

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Ambient Pollution and Heart Rate Variability

Diane R. Gold, Augusto Litonjua, Joel Schwartz, Eric Lovett, Andrew Larson, Bruce Nearing, George Allen, Monique Verrier, Rebecca Cherry and Richard Verrier

Circulation 2000;101:1267-1273

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2000 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/101/11/1267>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Ambient Pollution and Heart Rate Variability

Diane R. Gold, MD, MPH; Augusto Litonjua, MD, MPH; Joel Schwartz, PhD; Eric Lovett, PhD; Andrew Larson, BS; Bruce Nearing, PhD; George Allen, BS; Monique Verrier, BA; Rebecca Cherry, BA; Richard Verrier, PhD

Background—We investigated associations between ambient pollution levels and cardiovascular function in a repeated measures study including 163 observations on twenty-one 53- to 87-year-old active Boston residents observed up to 12 times from June to September 1997. Particles with aerodynamic diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) were measured continuously using a tapered element oscillating microbalance.

Methods and Results—The protocol involved 25 minutes per week of continuous Holter ECG monitoring, including 5 minutes of rest, 5 minutes of standing, 5 minutes of exercise outdoors, 5 minutes of recovery, and 20 cycles of slow breathing. Heart rate variability (HRV) was assessed through time domain variables: the standard deviation of normal RR intervals (SDNN) and the square root of the mean of the squared differences between adjacent normal RR intervals (r-MSSD). Mean 4-hour $\text{PM}_{2.5}$ levels ranged from 3 to 49 $\mu\text{g}/\text{m}^3$; 1-hour ozone levels ranged from 1 to 77 ppb. In multivariate analyses, significantly less HRV (SDNN and r-MSSD) was associated with elevated $\text{PM}_{2.5}$. During slow breathing, a reduction in r-MSSD of 6.1 ms was associated with an interquartile (14.3 $\mu\text{g}/\text{m}^3$) increase in $\text{PM}_{2.5}$ during the hour of and the 3 hours previous to the Holter session ($P=0.006$). During slow breathing, a multiple pollution model was associated with a reduction in r-MSSD of 5.4 ms ($P=0.02$) and 5.5 ms ($P=0.03$) for interquartile changes in $\text{PM}_{2.5}$ and ozone, respectively, resulting in a combined effect equivalent to a 33% reduction in the mean r-MSSD.

Conclusions—Particle and ozone exposure may decrease vagal tone, resulting in reduced HRV. (*Circulation*. 2000;101:1267-1273.)

Key Words: nervous system, autonomic ■ heart rate ■ epidemiology ■ electrophysiology ■ air pollution

Reduced heart rate variability (HRV) is a predictor of increased risk for cardiovascular mortality and morbidity.^{1,2} It may be a marker for poor health or it may be an etiologic factor, representing a disturbance of autonomic function that increases risk for cardiac events. Short-term increases in particle air pollution have been associated with increases in daily cardiovascular mortality and morbidity in studies from cities throughout the industrialized world.³ In response to particle exposure, heart rate or rhythm abnormalities without hypoxia or respiratory distress have been observed in animals⁴ and humans.⁵ These studies have led to the hypothesis that particle air pollution may influence cardiovascular risk in part through disturbance of autonomic function as reflected by changes in HRV. Recent studies in Maryland⁶ and Utah⁷ suggest associations between ambient particle levels and reduced HRV; other pollutant effects were not investigated. We assessed the relationship between short-

term changes in multiple air pollutants and short-term changes in HRV in a community-based elderly population.

Methods

Study Sample and Protocol

Between May and July 1997 volunteers were recruited from a Boston housing community, where the screening and testing office were located, on the ground floor of an apartment building. A questionnaire was administered regarding medications, pulmonary and cardiac symptoms, and smoking history. A resting 12-lead ECG was performed. Exclusion criteria included unstable angina, atrial flutter, atrial fibrillation, paced rhythm, or left bundle-branch block. Inclusion criteria included the ability to walk on level ground. Thirty-one individuals were screened and 21 entered the repeated measures study.

Each participant was given a day of the week and a time when weekly testing would be performed. Subjects were tested June through September from 9:00 AM to 2:00 PM, Monday through Friday, by a team of 2 technicians or physicians. Participants were administered a brief questionnaire regarding chest pain, doctor's visits, hospital visits, medication

Received July 21, 1999; revision received October 5, 1999; accepted October 12, 1999.

From the Channing Laboratory, Brigham and Women's Hospital and the Harvard Medical School (D.R.G., A. Litonjua, M.V., R.C.); the Environmental Epidemiology Program and the Environmental Science and Engineering Program, Department of Environmental Health, Harvard School of Public Health (D.R.G., J.S., G.A.); and the Institute of Prevention of Cardiovascular Disease, Beth Israel Deaconess Medical Center, Boston, Mass (E.L., A. Larson, B.N., R.V.); and Marquette Medical Systems, Milwaukee, Wis (A. Larson).

Although the research described in this article was funded by the US EPA, it has not been subjected to agency review and therefore does not necessarily reflect the views of the agency, and no official endorsement should be inferred. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Correspondence to Diane R. Gold, MD, MPH, The Channing Laboratory, Brigham and Women's Hospital, Harvard Medical Laboratory, 181 Longwood Avenue, Boston, MA 02115-5804. redrg@gauss.bwh.harvard.edu

© 2000 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

TABLE 1. Participant Characteristics

Characteristic	No. (%)
Sex	
Male	10 (48)
Female	11 (52)
Race/ethnicity	
Black, non-Hispanic	4 (19)
Hispanic	2 (9)
White	15 (72)
Cigarette smoking	
Never	8 (38)
Former	10 (48)
Current	3 (14)
Current asthma*	1 (5)
Coronary artery disease* (ever angina or heart attack)	6 (29)
Ever congestive heart failure*	2 (10)
Ever hypertension*	12 (57)
Medication use	
β -blocker	6 (29)
Calcium channel blocker	3 (14)
Angiotensin-converting enzyme inhibitors	6 (29)
Sympathomimetic†	1 (5)
Fair/poor health, yes	8 (38)
Illness kept in bed, past year	5 (24)

*Report of doctor's diagnosis of disease.

† β -agonist or theophylline.

changes, and whether the medication had been taken that morning. Continuous Holter monitoring with electrodes in a modified V5 and AVF position was performed during a protocol involving: (1) Five minutes of rest. Respiratory rate and 3 supine blood pressures were measured using a mercury column sphygmomanometer; (2) Five minutes of standing. After 2 minutes of equilibration, standing blood pressure was measured 3 times; (3) Five minutes of exercise outdoors. If the participant felt able, a standard walk was performed, involving one climb up a slight incline; (4) Five minutes of recovery. The participant lay down again and respiratory rate was recorded; (5) Three minutes, twenty seconds of slow breathing.⁸ For 20 respiratory cycles, the participant was asked to breath in for 5 seconds and then out for 5 seconds, with a technician coaching. The slow breathing portion enabled us to evaluate whether the effects of pollution on HRV were independent of respiratory rate, which might also be influenced by pollution levels.

Processing of Holter Recordings

Using a Marquette MARS Workstation, a trained engineer reviewed and, when necessary, corrected automatically determined readings of QRS complexes. Regions of noise and artifact (<1% of data) were eliminated. After correction, software facilities on the MARS were used to export beat timing and annotation information for analysis and creation of outcome variables through custom PC-based software written in the C language. Only normal-to-normal (NN) intervals between 150 and 5000 ms with NN ratios between 0.8 and 1.2 were included for analysis of heart rate variability. No tape contained >1% premature beats.

Two time domain measures of HRV were obtained. The standard deviation of normal RR intervals (SDNN) and the square root of the mean of the squared differences between adjacent normal RR intervals (r-MSSD) were calculated from all normal RR intervals for each portion of the protocol and the protocol overall.

TABLE 2. Ambient Pollution* and Temperature Levels During Holter Monitoring

Pollutant	No.	Mean	Range	Interquartile Range	NAAQS‡
PM _{2.5} , $\mu\text{g}/\text{m}^3$					
1-h mean	159	14.7	0–44.9	14.1	
4-h mean†	154	15.3	2.9–48.6	14.4	
24-h mean	163	15.5	2.3–45.1	12.0	65 (24 h)
Coarse Matter					
4-h mean	144	9.0	0.6–31.9	5.8	
O ₃ , ppb					
1-h mean	153	25.7	1.0–77	23.0	120 (1 h)
24-h mean	160	26.0	5–56	14.2	80 (8 h)
NO ₂ , ppb					
24-h mean	154	21.6	3–41	9.6	53 (1 y)
SO ₂ , ppb					
24-h mean	160	3.2	0–12.6	3.0	140 (24 h)
CO, ppm					
24-h mean	163	0.47	0.12–0.82	0.13	9 (8 h)
Temperature, °C					
24-h mean	163	24.3	14.0–31.7	5.7	

*Pollutants include daily particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ (PM_{2.5}), ozone (O₃), nitrogen dioxide (NO₂), and carbon monoxide (CO).

†The mean of the levels during the 4 hours before and including the time of Holter monitoring.

‡NAAQS indicates National Ambient Air Quality Standards (averaging time).

Exposure Monitoring

Airborne particles with an aerodynamic diameter ≤ 2.5 and $10 \mu\text{m}$ (PM_{2.5}, PM₁₀) were measured continuously 6 km from the study site, using the Model 1400A Tapered Element Oscillating Microbalance (TEOM). Because the TEOM sample filter is heated to 50°C, a season-specific correction was used to compensate for the loss of semivolatile mass that occurs at this temperature.⁹ Calibration factors were obtained by regressing continuous PM_{2.5} and PM₁₀ concentrations averaged over 24-hour periods on the corresponding collocated integrated 24-hour Harvard Impactor low-volume Teflon filter gravimetric measurements:

$$\text{corrected PM}_{2.5} = (\text{measured PM}_{2.5} + 2.00) / 0.944$$

for May through August ($r^2 = 0.99$)

Coarse matter was calculated by subtracting PM_{2.5} from PM₁₀. Continuous carbon monoxide (CO) data were collected within a quarter of a mile of the participant residence, with a ThermoEnvironmental (Franklin, Mass) Model 48 gas analyzer using a US EPA reference method. Ozone (O₃), NO₂, SO₂, temperature, and relative humidity measurements were obtained from the Massachusetts Department of Environmental Protection local monitoring site 4.8 miles from the study site.

Analysis

Continuous or categorical predictor variables treated as time invariant (or changing slowly) included age, sex, race/ethnicity, body mass index, and the diagnostic categories were derived from answers to the screening questionnaire and are summarized in Table 1. Time varying predictors included air pollutants, temperature, relative humidity, and medication use.

Data analyses dealt with the variable number of repeated measures on each subject. Although individual covariates were available for each subject and were used to control for individual differences, it

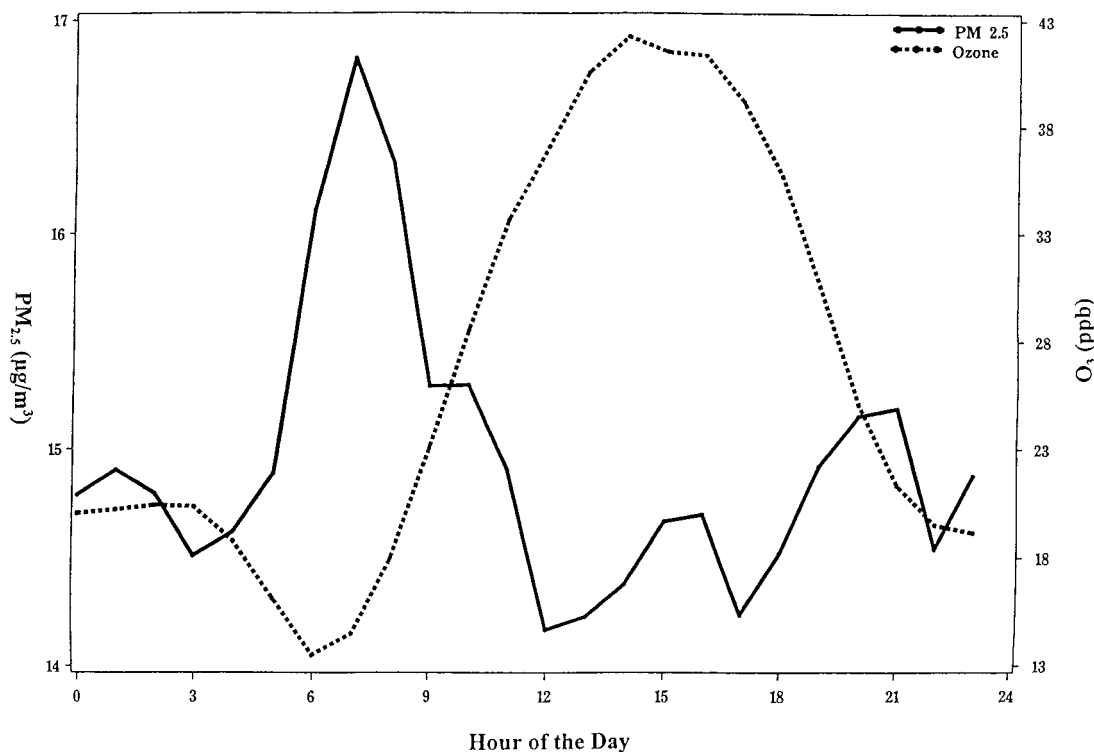


Figure 1. Mean 24-hour pattern of PM_{2.5} and O₃ hourly levels for the study period.

was believed unlikely that the measured covariates would explain all interindividual differences. Because each subject was not seen on each day of the study but rather once or twice a week, this created the potential for variations in the persons to be seen each day to confound time varying exposures such as air pollution. The primary approach we took to control for this was to construct fixed-effects models,¹⁰ fitting an individual intercept for each subject while still adjusting for time-varying covariates and individual traits, the most important of which was medication use.

Fixed-effects models have the advantage of adjusting for both measured and unmeasured time invariant characteristics of the individual, but the disadvantage of not providing estimates for specific measured time invariant subject characteristics. Through the mixed procedure of SAS,¹¹ a second set of random-effects models were used to evaluate the sensitivity of air pollution results to the choice of model and to define the primary effects and interactions with air pollution of subject characteristics, whose individual effects could not be evaluated in a fixed-effects model. Because there are multiple measurements on each subject, and those measurements may not be independent, a random subject effect was used in these regression analyses.

Weather and air pollution are continuous exposure measures and may not be related to electrophysiological measures in a linear fashion. To test this assumption, we repeated the analyses using generalized additive models in Splus.⁹ A generalized additive model fits the outcome as a sum of functions of each predictor not required to be linear. The shape of these functions is estimated from the data using nonparametric smoothing, and the significance of any deviations from linearity can be tested using nonparametric F tests.⁹ Fixed-effects models used nonparametric smoothing to adjust for temperature because it (temperature) did not always have a linear relationship with heart rate and HRV.

Results

A total of 163 Holter monitoring sessions were recorded for the 21 participants, 16 of whom had 6 or more observations. The median body mass index of the participants was 25.6

kg/m² (range, 18.5 to 33.3 kg/m²); the median age was 73.3 (range, 53 to 87 years).

Pollution levels and weather measurements in relation to the times of Holter monitoring are detailed in Table 2. Peak exposure times for PM_{2.5} were in the early morning, often during the 3- to 5-hour period before testing; O₃ levels were highest at midday (Figure 1). CO and SO₂ levels were low (Table 2).

During exercise, when sympathetic stimuli could be expected to take over from vagal tone, which dominates during rest periods,¹² heart rate rose (Table 3) and HRV (SDNN, r-MSSD) fell. Heart rate was lowest during slow breathing, the period designed to elicit vagal tone.

Although associations were found with shorter averaging periods for pollution, the largest and most precise estimates of associations between PM_{2.5} and heart rate occurred with the mean 24-hour PM_{2.5} (Table 4). Associations between PM_{2.5} and heart rate/HRV outcomes were not seen with pollution measures beyond 24 hours before testing.

Associations between 24-hour PM_{2.5} levels and diminished heart rate increased in magnitude and precision after adjusting for the previous 24-hour mean temperature (Table 4). Adjusting for 24-hour PM_{2.5}, overall heart rate rose as 24-hour temperature rose. A larger reduction in heart rate with PM_{2.5} was seen for smokers (3.8 versus 1.5 ms; $P=0.08$) and for those in fair-to-poor health (3.9 versus 1.3 ms; $P=0.02$).

For SDNN and r-MSSD, the size and precision of the estimates of associations with PM_{2.5} increased with each additional hour until the mean of the hour of and the 3 to 4 hours before testing. This timing approximated the number of hours since 6 to 7 AM, when particulate pollution levels peaked. Elevated PM_{2.5} levels over the hour of and the 3 hours before testing (4-hour PM_{2.5}) were associated with reduced

TABLE 3. Mean Heart Rate and Heart Rate Variability for 5 Protocol Periods

	First Rest	Standing	Exercise	Post exercise	Slow Breathing
Heart rate mean, beats/min	66.6 (0.9)	75.6 (1.0)	86.7 (1.0)	69.5 (0.9)	65.3 (0.8)
SDNN, ms	64.1 (2.4)	56.5 (2.1)	49.1 (1.7)	72.1 (3.0)	55.5 (2.0)
r-MSSD, ms	30.0 (1.8)	25.0 (1.4)	21.0 (0.8)	35.4 (2.1)	33.0 (1.9)

All values are mean (\pm SE).

overall HRV as measured by SDNN, but the associations were somewhat weaker than associations between $PM_{2.5}$ and r-MSSD (Table 4).

Associations between elevated $PM_{2.5}$ and reduced r-MSSD were robust and significant in all portions of the protocol other than exercise, with only small changes in the precision or magnitude of effect estimates with adjustment for temperature or heart rate (Table 4). Graphically, the assumption of a linear association between $PM_{2.5}$ and reduced r-MSSD appeared acceptable (Figure 2), and the deviation from a linear, no-threshold model was not significant ($P=0.69$). An interquartile increase in $PM_{2.5}$ ($14.35 \mu\text{g}/\text{m}^3$) was associated with a reduction in r-MSSD of 4 ms for the first rest period and 6 ms during slow breathing (Tables 5 and 6). The magnitude or precision of this estimate did not change significantly when extremes of exposure ($<5 \mu\text{g}/\text{m}^3$ and $>40 \mu\text{g}/\text{m}^3$) were omitted from the analyses.

Estimates for the associations between $PM_{2.5}$ and heart rate or HRV were similar regardless of the use of fixed- or random-effects models (Tables 4, 5, and 6). In separate random-effects models adjusting for $PM_{2.5}$, we examined age, body mass index, sex, smoking status, race, medication use, hypertension, coronary artery disease (history of angina or heart attack), history of congestive heart failure, and overall assessments of general health as predictors of heart rate and HRV. Subject characteristics with univariate associations were tested in multivariate models (Table 5). The increase in r-MSSD associated with β -blocker usage was ≈ 3 times the magnitude of the decrease in r-MSSD associated with $PM_{2.5}$.

Other pollutants, including coarse particulate matter, CO , O_3 , NO_2 , and SO_2 were considered as independent predictors and confounders of the associations between $PM_{2.5}$ and heart rate/HRV. In single pollutant models, both 24-hour mean

TABLE 4. Ambient $PM_{2.5}$ as a Predictor of Heart Rate and of Heart Rate Variability for 5 Protocol Periods

Outcome Variable	Predictor Variable	Model 1		Model 2 (With Heart Rate)		Model 3 (With 24-h Temperature)		
		Coefficient (SE)	P	Coefficient (SE)	P	Coefficient (SE)	P	
Heart rate, beats/min	24-h $PM_{2.5}$ ($\mu\text{g}/\text{m}^3$)	First rest	-0.10 (0.04)	0.02			-0.15 (0.06)	0.01
		Standing	-0.15 (0.05)	0.006			-0.20 (0.07)	0.007
		Exercise	-0.10 (0.05)	0.03			-0.21 (0.06)	0.002
		Second rest	-0.02 (0.05)	0.75			-0.11 (0.07)	0.13
		Slow breathing	-0.04 (0.04)	0.26			-0.09 (0.05)	0.09
		Overall	-0.09 (0.04)	0.04			-0.16 (0.06)	0.007
		SDNN, ms	4-h $PM_{2.5}$	First rest	-0.28 (0.16)	0.09	-0.22 (0.16)	0.17
Standing	-0.09 (0.15)	0.54		-0.17 (0.13)	0.20	-0.004 (0.17)	0.98	
Exercise	-0.25 (0.15)	0.09		-0.27 (0.14)	0.06	-0.24 (0.17)	0.16	
Second rest	-0.29 (0.20)	0.15		-0.27 (0.20)	0.18	-0.11 (0.22)	0.61	
Slow breathing	-0.16 (0.14)	0.26		-0.16 (0.14)	0.65	-0.20 (0.16)	0.23	
Overall*	-0.24 (0.10)	0.01		-0.26 (0.09)	0.004	-0.17 (0.11)	0.10	
r-MSSD, ms	4-h $PM_{2.5}$	First rest		-0.28 (0.09)	0.003	-0.27 (0.09)	0.005	-0.28 (0.11)
Standing		-0.28 (0.11)	0.01	-0.32 (0.11)	0.0003	-0.29 (0.12)	0.02	
Exercise		-0.09 (0.08)	0.26	-0.10 (0.08)	0.20	-0.13 (0.09)	0.13	
Second rest		-0.29 (0.12)	0.02	-0.27 (0.12)	0.03	-0.25 (0.14)	0.06	
Slow breathing		-0.35 (0.13)	0.01	-0.35 (0.14)	0.01	-0.42 (0.15)	0.006	
Overall*		-0.25 (0.08)	0.001	-0.26 (0.08)	0.0007	-0.29 (0.08)	0.0009	

All repeated measures regression models contain fixed-effects indicator variables for each of 21 participants and variables for whether the participant took a β -blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, or sympathomimetic medication on the testing day.

*Mean of the estimates of all 5 portions of the protocol, weighted by the SE.

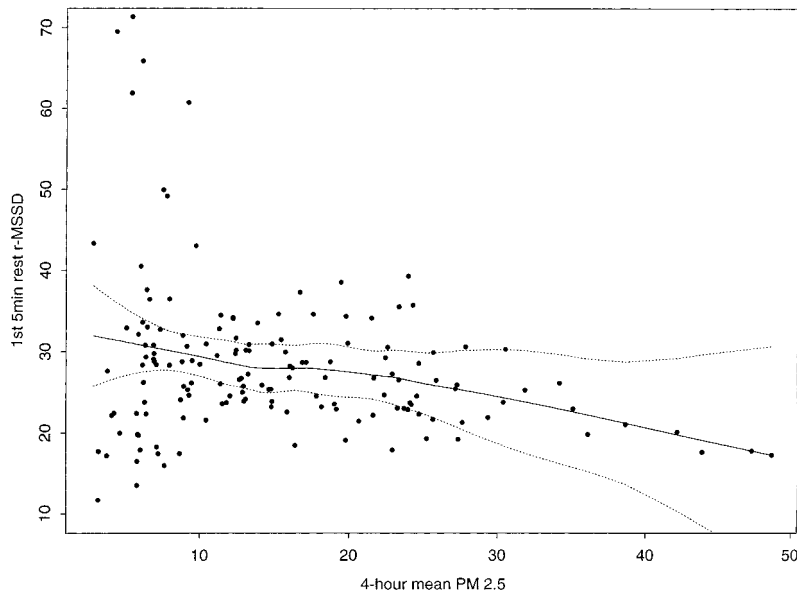


Figure 2. Covariate adjusted smoothed plot and 95% confidence limits of r-MSSD vs $PM_{2.5}$ averaged over the 4 hours before and including the hour during Holter monitoring. r-MSSD was adjusted for indicator variables for each of the participants and variables for whether the participant took a β -blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, or sympathomimetic medication on the testing day. ● represent individual covariate adjusted observations for each individual for each day.

NO_2 and SO_2 were associated with reduced heart rate in the first rest period, but not overall. Associations between these pollutants and heart rate for shorter pollution averaging periods were weaker. Multiple pollutant models also suggested an independent contribution of these gases to heart rate in the first rest period but not overall (Table 6). No other pollutants considered were associated with reduced heart rate in a significant or graphically plausible manner.

Increased levels of O_3 predicted reduced r-MSSD, with estimated effects similar to those of $PM_{2.5}$. The peak effect appeared to have a somewhat shorter averaging period for O_3 ,

compared with $PM_{2.5}$. Both 4-hour mean $PM_{2.5}$ and 1-hour mean O_3 were significant predictors of reduced r-MSSD during the slow breathing period, after outdoor exercise. The combined effect of the 2 pollutants on reduced r-MSSD was 11 ms or 33% of the mean r-MSSD during slow breathing. Coarse particulate matter, CO, SO_2 , and NO_2 were not associated with r-MSSD.

Discussion

This study suggests that both particulate and O_3 pollution may lead to short-term autonomic imbalance, reflected by changes in

TABLE 5. Predictors of Heart Rate and Heart Rate Variability (r-MSSD), Random Effects Models

Outcome Variable	Predictor Variables	Estimated Effect* (SE)	P
Model 1: heart rate, overall (beats/min)	24-h $PM_{2.5}$ †	-1.9 (0.7)	0.01
	24-h Temperature†, °C	1.5 (0.9)	0.09
	Current smoker	16.1 (4.3)	0.0003
	β -Blocker (0=not on)		
	On, didn't take	-10.0 (3.3)	0.003
	On, took in AM	-10.1 (2.8)	0.0004
Model 2: r-MSSD, first rest period (ms)	4-h $PM_{2.5}$	-4.2 (1.3)	0.0021
	Sex (0=Male)		
	Female	12.2 (7.4)	0.10
	β -Blocker (0=not on)		
	On, didn't take	6.1 (7.2)	0.39
	On, took in AM	13.4 (6.4)	0.04
	Calcium channel blocker (0=not on)		
	On, didn't take	10.4 (16.1)	0.52
On, took in AM	18.9 (11.7)	0.11	
Fair/poor health	-16.3 (7.7)	0.04	

*Effect estimated for interquartile changes in $PM_{2.5}$ and temperature. Interquartile range (Q^1-Q^3) for 24-h $PM_{2.5}$ is $12 \mu g/m^3$; for 4-h $PM_{2.5}$, $14.35 \mu g/m^3$; and for 24-h temperature, $5.7^\circ C$.

†24-h mean values.

TABLE 6. Estimated Effects of Pollution on Heart Rate Variability in Single and Multiple Pollutant Models

Outcome Variable (mean)	Model	Predictor Variable	Estimated Effect (SE)	P	Estimated Effect as Percent of Mean	
Heart rate, first rest period, beats/min (66.3)	1	24-h PM _{2.5}	-1.8 (0.7)	0.01	2.7	
	2	24-h NO ₂	-1.4 (0.6)	0.02	2.1	
	3	24-h SO ₂	-1.0 (0.5)	0.03	1.5	
	4	24-h PM _{2.5}	-1.6 (0.7)	0.03	2.4	
		24-h NO ₂	-1.0 (0.6)	0.09	1.6	
	5	24-h PM _{2.5}	-1.6 (0.7)	0.03	2.5	
		24-h SO ₂	-0.8 (0.5)	0.09	1.2	
	Overall heart rate, beats/min (74.9)	1	24-h PM _{2.5}	-1.9 (0.7)	0.01	2.6
		2	24-h NO ₂	-1.0 (0.6)	0.10	1.3
		3	24-h SO ₂	-0.5 (0.5)	0.30	
4		24-h PM _{2.5}	-1.8 (0.7)	0.01	2.4	
		24-h NO ₂	-0.6 (0.6)	0.32		
5		24-h PM _{2.5}	-1.9 (0.7)	0.01	2.6	
	24-h SO ₂	-0.2 (0.5)	0.60			
r-MSSD, first rest period, ms (30.1)	1	4-h PM _{2.5}	-4.0 (1.5)	0.009	13.3	
	2	1-h O ₃	-3.0 (1.8)	0.11	9.9	
	3	4-h PM _{2.5}	-3.7 (1.6)	0.02	12.5	
		1-h O ₃	-2.9 (1.7)	0.10	9.5	
r-MSSD, slow breathing period, ms (33.2)	1	4-h PM _{2.5}	-6.1 (2.2)	0.006	18.4	
	2	1-h O ₃	-5.9 (2.3)	0.01	17.9	
	3	4-h PM _{2.5}	-5.4 (2.2)	0.02	16.4	
		1-h O ₃	-5.5 (2.4)	0.03	16.6	

All repeated measures regression models contain fixed effects indicator variables for each of 21 participants and variables for whether the participant took a β -blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, or sympathomimetic medication on the testing day. Effect was estimated for interquartile changes in PM_{2.5} and temperature. Interquartile range (Q₁-Q₃) for 24-h PM_{2.5} is 12 $\mu\text{g}/\text{m}^3$; for 4-h PM_{2.5}, 14.35 $\mu\text{g}/\text{m}^3$; and for 24-h temperature, 5.7°C.

heart rate and HRV. For persons 65 and older, a 4.3% increase in daily deaths in Boston was observed for an interquartile change in PM_{2.5} of the same magnitude as seen in our study.¹³ Whether or not pollution-related short-term changes in HRV or autonomic balance can partially account for associations between particulate or O₃¹⁴ levels and cardiovascular morbidity or mortality is unknown. Between-person reduced HRV has been demonstrated to predict an increased risk for subsequent cardiac events in a population initially free of clinically apparent cardiac disease,² increased mortality in the elderly,¹ and sustained ventricular tachycardia.¹⁵ In these between-person comparisons, altered HRV may contribute to mortality either as an etiologic factor¹ or as a marker for poor health and subclinical coronary artery disease. If altered HRV is an etiologic factor for myocardial ischemia and fatal arrhythmias, it is hypothesized to work through sympathetic predominance and/or diminished parasympathetic tone.

Clinically, extreme within-person changes in autonomic function related to extremes either in sympathetic or parasympathetic output, can increase cardiac morbidity.¹⁶ Whether, for vulnerable populations, there are prognostic implications for more subtle within-person changes in autonomic balance as reflected in heart rate variability is unknown. We estimate a short-term pollution (PM_{2.5} + O₃) related reduction in r-MSSD of 13 ms (Table 6), similar in magnitude but opposite in effect compared with the increase

in r-MSSD observed in short-term follow-up in trials of effects of post-MI cardiac rehabilitation, β -blockers, or verapamil on HRV.¹⁷

Because r-MSSD estimates short-term variation in heart rate, reduction in r-MSSD suggest decreased parasympathetic influences on heart rate. Although short-term variation in heart rate is in part governed by respiratory variation, it is also influenced by other parasympathetic stimuli.¹² In our study, because the association between PM_{2.5} and reduced r-MSSD did not diminish after controlling respiratory rate in slow breathing or after adjusting for the observed respiratory rate during the first rest period, it is less likely that this association was solely a function of a pollution-related effect on respiration and a subsequent vagally mediated reflex effect on the heart. The reduction in r-MSSD in response to PM_{2.5} was also independent of effects of heart rate increases on r-MSSD.

The small negative association between 24-hour PM_{2.5} and heart rate does not fit with the hypothesis of an overall decrease in vagal tone or increase in sympathetic tone accompanying a high pollution episode. It is possible that the 24-hour averaged effect of PM_{2.5} differed from the more immediate effects of 4-hour PM_{2.5}. It is also plausible that in certain vulnerable populations particulate pollution leads to dysregulation of autonomic function, which can simultaneously reduce heart rate and HRV.

Our findings of particle-associated overall decreases in HRV are similar to those in Maryland⁶ but different from Utah (29 person-days)⁷ where increases in particle levels were associated with reduced SDNN but increased r-MSSD. Differences between the Boston and Utah findings may not be due to chance or sample size; the nature of the autonomic response to pollution may relate to the host and particle mass characteristics.

Pollution-related pulmonary inflammation may lead to systemic autonomic dysfunction through stimulation of vagal receptors in the lung. Derangements in cardiac neural conduction may also occur when inflammatory mediators or particles from the lung are transmitted via the general circulation to the heart. Killingsworth and colleagues have found pathological evidence for chemokines and particles in the myocardium of rats exposed to particle pollution.¹⁸

Limitations

Only time domain and not frequency domain variables were available for this study; however, the correlation between the 2 types of measures of long- and short-term cycles of HRV is high (eg, 0.93 for r-MSSD and high frequency HRV). Comparisons between our study results and others can only be approximate. Between studies, averaging time for measurement of r-MSSD varies between 5 minutes, 2 hours, and 24 hours. However, our overall mean value for r-MSSD (29 ms) was similar to that of the Framingham (33 ms) and other studies,² suggesting comparability for that measurement, which is less influenced by length of observation than measures reflecting long-term cycles.¹² Although the number of observations was sufficient to evaluate pollution effects on HRV, the number of subjects was insufficient to generalize regarding subject characteristics and HRV. Nevertheless, adjusting for subject characteristics was essential, because the effects of characteristics such as medication use were large. Except for measures of CO, measures of other pollution parameters were made up to 6 km from the study site; however, these parameters were demonstrated to be regionally distributed. Measurement error may influence the small correction factor for the loss of semivolatile organics from PM_{2.5} but is unlikely to influence the relationship between PM_{2.5} and r-MSSD. Lack of time activity, air conditioning use, and indoor pollution data are likely to increase error in the estimation of actual exposure; however, this is likely to bias the analysis toward the null.

Study Implications

This Boston study suggests that short-term changes in both PM_{2.5} and O₃ alter HRV, and therefore autonomic function. However, even if prospective studies find our results qualitatively or quantitatively reproducible, it will be necessary to assess whether short-term changes in HRV have prognostic value for either ischemic changes or malignant cardiac arrhythmias.

Acknowledgments

The authors thank Drs Douglas Dockery, Frank Speizer, and Peter Stone for their helpful criticism and suggestions; Gail MacCallum

for her technical support in Holter monitoring; Marcia Goetsch for her programming support; Joanne Maldonis for her secretarial support; and the Roxbury Tenants of Harvard for their enthusiastic participation in this study. This work was supported in part by the EPA Cooperative Agreement CR821762; the NIEHS Center Grants (ES0639 and ES 0002); NIEHS Public Health Service Environmental/Occupational Medicine Academic Award (K07-ES00266) of Dr Rose Goldman (to R.C.); and Harvard Medical School, with equipment contributions and technical assistance from Marquette Medical Systems.

References

1. Tsuji H, Venditti FJ Jr, Manders ES, Evans JC, Larson MG, Feldman CL, Levy D. Reduced heart rate variability and mortality risk in an elderly cohort: the Framingham Heart Study. *Circulation*. 1994;90:878–883.
2. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events: the Framingham Heart Study. *Circulation*. 1996;94:2850–2855.
3. Pope CA, Dockery DW, Schwartz J. Review of epidemiologic evidence of health effects of particulate air pollution. *Inhal Toxicol*. 1995;7:1–18.
4. Watkinson WP, Campen MJ, Costa DL. Cardiac arrhythmia after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. *Toxicol Sci*. 1998;41:209–216.
5. Pope CA III, Dockery DW, Kanner RE, Villegas GM, Schwartz J. Oxygen saturation, pulse rate, and particulate air pollution: a daily time-series panel study. *Am J Respir Crit Care Med*. 1999;159:365–372.
6. Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. *Environ Health Perspect*. 1999;107:521–525.
7. Pope CA III, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, Schwartz J, Villegas GM, Gold DR, Dockery DW. Heart rate variability associated with particulate air pollution. *Am Heart J*. 1999;138:890–899.
8. Freeman R, Weiss ST, Roberts M, Zbikowski SM, Sparrow D. The relationship between heart rate variability and measures of body habitus. *Clin Auton Res*. 1995;5:261–266.
9. Allen G, Sioutas C, Koutrakis P, Reiss R, Lurmann FW, Roberts PT. Evaluation of the TEOM method for measurement of ambient particulate mass in urban areas. *J Air Waste Manage Assoc*. 1997;47:682–689.
10. Statistical Sciences, S-Plus User's Manual. Version 3.2; Seattle: StatSci, MathSoft, Inc; 1993.
11. SAS Institute Inc. SAS/STAT8 Software. Changes and enhancements through release 6.12. Cary, NC: SAS Institute Inc; 1997.
12. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Special report: heart rate variability standards of measurement, physiological interpretation, and clinical use. *Circulation*. 1996;93:1043–1065.
13. Schwartz J, Dockery DW, Neas LM. Is daily mortality associated specifically with fine particles? *J Air Waste Manage Assoc* 1996; 46:2–14.
14. Touloumi G, Katsouyanni K, Zmirou D, Schwartz J, Spix C, Deleon A, Tobias A, Quenell P, Rabchenko D, Bacharova L, Bisanti L, Vonk JM, Ponka A. Short term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA Project. *Am J Epidemiol*. 1997; 146:177–185.
15. Odemuyiwa O, Malik M, Farrell T, Bashir Y, Poloniecki J, Camm J. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all-cause mortality, arrhythmic events and sudden death after acute myocardial infarction. *Am J Cardiol*. 1991;68:434–439.
16. Eddel GL. Psychologic stress, vasodepressor (vasovagal) syncope, and sudden death. *Ann Intern Med*. 1978;89(3):403–412.
17. Malfatto G, Facchini M, Sala L, Branzi G, Bragato R, Leonetti G. Effects of cardiac rehabilitation and beta-blocker therapy on heart rate variability after first acute myocardial infarction. *Am J Cardiol*. 1998;81:834–840.
18. Killingsworth CR, Alessandrini F, Murthy GGK, Catalano PJ, Paulauskis JD, Godleski JJ. Inflammation, chemokine expression, and death in monocrotaline-treated rats following fuel oil fly ash inhalation. *Inhal Toxicol*. 1997;9:541–565.