytokines (IL-6 and IL-8) than fine and ultrafine particles, and had similar potency as the other size fractions in stimulating the production of reactive oxygen species.

Previous investigations of the association between ambient air pollution and tachyarrhythmia in patients with implantable defibrillators have reported mixed results.[16–21] The first published pilot study of 33 patients suggested that

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TABLE 5. Results of Season-Specific GEE Models for the Associations of Daily Ambient Air Quality Measurements and Tachyarrhythmic Events in Patients With Implantable Cardioverter Defibrillators

Pollutant	Unit*	Warm Season (April 15 to October 14) OR (95% CI)	Cold Season (October 15 to April 14) OR (95% CI)
1 January 1993 – 31 December 2002			
24-h PM_{10}	10 $\mu g/m^3$	0.980 (0.939–1.022)	1.018 (0.981–1.057)
8-h ozone	25 ppb	0.998 (0.929–1.071)	0.917 (0.763–1.103)
1-h NO_2	20 ppb	1.003 (0.952–1.055)	1.005 (0.958–1.054)
1-h CO	1 ppm	1.051 (0.976–1.085)	0.989 (0.941–1.034)
1-h SO_2	20 ppb	1.029 (0.989–1.116)	0.986 (0.956–1.023)
1 August 1998 – 31 December 2002			
24-h $PM_{2.5}$	10 $\mu g/m^3$	0.977 (0.908–1.051)	1.022 (0.967–1.079)
24-h coarse PM	5 $\mu g/m^3$	1.010 (0.958–1.065)	1.050 (1.005–1.097)
24-h $PM_{2.5}$ water-soluble metals	0.03 $\mu g/m^3$	0.947 (0.886–1.013)	0.972 (0.886–1.067)
24-h $PM_{2.5}$ sulfate	5 $\mu g/m^3$	0.987 (0.910–1.070)	1.038 (0.927–1.163)
24-h $PM_{2.5}$ organic carbon	2 $\mu g/m^3$	0.992 (0.923–1.067)	1.014 (0.982–1.046)
24-h $PM_{2.5}$ elemental carbon	1 $\mu g/m^3$	0.995 (0.938–1.056)	1.023 (0.987–1.061)
24-h oxygenated hydrocarbons	15 ppb	1.032 (0.968–1.100)	0.976 (0.921–1.034)

*Approximately 1 standard deviation.

tachyarrhythmic events were associated with increased levels of NO_2, CO, and $PM_{2.5}$.[17] A larger study of 203 patients in the same population reported results generally consistent with the null, except for events after a recent ventricular tachyarrhythmia.[16] Associations with particles, NO_2, CO, and SO_2 were reported in patients who had a tachyarrhythmic event within the previous 3 days,[16] a potential interaction not observed in the present study. A case-crossover analysis on a subset of these patients reported positive associations of ventricular arrhythmias and $PM_{2.5}$ and ozone.[18] Another study of ventricular arrhythmias in 50 patients in Vancouver, Canada, reported no association between events and ambient air pollution levels in primary analyses; associations were observed for SO_2 in a subset of 16 patients with more than 6 months of follow-up and more frequent events.[21] An alternative analysis of a subset of that population using case-crossover methodology also yielded null results.[20] Most recently, a study of 56 patients living in St. Louis reported an increase in events of ventricular arrhythmia associated with an increase in ambient levels of SO_2.[19] Previous studies of patients with implantable defibrillators have not examined the association of coarse PM and ventricular tachyarrhythmias.[16–21]

We conducted several sensitivity analyses in order to evaluate the robustness of our primary GEE model. Most of the results were consistent with no association. The results from the GEE models controlling for minimum temperature, rather than maximum temperature were systematically more positive, although still largely consistent with the null. This difference may suggest residual confounding by temperature in the model with minimum temperature. In preliminary models that excluded all pollutant terms, maximum temperature was more strongly associated with tachyarrhythmic events than minimum temperature. Additionally, the regression parameters from models that included terms for both maximum and minimum temperature were more similar to those from models controlling for only maximum temperature rather than those controlling for only minimum temperature.

Outcome misclassification in the present study is likely to be minimal. An electrophysiologist or trained technician reviewed the intracardiac electrograms for each event detected by the implantable defibrillator at the time the information was downloaded. Detected events that were not ventricular in origin (eg, supraventricular tachycardia, sinus tachycardia, lead fracture, electromagnetic interference, or oversensing—-constituting approximately 25% of all detected events) were excluded from the analysis. We did not have an additional review of the electrograms by an electrophysiologist. Our collaborating electrophysiologist (J.J.L.) determined that such a review would have had limited usefulness given the routine review performed at each clinic, and would likely have led to reclassification of very few events. Any resulting bias to the null arising from outcome misclassification is likely to be small. Given the power of the study conferred by the large sample size, a strong association is not likely to be missed.

An additional issue in studies of this type is that personal exposure measurements are not available. In the current study involving 518 patients (far fewer than is typical of hospital admission or mortality studies), the longitudinal correlation of personal and ambient levels may be insufficient to support the use of the available ambient air quality data for etiologic investigation. Spatial heterogeneity of ambient air pollution could also have affected our results, possibly biasing them toward the null, because the centrally located monitor may not have accurately measured air pollutants for distant areas. The spatial variation and correlation between

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monitors for many of the pollutants studied here (NO_x, CO, SO_2, 24-hour $PM_{2.5}$, and the 24-hour $PM_{2.5}$ components of sulfates, organic carbon, and elemental carbon) have been examined.[24] Measurements from the ARIES monitoring station were consistent with those from the Air Quality System and other monitoring stations.[24] As expected, the spatial variability was greater for primary pollutants than for secondary pollutants.[24] These findings would tend to weaken but likely not eliminate associations with ambient air pollution levels for some pollutants. Thus, although the study provides evidence suggesting that a strong association of ventricular tachyarrhythmic events with the ambient pollutants assessed is unlikely, it does not eliminate the possibility of weak associations, nor does it contribute evidence regarding whether personal exposure may be a determinant of ventricular tachyarrhythmia. Additionally, behavior such as air conditioning use or time spent outdoors may affect personal exposure levels. This could affect the magnitude of the observed associations in comparison to other geographic locations.

Although the association between ambient air pollution and cardiovascular events has been noted in numerous epidemiologic studies, results from studies examining the association of air pollution and arrhythmic events in patients with implantable defibrillators have been less consistent. The present study does not support a strong association with ventricular tachyarrhythmic events in such patients. This study included more patients over a longer period of time with more fully characterized ambient air quality measures (including detailed measurements of $PM_{2.5}$ mass), than previous studies. Although we cannot exclude the possibility that potential misclassification of tachyarrhythmic events may have attenuated the magnitude of the results slightly, the likelihood of missing a strong association with ambient pollutant levels was low. We conducted several alternative analyses, all of which indicated a lack of an association; only coarse particulate matter provided any suggestion of a positive association. Future studies may provide further insight into these findings.

ACKNOWLEDGMENTS

We thank Keely Cheslack-Postava, Melissa Berkowitz, Amie May, Rebecca Gunter, Aimee Cunningham, and Laurie Gold for their assistance on the project. We are also grateful for the cooperation of the staff at the participating clinics.

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