Association of Short-term Ambient Air Pollution Concentrations and Ventricular Arrhythmias

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The authors evaluated the association between ventricular arrhythmias detected by implantable cardioverter defibrillators and ambient air pollution concentrations in the hours immediately before the arrhythmia. Patients given implantable cardioverter defibrillators at the New England Medical Center in Boston, Massachusetts, between mid-1995 and 1999 who lived within 40 km of a central monitoring site ($n = 203$) were followed until July 2002. The authors used a case-crossover design to study the association between ambient air pollution and up to 798 confirmed ventricular arrhythmias among 84 subjects. The authors found that interquartile range increases in 24-hour moving average particulate matter less than 2.5 μm in aerodynamic diameter and ozone were associated with 19% and 21% increased risks of ventricular arrhythmia, respectively. For each, there was evidence of a linear exposure response, and the associations appeared independent. These associations were stronger than associations with mean concentrations on the same calendar day and previous calendar days. The authors did not find associations with pollutant concentrations less than 24 hours before the arrhythmia. Cases with a prior ventricular arrhythmia within 72 hours had greater risk associated with air pollutants than did cases without a recent arrhythmia. These results confirm previous findings and suggest that matching of pollution periods to arrhythmias is important in detecting such associations.

air pollution; arrhythmias; heart arrest; tachycardia, ventricular; ventricular fibrillation

Episodes of particulate air pollution have been associated with increased hospital admissions for cardiovascular disease (1–9) and increased cardiovascular mortality (10–16). Understanding the mechanism(s) of these effects requires knowledge of the timing of the cardiovascular response following exposure to air pollution. Daily cardiovascular mortality and morbidity have generally been associated with air pollution on the same calendar day and previous calendar days (1–10, 13–15). An examination of potentially longer-lagged associations (up to 40 days) in Dublin, Ireland, showed that cardiovascular deaths were increased only for the day of and the 2 days following particulate air pollution episodes, while respiratory deaths were increased for weeks (16).

Associations with pollutant concentrations of shorter duration have been observed in a few studies. In Boston,

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Massachusetts, increased risk of myocardial infarction was associated with mean air pollution concentrations in the 2 hours preceding onset and independently within the 48 hours preceding onset (17). Heart rate variability was reduced in association with mean particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) in the previous 3–4 hours in a panel of elderly subjects (18) and in an occupationally exposed cohort (19, 20) in Boston.

Implantable cardioverter defibrillator (ICD) devices continuously monitor for ventricular arrhythmias and record the date and time of each detected arrhythmia. They also record an electrogram and beat-to-beat intervals immediately preceding, during, and after any such event. In the event of a life-threatening arrhythmia, the ICD can automatically administer pacing or a therapeutic shock to restore normal rhythm. These devices have been shown to be effective in the prevention of sudden cardiac death in high-risk patients (21–23).

Previous studies of ICD-detected ventricular arrhythmias or discharges have found positive but inconsistent associations with daily ambient air pollution concentrations (24–28). A pilot study of 100 ICD patients in Boston found an association between ICD-recorded discharges and mean nitrogen dioxide concentration in the previous 2 days (24). Subjects with frequent events (10 or more during 3 years of follow-up) experienced increased ICD discharges associated with carbon monoxide, nitrogen dioxide, $PM_{2.5}$, and black carbon (24). A follow-up study of confirmed ventricular arrhythmias in approximately 200 Boston ICD patients found increased risks associated with 2-calendar-day mean levels of nitrogen dioxide, $PM_{2.5}$, black carbon, carbon monoxide, ozone, and sulfur dioxide (25, 26). A study of 50 patients in Vancouver, Canada (27, 28), found no consistent relations between days with ICD discharges and daily ambient air pollution. All of these studies examined the association of calendar-day mean air pollution with ICD-detected arrhythmias on the same calendar day and previous calendar days but did not take advantage of the more precise time definition available from the ICD. Using the Boston study population noted above (25, 26), we evaluated the association between confirmed ventricular arrhythmias and short-term pollution concentrations, with specific interest in pollution levels less than 24 hours before the arrhythmia.

MATERIALS AND METHODS

Study population

A total of 203 patients implanted with a Guidant ICD (Cardiac Pacemakers, Inc., Minneapolis, Minnesota) at the New England Medical Center between June 1, 1995, and December 31, 1999, were followed until their last clinic visit before July 15, 2002. These ICDs recorded electrograms and were the most common ICD implanted at the New England Medical Center during the study period. We excluded each patient's first 14 days after implantation and any events that occurred during inpatient hospital visits. We restricted our analyses to patients with residential zip codes within 40 km (25 miles) of the monitoring station at the Harvard School of Public Health.

Outcome and clinical data

For each ICD-recorded episode of arrhythmia, the date, time, and intracardiac electrogram was recovered from the ICD. An electrophysiologist blinded to air pollution levels classified the arrhythmia according to preset criteria, including onset rate, regularity, QRS morphology during and prior to the episode, and response to therapy. In the few cases in which the patient had experienced a large number of ICD-detected episodes since the last clinic visit, such that early electrograms in the ICD memory were overwritten, arrhythmias were classified on the basis of beat-to-beat intervals (R-R intervals). Arrhythmias were classified as ventricular tachycardia, ventricular fibrillation, sinus tachycardia, atrial flutter, atrial fibrillation, supraventricular tachycardia (i.e., when the chamber was identified as the atrium but the specific arrhythmia type was not determined), or noise/oversensing. Ventricular tachycardia and ventricular fibrillation (both sustained and nonsustained) were classified as ventricular arrhythmias. All arrhythmias originating outside the ventricle, as well as events classified as noise/oversensing, were excluded. An episode was defined as a new arrhythmic event if there had been a period of at least 60 minutes since the previous event. Residence zip code, date of birth, race/ethnicity, clinic visit dates, and prescribed medications (beta blockers, other antiarrhythmic medications, and digoxin) were abstracted from patients' records. The Harvard School of Public Health Human Subjects Committee and the New England Medical Center Institutional Review Board approved this study.

Air pollution and weather data

Hourly barometric pressure, temperature, and dew point measurements were made at Logan International Airport and extracted from National Weather Service records (EarthInfo, Inc., Boulder, Colorado). Hourly ambient concentrations of gaseous criteria air pollutants in the greater Boston area were obtained from the Massachusetts Department of Environmental Protection. Nitrogen dioxide, sulfur dioxide, and ozone were measured consistently at six sites during this period. Carbon monoxide was measured at four urban sites established to monitor possible violations of the National Ambient Air Quality Standards. For each hour, we calculated a mean gaseous pollutant concentration using all reporting monitors for that hour. If one monitor was missing a value for an hour, any difference in the mean might reflect a change in the monitors used to compute the mean, rather than a change in pollutant concentration. To address this, we used the method proposed by Schwartz (29), which takes into account the yearly means and standardized deviations of individual monitors when computing averages across sites.

Concentrations of $PM_{2.5}$ were measured using a tapered element oscillating microbalance (model 1400A; Rupprecht and Patashnick, East Greenbush, New York) in South Boston (~5 km east of the Harvard School of Public Health) from April 1, 1995, to January 20, 1998, and at the Harvard School of Public Health from March 16, 1999, to July 31, 2002. Tapered element oscillating microbalance measurements were corrected for loss of volatile mass using

a season-specific correction factor (30), based on collocated 24-hour gravimetric $PM_{2.5}$ measurements. Black carbon was measured hourly by an Aethalometer (model 8021; McGee Scientific, Berkeley, California) in South Boston from April 1, 1995, to March 29, 1997, and at the Harvard School of Public Health from October 15, 1999, to July 31, 2002.

Statistical analysis

The association of air pollution with ventricular arrhythmias was analyzed using a case-crossover design (31), which has previously been used to study triggers of acute cardiovascular events (17, 28, 32–38). In this design, each subject contributes information as a case during the event periods and as a matched control during nonevent times. Because case periods and their matched control periods are derived from the same person and a conditional analysis is conducted, non-time-varying confounders such as underlying medical conditions and long-term smoking history are controlled by design. Variables that may be related to both air pollution and the occurrence of ventricular arrhythmias that vary over time (e.g., season and meteorologic conditions) are possible confounders.

Case periods were defined by the time each confirmed arrhythmic event began, rounded to the nearest hour. Control periods (3–4 per case) were selected by matching on weekday and hour of the day within the same calendar month (39). Hourly pollution concentrations and weather conditions were then matched to the case and control time periods for analysis.

Moving average air pollution concentrations

Based on the previous finding for cardiovascular events, we examined associations for the period between 3 and 48 hours prior to ICD-detected ventricular arrhythmias. We estimated the association of moving average air pollutant concentration in specific time periods prior to the arrhythmia (lags of 0–2, 0–6, 0–23, and 0–47 hours) for each pollutant ($PM_{2.5}$, black carbon, nitrogen dioxide, sulfur dioxide, ozone, and carbon monoxide). Conditional logistic regression analyses including a pollutant moving average and natural splines (3 df) for the mean temperature, dew point, and barometric pressure in the previous 24 hours were run separately for each pollutant moving average. Our models assumed that each outcome was independent, but many subjects had more than one event. If those subjects had different susceptibilities to air pollution on the basis of their clinical history and genetic characteristics, this would have induced correlation in our errors. Therefore, we included a frailty term (40) for each subject (akin to a random intercept) in all models. Odds ratios and 95 percent confidence intervals are presented for an interquartile range increase in mean concentration for each pollutant and averaging time. To assess the stability of pollutant-specific risk estimates after adjustment for other pollutant concentrations, we created two-pollutant models using 24-hour moving averages.

TABLE 1. Characteristics of 84 subjects with confirmed ventricular arrhythmias during follow-up, Boston Implantable Cardioverter Defibrillator Study, 1995–2002

Characteristic	No.	%*
Male gender	66	79
Race/ethnicity		
Caucasian	70	83
African American	4	5
Hispanic	7	8
Asian	1	1
Unknown	2	2
Age (years) at first event		
<45	6	7
45–54	11	13
55–64	21	25
65–74	29	35
≥75	17	20
Prescribed beta blockers	57	68
Prescribed digoxin	43	53
Prescribed other antiarrhythmic agents	21	25
Diagnosis at ICD† implantation		
Coronary artery disease	62	74
Congenital heart disease	1	1
Idiopathic cardiomyopathy	12	14
Hypertrophic cardiomyopathy	1	1
Long QT syndrome	1	1
Arrhythmogenic right valve dysplasia	2	2
Mitral valve prolapse	1	1
Normal	4	5
Ejection fraction (%)		
<25	23	27
25–34	32	38
35–44	29	35

* Percentages may not sum to 100% because of rounding.
† ICD, implantable cardioverter defibrillator.

Sensitivity analyses

The moving average models assumed that each of the hour-specific concentrations within the interval of the moving average had the same effect. We investigated whether relaxing that assumption and not putting any constraints on the shape of the lagged effect across the 24-hour period before the arrhythmia changed our findings and inference. Using the same conditional logistic regression models as those described above, we created unconstrained distributed lag models (41), replacing the 24-hour moving average term with 24 terms for the individual lag hours (lags 0–23). From each model, we used the exponentiated sum of the lag hours' regression coefficients times the interquartile range increase in 24-hour moving average concentration

TABLE 2.   Air pollution profile of the Boston, Massachusetts, metropolitan area from August 1995 to June 2002, Boston Implantable Cardioverter Defibrillator Study*

Parameter	No. of hours or days	25th percentile	50th percentile	75th percentile	Maximum
$PM_{2.5}$† ($\mu g/m^3$)‡					
Hourly	48,592	5.6	9.2	15.0	84.1
Daily	2,079	6.7	9.8	14.5	53.2
Black carbon ($\mu g/m^3$)§					
Hourly	36,789	0.44	0.77	1.35	23.93
Daily	1,555	0.58	0.94	1.41	7.32
Nitrogen dioxide (ppb†)					
Hourly	60,555	15.8	21.7	29.0	78.8
Daily	2,526	18.1	22.4	27.3	61.8
Sulfur dioxide (ppb)					
Hourly	60,620	2.6	4.3	7.5	71.6
Daily	2,526	3.2	4.8	7.3	31.4
Carbon monoxide (ppm†)					
Hourly	60,091	0.46	0.73	1.04	5.83
Daily	2,526	0.52	0.78	1.03	2.48
Ozone (ppb)					
Hourly	60,210	11.3	22.2	33.0	119.5
Daily	2,524	15.2	22.6	30.9	77.5
Temperature (°C)					
Hourly	60,449	3	11	18	36
Daily	2,526	4	11	18	32
Dew point (°C)					
Hourly	60,356	−3	6	13	25
Daily	2,526	−2	5	13	23
Barometric pressure (mmHg)					
Hourly	60,379	758	762	766	784
Daily	2,525	758	762	766	781

* Measured hourly. Total possible hours = 60,624. Total possible days = 2,526.

† $PM_{2.5}$, particulate matter less than 2.5 µm in aerodynamic diameter; ppb, parts per billion; ppm, parts per million.

‡ Concentrations were missing from January 21, 1998, to March 15, 1999.

§ Concentrations were missing from March 30, 1997, to October 15, 1999.

to estimate the cumulative risk for that time period. We estimated standard errors and 95 percent confidence intervals from the covariance matrix. We then compared results from these models with those from the moving average models.

Previous analyses have assessed associations of ICD-detected arrhythmias with calendar-day (midnight to midnight) air pollution concentrations (24–28). For comparison, we conducted the same conditional logistic regression analysis as described above but replaced the 24-hour moving average with the mean air pollution concentration for the calendar day of the event, and then again with the mean air pollution concentration for the previous calendar day. We then compared the odds ratios and 95 percent confidence intervals from these models with those from the model as-

sessing a 24-hour moving average. All odds ratios and 95 percent confidence intervals were scaled to the same interquartile range increase.

Exposure response

We stratified each case and control's mean air pollution concentrations into quintiles. We then used the same conditional logistic regression model as that described above, replacing the 24-hour moving average term with indicator variables for each quintile of 24-hour pollutant moving average concentration. We performed a test for trend using the same model but replacing the indicator variables with an ordinal variable (quintile's median value).

TABLE 3.   Odds ratios for ventricular arrhythmia associated with an interquartile-range increase in mean pollutant concentrations, Boston Implantable Cardioverter Defibrillator Study, 1995–2002

Pollutant and lag (hours)	Interquartile range	No. of subjects	No. of ventricular arrhythmias	Odds ratio	95% confidence interval
$PM_{2.5}*$ ($\mu g/m^3$)					
0–2	9.2	75	594	1.08	0.95, 1.21
0–6	8.8	75	588	1.11	0.98, 1.26
0–23	7.8	75	561	1.19	1.02, 1.38
0–47	6.8	75	533	1.12	0.95, 1.33
Black carbon ($\mu g/m^3$)					
0–2	0.90	60	436	0.90	0.78, 1.05
0–6	0.88	60	431	0.83	0.70, 1.00
0–23	0.83	60	425	0.93	0.74, 1.18
0–47	0.74	60	416	1.05	0.81, 1.38
Nitrogen dioxide (ppb*)					
0–2	12.8	84	797	1.05	0.92, 1.19
0–6	11.8	84	797	1.03	0.90, 1.17
0–23	9.2	84	796	1.10	0.97, 1.25
0–47	7.7	84	790	1.18	1.04, 1.35
Carbon monoxide (ppm*)					
0–2	0.56	84	798	1.01	0.87, 1.18
0–6	0.54	84	798	1.00	0.85, 1.17
0–23	0.51	84	798	1.03	0.84, 1.25
0–47	0.49	84	798	1.11	0.88, 1.40
Sulfur dioxide (ppb)					
0–2	4.7	84	798	1.07	0.97, 1.18
0–6	4.5	84	798	1.09	0.98, 1.20
0–23	4.1	84	798	1.09	0.97, 1.22
0–47	4.0	84	798	1.17	1.02, 1.34
Ozone (ppb)					
0–2	21.1	84	795	1.10	0.93, 1.29
0–6	19.6	84	792	1.16	0.98, 1.36
0–23	15.8	84	787	1.21	1.00, 1.45
0–47	15.3	84	779	1.18	0.95, 1.46

* $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; ppb, parts per billion; ppm, parts per million.

Effect modification by patient and event characteristics

We separately examined modification of the 24-hour mean $PM_{2.5}$ association by gender, race (White vs. non-White), age (<65 years vs. ≥65 years), low preimplantation ejection fraction (<25 percent vs. ≥25 percent), prescribed beta blockers, digoxin, and other antiarrhythmic medications (i.e., amiodarone, mexiletine, quinidine, or sotalol). For each characteristic, we added an interaction term to the conditional logistic regression model with the 24-hour mean $PM_{2.5}$ concentration (lags 0–23). Since each subject's prescription drug use could change over the course of follow-up, each event/case's prescription drugs were defined by a report of prescription at the subject's most recent clinic follow-up visit. We also assessed effect modification by recent ventricular arrhythmias, defined as a ventricular ar-

rhythmia within 72 hours of each case and control period. We included both an interaction term and a main-effect term for those recent ventricular arrhythmias in the conditional logistic regression model described above.

We used SAS software (version 8.2; SAS Institute, Inc., Cary, North Carolina) to construct all data sets and to calculate descriptive statistics. We used S-Plus software (version 6.2; Insightful, Inc., Seattle, Washington) for all modeling.

RESULTS

There were 203 subjects enrolled in the study with residential zip codes within 40 km of the central particle monitoring site at the Harvard School of Public Health. Mean follow-up time was 3.1 years (standard deviation, 1.8).

TABLE 4. Odds ratios for ventricular arrhythmia associated with an interquartile range increase in 24-hour moving average pollutant concentration in two-pollutant models, Boston Implantable Cardioverter Defibrillator Study, 1995–2002

Pollutants included in model	Interquartile range	No. of subjects	No. of ventricular arrhythmias	Odds ratio	95% confidence interval
PM$_{2.5}$*	7.8 μg/m^3	75	550	1.18	1.01, 1.37
Ozone	15.8 ppb*			1.18	0.94, 1.49
PM$_{2.5}$	7.8 μg/m^3	75	559	1.22	1.00, 1.49
Nitrogen dioxide	9.2 ppb			0.96	0.79, 1.18
PM$_{2.5}$	7.8 μg/m^3	75	561	1.18	0.98, 1.43
Sulfur dioxide	4.1 ppb			1.00	0.84, 1.20
Ozone	15.8 ppb	84	786	1.28	1.06, 1.56
Nitrogen dioxide	9.2 ppb			1.15	1.00, 1.31
Ozone	15.8 ppb	84	787	1.28	1.06, 1.56
Sulfur dioxide	4.1 ppb			1.12	0.99, 1.27

* PM$_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; ppb, parts per billion.

Ninety-five patients had a total of 1,574 recorded ICD events (933 separated by more than an hour). There were 798 electrophysiologist-confirmed ventricular arrhythmias among 84 subjects. Since PM$_{2.5}$ and black carbon were not measured during the entire study period, all analyses involving PM$_{2.5}$ included, at most, 595 ventricular arrhythmias from 75 subjects, and all analyses involving black carbon included, at most, 436 ventricular arrhythmias from 60 subjects.

Subjects with confirmed ventricular arrhythmias were predominantly White males with an average age of 64 years (range, 19–90 years) (table 1). At their first clinic visit, 68 percent of patients were prescribed beta blockers, 53 percent digoxin, and 25 percent other antiarrhythmic medications (i.e., amiodarone, mexiletine, quinidine, or sotalol). Eight subjects (10 percent) were not prescribed any of these medications. For 58 percent of the ventricular arrhythmias, subjects were prescribed beta blockers at the follow-up visit immediately preceding the arrhythmia. For 56 percent of the ventricular arrhythmias, subjects were prescribed digoxin, and for 55 percent, they were prescribed other antiarrhythmic medications. Coronary artery disease was the predominant implantation diagnosis. Sixty-five percent had an ejection fraction less than 35 percent, while 27 percent had an ejection fraction less than 25 percent (table 1).

Twenty-three percent of patients had only one event (2 percent of all events), while 29 percent of patients had 10 or more events (77 percent of all events). Ventricular arrhythmias were most frequent in the afternoon (2–3 p.m.) and evening (6–9 p.m.) and least frequent at night (10 p.m.–6 a.m.).

Descriptive data on Boston's air pollution during the study period, measured hourly and daily, are shown in table 2. Hourly mean PM$_{2.5}$, nitrogen dioxide, carbon monoxide, sulfur dioxide, and black carbon concentrations were highest in the early morning (6–7 a.m.), while levels of nitrogen dioxide and carbon monoxide had additional early evening peaks (4–7 p.m.). Hourly mean ozone concentrations were highest at midday (1 p.m.). Mean pollutant concentrations were higher on weekdays than on weekends for all pollutants but ozone, which was higher on weekends than on weekdays.

Moving average air pollution concentrations

We found increased risks of ventricular arrhythmias associated with moving average PM$_{2.5}$ in the previous 3, 7, 24, and 48 hours, although the strongest PM$_{2.5}$ associations were found for the moving average over the previous 24 hours (table 3). We found similar associations for ozone, with the strongest associations being observed for the 24-hour moving average. We found positive associations for the moving average nitrogen dioxide and sulfur dioxide concentrations, with the strongest associations being seen for the 48-hour moving average. We did not find positive associations with any of the moving averages of black carbon or carbon monoxide in the 24 hours before the arrhythmia, although the 7-hour moving average black carbon concentration showed a protective effect (table 3).

When we modeled the 24-hour moving average PM$_{2.5}$ and ozone concentrations jointly, both pollutants were associated with increased risk (table 4). When we modeled PM$_{2.5}$ and nitrogen dioxide jointly and then PM$_{2.5}$ and sulfur dioxide jointly, PM$_{2.5}$ remained associated with increased risk in both models, but nitrogen dioxide and sulfur dioxide did not. When we modeled ozone and nitrogen dioxide jointly and then ozone and sulfur dioxide jointly, all three pollutants remained associated with increased risk (table 4). Since it appeared that only PM$_{2.5}$ and ozone acted independently, subsequent analyses focused only on these pollutants.

Sensitivity analyses

Using unconstrained distributed lag models, we found positive associations with PM$_{2.5}$ (odds ratio (OR) = 1.20, 95 percent confidence interval (CI): 1.02, 1.41) and ozone (OR = 1.22, 95 percent CI: 1.01, 1.49) in the 24 hours
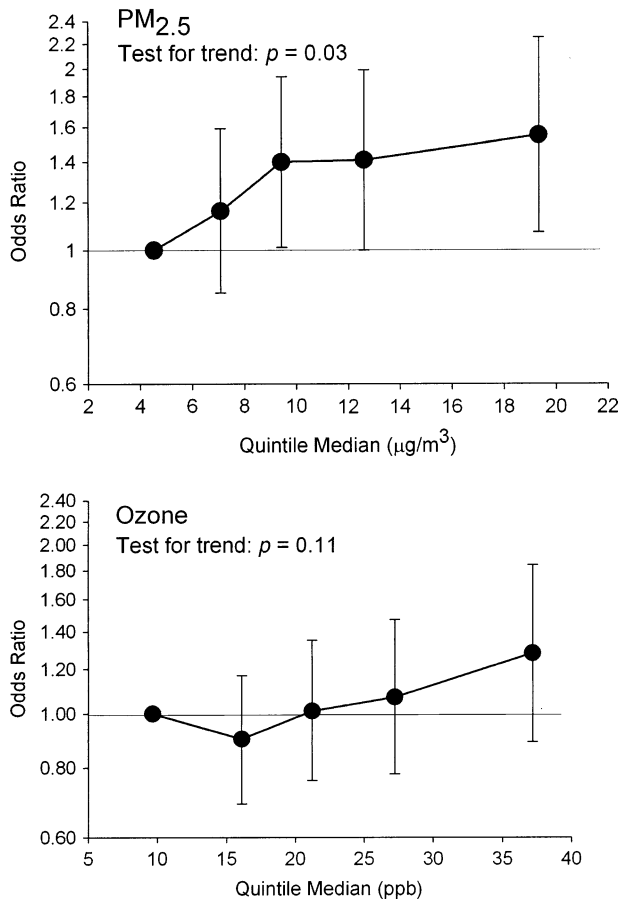
FIGURE 1. Odds ratios for ventricular arrhythmia associated with quintiles of pollutant concentration (24-hour moving average particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) and 24-hour moving average ozone) as compared with quintile 1, Boston Implantable Cardioverter Defibrillator Study, 1995–2002. Bars, 95% confidence interval.

TABLE 5.   Odds ratios for ventricular arrhythmia associated with a 7.8-μg/m³ increase in 24-hour moving average $PM_{2.5}$* concentration, by level of effect modifier, Boston Implantable Cardioverter Defibrillator Study, 1995–2002

Effect modifier	Odds ratio	95% confidence interval	No. of ventricular arrhythmias	Interaction p value†
Age (years)				
<65	1.25	0.99, 1.59	182	0.55
≥65	1.16	0.97, 1.38	379	
Race				
White	1.21	1.03, 1.41	495	0.43
Non-White	1.04	0.72, 1.49	66	
Gender				
Male	1.18	1.01, 1.38	493	0.79
Female	1.24	0.87, 1.77	68	
Use of beta blockers				
Yes	1.14	0.94, 1.39	303	0.53
No	1.24	1.01, 1.52	256	
Use of other antiarrhythmic medications				
Yes	1.18	0.97, 1.43	323	0.93
No	1.19	0.98, 1.46	238	
Use of digoxin				
Yes	1.14	0.94, 1.38	306	0.71
No	1.19	0.97, 1.47	244	
Ejection fraction (%)				
<25	1.25	0.99, 1.59	136	0.55
≥25	1.15	0.96, 1.38	425	

* $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter.

† Chi-squared test (1 df). All p values are two-sided.

before the arrhythmia. Both cumulative risk estimates were almost identical to those of the 24-hour moving averages.

The estimated odds ratio for the 24-hour moving average $PM_{2.5}$ concentration was substantially larger than the odds ratios for the mean $PM_{2.5}$ concentration on the same calendar day (OR = 1.08, 95 percent CI: 0.94, 1.24) and the previous calendar day (OR = 1.12, 95 percent CI: 0.97, 1.28). Similarly, for ozone, the odds ratio for the 24-hour moving average concentration was larger than the estimated odds ratios for the same-calendar-day concentration (OR = 0.96, 95 percent CI: 0.80, 1.15) and the previous-calendar-day concentration (OR = 0.97, 95 percent CI: 0.81, 1.16).

Exposure response

We assessed the exposure-response relationship for the association between ventricular arrhythmias and quintiles of 24-hour moving average $PM_{2.5}$ and ozone concentration

(figure 1). Risk generally increased with quintiles of $PM_{2.5}$ and ozone, but the test for trend was statistically significant only for $PM_{2.5}$.

Effect modification by patient and event characteristics

We found that the response to 24-hour mean $PM_{2.5}$ concentrations was similar across patient age, gender, race, preimplantation ejection fraction, prescribed beta blockers, digoxin, and other antiarrhythmic drugs (table 5). Having a ventricular arrhythmia was a strong predictor of a subsequent event. The risk of having a ventricular arrhythmia, given that another occurred within the previous 72 hours, was 3.08 (95 percent CI: 2.50, 3.81). Subjects who had a ventricular arrhythmia within 72 hours also had greater risk of ventricular arrhythmia associated with $PM_{2.5}$, black carbon, nitrogen dioxide, carbon monoxide, and sulfur dioxide than did those without such a recent event.

TABLE 6. Odds ratios for ventricular arrhythmia associated with an interquartile range increase in the 24-hour moving average pollutant concentration (mean of pollutant lags 0–23 hours), according to the presence or absence of a recent confirmed ventricular arrhythmia within the previous 72 hours, Boston Implantable Cardioverter Defibrillator Study, 1995–2002

Pollutant	Interquartile range	Recent event			No recent event			Interaction *p* value†
		No.	OR*	95% CI*	No.	OR	95% CI	
$PM_{2.5}$*	7.8 μg/m³	179	1.32	1.04, 1.69	382	1.10	0.92, 1.31	0.18
Black carbon	0.83 μg/m³	131	1.56	0.98, 2.47	294	0.82	0.63, 1.07	0.01
Nitrogen dioxide	9.1 ppb*	275	1.40	1.11, 1.77	521	0.98	0.84, 1.13	0.01
Carbon monoxide	0.51 ppm*	276	1.26	0.96, 1.65	522	0.89	0.71, 1.12	0.02
Sulfur dioxide	4.1 ppb	276	1.20	1.01, 1.44	522	0.96	0.83, 1.10	0.03
Ozone	15.7 ppb	270	1.04	0.78, 1.37	517	1.28	1.05, 1.58	0.14

* OR, odds ratio; CI, confidence interval; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; ppb, parts per billion; ppm, parts per million.

† All *p* values are two-sided.

Conversely, ozone was associated with increased risk among subjects without a recent event but not among subjects with recent events (table 6).

DISCUSSION

In this sample of ICD patients, we found a 19 percent increase in the risk of ICD-detected ventricular arrhythmias associated with each 7.8-μg/m³ increase in mean $PM_{2.5}$ in the previous 24 hours and a 21 percent increase in risk associated with each 15.8-parts-per-billion (ppb) increase in mean ozone over the same time period. For each, there was evidence of a linear exposure response, and these associations appeared independent. We found interquartile range increases in 24-hour moving average nitrogen dioxide (9.2 ppb) and sulfur dioxide (4.1 ppb) to be associated with 10 percent and 9 percent increased risks of ventricular arrhythmia, respectively, with larger increases in risk associated with the 48-hour moving averages. However, there was no risk associated with either 24-hour moving average nitrogen dioxide or sulfur dioxide after we controlled for $PM_{2.5}$, which suggests that they were confounded by or surrogates of $PM_{2.5}$. We found larger increases in risk associated with 24-hour moving averages compared with the shorter time periods. For all pollutants, we found no evidence of a cardiac response associated with concentrations in the few hours before the arrhythmia. When we relaxed our constraints on the shape of the distributed lag function and assessed the cumulative risk across the 24 hours before the arrhythmia using unconstrained distributed lag models, we found almost identical results. Furthermore, we found larger increases in risk for the 24-hour moving average than for mean concentrations on the same calendar day and previous calendar days. Cases who had had a prior ventricular arrhythmia within 72 hours had greater risk associated with black carbon, nitrogen dioxide, sulfur dioxide, and carbon monoxide than those cases without a recent ventricular arrhythmia, suggesting that, in this population, much of the risk associated with changes in ambient air pollution lies among cases with more irritable or unstable myocardium.

There did not appear to be effect modification by age, race, gender, prescribed beta blockers, digoxin, other antiarrhythmic agents, or a low ejection fraction.

Our findings are stronger than those reported in an analysis of these same patients using calendar-day mean pollution concentrations (25, 26). In those analyses, we reported smaller increases in risk of 2–16 percent associated with each interquartile range increase (using the same interquartile range increase as in this analysis) in mean pollutant concentrations for the day of the arrhythmia and the day before the arrhythmia. Our results are stronger than those reported by Peters et al. (24), who found an 8 percent increased risk of an ICD discharge associated with daily mean nitrogen dioxide and a 5 percent increase in risk associated with carbon monoxide (both scaled to the same increment in air pollution used here). Our findings differ from those of Vedal et al. (27) and Rich et al. (28), who found no consistently increased risk associated with pollutants among all study subjects in Vancouver.

Our finding of greater risk associated with pollutants for cases with a prior ventricular arrhythmia within 72 hours, using 24-hour moving averages, is consistent with our previous analysis using 2-calendar-day mean concentrations (25, 26). It is also consistent with the effects shown for patients with frequent events (defined as 10 or more events during 3 years of follow-up) in the Boston pilot study (25). One of the few positive associations seen in the Vancouver study was for 2-day-lagged sulfur dioxide in the 16 subjects with two or more events per year (28). Our finding is consistent with this result as well, suggesting that air pollution's effects may be greatest in the presence of an electrically unstable substrate.

There are several potential explanations for the stronger estimated associations with the moving average data as compared with calendar-day data. First, the case-crossover design and conditional analysis used in the current study controlled for season, time trends, and weekday (and any interaction between them) by design, thereby eliminating any residual confounding present in the previous analyses, where these factors were controlled through modeling. Second, in this analysis, onset of ventricular arrhythmia

was defined by the start time recorded by the ICD device, and ambient air pollution concentrations for the 24 hours before onset were then analyzed. In analyses based on the calendar day of the ventricular arrhythmia, the timing/matching of the air pollution concentrations prior to the arrhythmia is not as well defined. The calendar-day mean ambient air pollution level could be mismatched to the 24 hours before the arrhythmia by as much as 24 hours and on average by 12 hours, assuming a uniform distribution of arrhythmias throughout the day. If the etiologically important pollutant concentrations lie within the 24 hours prior to the arrhythmia, this can be an important source of exposure misclassification. Such misclassification should be nondifferential with respect to the arrhythmia and should lead to underestimates of risk. Both reasons may explain the much weaker associations observed in our own (24–26) and other (27, 28) earlier studies, which assessed the association of ICD-detected arrhythmias and calendar-day mean air pollution.

The finding of associations with 24-hour mean ambient air pollution but not with shorter time periods could imply a cumulative effect across the previous 24 hours. Alternatively, these associations could reflect the net effect of a single hour of ambient air pollution distributed over the succeeding 24 hours. However, this study design did not allow us to differentiate these two interpretations of the data.

These findings suggest that ambient air pollution is associated with an increased incidence of ventricular arrhythmias among patients with ICDs. Furthermore, those subjects experiencing clusters of ventricular arrhythmias in time (here within 72 hours) may be particularly susceptible to the effects of air pollution. Understanding the underlying mechanism by which air pollutants affect cardiovascular morbidity and mortality is crucial to further defining susceptible populations. However, in order to do so, we first must understand the time periods of highest risk and the air pollutants responsible for that risk.

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