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Effects of Personal Exposure to Ambient Fine Particulate Matter on Acute Change in Nocturnal Heart Rate Variability in Subjects without Overt Heart Disease

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Abstract

The immediate effect within minutes to hours of personal exposure to ambient fine particulate matter (PM_{2.5}) on cardiac autonomic function is limited, particularly at night. Our study aimed to assess the lagged association between personal exposure to PM_{2.5} and nocturnal heart rate variability (HRV). Repeated measures panel study among 21 community adults recruited from a local health clinic during the period of March 1, 2004 to August 31, 2004, in Boston, Massachusetts, in the United States. Ambulatory electrocardiogram (ECG) and continuous monitoring of personal exposure to PM_{2.5} and were measured for up to two consecutive days. We calculated 5-min time-specific average PM_{2.5} exposure for each participant. Mixed effects models were fit for 5-min standard deviation of normal-to-normal intervals (SDNN) and 5-min heart rate (HR) in relation to 5-min PM_{2.5} exposure lagged in 5-min intervals up to 4 hours. We found an 8.4% decrease in nocturnal SDNN (95% CI: –11.3% to –5.5%) and a 1.9% increase in nighttime HR (95% CI: 1.1% to 2.7%) for an interquartile range (IQR) increase in PM_{2.5} (13.6 µg/m³), after adjusting for confounders. Significant decreases in nocturnal SDNN associated with PM_{2.5} exposure occurred within 2.5 hours. The largest decrease in nocturnal SDNN of –12.8% (95% CI: –16.4 to –9.1%) that was associated with PM_{2.5} exposure was found with a lag of 25 minutes. Rapid changes in nocturnal HRV associated with personal PM_{2.5} exposure occurred within the

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Disclosures

None declared.

previous 2.5 hours, with the largest effects at 25 minutes, suggesting immediate cardiac autonomic effects of fine particulate exposure.

Keywords

lag; air pollution; night HRV; epidemiology

In 2012, the U.S. Environmental Protection Agency (EPA) strengthened the annual National Ambient Air Quality Standard (NAAQS) for ambient fine particulate matter of less than 2.5 μm in mean aerodynamic diameter ($\text{PM}_{2.5}$) to 12 micrograms per cubic meter ($\mu\text{g}/\text{m}^3$) from 15 $\mu\text{g}/\text{m}^3$ in 1997 to protect public health. A body of epidemiological evidence has demonstrated the association between exposure to $\text{PM}_{2.5}$ and cardiovascular events including ischemic heart disease (IHD), myocardial infarction (MI), stroke, arrhythmia, and heart failure exacerbation.^{1–3} Cardiac autonomic function, mainly indicated by heart rate variability (HRV), has been suggested as one of the hypothesized mechanisms linking PM exposure with adverse cardiac events^{4–10}. These epidemiologic studies showed heterogeneous time-lagged effects of $\text{PM}_{2.5}$ exposure on reduced HRV. However, to our knowledge, studies have not yet explored the very acute effects of personal $\text{PM}_{2.5}$ exposure within minutes to hours on HRV. To provide further insights into the time course of the very acute effects of $\text{PM}_{2.5}$ exposure on cardiac autonomic function, the present study was designed to investigate the association between personal exposure to $\text{PM}_{2.5}$ lagged in 5-min intervals up to 4 hours, and nocturnal HRV in a community-based general adult population; as nocturnal HRV better captured cardiac autonomic effects of personal $\text{PM}_{2.5}$ exposure in occupationally exposed¹¹ and general population adults.¹²

Methods

This repeated-measures panel study was designed to investigate the time course of the effects of personal $\text{PM}_{2.5}$ exposure on cardiac autonomic dysfunction. The study population has been described previously.^{12,13} Briefly, the study participants consisted of 21 adults, who did not have overt evidence of heart disease, that were recruited from a local health clinic in an inner city neighborhood of Boston, Massachusetts, during the period of March 1, 2004 to August 31, 2004. Each participant completed a modified American Thoracic Society (ATS) questionnaire,¹⁴ which also included information on socio-demographic factors (age, gender, and smoking status) and medication use. Information on medication use included statins, non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensive medications (beta blocker, calcium channel blocker or ACE inhibitors/angiotensin receptor blockers), or aspirin which were taken at least once during the study period. All participants completed continuous monitoring of ECG and personal $\text{PM}_{2.5}$ up to two consecutive days. The study was approved by the Institutional Review Boards of the Harvard School of Public Health and the Upham's Corner Neighborhood Health Center. All subjects gave written informed consent prior to participate in the study.

We used nocturnal HRV and nocturnal HR, for a period of 7 hours from 00:00 am to 07:00 am, as measures of cardiac autonomic response to $\text{PM}_{2.5}$ exposure.^{11,12} The ECG of each individual was measured continuously for up to two 24-hr periods using a five-lead ECG

Holter monitor, Dynacord 3-Channel Model 423 (Raytel Cardiac Services, Windsor, Connecticut). Of the 21 individuals, 18 subjects were monitored entire period and three individuals did not have nocturnal HRV (Figure 1). The ECG monitoring protocol has been provided previously.¹² Briefly, the holter monitor was calibrated 15 minutes before placing electrodes. Separate electrodes were placed on the participant's skin, and if necessary, the area was shaved for proper adhesion, and the leads were periodically checked by study staff. Each 24 hour recording was sent to Raytel Cardiac Services for processing and analysis using a StrataScan 563 (DelMar Avionics, Irvine, California) and then screened to correct data artifacts. A trained professional with no exposure information performed all analyses and edited all normal or abnormal findings based on standard criteria. The mean of SD of normal-to-normal intervals (SDNN, in milliseconds), as a time-domain HRV measure, and the mean heart rate (HR, in beats per minute) were calculated in standard 5-minute segments throughout the entire recording and matched with the corresponding personal 5-min PM_{2.5} intervals.

Continuous real-time personal PM_{2.5} concentrations were obtained for each individual with the TSI S_{IDE}P_{AK} Model AM510 Personal Aerosol Monitor, which uses light-scattering technology to determine mass concentration (TSI Inc., Shoreview, MN). Each S_{IDE}P_{AK} was fit with a PM_{2.5} inlet impactor. The air sample was drawn through a 1.2 meter long Tygon tube into the impaction inlet at a flow rate of 1.7 L/min, adjusted using a DryCal DC-Lite Primary Air Flow Meter (BIOS, Butler, New Jersey, USA). The PM_{2.5} monitor was placed in a padded pouch, with the inlet tubing secured in the participant's breathing zone, and attached to each participant. Participants were instructed to wear their monitors throughout the day and to place the monitor by their bed when sleeping at night. The monitor collected PM_{2.5} concentrations every 10 seconds and reported 5-minute averages.

We analyzed data using PROC MIXED in the SAS statistical package version 9.4 (SAS Institute Inc, Cary, North Carolina, USA). We treated exposure (PM_{2.5}) and outcome variables (nocturnal SDNN and nocturnal HR) as repeated measurements in 5-min segments. Dependent variables, 5-min nocturnal SDNN and 5-min nocturnal HR, were log₁₀-transformed to improve normality and stabilize the variance. Linear mixed effects models with random intercepts and unstructured covariance were used to estimate the percent changes as $(10^{[\beta \times \text{IQR}]} - 1) \times 100\%$, where β is the estimated regression coefficient and IQR is the interquartile range, in 5-min SDNN and 5-min HR for IQR increase in 5-min PM_{2.5}. To assess lagged effects of PM_{2.5}, we used 5-min lags up to 4 hours (total 48 lags calculated by 12 lags per hour $\times$ 4 hour) of PM_{2.5} matched on the time of continuous ECG for each subjects. In these lag models, one lag indicates a 5-min separation between the exposure and the outcome. We adjusted each model for age, gender, smoking status (current smoker and non-smoker), use of statins, NSAIDs, antihypertensive medications (beta blocker, calcium channel blocker or ACE inhibitors/angiotensin receptor blockers), and aspirin. Results are given as estimated percent changes with their 95% confidence intervals (CIs) in 5-min HRV and 5-min HR per IQR increase in 5-min PM_{2.5} exposure (13.6 $\mu\text{g}/\text{m}^3$).

Results

The demographic and clinical characteristics of each study participant are shown in Table 1. Subjects were on average 44 years of age; 81% were female, 29% were current smokers, and 48% took regular medications including any of statin (10%), NSAIDs (29%), antihypertensive medications (43%), or aspirin (14%). Of the 21 participants, 15 participants (71%) had one or more diseases including diabetes (9.5%), chronic bronchitis (9.5%), asthma (33.3%) or hypertension (57.1%).

Figure 2 shows adjusted lag associations of nocturnal SDNN and nocturnal HR with an IQR ($13.6 \mu\text{g}/\text{m}^3$) increase of personal $\text{PM}_{2.5}$. Greater decreases in nocturnal SDNN associated with $\text{PM}_{2.5}$ exposure occurred within 2.5 hours: the largest decrease in nocturnal SDNN of -12.80% (95% CI: -16.36% to -9.09%) and the largest increase in nocturnal HR of 2.27% (95% CI: 1.22% to 3.33%) associated with $\text{PM}_{2.5}$ exposure were found with a lag of 25 minutes and 20 minutes, respectively. When we adjusted for multiple comparisons using a Bonferroni correction and false discovery rate (FDR) estimation, strong and consistent associations were found within the lags of 25 minutes of $\text{PM}_{2.5}$ exposure (Supplement Table 1)."

Results were similar when we additionally adjusted for ethnicity since ethnic differences in HRV has been reported¹⁵: the largest decrease in nocturnal SDNN of -13.41% (95% CI: -17.11% to -9.55%) and the largest increase in nocturnal HR of 2.36% (95% CI: 1.31% to 3.42%) associated with $\text{PM}_{2.5}$ exposure were found with a lag of 25 minutes. Results were also similar when the analysis was additionally adjusted for diabetes: the largest decrease in nocturnal SDNN of -12.47% (95% CI: -16.10% to -8.69%) and the largest increase in nocturnal HR of 2.29% (95% CI: 1.23% to 3.36%) associated with $\text{PM}_{2.5}$ exposure were found with a lag of 25 minutes.

We also analyzed the lagged associations of nocturnal HRV with $\text{PM}_{2.5}$ classified by three groups: low exposure ($<12 \mu\text{g}/\text{m}^3$) based on a new annual NAAQS, medium exposure (12 to $24 \mu\text{g}/\text{m}^3$), and high ($\geq 24 \mu\text{g}/\text{m}^3$) exposure. Similar patterns of associations of nocturnal HRV with 5-min lagged $\text{PM}_{2.5}$ exposure were found; particularly, subjects with high and medium $\text{PM}_{2.5}$ exposure had 37.1% (95% CI: -46.0% to -26.7%) and 23.8% (95% CI: -29.7% to -17.5%) lower nocturnal SDNN than individuals with the low $\text{PM}_{2.5}$ exposure with a lag of 25 minutes (Supplement Table 2).

Discussion

In this community-based repeated measures panel study, we found lagged associations between personal exposure to $\text{PM}_{2.5}$ and rapid changes in cardiac autonomic function. Greater reductions in nocturnal HRV associated with $\text{PM}_{2.5}$ exposure occurred within 2.5 hours: the largest decrease in nocturnal SDNN associated with $\text{PM}_{2.5}$ exposure was found with a lag of 25 minutes, suggesting very rapid responses.

Although, to our knowledge, there is no previous study that assessed the short-term lag association between personal $\text{PM}_{2.5}$ exposure and nocturnal HRV in individuals, who were assumed to be asleep at night and hence limiting the influence of physical activity and

mental stress on HRV, a body of epidemiologic evidence suggests that particulate air pollution has been associated with cardiac autonomic dysfunction.^{4–10, 16–18} But these studies have shown various lagged effects of PM_{2.5} exposure that occurred within hours or same day of exposure^{4,5, 8–10} or longer time lags for more than one day^{16–18} using data from fixed ambient monitoring sites, which may lead to exposure misclassification, other than individual level. Only a few studies monitored individual-level PM_{2.5} and found acute effects on HRV.^{5,7,19} In community-dwelling adults from the APACR (Air Pollution and Cardiac Risk and its Time Course) study,⁵ the effects of personal PM_{2.5} on decreased cardiac autonomic modulation (CAM) measures occurred acutely, with the strongest effects occurring between 4 and 6 hours within 6 hours after elevated PM_{2.5} exposure, but potential confounders such as medication use were not considered in the models. In an occupational cohort of boilermaker welders, a biphasic cardiac autonomic response with acute (2 hours) and delayed (9–13 hours) was associated with a decline in SDNN index (SDNNi), the mean of the SDNN for all 5-min segments.⁷ That study may not be generalizable, however, because only young male workers who may be exposed to relatively high levels of occupational PM_{2.5} (mean: 1.12 mg/m³) were studied, and the composition of welding fume particles may not be similar to urban ambient air. In a controlled human exposure chamber study,¹⁹ decreases in HRV were observed following 2 hour exposures to concentrated ambient particles (CAPs) in concentrations of 5–200 µg/m³ among elderly participants, but not among young volunteers. Because physical activity and mental stress could influence HRV,²⁰ young volunteers exercised intermittently (alternating 15 minutes of rest and 15 minutes of moderate exercise on a cycle ergometer) during the exposure to assess the effects of particulate exposure. In the current population, there was a relatively weak association between personal PM_{2.5} and daytime HRV compared to nocturnal HRV associations with PM_{2.5} exposure.¹²

The mechanisms responsible for the acute cardiovascular effect of the PM exposure are not fully elucidated, but it may be biologically plausible, as particles could stimulate afferent nerves in the lungs which influence the autonomic nervous system.²¹ In a human study of healthy volunteers, inhaled particles rapidly pass into the systemic circulation within minutes: detected in blood at 1 minute, reached a maximum concentration between 10 and 20 minutes.²² In the systemic circulation, particles can cause oxidative stress directly or via acute pulmonary inflammation through the generation of reactive oxygen species (ROS) and proinflammatory cytokines.²³ These products may play a role in decreased HRV, reflecting the influence of both sympathetic and parasympathetic system. The acute effect of PM exposure observed in this study may occur via direct mechanisms involving direct activation of pulmonary neural reflex arcs.² In addition, impaired cardiac autonomic function, which is assessed by decreased HRV, is one of the most studied potential mechanisms that link fine particulate air pollution and cardiac diseases as previous studies have shown the acute, within hours, adverse cardiac effects of fine particulate air pollution including myocardial infarction,²⁴ prolonged ventricular repolarization,²⁵ ST segment depression, an ECG marker of myocardial ischemia,^{8,26} and cardiac arrhythmia.²⁷

The major limitation of this panel study includes the relatively small number of study participants and predominantly female population, limiting generalizability. To maximize statistical power in the small number of subjects, we used repeated measurements and

adopted linear mixed effects models to detect the associations between personal PM_{2.5} and nocturnal HRV. Another limitation is that we are unable to provide information on which constituents of PM_{2.5} result in the observed detrimental cardiac autonomic effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Overview of study design and measurements

Figure 2.

Adjusted percent changes and 95% CIs in nocturnal SDNN and nocturnal HR for an IQR increase in PM_{2.5} (13.6 µg/m³). Models were adjusted for age, gender, smoking status, use of statin, use of NSAIDs, use of hypertension medication (beta blocker, calcium channel blocker or ACE inhibitors/angiotensin receptor blockers), and use of aspirin. Circle black/white symbols indicate the effect estimate.

Table 1

Characteristics of the study subjects (N=21)

Subject	Age	Gender	Race	Smoker	Statin	NSAIDs	Aspirin	AHT [†]	SDNN (msec, mean±SD)			Heart rate (bpm, mean±SD)			PM _{2.5} (µg/m ³ , mean±SD)		
									Entire recording	Night	Night	Entire recording	Night	Night	Entire recording	Night	Night
1	21	F	B	N	-	-	-	-	69.7±29.7	74.4±31.8	83.3±15.2	71.0±9.2	15.5±5.7	10.0±2.6			
2	23	M	B	N	-	-	-	-	70.3±32.4	84.1±39.5	73.6±13.9	58.6±4.8	9.5±9.4	6.6±2.3			
3	23	F	B	N	-	-	-	-	67.0±25.5	74.0±24.3	82.9±15.7	69.7±5.7	18.1±4.2	20.5±4.1			
4	25	F	B	N	-	-	-	-	68.7±23.2	77.8±26.2	71.6±10.8	57.3±4.7	12.8±24.4	6.4±1.3			
5	26	F	B	N	-	-	-	-	102.5±24.7	-	66.2±10.0	-	8.8±15.6	4.1±0.6			
6	33	F	B	S	-	-	-	-	28.6±12.0	35.9±13.2	101.2±13.4	86.8±5.5	52.4±97.3	-			
7	39	F	H	N	-	-	-	+	41.0±25.4	57.9±19.7	74.7±10.1	66.4±5.7.3	10.3±13.9	4.1±3.5			
8	41	F	B	N	-	-	-	+	54.0±22.0	60.0±27.8	79.3±14.6	63.7±8.5	6.4±4.7	6.3±1.5			
9	43	F	B	S	-	-	-	+	41.3±19.4	-	88.1±13.0	-	175.8±88.9	-			
10	45	F	H	N	-	-	-	-	57.4±21.0	58.4±22.4	84.1±12.3	81.0±11.3	4.6±6.3	0.4±0.3			
11	45	F	B	N	-	-	-	-	46.9±16.4	52.6±17.4	82.9±12.6	72.1±5.9	6.1±8.1	3.2±0.6			
12	45	F	H	N	-	+	-	-	42.7±17.6	54.7±25.5	83.6±12.6	66.0±4.3	18.8±72.4	2.1±0.6			
13	46	F	B	N	-	-	-	-	54.0±20.6	52.9±23.3	83.4±12.8	76.3±19.3	13.4±48.2	3.5±1.3			
14	47	F	B	N	-	-	-	-	29.9±11.6	34.2±13.3	98.2±10.1	87.3±7.9	9.7±8.6	6.6±4.6			
15	51	M	H	S	-	+	+	+	28.4±17.9	55.4±19.3	96.4±10.8	79.2±6.4	24.9±50.7	21.9±12.6			
16	54	F	B	N	-	+	+	+	34.5±14.2	37.4±16.8	94.7±12.4	84.4±10.0	63.5±58.7	9.3±6.6			
17	55	M	B	S	-	-	-	+	36.8±29.4	55.2±55.5	78.4±7.6	75.0±7.4	64.7±86.7	49.7±22.9			
18	61	F	B	N	+	+	-	+	54.5±23.6	56.9±32.1	79.5±10.6	66.9±4.3	12.6±27.9	7.2±0.9			
19	66	F	H	N	-	+	-	+	50.4±19.7	48.1±25.8	70.1±6.5	69.5±6.4	13.5±5.2	12.3±2.6			
20	68	F	B	S	+	+	+	+	34.3±10.3	-	76.1±6.1	-	26.7±51.3	-			
21	69	M	W	S	-	-	-	-	30.8±11.9	27.5±10.9	82.4±6.4	85.8±5.1	218.6±251.4	12.8±30.1			
Mean	44								49.6±27.2	55.2±30.0	82.8±14.8	73.4±12.3	29.8±77.7	10.7±15.0			

F, female; M, male; B, non-Hispanic black; H, Hispanic; W, white; N, non-smoker; S, current smoker; AHT, anti-hypertensive medication.

[†] Antihypertensive medication includes any of beta blocker, calcium channel blocker or ACE inhibitor/angiotensin receptor blockers.