HEI

STATEMENT

Synopsis of Research Report 186

HEALTH EFFECTS INSTITUTE

Particle Exposures as Triggers for Acute ECG Changes

BACKGROUND

A large number of epidemiologic studies have reported associations between higher exposure to particulate matter (PM) from combustion sources and increased cardiovascular mortality and hospitalization in vulnerable individuals, such as those with lung or heart disease and in older adults. Current and past research has aimed at identifying the pathophysiologic mechanisms responsible for these associations. Numerous studies have also shown that short-term exposures to PM and other pollutants are associated with changes in cardiac rhythm, such as HRV, and with alterations in the morphology of electrocardiogram (ECG) waveforms, providing insights into the interplay among pollutants, the heart, and the parasympathetic and sympathetic nervous systems.

APPROACH

The goal of the study by Rich, Peters, and colleagues was to reanalyze existing ECGs from four previous studies conducted by their teams to evaluate the associations between short-term (from 5 minutes to 6 hours) increases in exposure to fine PM (PM ≤ 2.5 µm in aerodynamic diameter [$PM_{2.5}$]) and ultrafine PM (PM ≤ 0.1 µm in aerodynamic diameter [UFP]) and changes in cardiac rhythm. The investigators were interested in assessing the effects of these particles on HRV and other ECG variables on shorter timescales than most previous studies. The ECGs were obtained using a portable recorder known as a

What This Study Adds

- Rich, Peters, and colleagues analyzed the ECGs of more than 200 individuals from two completed panel studies and two completed controlled-exposure studies in relation to increases in exposure to ultrafine particles (UFPs) and ambient fine particles ($PM_{2.5}$) in the previous 6 hours. Through a statistical approach known as factor analysis, they identified three ECG variables that were common across the studies: SDNN, a marker of total heart rate variability (HRV); RMSSD, a marker of parasympathetic regulation; and T-wave complexity, a marker of repolarization.
- Increases in recent exposures (previous 2 to 5 hours) to UFPs and $PM_{2.5}$ were associated with changes in SDNN; increases in exposure to $PM_{2.5}$ over the same period were associated with changes in RMSSD. Very recent exposures (less than 1 hour before) were not associated with any ECG changes.
- The observed associations are not likely to be of clinical significance but provide evidence of particle-related subclinical physiological changes and increase our confidence in the use of HRV parameters as reproducible intermediate markers potentially relevant to the association between air pollution and cardiovascular outcomes.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. David Q. Rich at the University of Rochester School of Medicine and Dentistry, Rochester, New York; Dr. Annette Peters at the Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; and their colleagues. The complete report, "Ambient and Controlled Particle Exposures as Triggers for Acute ECG Changes" (© 2016 Health Effects Institute), can be obtained from HEI or our Web site (see last page).

Holter monitor, worn by the subjects during the observation periods. The four previous studies were:

- The Augsburg panel study of individuals with diabetes or impaired glucose tolerance and individuals without the glutathione S-transferase M1 (*GSTM1*) gene (which is involved in the detoxification of oxidative-stress products);
- The Rochester panel study of patients with a history of acute coronary artery syndromes; and
- Two Rochester controlled-exposure studies of healthy volunteers and volunteers with diabetes.

Exposure Assessment

For the panel studies, the investigators estimated 1-hour average exposures to UFPs and $PM_{2.5}$ from ambient air measurements and, for the Augsburg study only, 5-minute average exposures to UFPs from personal air measurements. For the controlled-exposure studies, they estimated 1-hour and 5-minute average UFP exposures from chamber measurements of concentrated ambient UFPs or laboratory-generated elemental carbon particles. There were large differences between studies in the UFP concentrations.

Statistical Analyses

To reduce the number of variables in their statistical models, the investigators performed separate factor analyses of the hourly ECG variables and, for subsequent analysis, selected the three that had the highest correlation with a factor and were common to all four studies: SDNN (a marker of overall HRV), RMSSD (a marker of parasympathetic modulation), and T-wave complexity (a marker of repolarization).

The investigators used an additive mixed model as their basic statistical model, although the modeling approach varied somewhat across studies. They analyzed the three selected ECG variables (1-hour or 5-minute averages) in relation to the previous 1-hour average pollutant concentrations (up to 6 hours) or the previous 5-minute average pollutant concentrations (up to 60 minutes), reporting results as the percent change per interquartile increase in pollutant concentrations at each lag. They tested nine hypotheses in all: six about associations between 1-hour average UFP and $PM_{2.5}$ concentrations and 1-hour averages for the three ECG variables and three about associations between 5-minute average UFP concentrations and 5-minute averages for the same ECG variables.

RESULTS AND INTERPRETATIONS

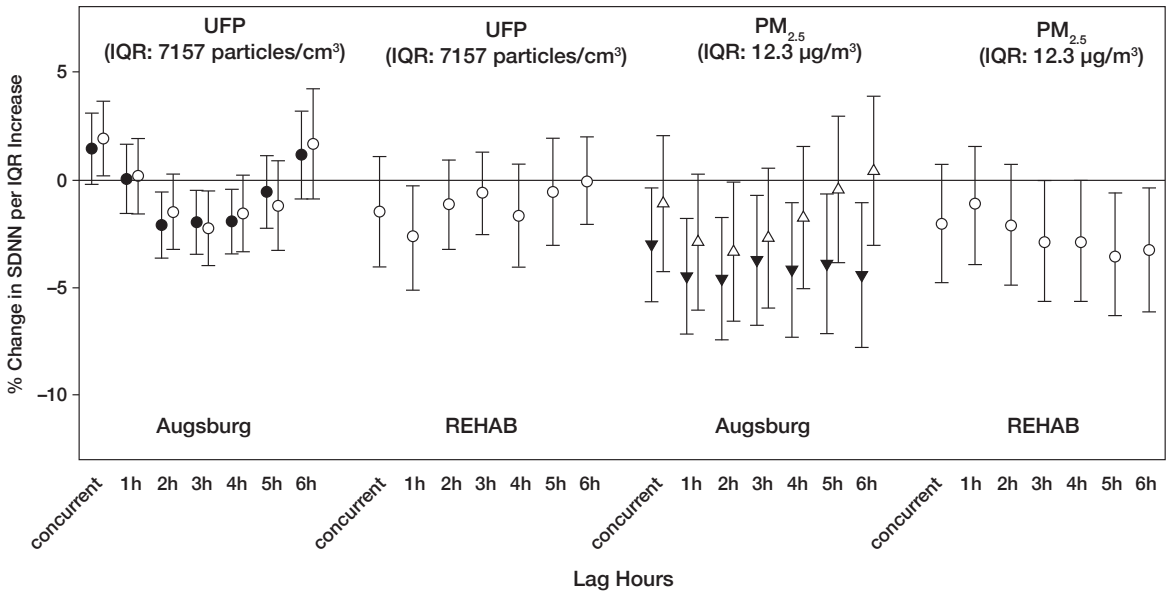
The analyses supported the hypotheses that higher exposures to UFPs and $PM_{2.5}$ are associated with lower total HRV (as assessed by SDNN) during the subsequent 2 to 5 hours (Figure 1) and that higher exposures to $PM_{2.5}$ are associated with lower RMSSD. These results are consistent with those reported by other studies. No associations were found with T-wave morphology. The study did not support the hypothesis that very recent (less than 1 hour) exposures to $PM_{2.5}$ or UFPs are associated with rapid ECG changes.

In its independent assessment of the study, the Health Review Committee concluded that the study was carefully conducted and made efficient use of existing data obtained from relevant populations to address important questions about associations between markers of cardiac function and recent exposure to PM. The investigators' inability to replicate many of their hypotheses across the four studies may have been caused, at least in part, by the pronounced differences in participant characteristics, exposure sources, compositions, concentrations, and study designs, coupled with the stringent criteria used to evaluate whether a hypothesis was replicated.

The Committee thought that the use of factor analysis to reduce the number of ECG outcome variables to model was novel and achieved its intended purpose. However, the use of a separate factor analysis for each study resulted in between-study differences in the number of factors and variables identified, raising doubts about the generalizability of this approach to other studies. The Committee also raised some concerns about the use of different statistical models to analyze the data from each of the studies.

The Committee agreed with the investigators' conclusion that recent exposures to UFPs and $PM_{2.5}$ are associated with subclinical alterations in markers of HRV and noted that the observed associations should not be interpreted to imply that ambient PM triggers the cardiac responses. These conclusions are broadly consistent with those of earlier studies, although the analyses presented in the current study are more detailed and extensive than those in many of the earlier studies and represent an important addition to the literature. The Committee also agreed

with the investigators that the observed associations are not likely to be of clinical significance but rather provide evidence of particle-related subclinical physiologic changes by which air pollution may increase the risk of acute cardiovascular events. The Committee did not think the investigators' conclusion that exposures to UFPs and $PM_{2.5}$ were independently associated with decreases in SDNN was clearly supported by the results. The combined results from the four studies increase confidence in the use of HRV parameters as reproducible intermediate markers potentially relevant to the associations between air pollution and cardiovascular outcomes.



Statement Figure 1. Percent change in SDNN (1-hour average) associated with each IQR increase in UFP and $PM_{2.5}$ concentrations in the concurrent hour and at lags 1 to 6 hours for the Augsburg (columns 1 and 3) and REHAB (columns 2 and 4) studies. For the Augsburg study, black symbols represent subjects in the group with diabetes or IGT, and white symbols represent healthy subjects in the group with a genetic susceptibility. For the REHAB study, the results were scaled to the same IQR increase as the Augsburg study. (1h = first hour before the measurement; 2h = second hour before the measurement, etc.)

Research Report 186

Ambient and Controlled Particle Exposures as Triggers for Acute ECG Changes

David Q. Rich, Annette Peters, Alexandra Schneider, Wojciech Zareba, Susanne Breitner, David Oakes, Jelani Wiltshire, Cathleen Kane, Mark W. Frampton, Regina Hampel, Philip K. Hopke, Josef Cyrys, and Mark J. Utell

HEALTH EFFECTS INSTITUTE

75 Federal Street, Suite 1400
Boston, MA 02110, USA
+1-617-488-2300 phone
+1-617-488-2335 fax

pubs@healtheffects.org
www.healtheffects.org

Recycled paper