Increased Risk of Paroxysmal Atrial Fibrillation Episodes Associated with Acute Increases in Ambient Air Pollution

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OBJECTIVES: We reported previously that 24-hr moving average ambient air pollution concentrations were positively associated with ventricular arrhythmias detected by implantable cardioverter defibrillators (ICDs). ICDs also detect paroxysmal atrial fibrillation episodes (PAF) that result in rapid ventricular rates. In this same cohort of ICD patients, we assessed the association between ambient air pollution and episodes of PAF.

DESIGN: We performed a case–crossover study.

PARTICIPANTS: Patients who lived in the Boston, Massachusetts, metropolitan area and who had ICDs implanted between June 1995 and December 1999 (n = 203) were followed until July 2002.

EVALUATIONS/MEASUREMENTS: We used conditional logistic regression to explore the association between community air pollution and 91 electrophysiologist-confirmed episodes of PAF among 29 subjects.

RESULTS: We found a statistically significant positive association between episodes of PAF and increased ozone concentration (22 ppb) in the hour before the arrhythmia (odds ratio = 2.08; 95% confidence interval = 1.22, 3.54; p = 0.001). The risk estimate for a longer (24-hr) moving average was smaller, thus suggesting an immediate effect. Positive but not statistically significant risks were associated with fine particles, nitrogen dioxide, and black carbon.

CONCLUSIONS: Increased ambient O3 pollution was associated with increased risk of episodes of rapid ventricular response due to PAF, thereby suggesting that community air pollution may be a precipitant of these events.

within the same calendar month (Lumley and Levy 2000). We calculated average pollution concentrations and weather conditions during the hour and during the 24 hours before the case and control time periods for this analysis.

Conditional logistic regression models, including the mean pollutant concentration in the hour of the arrhythmia (lag hour 0) and natural splines [3 degrees of freedom (df)] for the mean temperature, dew point, and barometric pressure in the 24 hr before the arrhythmia, were run separately for each pollutant (PM$_{2.5}$, black carbon, NO$_2$, CO, SO$_2$ and O$_3$). Different individuals may have different cardiac responses to pollution, based on their clinical history and genetic characteristics. Therefore, we included a frailty term (Therneau and Grambsch 2000) for each subject (akin to a random intercept) in all the above models. Odds ratios (ORs), 95% confidence intervals (CIs), and p-values for statistical significance testing are presented for an interquartile range increase in each pollutant. We considered associations with longer exposures before the PAF episode using the mean of the pollutant in the previous 24 hr (lag hours 0–23).

To assess the sensitivity of our results to the influence of outliers, we ran analyses, trimming the highest 5% and lowest 5% of air pollution concentrations. For O$_3$, which has a strong seasonal pattern, we examined whether the association between PAF and O$_3$ concentration was limited to the 6 months with the highest mean ambient temperature (May–October) by adding an O$_3$/warm month interaction term to the conditional logistic regression model. We assessed the linearity of the PAF and O$_3$ association by replacing the linear air pollution term with a penalized spline (3 df) in the conditional logistic regression model. We plotted the covariate adjusted log OR for the risk of PAF in the spline and linear models versus 1-hr O$_3$ concentration.

We used SAS (version 9.1; SAS Institute Inc., Cary, NC) software to construct all datasets and to calculate descriptive statistics. We used S-Plus 6.2 (Insightful Inc., Seattle, WA) software for all modeling.

**Results**

There were 203 ICD patients enrolled in the study who lived within 40 km of the Harvard School of Public Health with a mean (± SD) follow-up time of 3.1 ± 1.8 years (maximum = 7.0 years). Ninety-five patients had a total of 1,574 recorded ICD events, 933 of which were separated by > 1 hr. Ninety-one (9.8 %) of these events, among 29 subjects, were confirmed episodes of PAF. Because PM$_{2.5}$ and black carbon were not measured during the entire study period, analyses of PM$_{2.5}$ included at most 52 episodes of PAF from 22 subjects, and analyses of black carbon included at most 46 episodes of PAF from 18 subjects.

The 29 subjects with PAF episodes were primarily male (79%) and white (79%), and they ranged in age from 45 to 78 years (mean, 65 years). At their first clinic follow-up visit, 69% of subjects were listed as being prescribed beta-blockers, 57% digoxin, and 24% other antiarrhythmics (i.e., amiodarone, quinidine, sotalol, or mexiletine). Two subjects (7%) were not prescribed any of these medications. The most common diagnoses at implantation were coronary artery disease (76%) and idiopathic cardiomyopathy (22%). Before ICD implantation, 55% of subjects had left ventricular ejection fractions < 35%. Subjects’ ICDs were programmed with ventricular tachycardia detection rates (i.e., ventricular rate threshold above which the electrogram and date/time for a tachyarrhythmia would be recorded) that had a 10th to 90th percentile range of 140 to 200 beats/min (median = 175).

Of the 29 subjects who experienced at least one episode of PAF, 15 (52%) experienced > 1 event, while 2 (7%) experienced ≥ 10. Twenty (69%) also experienced a ventricular arrhythmia during follow-up. Episodes of PAF were more frequent in the late morning (0900–1100 hr), with a smaller evening peak (1800–2000 hr).

The distributions of air pollution concentrations and meteorologic characteristics in Boston during the study period, averaged hourly and daily, are summarized in Table 1. The highest average PM$_{2.5}$ and black carbon concentrations were observed early in the morning (0600–0800 hr), highest NO$_2$ in the early morning (0600–0800 hr) and early evening (1600–2100 hr), and highest O$_3$ at midday (1200–1400 hr). Further detail has been provided previously (Dockery et al. 2005b).

We found a statistically significant increased risk of PAF associated with mean O$_3$ concentration in the concurrent hour (lag hour 0; Table 2). The estimated relative odds for the 24-hr moving average concentration was positive (OR > 1), but not statistically significant. We did not find statistically significant associations with any other pollutant in the concurrent hour, but associations were positive for PM$_{2.5}$ and NO$_2$. Risk estimates for 24-hr average PM$_{2.5}$, NO$_2$, and black carbon were positive, but none was statistically significant. Risk estimates for 24-hr average CO and SO$_2$ were protective (OR < 1), but neither was statistically significant (Table 2).

For O$_3$ in the concurrent hour, there was little change in risk of PAF when we excluded the top 5% and bottom 5% of concentrations (OR = 2.15, 95% CI = 1.04–4.44, p = 0.04). The association between PAF and O$_3$ in the concurrent hour in the cold months (OR = 2.21; 95% CI = 0.98–4.98; p = 0.06) was
comparable to that in the warm months (OR = 1.98; 95% CI = 1.05–3.73; \( p = 0.04 \)), with no significant interaction (\( p = 0.84 \)).

Figure 1 shows the covariate adjusted log OR for the risk of PAF versus 1-hr \( O_3 \) concentration modeled using first a linear term and then a penalized spline (3 df). We found no evidence of a deviation from linearity (non-linear term, \( p = 0.63 \)).

**Discussion**

In a study designed to assess the association of ambient air pollution with ventricular arrhythmias among ICD patients, 91 of the ICD-detected episodes were identified by electrophysiologist review as PAF. Although these episodes of PAF were likely an underrepresentation of all those PAF episodes experienced by these patients, they provided a unique opportunity to assess associations between air pollution and episodes of PAF. We found a statistically significant 2-fold increase in risk of PAF episodes associated with each 22-ppb increase in mean ambient \( O_3 \) concentration in the concurrent hour. We found no evidence that this association was nonlinear.

An earlier study reported a 10.5% increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy compared to the population mean rate of supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in supraventricular ectopy (~3.5 beats/hr) increase in 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O$_3$ concentrations were highest on warm sunny days, and highest during the afternoon hours. However, we found a statistically significant association with O$_3$ after adjustment for temperature, and we found no evidence that the O$_3$ associations were restricted to the six warmest months.

We also found positive associations with PM$_{2.5}$, NO$_2$, and black carbon, but the CIs were wide and the risk estimates were not statistically significant. The number of PAF episodes with matching O$_3$ and NO$_2$ concentrations was small (n = 52), and they were even smaller for PM$_{2.5}$ (n = 46), which resulted in reduced power to detect any associations. Thus, this small number of confirmed PAF episodes dictated caution in our interpretation of specific associations. Although we have highlighted the association with O$_3$ in the concurrent hour, it remains unknown whether our finding of an association between transient ambient air pollution concentrations and PAF is limited to this particular subset of PAF episodes, however, is unknown. Studies using devices programmed to detect a wider range of PAF episodes with more precise data on the timing of arrhythmia initiation are required to confirm and quantify this association further.

A problem in studying incidence of PAF is the definition of time of onset of new episodes. Although the ICD device provides a detection time for each episode of PAF, this is the time recorded by the ICD. This situation would lead to mismatching of air pollution concentrations to case and control time periods. However, this exposure misclassification would be nondifferential with respect to case/control status. Therefore, it would have resulted in a bias toward the null, underestimates of risk.

Episodes of PAF also may have been misclassified, however, any outcome misclassification, if present, was likely independent of air pollution levels and nondifferential. This misclassification would have produced wide CIs, a bias toward the null, and underestimates of risk.

Our analysis was limited to a subset of all PAF episodes that these subjects experienced. PAF episodes with ventricular response rates that remained below the ICD’s preset detection criteria for the duration of the arrhythmia would not have been recorded. These under-detected episodes likely represented a substantial fraction of the PAF episodes experienced by these patients. However, we used the case–crossover method, where each person serves as his or her own control, and event times are contrasted with matched control times. Such misclassification would have resulted in a loss of power, but no bias in our risk estimates. Whether our finding of an association between transient ambient air pollution concentrations and PAF is limited to this particular subset of PAF episodes, however, is unknown. Studies using devices programmed to detect a wider range of PAF episodes with more precise data on the timing of arrhythmia initiation are required to confirm and quantify this association further.

REFERENCES


