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ORIGINAL ARTICLE

Effects of fine particulate on heart rate variability in Beijing: a panel study of healthy elderly subjects

Xiaofeng Jia · Xiaoming Song · Masayuki Shima · Kenji Tamura · Furong Deng · Xinbiao Guo

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Abstract
Purpose This study aims to investigate the effects of ambient fine particulate (particulate matter with an aerodynamic diameter of 2.5 μm or less, $PM_{2.5}$) exposure within several minutes on Heart Rate Variability (HRV) of the healthy elderly subjects in the general environments (indoor and outdoor).
Methods This study is conducted by measuring the real-time indoor and outdoor exposure variables ($PM_{2.5}$, Temperature, and relative humidity) and heart rate variability (HRV), a marker of cardiac autonomic function measured by 24-h ambulatory electrocardiogram monitoring in a panel of 30 healthy elderly subjects in Beijing. Associations between personal 5-min $PM_{2.5}$ concentrations and concurrent 5-min HRV frequency indices are investigated using the mixed linear model.
Results High Frequency (HF) and Low Frequency (LF) increase, respectively by 1.30% (95% CI, 0.16–2.45%) and 1.34% (95% CI, 0.38–2.30%) per 10 $\mu g/m^3$ increases of $PM_{2.5}$ in the polled data analysis after the potential confounders are adjusted. When the indoor and outdoor periods are separated, positive associations are found between $PM_{2.5}$ and HRV when the subjects are indoors; however, there is no association when the subjects are outdoors.
Conclusions We conclude that $PM_{2.5}$ exposure within several minutes leads to increases of HRV of the healthy older subjects, which may increase the cardiac risks. Prominent effect of $PM_{2.5}$ on HRV is found when they are indoors, while the effect is not obvious in outdoor environment.

Keywords Fine particulate matter · Indoor air pollution · Heart rate variability · Healthy elderly subjects · Epidemiology

Abbreviations

AIC	Akaike's information criteria
ANS	Autonomic nervous system
$\mu g/m^3$	Micrograms per cubic meter
BMI	Body mass index
CI	Confidence interval
ECG	Electrocardiogram
HF	High frequency
HRV	Heart rate variability
kg/m^2	Body weight in kilograms divided by height in square meters
LF	Low frequency
LFHFR	Low-frequency/high-frequency ratio
L/min	Liters per minute
$msec^2$	square millisecond
$PM_{2.5}$	Particulate matter with an aerodynamic diameter $\leq$ 2.5 μm
RH	Relative humidity
SD	Standard deviation
SE	Standard error
Temp	Temperature

X. Jia · X. Song · F. Deng · X. Guo (✉)
Department of Occupational and Environmental Health Sciences, Peking University School of Public Health, 38 Xueyuan Road, 100191 Beijing, China
e-mail: guoxb@bjmu.edu.cn

M. Shima
Hyogo College of Medicine, Nishinomiya, Japan

K. Tamura
National Institute for Environmental Studies, Tsukuba, Japan

Introduction

Previous studies show that fine particulate matter (particulate matter with an aerodynamic diameter of 2.5 μm or less, $PM_{2.5}$) exposure has short-term effects on the increase of cardiovascular disease morbidity and mortality (Kan et al. 2007; Peters et al. 2001; Brook et al. 2010) and the disturbed heart rate variability (HRV) is reported to be the major contributor to the trigging of cardiac electro-physiologic diseases (Tsuji et al. 1996; Thayer and Lane 2007).

Heterogeneous associations between $PM_{2.5}$ and HRV indices are reported in previous studies, in which elderly individuals with compromised health status were chosen as subjects, and outdoor $PM_{2.5}$ measurements based on the ambient stationary monitors were conducted as exposure evaluations (Chuang et al. 2007; Wheeler et al. 2006; Lipsett et al. 2006; Schwartz et al. 2005; Park et al. 2005; Gold et al. 2000; Zanobetti et al. 2010). However, until recently, the associations between $PM_{2.5}$ and HRV of the healthy elderly subjects in the indoor and outdoor general environments have not been studied. Due to the disturbance from the health status and biased exposure evaluation, there is a great limitation in inferring the above associations from the current studies. It has been demonstrated that health conditions and drug mediations may greatly modify the associations between $PM_{2.5}$ and HRV (de Hartog et al. 2009; Wheeler et al. 2006; Park et al. 2005). Besides, exposure evaluation based on the stationary monitoring station conducted in former studies is also reported to mask or disturb the effects of $PM_{2.5}$ on HRV indices (Suh and Zanobetti 2010).

In this study, we conducted the personal $PM_{2.5}$ exposure evaluation by micro-environment analysis method and evaluated the associations between $PM_{2.5}$ and HRV indices in a panel of healthy elderly subjects. We also investigated different associations in indoor and outdoor environments.

Materials and methods

Study protocol

This study was conducted in the community located in the North-Western Beijing along the 4-ring road, which was surrounded by busy traffic roads. The ambient $PM_{2.5}$ maintains at relatively high level and mainly comes from the traffic emission (Chan and Yao 2008).

Our study period was from August 2008 to September 2008 (summer in Beijing). The measurements were conducted on the weekdays (from Monday to Friday) in order to exclude the unusual activity on the weekends.

Panel participants' recruitment

Forty-one elderly subjects (age > 50 years) living in the community were initially recruited through annual health checkups at the Community Health Center. Before the study period, everyone received a physical examination (including the blood pressure, X-ray chest perspective, height and weight measurement, and the examinations of blood markers) and completed a questionnaire. The subjects were included from the following criteria: (1) Non-current-smokers who have no home or occupational exposure to smoke, dusts, or fumes; (2) Suffering from no obesity (BMI $\leq$ 30 kg/m^2), and no history of diabetes, hypertension or other chronic diseases, and common cardiopulmonary diseases (atrial fibrillation, second-degree heart block, left bundle branch block, paced rhythm, unstable angina, myocardial infarction, pneumonia, asthma, or chronic obstructive pulmonary disease); (3) Having normal hemogram indices. Thirty-nine subjects met our inclusive criteria, and finally 30 subjects were included in our panel (eight subjects did not receive the HRV measurement and one subject received Holter monitoring for less than 5 h, which is too short to be acceptable). Most of them are retirees and the scopes of their activities were usually within 1 km around the community. The study was approved by the Institutional Review Board of Peking University Health Science Center, and all the subjects signed an informed consent before the study.

Continuous ambulatory HRV monitoring

Participants were hooked up to the Holter monitors by the trained technicians. The participant's skin was shaved if necessary, cleaned, and slightly abraded to ensure proper lead contact. Every subject wore the Holter Recorder for 24 h from the 9:00 am to 9:00 am the next day. On the testing day, the subjects were asked to follow their regular daily routine and complete a standard time-activity pattern diary, including: time intervals (30 min a segment), places (indoor or outdoor; 1/0), sporting (yes or no; 1/0), cooking (yes or no; 1/0), cleaning (yes or no; 1/0), sleeping (yes or no; 1/0), windows-open (yes or no; 1/0), etc. during the HRV recording.

The ambulatory electrocardiogram (ECG) was recorded using the Holter monitors (H12+, Ver 1.0, Motara Instrument Inc., Milwaukee, WI, USA). The power spectral density (HF and LF) was calculated in 5-min segments for the entire recording using the Fast Fourier Transform (FFT) with PC-based software (H-Scribe, Ver3.7, Motara Instrument Inc., Milwaukee, WI, USA). Two frequency indices were chosen by the power spectral density analysis as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Anonymous 1996; Stein et al. 1994):

high-frequency component (HRV-HF; 0.15–0.40 Hz), low-frequency component (HRV-LF; 0.04–0.15 Hz), and the LFHFR, which is the ratio of LF/HF. Trained personnel performed all analyses. All recordings could either be accepted or rejected according to the recommended standard criteria (Anonymous 1996), and the 5-min recordings with less than 300 beats were excluded to ensure the quality of the HRV testing. Since sleep may greatly disturb the HRV modification (Chan et al. 2004; Chuang et al. 2005), we distinguished the wakeful and sleeping period according to the time-activity diary and used measurements when subjects were awake for data analysis.

Monitoring of indoor/outdoor pollutants and meteorological parameters

The real-time meteorological data and $PM_{2.5}$ concentration (indoor and outdoor) were measured concurrently with the ambulatory HRV testing. As the subjects spent most of their wakeful period in the living room, the indoor monitors were conducted in the living room of the subjects who undergo the HRV test. The outdoor monitors were placed on the six-floor rooftop of the residential building (18 m in height) in the community with no emission sources nearby.

The temperature (Temp) and Relative Humidity (RH) (indoor/outdoor) were recorded by the HOBO Pro V2 Temp/RH (Onset Corp., Pocasset, MA, USA) every 1 min. The relative $PM_{2.5}$ concentrations per minute were measured by a digital dust monitor (LD-3 K; Sibata Scientific Technology Inc., Tokyo, Japan), which was a portable monitor based on the light scattering principle by measuring the intensity of the laser beam scattered by fine particulates. Conversion coefficients were calculated based on the mass concentrations measured simultaneously using the filtration sampling method to convert relative concentrations to mass concentrations. We used collocated portable air samplers (MP-Σ300; Sibata Scientific Technology Inc., Tokyo, Japan) equipped with cascade impactors (ATPS-20H; Sibata Scientific Technology Inc., Tokyo, Japan) with a flow rate of 1.5 l/min (the cut-off points of aerodynamic diameter were 2.5 and 2.5–10 μm, respectively) to measure the mass concentrations while the LD-3 K monitoring worked simultaneously in the same place. After gravimetric analysis, the daily average $PM_{2.5}$ mass concentration was used to calibrate the real-time mass concentration by the following formula:

$$\begin{aligned}&\text{Calibrated real time } PM_{2.5}\text{mass concentration}\\&= \text{real time } PM_{2.5}\text{relative concentration}\\&\times \begin{pmatrix}\text{measured daily average } PM_{2.5}\text{mass concentration}\\ \div \text{daily average real time } PM_{2.5}\text{concentration}\end{pmatrix}\end{aligned}$$

All the minute-average variables ($PM_{2.5}$, Temp, and RH) were aggregated to 5-min average variables synchronized with the 5-min HRV indices testing.

Calculation of personal levels of exposure variables

The personal level of exposure variables was calculated by the micro-environment analysis method. We calculated the personal exposures of 5-min average of $PM_{2.5}$, Temp, and RH indicated by the $PM_{2.5p}$, T_p, and RH_p using the following formula:

$$X_p = |place - 1| \times X_0 + place \times X_i$$

X_p is the personal level of variables, *place* is the subject's location during the 5-min interval (1/0, indoor/outdoor), and the X_i, X_0 are the indoor and outdoor levels of variables, respectively.

Statistical methods

We used nonparametric test (Wilcoxon test) for the indoor-outdoor comparisons of the $PM_{2.5}$ and HRV indices. The response variables HF, LF, and LFHFR were $\log_{10}$ transformed to improve the normality and stability. The mixed linear regression model was applied to estimate the effects of 5-min $PM_{2.5}$ on simultaneous $\log_{10}$ transformed 5-min average HRV indices for its advantage of analyzing repeated measurements. The mixed model was fit and assumed that:

$$Y_{it} = b_0 + u_i + b_1 x_1 + \ldots + b_p x_p + \beta\text{Pollutant} + \varepsilon_{it}$$

Y_{it} is the 5-min logarithm of HRV in subject i at time t, b_0 is the overall intercept, and u_i is the separate random intercept for subject i. x_1–x_p are covariates measured simultaneously.

A random intercept for each subject, as well as the fixed covariates such as gender, age, BMI, time of day, hear rate, T_p, RH_p, and activity were included in the model. We conducted the sensitivity analysis by analyzing two models to examine the potential instability from the covariates selection and the nonlinearity associations between meteorological data (temperature and RH) and HRV indices. In model 1, only $PM_{2.5}$ was chosen as the fixed effect in the model analysis (with no covariates adjusted). Model 2 included the $PM_{2.5}$ and the selected linear (gender, age, BMI, time of day, hear rate, T_p, RH_p, and activity) and nonlinear terms (quadratic temperature/RH) covariates as fixed effects. The autoregressive-1 (AR-1) was specified as covariance structure in the model analysis. Statistical analyses were performed using the mixed procedure in the SAS (proc mixed in SAS version 9.1; SAS institute inc., Cary, NC, USA). Model selection was based on minimizing AIC.

Several different $PM_{2.5}$ moving averages (15-, 30-min and 1-, 2-, 4-, 6-h) and the 5-min average $PM_{2.5}$ at different lag time before every 5-min average HRV measurement were conducted for lag effect evaluation. We estimated the

percent change in every HRV parameter for 10 μg/m^3 increase of $PM_{2.5}$ as $[10^{(\beta \times 10)} - 1] \times 100\%$, with 95% confidence intervals (CIs) $\{10^{[10 \times (\beta \pm 1.96 \times SE)]} - 1\} \times 100\%$, where β and SE were the estimated regression coefficient and its standard error (Wu et al. 2010).

Results

All the 30 subjects (12 men and 18 women) took part in the 24-h HRV measurements successfully. The demographic and healthy characteristics are shown in Table 1. The age of the subjects ranges from 51 to 73 years. Almost all the indices in Table 1 are within the normal reference range, which ensure the stable baseline of health status. The cholesterol and triglycerides levels (two additional indices) of 5 individuals were beyond the normal reference range (cholesterol, 3.38–5.72 mmol/l; triglycerides, 0.39–1.63 mmol/l).

The Holter measurements in our study on average covered 22 h (11.8 h were in wakefulness), in which 650 5-min HRV and 335 5-min $PM_{2.5}$ data were missed, and 3,265 data were used in the model analysis. Distributions of exposure variables in indoor and outdoor environments are shown in Table 2. The values are expressed by Median (1–99% percentile) because of the skewed distribution. The fluctuation of the 5-min average $PM_{2.5}$ is wide, which ranges from 0.18 to 255.39 μg/m^3. The median of 5-min average $PM_{2.5}$ is higher when the subjects are indoors than when they are outdoors (45.58 vs. 37.52 μg/m^3, Wilcoxon test, $p = 0.001$). Table 3 shows distributions of the 5-min average HRV frequency indices in different places (indoor/outdoor). After the exclusion of the noises, the samples of 5-min Holter recordings of the subjects in the model analysis were 116 ± 34. HF is higher when the subjects are indoors than outdoors (HF: median 231.0 vs. 154.0 msec^2, $p < 0.001$), and LFHFR is much lower when indoors (LFHFR: median 1.29 vs. 1.59, $p < 0.001$).

Table 1 Personal characteristics of study subjects ($n = 30$)

Characteristics[a]	
Men (%)	12 (40%)
Age (years)	
Mean ± SD	57.9 ± 5.4
Range	51–73
BMI (kg/m^2)	
Mean ± SD	24.38 ± 2.58
Range	19.14–29.09
Seated blood pressure (mm Hg)	
Systolic	117.34 ± 11.39
Diastolic	77.86 ± 6.07
Serum lipid indices (mmol/l)	
Cholesterol	5.27 ± 0.92
Triglycerides	1.53 ± 0.87
High-density lipoprotein	1.46 ± 0.36
Low-density lipoprotein	2.50 ± 0.68
Fibrinogen (g/l)	3.19 ± 0.51

kg/m^2, body weight in kilograms divided by height in square meters; mmol/l, millimoles per liter

[a] Data are presented as arithmetic mean (AM) ± standard deviation (SD) unless otherwise indicated

We used two models to evaluate the effects of 5-min $PM_{2.5}$ on the simultaneous HRV indices and found slight changes, which showed the stability and reliability of the associations between $PM_{2.5}$ and HRV indices (shown in Table 4). In model 2, HF and LF increase, respectively by 1.30% (95% CI, 0.16–2.45%) and 1.34% (95% CI, 0.38–2.30%) per 10 μg/m^3 increase of $PM_{2.5}$ in the pooled data analysis (combining the indoor and outdoor data). If we separate the indoor and outdoor periods, 10 μg/m^3 increases of $PM_{2.5}$ associate with the 1.67% (95% CI, 0.38–2.97%) and 1.30% (95% CI, 0.21–2.39%) increases of HF and LF when subjects are indoors; however, no significant associations with HRV indices are found when the subjects are outdoors ($p > 0.10$). Figure 1 shows the lag effects in model 2 analysis. No prominent lag effects were found between 5-min average $PM_{2.5}$ at different lag time and HRV indices. In the moving average analysis, HF shows no prominent lag effects, whereas LF showed stronger associations on the 6-h moving average $PM_{2.5}$. Figure 2 shows the subject-specific effect estimates in model 2 of pooled analysis. For HF, 19 subject special estimated effects are positive, and 11 are negative; while 20 positive and 10 negative for LF. Most of the effect estimates for HF and LF are positive despite the heterogeneity.

Discussion

In this study, we measure the exposure to $PM_{2.5}$ within several minutes and the changes in HRV frequency indices of healthy elderly subjects in general environments. Previous studies focused mostly on the elderly subjects with cardiovascular or pulmonary diseases; however, less attention has been paid to the healthy elderly subjects. We chose the healthy elderly subjects and excluded the confounders of health status and medicine mediations. The real-time micro-environment monitoring design of variables ($PM_{2.5}$ and the meteorological data) in our study is based on the concurrent indoor/outdoor monitoring and the routine activity diary and may represent a substantial improvement over most studies only relying on central monitors.

Former studies mainly focused on health effects of ambient $PM_{2.5}$, paying little attention to the $PM_{2.5}$ in indoor

Table 2 Distributions of exposure variables in the general environment

Exposure variables[a]	Outdoor		Indoor		Personal		p value[d]
	N[b]	Median (1–99% per)[c]	N	Median (1–99% per)	N	Median (1–99% per)	
5-min average $PM_{2.5}$ ($\mu g/m^3$)	735	37.52 (0.19–214.50)	2,530	45.58 (0.16–258.73)	3,265	44.09 (0.18–255.39)	0.001
5-min average T_{emp} (°C)	735	27.69 (20.50–42.42)	2,530	28.05 (25.07–30.10)	3,265	28.02 (21.04–40.85)	0.02
5-min average RH (%)	735	59.99 (20.27–94.73)	2,530	57.54 (36.79–72.85)	3,265	57.96 (27.95–94.59)	0.12

[a] All the exposure variables were during the wakeful period and then divided by environments (outdoor/indoor)

[b] Sample size (observation windows) after excluding all abnormities and noises in the model analysis

[c] Values are Median (1–99% percentile)

[d] p values of the outdoor-indoor difference for exposure variables using the Wilcoxon two-sample test

Table 3 Distribution of 5-min average HRV frequency indices in the general environment

Variables/place[a]	N[b]	p value[c]	Percentile				
			5	25	50	75	95
5-min HF power ($msec^2$)		$p < 0.001$					
Outdoor	735		22.0	59.0	154.0	474.0	2,732.0
Indoor	2,530		27.0	96.0	231.0	565.0	2,256.0
Pooled	3,265		26.0	84.0	214.0	543.0	2,349.0
5-min LF power ($msec^2$)		$p = 0.50$					
Outdoor	735		40.0	120.0	298.0	744.0	1,962.0
Indoor	2,530		43.0	141.0	309.0	707.0	1,951.0
Pooled	3,265		42.0	137.0	306.0	712.0	1,952.0
5-min LFHFR		$p < 0.001$					
Outdoor	735		0.39	0.80	1.59	3.17	7.41
Indoor	2,530		0.26	0.68	1.29	2.41	6.51
Pooled	3,265		0.28	0.71	1.35	2.64	6.68

[a] All the HRV were measured during the wakefulness period and then divided by environments (outdoor/indoor). Pooled indicates variables combing the indoor and outdoor data

[b] Sample size (observation windows) after excluding all abnormities and noises in the model analysis

[c] p values of the outdoor-indoor difference for 5-min HRV indices using the Wilcoxon two-sample test

environment. Since the elderly subjects spend most of their time indoors (78.0% of the wakeful period in our study was indoors), it is very important to pay more attention to indoor environment. Our study is the first investigation into the different effects of $PM_{2.5}$ in the indoor and outdoor environments on HRV.

The frequency domain analysis used in our study has been recommended as a useful tool for achieving a more precise assessment of autonomic function and proved to be capable of describing the autonomic contribution to cardiac oscillation more accurately than time domain measures in short-term HRV recordings. High-Frequency spectral power reflects primarily parasympathetic influences, whereas Low-Frequency power has been shown to reflect both sympathetic and parasympathetic influences. LFHFR represents the relative balance between the sympathetic and parasympathetic nerves (Anonymous 1996; Rajendra Acharya et al. 2006). We chose the frequency domain analysis with focus on HF and LF power, which had also been applied successfully in prior air pollution studies (Holguin et al. 2003; Park et al. 2008).

Many previous epidemiological studies evaluating the associations between $PM_{2.5}$ and HRV indices reported heterogeneous results. Some studies reported positive associations (Riediker et al. 2004; Magari et al. 2002; Gong et al. 2003), whereas others reported the negative (Schwartz et al. 2005; Gold et al. 2000; Pope et al. 2004) or zero association (Sullivan et al. 2005; Barclay et al. 2009). In our study, $PM_{2.5}$ leads to the increase of HRV frequency indices of the healthy elderly subjects in pooled data analysis, which is consistent with some previous epidemiological and animal experimental

Table 4 Estimated effects of 5-min $PM_{2.5}$ average on 5-min HRV indices in general environments

Variables/ models	Pooled		Outdoor		Indoor	
	Percent changes (95% CI)	Slope (p value)	Percent changes (95% CI)	Slope (p value)	Percent changes (95% CI)	Slope (p value)
5-min HF power						
Model 1[a]	1.35 (0.23 to 2.49)**	0.58 (0.018)	0.65 (−2.58 to 3.99)	0.28 (0.699)	1.16 (−0.04 to 2.36)*	0.50 (0.058)
Model 2[b]	1.30 (0.16 to 2.45)**	0.56 (0.025)	−2.93 (−6.35 to 0.62)	−1.29 (0.105)	1.67 (0.38 to 2.97)**	0.72 (0.011)
5-min LF power						
Model 1	1.11 (0.18 to 2.04)**	0.48 (0.019)	−0.41 (−3.03 to 2.27)	−0.18 (0.754)	0.99 (−0.01 to 2.00)*	0.43 (0.053)
Model 2	1.34 (0.38 to 2.30)**	0.58 (0.006)	−2.25 (−5.13 to 0.71)	−0.99 (0.133)	1.30 (0.21 to 2.39)**	0.56 (0.019)
5-min LFHFR						
Model 1	−0.21 (−0.91 to 0.50)	−0.09 (0.567)	−1.05 (−3.06 to 1.00)	−0.46 (0.317)	−0.14 (−0.90 to 0.63)	−0.06 (0.746)
Model 2	0.05 (−0.67 to 0.78)	0.02 (0.885)	0.70 (−1.64 to 3.10)	0.30 (0.561)	−0.34 (−1.17 to 0.49)	−0.15 (0.416)

** $p < 0.05$, * $p < 0.10$

Coefficients are expressed as percent changes (95% CIs) per 10 μg/m^3 increase of $PM_{2.5}$ concentration and the Slope × 1,000 (p value)

[a] Model 1 with no covariates adjusted

[b] Model 2 with linear covariates (gender, age, BMI, time of day, hear rate, T_p, RH_p, and activity) and non-linear covariates (quadric terms of T_p/RH_p) adjusted

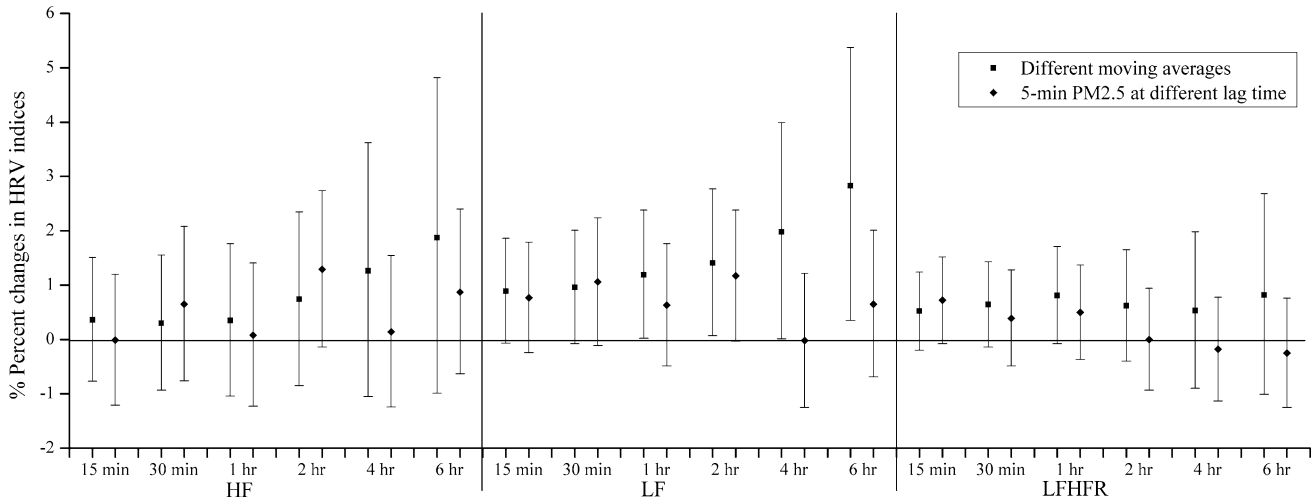

Fig. 1 Percent changes of HRV indices per 10 μg/m^3 increase of $PM_{2.5}$ at different lag time intervals. Percent changes (95% CIs) of 5-min HRV frequency indices per 10 μg/m^3 increase of $PM_{2.5}$ at different lag time intervals (from 15 min to 6 h) in model 2 analysis. The *square* indicates the HRV changes of $PM_{2.5}$ at different moving averages. The *diamond* indicates the HRV changes of 5-min average $PM_{2.5}$ at different lag time

studies (Godleski et al. 2000; Elder et al. 2007; Tankersley et al. 2004) (shown in Table 5). Studies on the mechanisms support the positive associations between $PM_{2.5}$ exposure and HRV indices. The $PM_{2.5}$ depositing in lung may stimulate the broncho-pulmonary C-fibers afferents and mediate the cardio-pulmonary parasympathetic reflex, which induce the shift toward predominance of parasympathetic stimulation indicted by the increased HRV indices (Coleridge and Coleridge 1984; Lee and Pisarri 2001).

We also noticed that some other studies reported negative associations between ambient $PM_{2.5}$ and HRV indices. The reasons for the discrepancy may be as follows:

1. Many previous studies focusing on elderly participants with compromised health status reported decreased HRV (de Hartog et al. 2009; Wheeler et al. 2006; Lipsett et al. 2006; Chuang et al. 2005); however, we found no report about the study on the health elderly subjects in the general environments. The health status

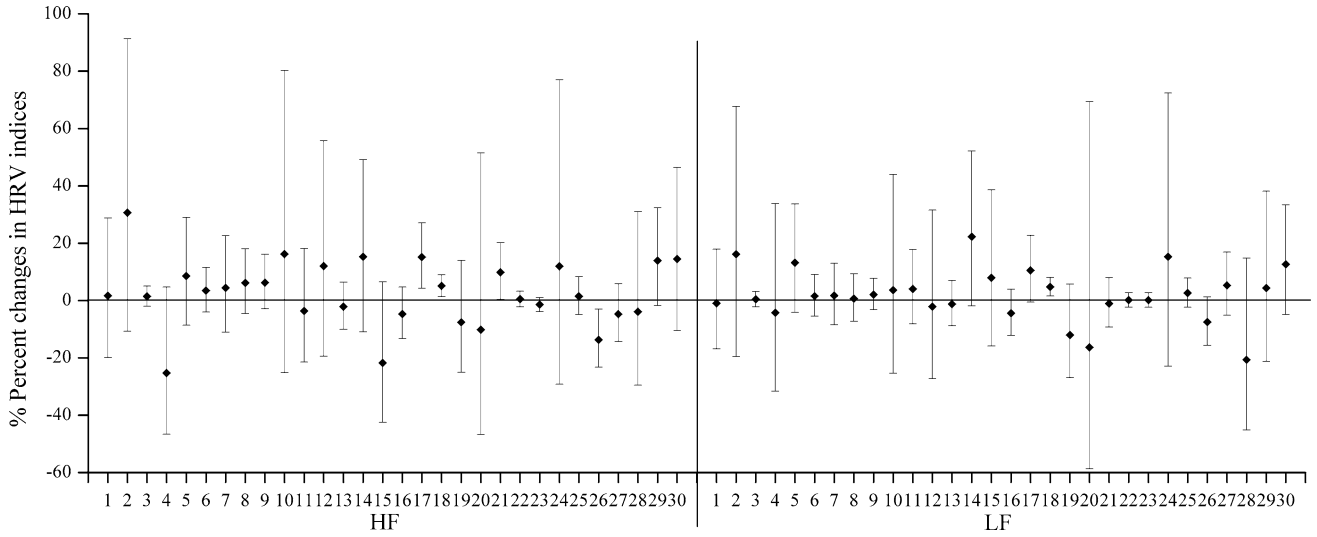

Fig. 2 Subject-specific effect estimates of HRV indices per 10 μg/m^3 increase of 5-min average $PM_{2.5}$. Subject-specific effect estimates (percent changes with 95% CIs) for 5-min HRV frequency indices per 10 μg/m^3 increase of 5-min average $PM_{2.5}$ in model 2 analysis. The *x*-axis indicates different subjects (subjects 1–12 are men; subjects 13–30 are women)

may be the most important modifier of the $PM_{2.5}$ mediated HRV response. Wheeler et al. (2006) reported increased effects of $PM_{2.5}$ on HRV for the panel of COPD subjects ($n = 18$), but no associations for the MI subjects panel ($n = 12$) (Wheeler et al. 2006). Therefore, the results in our study, which focused on the healthy subjects, cannot be compared directly with that of other published studies on subjects with compromised health. Our study provides the first evidences for the associations between $PM_{2.5}$ and HRV in healthy elderly subjects.

2. The different analysis methods of HRV in air pollution studies (long-term 24-h average HRV indices measurements and short-term 5-min special protocol testing, etc.) may lead to different inferences of $PM_{2.5}$ effect on HRV. The several minutes frequency domain indices are not perfectly synonymous to the 24-h measures (Anonymous 1996). Our study focused on the acute effects of $PM_{2.5}$ several minutes exposure on HRV indices. To allow for the maximal comparability between exposure and outcome variables, we chose the 5-min short-term epoch analysis instead of the 24-h period measurements.
3. Different compositions of the $PM_{2.5}$ may also be responsible for the heterogeneous associations. Magari et al. (2002) reported that the increases in the HRV were associated with lead and vanadium in the $PM_{2.5}$, whereas no statistical associations were found with nickel concentrations in the 39 boilermakers (Magari et al. 2002). Riediker (2007) also reported that the proportion of different metal components and organic components induced different effects of $PM_{2.5}$ on HRV indices in 9 male highway patrol troopers (Riediker 2007). Timonen et al. (2006) reported the negative, positive and zero associations between $PM_{2.5}$ and HF, respectively, in subject panels of Helsinki Erfurt and Amsterdam and suggested that the sources of $PM_{2.5}$ were the underlying modifiers (Timonen et al. 2006). Though no studies investigate the different $PM_{2.5}$ compositions in Beijing and other study centers, different compositions may still be the underlying mechanisms, which need further studies.

Our study shows the positive associations between $PM_{2.5}$ and HRV in indoor environment when separating the indoor and outdoor environments analysis. To our knowledge, no study has been conducted on the associations between $PM_{2.5}$ and HRV in indoor environment. Since the subjects spent most of daily time indoors, the positive associations in the pooled data analysis may possibly come from the indoor environment. The associations between $PM_{2.5}$ and HRV in indoor environment in our study cannot be compared directly with previous studies that observed the effects of ambient $PM_{2.5}$ on HRV indices. In our study, the gas stove cooking and the re-suspension by indoor activity (cleaning, walking, etc.) are the major sources of indoor $PM_{2.5}$, which is different from outdoor $PM_{2.5}$ in sources and components (Pekey et al. 2010; Afshari et al. 2005).

No significant associations are found between $PM_{2.5}$ and HRV of the healthy elderly subjects when the subjects are outdoors, which is consistent with some previous studies about ambient $PM_{2.5}$ and HRV indices of the unhealthy elderly individuals (Sullivan et al. 2005; Barclay et al.

Table 5 Short-term increased effects of fine particulate on hear rate variability—observational and animal studies

References	Study design	Exposure	Response
Riediker et al. (2004)	Panel study in 9 young subjects (aged 23–30 years, men, healthy and nonsmoking) for 4 successive days	During the working period, 9-h exposure session at 24.1 $\mu g/m^3$ to $PM_{2.5}$ per day	HF ↑ (14.8% of mean) SDNN ↑ (11.7% of mean) and LFHFR ↓ (−21.5% of mean) per 10 $\mu g/m^3$ increase of $PM_{2.5}$
Magari et al. (2002)	Panel study in 39 subjects (aged 18–59 years, men, healthy boilermaker workers) for continuous 24-h HRV testing	During the work period, personal $PM_{2.5}$ at 1.16 $\mu g/m^3$ of mean, lead exposure at 0.37 $\mu g/m^3$ of mean and vanadium at 0.76 $\mu g/m^3$ of mean.	SDNN ↑ (11.30 and 3.98 ms of mean) for every 1 $\mu g/m^3$ increase of the lead and vanadium concentrations of $PM_{2.5}$
Wheeler et al. (2006)	Panel study in 18 COPD patients (aged 49–76 years) for five or more days (5-min HRV protocol testing per day)	4-h average ambient $PM_{2.5}$ concentrations at 17.8 $\mu g/m^3$ (measured by ambient stationary monitors)	LF ↑ (35.9% of mean) SDNN ↑ (8.3% of mean) per inter-quartile range increases in 4-h ambient $PM_{2.5}$ (11.65 $\mu g/m^3$)
Peretz et al. (2008)	Experimental study in 16 adult volunteers (aged from 24–48 years, 3 healthy and 13 with metabolic syndrome)	2-h exposure sessions at 200 $\mu g/m^3$ to diesel exhaust	HF ↑ (0.33 mes^2 of mean) and LFHFR ↓ (−0.74 of mean) at 3-h after exposure, without lag effects
Gong et al. (2003)	Experimental study in 24 subjects (aged 18–45 years, 12 healthy and 12 asthmatic nonsmoking volunteers)	2-h exposure sessions at 174 $\mu g/m^3$ to concentrated ambient particulates in the $PM_{2.5}$ size (CAP)	Normalized HF ↑ ($p < 0.05$) after the exposure and LFHFR ↓ ($p < 0.05$) with CAP relative to FA (filter air)
Godleski et al. (2000)	Animal experiment in coronary occlusion compromised dogs exposed to concentrated air fine particulates by inhale	85–1,056 $\mu g/m^3$ × 6 h/days × 3 days exposure to concentrated $PM_{2.5}$	LF ↑, HF ↑, LFHFR ↑
Elder et al. (2007)	Animal experiment in aged, spontaneously hypertensive rats exposed to ultra fine particulate by inhale	1.95–5.62 × $10^5/cm^3$ × 6 h/days × 14 days exposure to vehicle exhaust emissions (median diameter = 15–20 nm)	Normalized HF ↑, LF ↑, HR ↓
Tankersley et al. (2004)	Animal experiment in senescent mice exposure to carbon black by inhale	<200 microgram/m^3 × 3 h/days × 3 days exposure to carbon black	rMSSD ↑, LFHFR ↓, HR ↓

rMSSD: root mean square of successive differences in normal beat intervals, is highly correlated with HF in the biological plausibility; Normalized HF = HF/(TP-VLF), TP: total power, VLF: very low frequency index; SDNN: SD of NN-intervals; ↑: significant increase; ↓: significant decrease

2009). The absence of the association in our study may be the result of the higher HRV levels of the healthy elderly subjects and the lower $PM_{2.5}$ exposure level when the subjects are outdoors. We also noticed the negative estimates of coefficient in model 2 analysis of outdoor $PM_{2.5}$ on HRV ($p > 0.10$). The insignificant associations may be caused by potential impreciseness in the exposure evaluation of outdoor $PM_{2.5}$ conducted on the rooftop of the residential building and the smaller number of outdoor HRV measurements ($n = 735$).

On the other hand, the differing associations in indoor and outdoor environment for the subjects may be caused by the differences in $PM_{2.5}$ concentrations and compositions and the different HRV baseline status. Our study shows the lower HF levels when the subjects are outdoors than indoors, which may be associated with the more exercise in outdoor environment (Arai et al. 1989). The detailed mechanisms still need further studies.

The dysfunction of the cardiac ANS, expressed both by the increased HRV indices (de Bruyne et al. 1999) and decreased HRV indices (Tsuji et al. 1996; Thayer and Lane 2007), are important mechanisms of cardiovascular diseases morbidity and mortality. Stone et al. (1999) have described two possible mechanisms in which $PM_{2.5}$ increases cardiovascular risk by affecting HRV. They suggest that the adverse effects of $PM_{2.5}$ can be mediated either through a sympathetic stress response which leads to the decreased HRV and tachyarrythmias or through a vagal (parasympathetic) response which leads to increased HF, increased HRV, and bradyarrythmias (Stone and Godleski 1999). Increased HRV (especially for the indices representing the parasympathetic activity) are reported to be associated with sinus node dysfunction (Bergfeldt et al. 1995) and the vagal (parasympathetic) response, which may predispose individuals to potentially fatal arrhythmias (Kasanuki et al. 1997) and paroxysmal atrial fibrillation (Bettoni and Zimmermann 2002).

Many previous studies find effects of particles on HRV within hours of exposure (Schwartz et al. 2005; Park et al. 2005), but it is less clear whether $PM_{2.5}$ can exert such an acute effect of several minutes exposure on the autonomic nervous system. The 5-min concurrent and continuous monitoring of exposure and outcome variables in our study is suitable for the transient effects analysis. However, due to the great loss of valid data in the lag effects evaluation,the associations between $PM_{2.5}$ and HRV in the lag effect evaluation cannot be compared directly with the associations between concurrent 5-min $PM_{2.5}$ and 5-min HRV indices. Our study can only provide limited evidence for the lag effects of $PM_{2.5}$ on healthy elderly subjects, which still need further studies. The heterogeneous effects of $PM_{2.5}$ among subjects shown in the subject-specific evaluation may because of the gene polymorphisms (Ren et al. 2010).

Our study had some limitations. Although we had rather stringent inclusive criteria for the study subjects, they were not a strictly randomly selected sample group. In addition, the diary intervals were on a 30-min basis, which may also introduce potential misclassifications. The study was carried out during the Olympic Games in Beijing when the traffic was restricted strictly. The characteristics of the air $PM_{2.5}$ in this period were lower concentrations and fewer traffic-related sources. The potential influences of the changed concentrations and components in the $PM_{2.5}$ on HRV induces need further studies.

Conclusions

In conclusion, our findings provide the evidence that several minutes $PM_{2.5}$ exposure increases HRV of the healthy elderly subjects, which may increase the cardiac risks. Prominent effect of $PM_{2.5}$ on HRV is found when they are indoors, while the effect is not obvious in outdoor environment.

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Conflict of interest All authors declare they have no potential competing financial interest.

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