HEI

STATEMENT

Synopsis of Research Report 124 Part II

HEALTH EFFECTS INSTITUTE

Association of Particulate Air Pollution with Arrhythmias Recorded by Implanted Defibrillators

INTRODUCTION

Epidemiologic studies have reported associations between short-term changes in concentrations of particulate matter (PM) or its components and hospital admissions for and increased mortality from cardiovascular diseases. How exposure to PM may be linked to exacerbation of cardiovascular disease is not well understood. In 1998 HEI issued Request for Applications 98-1, "Characterization of Exposure to and Health Effects of Particulate Matter", to characterize exposure to and evaluate the health effects of PM. A key component of the RFA was to evaluate the effects of exposure to ambient particles in people who might be more susceptible to particle effects than healthy individuals; people with cardiovascular conditions are considered one of those groups.

HEI funded two researchers to conduct epidemiologic studies to assess the possible impact of short-term exposure to PM on important cardiovascular events. One was Dr Annette Peters (GSF-National Research Center for Environment and Health, Neuherberg, Germany) who studied the effects of air pollution on the induction of nonfatal myocardial infarction. The second was Dr Douglas Dockery (Harvard School of Public Health, Boston MA), whose study is described here.

APPROACH

Dockery and colleagues hypothesized that short-term increases in ambient (outdoor) concentrations of PM would increase the risk of possibly life-threatening arrhythmias—rapid, and in some cases rapid and irregular, heart rhythms—in patients with implanted cardioverter defibrillators (ICDs). An ICD is programmed to respond when the heart rate exceeds a preset number of beats per minute. The ICD records and stores the heartbeat pattern before, during, and after every detected arrhythmic episode. (If necessary, the ICD delivers an electrical stimulus to return the heart rate to a normal rhythm.) By evaluating the patients' ICD tracings, the investigators assessed whether pollutant concentrations were associated with arrhythmias recorded by the ICD.

Many patients with cardiovascular disease and different cardiac conditions are fitted with an ICD to immediately treat arrhythmias that develop in the lower chambers of the heart, the ventricles. If not treated rapidly, ventricular arrhythmias may cause sudden death. Thus, ICDs are designed to react to ventricular arrhythmias with a rapid heart beat because they are life-threatening. Arrhythmias may also originate in the upper chambers of the heart, the atria; these atrial arrhythmias (generally referred to as supraventricular arrhythmias) are not immediately life-threatening. Most supraventricular arrhythmias do not stimulate a rhythm in the ventricles rapid enough to trigger an ICD electrogram tracing.

Single-chamber ICDs monitor only the ventricles; newer dual-chamber ICDs monitor both the ventricles and the atria, making it easier to distinguish between ventricular and supraventricular arrhythmias when tracings are reviewed later.

Dockery and colleagues studied 195 patients treated at the New England Medical Center's Cardiac Electrophysiology and Pacemaker Laboratory in Boston MA. The patients were Massachusetts residents who lived within 40 km (25 miles) of the Harvard School of Public Health and who had been followed for more than 60 days (average follow-up 3.2 years). Of the 195 patients, 81% had single-chamber ICDs and 19% had dual-chamber ICDs. The average age at implantation was 63.6; 74% of the participants were male; and 83% were white. For their cardiac conditions, the majority of patients were prescribed multiple cardiac medications, predominantly β-blockers, antiarrhythmic drugs, and digoxin.

Continued

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr Douglas W Dockery at the Harvard School of Public Health, Boston MA. The complete report, Research Report 124, *Particulate Air Pollution and Nonfatal Cardiac Events. Part II: Association of Air Pollution with Confirmed Arrhythmias Recorded by Implanted Defibrillators*, can be obtained from HEI or our website (see reverse side).

The investigators measured concentrations of different fractions of PM and its components: fine particles ($PM_{2.5}$; aerodynamic diameter $\leq$ 2.5 µm), ultrafine particles (measured as particle number concentration; generally representative of particles with aerodynamic diameter $\leq$ 0.1 µm), black carbon (BC; the carbon component of PM that absorbs light), and sulfate. However, because they had information about ultrafine particles and sulfate levels for less than 3 years of the 7-year study period, they included these PM components in only a few of their analyses.

They also obtained information about concentrations of the gaseous pollutants nitrogen dioxide (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), and ozone (O_3) in the Boston metropolitan area. The effects of pollutant concentrations on the day of the event (lag day 0) and up to 3 days before the event (lag days 1–3) were assessed as single days, as the mean of lag days 0 and 1, and as the distributed lag, that is, estimated for all lag days simultaneously.

Dockery and colleagues used logistic regression models to determine whether exposure to pollutants was associated with arrhythmias. For many analyses the investigators reported estimates of effects of individual pollutants on all arrhythmias combined, and separately on ventricular and supraventricular arrhythmias. They also used the patients' clinical information in some analyses to determine whether specific characteristics would modify a pollutant's effects. The effect modifiers evaluated were diagnosis at ICD implantation (these included coronary artery disease compared with other cardiac diagnoses; ejection fraction [the fraction of total blood pumped out of the ventricle with every heartbeat]; and a history of heart attacks); cardiac medications prescribed; multiple arrhythmias during the follow-up period; and more than one arrhythmia within 3 days. They also evaluated whether the distance of patients' residences from the air pollution monitors affected the estimates of a pollutant's effects.

This study followed a smaller pilot study in Boston by Dockery and colleagues that also examined pollutant effects on patients with implanted ICDs. That study had reported weak associations between ICD discharges and ambient concentrations of PM and NO_2; associations were stronger in a subgroup analysis of those who had had multiple ICD discharges.

RESULTS AND INTERPRETATION

Unlike the pilot study, the cardiologist on the current study evaluated all the ICD tracings recorded (1912) and excluded 232 events because they did not meet the criteria for an arrhythmia; he identified 1342 tracings as ventricular and 346 as supraventricular arrhythmias. At least one ventricular or supraventricular arrhythmia was identified in 92 of the 195 patients.

Associations between $PM_{2.5}$ or BC and ventricular arrhythmias or all arrhythmias combined were weakly positive (and not statistically significant) at lag days 0 and 1, and were not found at days 2 and 3. Associations between $PM_{2.5}$ or BC and supraventricular arrhythmias were larger but also nonsignificant. Associations between CO, NO_2, or O_3 and the different types of arrhythmias were similar to those reported for $PM_{2.5}$ and BC in parallel analyses.

Associations for SO_2 with all arrhythmias combined or ventricular arrhythmias were positive (increase in relative risks of 6%–14%) at lag days 0, 1, 2, and 3. When analyzed as single days, for all arrhythmias combined these increases were statistically significant for days 0, 2 and 3; and for ventricular arrhythmias they were statistically significant for days 2 and 3. Larger associations (increase in relative risks of 15%–25%) were reported for SO_2 with supraventricular arrhythmias; the relative risk was statistically significant for lag day 1.

Of the several possible effect modifiers evaluated, few showed any effects. However, experiencing a ventricular arrhythmia within the 3 days before another ventricular arrhythmia increased the relative risk associated with $PM_{2.5}$, BC, SO_2, CO, and NO_2 concentrations (an increase in relative risk of 28%–75%, depending on the pollutant). Taking β-blockers was associated with decreased effects of pollutants on supraventricular arrhythmias. No consistent pattern of altered risk was found in relation to a patient's distance of residence from the pollutant monitors. These associations, produced by appropriate exploratory analyses, need to be validated in future studies.

CONCLUSIONS

This important study investigated specific hypotheses about exposure to particulate pollutants and the induction of a major clinical endpoint, cardiac arrhythmias that could be fatal if not for the intervention of the ICD. Overall, the study's results indicate that, in patients with an ICD, ambient concentrations of $PM_{2.5}$ or BC on the day of or up to 3 days before the event are only weakly, if at all, associated with the induction of any type of nonfatal arrhythmia. These results reported for particulate pollutants parallel some of those described in the investigators' earlier pilot study in the Boston area. Thus, these results do not strongly support one of the investigators' main study hypotheses, that increased ambient concentrations of particulate air pollutants would be associated with increased incidence of arrhythmias. For sulfate and ultrafine particles, fewer measurements were made and not many analyses were performed or reported. Thus, conclusions are difficult to draw from the results in this report about associations between these particulate pollutants and arrhythmias.

Compared with all other pollutants, associations between arrhythmias and SO_2—a pollutant derived primarily from stationary sources in this study area—were more likely to be statistically significant and more robust, especially for supraventricular arrhythmias. It is not clear, however, whether the associations reported for SO_2 and arrhythmias are due to SO_2 per se or reflect the activity of another pollutant associated with SO_2. NO_2, CO, and O_3 showed weak associations with all arrhythmias combined, similar to those reported for $PM_{2.5}$ and BC. These results differ from the pilot study, in which NO_2 was the only pollutant, gaseous or particulate, found to be significantly associated with ICD discharges in the overall study population.

The sources that emit the different pollutants are not clear: in the area of the current study, NO_2, CO, and $PM_{2.5}$ are associated primarily with vehicular emissions but SO_2 is associated primarily with stationary sources. Methods are needed to accurately identify the sources of emissions and to evaluate the relative contributions to health effects from stationary and mobile sources.

A strength of this study was the care taken to characterize the tracings recorded by the ICDs. This allowed nonarrhythmic events to be excluded from the analyses and ventricular arrhythmias to be distinguished from supraventricular arrhythmias. As expected, because the ICD is programmed to primarily treat arrhythmias that originate in the ventricles, the majority of arrhythmias identified were ventricular in origin. Thus, effect estimates for particulate or gaseous pollutants and ventricular arrhythmias were similar to those reported for all arrhythmias combined.

The estimated effects of particulate pollutants and SO_2 on supraventricular arrhythmias were larger than those reported for ventricular arrhythmias and all arrhythmias combined. These results are intriguing and suggest new avenues for research on the cardiovascular effects of air pollution.

The results about supraventricular arrhythmias should be interpreted with caution, however. Of the tracings recorded, supraventricular arrhythmias comprised only 15%; thus the statistical power to draw conclusions about associations between pollutant concentrations and this type of arrhythmia is somewhat low. In addition, the supraventricular arrhythmias recorded by ICDs used in this study are only a small set of the total supraventricular arrhythmias that actually occur.

Another strength of this study was using information on each patient's cardiac history, function, and medications to explore whether these characteristics would modify the effects of pollutants on arrhythmias. Possibly of most clinical significance, several pollutants—$PM_{2.5}$, BC, NO_2, CO, and SO_2—showed a significant positive association with ventricular arrhythmias among patients who had had another ventricular arrhythmia within the previous 3 days. In studies in which multiple subgroup analyses are performed, some results may be due to chance; thus, these associations should be interpreted cautiously. Given that the results were similar for many of the pollutants, they also increase the challenge of determining whether a particular pollutant or source may be responsible for the observed associations or may vary simultaneously over time with the responsible pollutant or pollutants. Nonetheless, they suggest that air pollutant effects may be most important for individuals in whom cardiac electrophysiology is most compromised.

Although the results of this study are not definitive, they suggest topics for further research that could be fruitful. Obviously, a study in which a substantially larger number of arrhythmias are recorded, through increasing the number of subjects involved, the length of follow-up, or both, is needed. The results also indicate that future studies need to pay careful attention to distinguishing supraventricular from ventricular arrhythmias; newer generations of ICDs should facilitate this distinction. Given the intriguing results related to supraventricular arrhythmias, other methods for investigating the effects of exposure to pollutants on this common subset of cardiac arrhythmias should be sought. At this point it is still not clear whether effects on cardiac arrhythmias are an important mechanism through which exposure to air pollution, and especially particulate pollution, exerts an effect on cardiovascular conditions.

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

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