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Personal Coronary Risk Profiles Modify Autonomic Nervous System Responses to Air Pollution

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Learning Objectives

- Compare and contrast the results of crude and adjusted analyses of relationships among increasing exposure of young male boilermakers to fine airborne particles ($PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less), heart rate (HR), and heart rate variability (HRV).
- Relate whether and how the HR and HRV responses associated with increasing pollution correlate with the risk of coronary artery disease as estimated using the Framingham index.
- State the likeliest explanation for adverse electrophysiological responses to high levels of $PM_{2.5}$.

Abstract

Objective: *We investigated whether $PM_{2.5}$-mediated autonomic modulation depends on individual coronary risk profiles.* ***Methods:*** *Five-minute average heart rate (HR) and heart rate variability (HRV, including standard deviation of normal-to-normal intervals [SDNN], square root of the mean squared differences of successive NN intervals [rMSSD], high frequency [HF]) were measured from 24-hour ambulatory electrocardiograms, and personal $PM_{2.5}$ exposures were monitored in a prospective study of 10 male boilermakers (aged 34.3 ± 8.1 years). We used the Framingham score to classify individuals into low (score = 1–3) and high (score = 5–6) risk categories. Mixed-effect models were used for statistical analyses.* ***Results:*** *Each 1-mg/m³ increase in the preceding 4-hour moving average $PM_{2.5}$ was associated with HR increase (5.3 beats/min) and HRV reduction (11.7%, confidence interval [CI] = 6.2–17.1% for SDNN; 11.1%, CI = 3.1–19.1% for rMSSD; 16.6%, CI = 1.5–31.7% for HF). Greater responses (2- to 4-fold differences) were observed in high-risk subjects than in low-risk subjects.* ***Conclusions:*** *Our study suggests that adverse autonomic responses to metal particulate are aggravated in workers with higher coronary risk profiles.* (J Occup Environ Med. *2006;48:1133–1142*)

Air pollution is increasingly appreciated as a threat to cardiovascular health.[1] Striking increases in death rates after several air pollution disasters in the United States and Europe in the mid-20th century are well documented.[2,3] Large cohort studies have consistently demonstrated that long-term exposures to ambient air pollutants, especially fine particles ($PM_{2.5}$; particulate matter with aerodynamic diameter ≤2.5 μm), are associated with increased cardiopulmonary mortality and morbidity.[4–6] Compelling data from time-series analyses and case-crossover studies have linked short-term increases in particulate exposures to increased incidences of cardiac arrhythmia, myocardial ischemia, myocardial infarction, and hospitalizations for congestive heart failure and ischemic heart diseases.[7–12] Among several hypothesized mechanistic pathways for PM-related adverse cardiac effects is autonomic nervous system activity[13] as assessed by heart rate variability (HRV). The association between PM exposures and decreased HRV has been documented both in the elderly[14,15] and young healthy adults.[16,17] Human chamber experiments with concentrated ambient air pollutants and laboratory studies with a rat myocardial infarction model provide parallel results supporting these clinical observations.[18,19] Decreased HRV is associated with an increased long-term risk for coronary events and cardiovascular mortality[20]; decreased HRV also precedes acute cardiac events, including sudden cardiac death and arrhythmia.[21]

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This study was supported by NIH grants ES09860 and ES00002.

Jiu-Chiuan Chen has no commercial interest associated with this research.

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DOI: 10.1097/01.jom.0000245675.85924.7e

Some subpopulations are more sensitive to particulate pollutants than others and develop more severe health effects, particularly the elderly and patients with congestive heart failure, diabetes, chronic coronary artery disease, and lower respiratory diseases.[22,23] Experimentally, particulate exposures can exacerbate acute myocardial ischemia in animals.[24] Although accumulating data from both human studies and controlled experiments have suggested that decreases in HRV be one of the mechanisms leading to the acute cardiac events associated with high levels of air pollution, it remains unclear whether the air pollution-mediated autonomic modulation depends on an individual's coronary risk profile.

The use of "multiple-risk-factor assessment equations" (eg, Framingham score) has long been recognized as a useful tool for assessing global cardiac risk in clinical practice.[25] In a scientific statement on "Air Pollution and Cardiovascular Diseases" recently issued by the American Heart Association,[26] the panel experts alerted those "at-risk" patients (eg, profiled by the Framingham score system) to the adverse health hazards of elevated air pollution. Previous clinical studies have described significantly decreased HRV among individuals with conventional coronary artery disease (CAD) risk factors[27] such as male gender, aging, high blood pressure, high total cholesterol, and low high-density lipoprotein. To investigate whether individual CAD risk profiles and PM exposures have independent influences or interact with each other with respect to their joint effects on autonomic nervous system, we conducted a short-term prospective study in an occupational panel of men who are exposed regularly to high levels of particulates in the workplace.

Materials and Methods

Study Population

Study protocols were approved by the Human Subject Committee of Harvard School of Public Health and written informed consent was obtained from each participant. The study population came from a cohort of apprentice boilermakers in eastern Massachusetts. Between January 25 and February 8, 2003, 26 subjects were recruited for this phase of study to assess acute cardiopulmonary and inflammatory responses to particulates. None met any predetermined exclusion criteria (unstable angina, bundle branch or atrioventricular block, atrial fibrillation or flutter, or other rhythms or clinical symptoms compromising HRV analysis). Of all 26 eligible workers, 12 volunteered for this study. All workers were in the welding school on the sampling day and were exposed to fine particulates while they were arc welding, grinding, cutting, or involved in other activities on mild steel.

Personal Characteristics

We used a modified American Thoracic Society questionnaire to collect information on respiratory symptoms, personal medical histories, and current use of medication. Also, we solicited information on demographic features, lifestyle factors (smoking, drinking, exercise, and so on), and recent occupational activities. Because HRV is potentially affected by daily activities, all workers were asked to record the times when they performed different occupational activities in the workplace and also times spent in usual daily activities such as cigarette smoking, coffee drinking, eating, alcohol consumption, exercising, and sleeping.

Ambulatory Electrocardiogram Monitoring

Twenty-four-hour ambulatory electrocardiogram (AECG) recordings were performed using Applied Cardiac Systems A.M. cassette recorders (Laguna Beach, CA). Recorded signals from two leads (aVF and modified V_5) were synchronized with personal air samplers. Recordings were analyzed in the AECG Core Laboratory at Brigham and Women's Hospital, Boston, Massachusetts.

Analysis of Heart Rate Variability

Using a Marquette MARS Workstation (Milwaukee, WI), an AECG research specialist reviewed and, when necessary, corrected automatically determined categorization of QRS complexes into normal or ectopic beats. After regions of noise and artifact were eliminated, software facilities on the MARS were used to export beat timing and annotation information for analysis and creation of response variables through customized PC-based software written in C-language. Only normal-to-normal (NN) intervals between 150 and 5000 ms with NN ratios between 0.8 and 1.2 were submitted to HRV analyses. All HRV measures were computed on each 5-minute epoch from a rate tachogram constructed from acceptable NN intervals.[28] For time-domain parameters (SDNN [standard deviation of normal-to-normal intervals] in msec, rMSSD [square root of the mean squared differences of successive NN intervals, in msec], pNN50 [the proportion of consecutive NN intervals that differ by more than 50 ms, in %], and average heart rate [HR; in beats/min]), the tachogram gaps were set to the mean tachogram rate over all available intervals to avoid spurious variance that might result from interpolation, and all variance measures were appropriately scaled for the available tachogram duration. Frequency-domain measures of HRV[29,30] are estimated from computing the tachogram periodogram, scaling the periodogram by applying the Parseval identity, and summing the appropriate coefficients in frequency regions of interest. Spectral measures included low-frequency (LF) power (0.04–0.15 Hz), high-frequency (HF) power (0.15–0.4 Hz), and the LF-to-HF ratio (LF/HF).

The HF power was used as the index of vagal activity, the LF as the index of combined vagal and sympathetic activities, and the LF/HF as the

index of sympathovagal balance. Our empiric quality control data indicated an excellent agreement (intraclass correlation coefficient >0.95) between results of repeated analyses for all time-domain and frequency-domain parameters.

Measurement of Particulate Exposure

$PM_{2.5}$ was the main particulate exposure characterized in this study, and both occupational and nonoccupational sources were noted. Welding fume, which has a rich content of ultrafine particles (diameters ≤0.1 μm) and transition metals,[31] was the main occupational source of $PM_{2.5}$. Nonoccupational exposures resulted from tobacco smoke, food preparation, vehicle exhaust, and so on. DustTrak (TSI Incorporated, St. Paul, MN) model 8520 aerosol monitor, which measures airborne particles using light-scattering technology, was used to monitor $PM_{2.5}$ within the participant's breathing zone for 24 hours continuously. Based on all 1-minute average $PM_{2.5}$ concentrations, moving averages from ≥5 minutes were generated. Subjects were instructed to wear the monitors while they were awake and to place the DustTrak on a nightstand while they were sleeping. For participants who slept on the preceding night in the same room as on the sampled night, their previous night $PM_{2.5}$ concentrations were approximated by data from the sampled night. Otherwise, the previous night's $PM_{2.5}$ data were omitted. Because animal models have demonstrated significant electrophysiological changes several hours after PM exposures,[32,33] we only used 4-hour moving averages in the statistical analyses to parallel previous reports.[15,16] In addition, we quantified cross-shift $PM_{2.5}$ exposures using a Model 200 Personal Exposure Monitor (PEM; MSP Corp., Minneapolis, MN) to collect gravimetric air samples. We have documented a good agreement (Spearman's r >0.90) between real-time readings by DustTrak and PEM measures in this occupational setting.[34]

Assessment of Coronary Artery Disease Risk Profiles

We used the Framingham CAD index to profile participants' personal CAD risk.[35] This index combines seven conventional CAD risk factors (age, gender, blood pressure, total cholesterol or low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, diabetes, and smoking) to predict total coronary risk (for developing angina pectoris, myocardial infarction, or coronary disease death) over a course of 10 years. We verified personal information on diabetes and smoking by structured interviews and urine tests for sugar and cotinine. Two to three blood pressure determinations were made by the same physician after subjects had been sitting and resting for 10 to 15 minutes before the work shift, and the average was used for analyses. Blood samples were drawn after an overnight fast and were analyzed at a qualified laboratory, which determined the overall lipid profiles, including total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol, using validated methods in accordance with National Institutes of Health/National Cholesterol Education Program recommendations.

Statistical Analysis

Because our study subjects were freely moving during concurrently continuous AECG and personal $PM_{2.5}$ exposure monitoring, there were unavoidable time periods when either AECG tracings contained much noise or real-time PM readings were missing. To reduce the artifacts of these measurements, we restricted our analyses to those AECG segments with >90% valid beats matched to those 5-minute epochs with uninterrupted measures of $PM_{2.5}$ in the preceding 4 hours. Also, the length of AECG recording sessions was not uniform across all subjects. As a result, we had an unbalanced data structure with different numbers of repeated measures (range, 20–284) of 5-minute epochs that were not equally spaced in time. To account for the autocorrelation of repeated measures within each subject, for each response variable, we constructed several mixed-effect models with different autocorrelation structures, including an exchangeable autocorrelation for all repeated measures, a first-order autoregressive covariance, and a time-dependent covariance structure with an exponential function of temporal distances (such that the correlations of repeated measurements are smaller for observations that were further apart). The autocorrelation plots of residuals were used to evaluate the appropriateness of assumed autocorrelation structures. The Akaike Information Criteria (AIC) were used for selecting optimal models. The 5-minute HRV variables were log-transformed due to its right-skewed distribution of residuals. In crude analyses, we constructed a simple model by regressing log (HRV) and HR on preceding 4-hour average $PM_{2.5}$ (base models). Effects of each component risk factor of Framingham score on HRV were then evaluated by entering the corresponding component score into the base models. In adjusted models, we included time-independent covariates (Framingham score, body mass index, drinking habit) and recorded time-varying activities (smoking, coffee drinking, alcohol drinking, eating, exercising, and sleeping; each entered as an indicator variable). We also accounted for circadian patterns of HRV and HR by adding three indicator variables representing time of day (morning [7–11 AM], afternoon [12–5 PM], evening [6–10 PM], and nighttime [11 PM–6 AM]). All mixed-effects models include a subject-specific random effect to account for any unmeasured between-subject difference in average HR and HRV measures. To further adjust the influence of ventilation, for all HRV models, we additionally adjusted for average HR, which has been shown to strongly correlate with ventilation in ambulatory subjects.[36,37] The potential modification of the PM-mediated autonomic modulation by individual CAD risk profiles was then examined by testing the interaction term of $PM_{2.5}$ and Framingham score.

Sensitivity analyses explored potential biases arising from influential observations, model form misspecification, and residual confounding by covariates. All these statistical analyses were carried out using SAS 9.0 software package (SAS Institute, Cary, NC) using PROC MIXED procedures. Based on the optimal AIC, the SP(POW) option was used to model the covariance structures for SDNN, pNN50, and LF/HF, whereas the AR(1) was used for HR, rMSSD, LF, and HF.

Results

All 12 participants of AECG study were male; 11 of them were white. The average age ± standard deviation was 33.4 ± 8.8 years. As compared with other 14 eligible workers who did not volunteer, AECG subjects on average had entered this occupation for a shorter period (3.8 ± 5.2 vs 7.0 ± 10.9 years, $P = 0.24$ for rank-sum test) and fewer (33% vs 50%, $P = 0.45$ for Fisher exact test) were active smokers. However, their age, history of hypertension (8%) and chronic bronchitis (8%), and blood lipid profiles (total cholesterol, LDL, HDL, and triglycerides) were similar. No participant had reported or had laboratory evidence of diabetes. In addition, measured cross-shift time-weighted average $PM_{2.5}$ concentrations (1.92 ± 1.22 vs 1.69 ± 1.01 mg/m^3, $P = 0.61$ for rank-sum test) and Framingham scores (2.1 ± 2.8 vs 1.9 ± 3.4) were also comparable. These similar personal characteristics, CAD risk profiles, and PM exposure levels indicate that our study subjects are representative of a young working population of boilermakers. In general, the 10-year average total CAD risk in this occupational cohort was approximately 5%, slightly higher than the average 3% for men of similar age.[35]

Ten of the 12 AECG subjects provided usable data from both simultaneous HRV and $PM_{2.5}$ monitoring. Defective AECG recording and air sampler technical failure prompted omission of two subjects. Personal characteristics, distribution of each CAD risk factor, individual Framingham score, and cross-shift exposure to $PM_{2.5}$ in these 10 subjects are described in Table 1. None of them was taking any medication at the time of examination. Because Framingham scores were not evenly distributed, we divided the subjects into two subgroups (relatively low vs high risk) based on their predicted 10-year cumulative risk (3% to 5% vs 8% to 10%). The correlation of Framingham index with its component score was 0.41 for age, 0.29 for smoking score, 0.41 for high blood pressure, 0.37 for total cholesterol, and 0.22 for HDL score. No single risk factor had predominant contribution to the difference in predicted CAD risk between the high-risk and low-risk subgroups. No significant correlation between cross-shift $PM_{2.5}$ concentrations and individual CAD risk profiles could be identified. SDNN index (mean of standard deviation of all RR intervals for all 5-minute segments throughout the entire recordings) was 145 ± 38 msec. Average HR within 5-minute epoch was 84 ± 4 beats/min (range, 47–130 beats/min). Average 5-minute HRV indices was 69 ± 6 msec for SDNN, 57 ± 9 msec for rMSSD, 14 ± 4 for pNN50, 2126 ± 509 ms^2 for LF, and 816 ± 197 ms^2 for HF. The 4-hour moving average $PM_{2.5}$ concentration

TABLE 1
Personal Characteristics of Study Subjects With Complete Ambulatory Electrocardiogram and Personal $PM_{2.5}$ Monitoring Data

Characteristics	Total ($N = 10$)	Coronary Risk Category: Low ($N = 7$)	Coronary Risk Category: High ($N = 3$)
Framingham score	3 ± 2	1, 1, 2, 2, 2, 2, 3	5, 5, 6
10-year coronary artery disease risk*	5%	3% to 5%	8% to 10%
Active smoker†	40%	0, 0, 1, 1, 0, 0, 0	1, 1, 0
	Mean ± SD (median)		
Age (yr)	34 ± 8 (33.5)	28, 40, 23, 46, 38, 30, 37	26, 39, 46
Tenure (yr)	4 ± 6 (2.3)	2.5, 2, 2, 2, 1, 3, 3	2, 4, 20
Body mass index (kg/m^2)	29 ± 4 (30)	32, 30, 22, 32, 35, 30, 30	25, 25, 30
Systolic blood pressure (mm Hg)	129 ± 10 (131)	127, 132, 129, 113, 139, 133, 116	119, 132, 145
Diastolic blood pressure (mm Hg)	79 ± 9 (75)	76, 86, 70, 74, 89, 72, 67	84, 73, 95
Total cholesterol (mg/dL)	218 ± 55 (208)	263, 205, 177, 121, 178, 210, 277	308, 245, 200
Low-density lipoprotein cholesterol (mg/dL)	139 ± 41 (134)	176, 133, 120, 67, 91, 134, 175	202, 166, 125
High-density lipoprotein cholesterol (mg/dL)	44 ± 7 (42)	45, 57, 40, 43, 41, 38, 43	56, 40, 41
$PM_{2.5}$ exposure‡ (mg/m^3)	1.78 ± 1.25 (2.13)	3.39, 0.02, 0.17, 2.5, 3.07, 1.8, 2.19	2.06, 0.07, 2.49
Number of valid repeated measurement§	172 ± 100 (167)	20, 194, 136, 83, 269, 283, 137	262, 136, 284

*Cumulative risk for developing angina pectoris, myocardial infarction, or coronary disease death estimated from the Framingham Heart Study.

†Active smoker: 1 = yes; 0 = no.

‡$PM_{2.5}$: cross-shift concentration of fine particulate matter measured by gravimetric methods.

§Five-min segments with >90% valid beats and complete $PM_{2.5}$ data in preceding 4 hr.

SD indicates standard deviation.

was 0.73 ± 1.06 mg/m^3, ranging from nearly nondetectable to 4.23 mg/m^3. The autocorrelation within repeated measures of 5-minute HRV with a common first-order autoregressive structure was 0.54 for log(SDNN), 0.60 for log(rMSSD), 0.79 for log-(pNN50), 0.57 for log(LF), and 0.62 for log(HF), whereas the autocorrelation was 0.68 continuously monitored $PM_{2.5}$ concentration.

Crude Analyses for Effects of $PM_{2.5}$ and Framingham Score

We illustrated in Table 2 the effects of $PM_{2.5}$ and individual CAD risk profiles on autonomic nervous system activities as reflected by the changes in average HR, SDNN, rMSSD, and HF. For each 1-mg/m^3 increase in 4-hour average $PM_{2.5}$, average HR increased by 5.9 beats/min (95% confidence interval [CI] = 4.1% to 7.7); 5-minute HRV decreased by 5.2% (CI = 1.5% to 8.9%) for SDNN, 2.9% (CI = −2.9% to 8.6%) for rMSSD, and 13.1% (CI = 2.0% to 24.2%) for HF. Although no statistically significant increase in HR associated with Framingham score was found, there was a consistent pattern of negative association between Framingham score and HRV. Each unit increase in Framingham score was associated with HRV reduction by 11.3% (CI = 1.6% to 20.9%) in SDNN, 17.5% (CI = 2.7% to 32.3%) in rMSSD, and 28.3% (CI = 3.3% to 53.3%) in HF after adjusting for effects of $PM_{2.5}$. In contrast, no single component CAD risk score revealed any consistent pattern of significant associations across HRV measures, although blood pressure and total cholesterol scores had statistically significant associations with reduction in SDNN and rMSSD, respectively.

Adjusted Analyses for Effects of $PM_{2.5}$ and Effect Modification by Coronary Artery Disease Risk Profiles

After the adjustment for individual's CAD risk profiles, body mass index, drinking habit, and the changes of time-varying activities and circadian rhythm

TABLE 2
Effects of $PM_{2.5}$ Exposure and Coronary Artery Disease Risk Profiles on Heart Rate Variability and Heart Rate

Predictor Variables	Effects on Heart Rate*		Effects on SDNN*		Effects on rMSSD*		Effects on HF*	
	β† (95% CI)	*P* Value	β† (95% CI)	*P* Value	β† (95% CI)	*P* Value	β† (95% CI)	*P* Value
Main exposure variable								
4-hr average $PM_{2.5}$(per mg/m^3)	5.9 (4.1 to 7.7)	<0.001	−5.2 (−1.5 to −8.9)	0.006	−2.9 (−8.6 to 2.9)	0.33	−13.1 (−24.2 to −2.0)	0.02
Coronary artery disease risk factors Component score (per unit)								
Age score	3.5 (−0.2 to 7.3)	0.06	−6.4 (−24.3 to 11.6)	0.49	−1.6 (−30.1 to 26.8)	0.91	−23.3 (−67.6 to 21.0)	0.30
Smoker score	−2.4 (−7.3 to 2.5)	0.33	15.0 (−3.5 to 33.6)	0.11	10.7 (−21.4 to 42.7)	0.51	29.9 (−20.8 to 80.6)	0.25
Blood pressure score	5.0 (−1.9 to 11.8)	0.15	−28.6 (−54.3 to −3.9)	0.02	−34.7 (−77.2 to 7.8)	0.11	45.6 (−120 to 28.9)	0.23
Total cholesterol score	−1.6 (−4.6 to 1.4)	0.30	−9.6 (−21.0. 1.8)	0.10	−16.9 (−33.1 to −0.8)	0.04	−23.5 (−53.1 to 6.2)	0.12
High-density lipoprotein cholesterol score	13.9 (7.9 to 19.8)	<0.001	−10.2 (−56.0 to 35.6)	0.66	−9.3 (−80.5 to 61.9)	0.80	−0.9 (−117 to 118)	0.99
Framingham score (per unit)	1.2 (−1.7 to 4.2)	0.42	−11.3 (−20.9 to −1.6)	0.02	−17.5 (−32.3 to −2.7)	0.02	−28.3 (−53.3 to −3.3)	0.03

*Effects of $PM_{2.5}$ adjusted for Framingham score and effects of coronary artery disease risk factors adjusted for $PM_{2.5}$.
†Regression coefficients from generalized estimating equation models interpreted as beat/min change in heart rate or percent change in 5-min heart rate variability measures for each unit change of predictor variables.
SDNN indicates standard deviation of normal-to-normal intervals (NN); rMSSD, square root of the mean squared differences of successive NN intervals; HF, high-frequency power (0.15–0.4 Hz); CI, confidence interval.

TABLE 3
Effects of $PM_{2.5}$ on Autonomic Nervous System Activities Across Subgroups With Different Coronary Risk Profiles*

	Main Effect Models β (95% CI)†	*P* Value	Effects Modification by Coronary Risk Category: Low β (95% CI)†	High β (95% CI)†	*P* Value‡
Effect on heart rate (beats/min per mg/m^3)	4.7 (3.0 to 6.3)	<0.001	3.3 (1.3 to 5.4)	6.4 (4.1 to 8.7)	0.04
Effects on time-domain HRV (% per mg/m^3)					
SDNN	−11.7 (−17.1 to −6.2)	<0.001	−8.1 (−14.7 to −1.5)	−15.5 (−22.1 to −8.9)	0.06
rMSSD	−11.1 (−19.1 to −3.1)	0.007	−6.7 (−16.6 to 3.1)	−15.4 (−25.1 to −5.7)	0.13
pNN50	−9.1 (−24.8 to 6.6)	0.26	−0.9 (−20.2 to 18.3)	−18.7 (−39.1 to 1.7)	0.15
Effects on frequency domain HRV (% per mg/m^3)					
LF	−16.6 (−28.8 to −4.3)	0.008	−10.9 (−26.0 to 4.1)	−21.5 (−36.3 to −6.8)	0.22
HF	−16.6 (−31.7 to −1.5)	0.03	−6.5 (−25.1 to 12.1)	−26.3 (−44.6 to −8.0)	0.07
LF/HF	−2.1 (−10.5 to 6.3)	0.62	−7.1 (−17.3 to 3.1)	3.1 (−7.1 to 13.3)	0.09

*As defined in Table 1 for low (Framingham score 1–3) and high (Framingham score 5–6) coronary risk categories.

†Regression coefficients with 95% confidence intervals estimated from mixed effects models adjusted for time of the day (morning, afternoon, nighttime) and time-varying activities (eating, smoking, coffee drinking, alcohol drinking, exercising, and sleeping); additionally adjusted for 5-min heart rate in all HRV models.

‡*P* value comparing low vs high coronary risk subgroup.

HRV indicates heart rate variability; SDNN: standard deviation of normal-to-normal intervals (NN); rMSSD, square root of the mean squared differences of successive NN intervals; pNN50, proportion of consecutive NN intervals that differ by more than 50 ms; LF, low-frequency power (0.04–0.15 Hz), HF, high-frequency power (0.15–0.4 Hz); LF/HF, LF-to-HF ratio; CI, confidence interval.

in autonomic nervous system activity (main effect models; Table 3), exposure to high-level of $PM_{2.5}$ was significantly associated with increased HR and reduced HRV, although the association with pNN50 did not reach statistical significance. The negative correlation between Framingham score and HRV reduction (16.7% for SDNN, 21.6% for rMSSD, and 35.5% for HF for one-unit increase in Framingham score) remained statistically significant (all $P < 0.05$) in the adjusted analyses. We also noticed that those in the high coronary risk category (Framingham score = 5–6) systematically had a greater response to high level of $PM_{2.5}$ than the subgroup of low coronary risk (Framingham score = 1–3). For instance, each 1-mg/m^3 increase in $PM_{2.5}$ was associated with a 3.3-beat/min increase in average HR among those in the low coronary risk category and a 6.4-beat/min increased in average HR among those in the high coronary risk category. For low-risk subjects, each 1-mg/m^3 increase in $PM_{2.5}$ was associated with 6.7% reduction in rMSSD and 6.5% reduction in HF, whereas the corresponding responses were 15.4% and 26.3% for high-risk subjects. Although only the between-subgroup comparison of the PM-mediated effect on average HR was statistically significant, probably due to the small sample size, there was a very consistent pattern of effect modification by individual's coronary risk profile across all time and frequency main measures of HRV. Autocorrelation plots did not reveal any remaining secular trend in the residuals of constructed mixed-effect models with optimal AIC, indicating a goodness-of-fit to our data.

Sensitivity Analyses

Further analyses were performed to examine whether our findings could have resulted from any potential bias related to extremes in data or residual confounding. We chose to focus our sensitivity analyses on HF because it was recommended as the most desirable measure of HRV from short-term recordings.[38] First, because HF data have a right-skewed distribution, to evaluate whether some extreme measurements were driving the observed association, we conducted a restricted analysis by excluding those with HF above the 75th percentile. We found that the negative $PM_{2.5}$–HF HRV association remained statistically significant (−11.3%; CI = −23.5 to −0.2), and a much more prominent response was found in high-risk than in low-risk subjects (−22.4% vs 1.0%, $P = 0.004$). Second, because we only had three subjects in the high-risk category, we evaluated whether our findings could have been overinfluenced by any single subject. We reconstructed the mixed-effect model each time we deleted one high-risk subject. Results of these updated models showed that the negative effect of $PM_{2.5}$ on HF HRV persisted (with respective effect estimate −17.3% [CI = −33.0 to −1.6], −7.4% [CI = −24.8 to 10.1], and −20.9% [CI = −36.9 to −5.0]), and the pattern of observing greater responses in the high-risk category remained (with respective *P* value 0.18, 0.04, and 0.08). Third, because lower HRV

during working hours with high PM exposures and higher HRV off work with low PM. exposures were observed, the residual confounding by circadian rhythms of HRV was considered. After adding to our model (Table 3 adjusted analyses) 23 indicator variables representing hourly changes in HRV, we found that the negative association between $PM_{2.5}$ and HF HRV remained statistically significant (−18.6%; CI = −37.0 to −0.2), and the observed response to $PM_{2.5}$ was still greater in high-risk than in low-risk subjects (−28.1% vs −8.2%, $P = 0.07$). Finally, previous air pollution studies on HRV changes have estimated the short-term effects of $PM_{2.5}$ on HRV using fixed-effect models.[14,15,39] When we reanalyzed our data by the fixed-effect models with 10 individual intercepts, the $PM_{2.5}$–HF association remained statistically significant (−13.9%; CI = −25.3 to −2.4), and the observed effect was more prominent in high-risk than in low-risk subgroups (−25.2% vs 0.3%, $P < 0.001$).

Discussion

We illustrated the use of the Framingham index as a multiple-risk-factor equation for the risk stratification on the autonomic nervous system responses to air pollution. Our study results suggest that particulate air pollution may differentially affect HRV and HR measures based on an individual's CAD risk profile. In subjects with an increased CAD risk (Framingham scores of 5–6), $PM_{2.5}$ exposure was associated with increase in HR and reduction in HRV that were several folds greater than the responses observed among individuals with a low risk profile (Framingham score of 1–3) when exposed to the same level of $PM_{2.5}$. These observations support not only the general concept that particulate air pollution adversely affects HRV, but also provides evidence that particulate air pollution affects individuals differentially based on their underlying cardiac risk.

Associations of HRV and HR with $PM_{2.5}$ exposures in this population of young men exposed to high levels of particulate pollutants are consistent with previous findings[14–17,40–42] and reinforce the conclusion that air pollution is an insidious and pervasive component of cardiac risk. We found that $PM_{2.5}$ exposures increased average HR and decreased HRV, even after accounting for potentially confounding effects of many time-varying factors. In our study population, high levels of $PM_{2.5}$ exposure were statistically significantly associated with reduced HRV for both time-domain (SDNN, rMSSD) and frequency-domain measures (LF, HF). Although the PM-associated increase in HR may indicate either activated sympathetic stress response or diminished vagal control, the consistently negative $PM_{2.5}$–HF association suggests that the adverse electrophysiological responses to high levels of $PM_{2.5}$ is predominated by reducing cardiac vagal control. This PM-mediated parasympathetic modulation was also found in several panels[40,43,44] and population-based studies.[41,42] Interestingly, no PM–HF associations were also reported previously,[45,46] and increased parasympathetic activities were found in one recent study on a group of young healthy patrol troopers[47] exposed to in-vehicle $PM_{2.5}$ and one experimental study of young healthy volunteers challenged with carbon particle.[48] Many factors such as differences in population characteristics, PM mixtures, and degree of exposure measurement errors might have caused these discrepancies. Given the heterogeneity in individuals' autonomic responses to PM, it may be equally important to further investigate the significance of PM-mediated autonomic modulation across different populations, because adverse consequences of altered autonomic modulation has been reported for increased and for decreased HRV as well.[49]

Studying the population susceptibility to the adverse effects of air pollution is an important task of profound public health significance.[50] Identifying susceptible subpopulations can shed light on the potential toxicokinetic and toxicodynamic mechanisms linking air pollution to adverse endpoints.[26] Previous studies have attempted to identify subpopulations susceptible to acute HRV responses to PM exposure, but the results were varied. Among 21 Boston residents aged 53 to 87,[15] smokers were found to have a greater reduction in HRV associated with $PM_{2.5}$ exposures than nonsmokers ($P = 0.08$). Other results, including those from one panel study of 34 elderly subjects in Mexico City[40] and the secondary analyses of extant data from the Normative Aging Study (NAS)[42] and the Atherosclerosis Risk in Communities Study (ARIC),[41] revealed a greater HRV reduction associated with PM exposure in those with hypertension than those without hypertension. Diabetes mellitus was found to modify the associations between $PM_{2.5}$ and HRV in the NAS, but there was no consistent pattern for both time- and frequency-domain measures. No greater response was observed for the PM_{10}–HRV association in the diabetic population of the ARIC study. Because most of these studies were conducted on the elderly population with prevalent comorbidities, it remained unclear whether the observed greater PM–HRV associations were imparted by the CAD risk factors per se or due to the effects of corresponding treatment.

Study Strengths

The use of Framingham score in the context of risk stratification for PM-mediated adverse cardiovascular effects may have several desirable features. As mentioned, like other "multiple-risk-factor assessment equations," the Framingham score has long been recognized by cardiologists as a useful tool for assessing global cardiac risks.[25] If our findings of effect modification by individual CAD risk profiles are further confirmed in larger community-based studies, it will speak to the additional use of this clinical tool to identify

high-risk populations for either risk communication or targeted prevention. Most of previous epidemiologic studies on susceptibility assumed a homogeneity in PM–HRV effect for each considered conventional CAD risk factor and disregarded the possibility that PM–HRV association may vary by the severity of comorbid conditions. In contrast, the formulation of Framingham score (and other multiple-risk-factor assessment equations) has quantitatively accounted for the varied degrees of comorbidities (eg, the blood pressure and HDL levels). As shown in Table 2, when we analyzed component risk factors independently, no single CAD risk factor had a consistent pattern of associations with different HRV measures, and none of the CAD risk factors showed significant interaction with PM–HRV effect. In contrast, when the overall risk profiles were analyzed jointly, an individual's Framingham score showed a very consistent effect on HRV measures both in crude and adjusted analyses. Also, compared with those in the low-risk category, high-risk individuals appeared to have greater HRV reduction in response $PM_{2.5}$ (Table 3). In addition, previous studies implicitly assumed that individuals' susceptibility to PM–HRV effect was contributed independently by the conventional CAD risk factors under study, and none evaluated the effect of air pollution on HRV based on composite CAD risk scores. From the mechanistic perspectives, the use of Framingham score to assess susceptibility is appealing because it is more plausible that individuals' biophysical characteristics *jointly* rather than *independently* define the measure and degree of susceptibility contributed by differential toxicokinetic and/or toxicodynamic responses to PM. Furthermore, the use of direct personal measures of particulate air pollution also distinguishes our study. Previous studies used ambient outdoor air samples to approximate personal exposures, potentially introducing substantial measurement errors, because study subjects may have spent significant time indoors. Environmental measures of short-term $PM_{2.5}$ by fixed-site monitors generally do not correlate well with direct personal $PM_{2.5}$ measures.[51]

Implications for Further Research

If further confirmed, the notion of PM–HRV effect modification by Framingham score suggests there are common features of toxicokinetic and/or toxicodynamic responses to PM across subjects with different CAD risk profiles. Air pollution exposure biologists may consider searching for pathways that jointly determine the shared toxicokinetic susceptibility to PM-mediated HRV effects among those with different CAD risk profiles. It is also possible that people with different conventional CAD risk factors (such as smoking, high blood pressure, and dyslipidemia in our population) carry similar pathophysiological characteristics (eg, hypersympathetic state, impaired neurocardiologic control of vagal tone) that impart toxicodynamic susceptibility to the PM-mediated cardiac effects. Exposure characteristics of workplace particulates in our study have other mechanistic implications for PM-mediated cardiovascular effects. First, particulate exposure levels in this occupational setting are much higher than ambient particulate concentration. Studies on populations mostly exposed to ambient levels need to be conducted to examine whether modification of PM effect by coronary risk profiles is dose-dependent. Second, welding fume is known to have a rich content of transition metals.[31] To understand the health effects of different particulate compositions and to control for most dangerous pollutants, the relative toxicity of specific components accountable for acute cardiovascular effects related to poor ambient air quality should be examined, including metal constituents.

Study Limitations

We recognize several study limitations. First, measured changes in 5-minute HRV reflect only short-term autonomic modulation in response to particulates. Although we observed consistent acute PM-mediated HRV reduction in both time and frequency domains and previous studies have showed that HRV measured in short durations predicts both long-term CAD risk and sudden cardiac death in patients with chronic heart failure,[21] the definitive clinical significance of such changes should be elucidated. Second, external validity or generalizability of our results may be limited by the small sample size of 10 subjects. Whether regular exposure to high levels of toxic particulates makes subjects more susceptible to acute PM effects than in the general population is unknown. However, the internal validity of our findings is supported by the representativeness of our study subjects. Finally, the current study did not measure other copollutants such as O_3, CO, and NO_2. Findings on these copollutants in relation to HRV are limited and inconsistent. Levels of O_3 and CO within the welders' breathing zone were negligible,[52] and personal indoor measures of $PM_{2.5}$ do not covary with personal measures of O_3, NO_2, and SO_2.[53] Thus, the likelihood of such unmeasured confounding is low.

Conclusions

Adverse cardiovascular responses to $PM_{2.5}$ exposures, reflected by decreased HRV and increased HR, are aggravated in young men with higher CAD risk profiles but without overt CAD who are exposed to high levels of metal particulates. These findings support the role of disturbances in autonomic nervous system activity in PM-associated acute cardiovascular effects.

Acknowledgments

The authors thank Ema Rodrigues, Jaime Hart, Tzu-Min Yeh, Jonathan Natkin, and Dr Sutapa Mukherjee for their important contribution to data collection. The authors are indebted to Sandra Verrier for her editorial

help. Special thanks to the staff and members of the International Brotherhood of Boilermakers, Iron Ship Builders, Blacksmiths, Forgers and Helpers of Local No. 29, Quincy, Massachusetts.

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