Original Article

Relationship between Ambient Fine Particles and Ventricular Repolarization Changes and Heart Rate Variability of Elderly People with Heart Disease in Beijing, China*

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Abstract

Objective To explore the effects of particulate matters less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) on heart repolarization/depolarization and heart rate variability (HRV).

Methods We conducted a panel study for elderly subjects with heart disease in Beijing from 2007 to 2008. $PM_{2.5}$ was measured at a fixed station for 20 h continuously each day while electrocardiogram (ECG) indexes of 42 subjects were also recorded repeatedly. Meteorological data was obtained from the China Meteorological Data Sharing Service System. A mixed linear regression model was used to estimate the associations between $PM_{2.5}$ and the ECG indexes. The model was adjusted for age, body mass index, sex, day of the week and meteorology.

Results Significant adverse effects of $PM_{2.5}$ on ECG indexes reflecting HRV were observed statistically and the strongest effect of $PM_{2.5}$ on HRV was on lag 1 day in our study. However, there were no associations between $PM_{2.5}$ and ECG indexes reflecting heart repolarization/depolarization. Additionally, the effects of $PM_{2.5}$ on subjects with hypertension were larger than on the subjects without hypertension.

Conclusion This study showed ambient $PM_{2.5}$ could affect cardiac autonomic function of the elderly people with heart disease, and subjects with hypertension appeared to be more susceptive to the autonomic dysfunction induced by $PM_{2.5}$.

Key words: $PM_{2.5}$; Repolarization; Heart rate variability; Elderly; Panel study

Biomed Environ Sci, 2013; 26(8):629-637 doi: 10.3967/0895-3988.2013.08.001 ISSN:0895-3988

www.besjournal.com(full text) CN: 11-2816/Q

INTRODUCTION

Multiple epidemiological studies have showed that ambient particulate matter (PM) is associated with increased cardiovascular hospital admission, morbidity and mortality in the exposed population[1-6]. Among all people elderly individuals with underlying cardiopulmonary disease are at the greatest risk[7-8]. Although this association has been

*This study was supported by the National Natural Science Foundation of China (Grant No. 20637020).

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Received: April 10, 2013; Accepted: July 8, 2013

well established, the underlying physiological mechanisms are still not fully understood. At present, poor myocardial substrate (current state of the myocardium), myocardial vulnerability and altered cardiac autonomic function (sympathetic activation or/and parasympathetic withdrawal), which are known as the "cardiac death triangle"[9], are believed to be key factors leading to cardiac events[10]. It has been postulated that PM might be a trigger of these factors, especially among vulnerable subjects[10].

Changes in myocardial substrate can be detected by analyzing the features of electrical activity in myocardium using electrocardiogram (ECG) methods such as repolarization/depolarization parameters[9,11-12]. Henneberger et al. (2005)[9] found that repolarization duration in 56 males with ischemic heart disease increased significantly in response to exposure to $PM_{2.5}$ Liao et al. (2010)[13] observed that elevated $PM_{2.5}$ could lead to longer ventricular repolarization but have no immediate impact on ventricular depolarization in samples of nonsmoking adults who lived in communities in central Pennsylvania. However, to date, epidemiologic evidence linking exposure $PM_{2.5}$ to repolarization/depolarization parameters is still limited[11-12].

HRV is a measure of cardiac autonomic function. It has been reported to be a predictor of increased risk of population mortality, myocardial infarction and other cardiovascular diseases[14-17]. Evidence for a positive association between PM and alterations in HRV have been illustrated[18-19], however, some studies have also observed negative[20-23] or zero[24-25] association between ambient $PM_{2.5}$ level and HRV. The inconsistency of these findings highlights the need for further exploration to gain a better understanding of the relationship between ambient $PM_{2.5}$ and HRV in exposed populations.

In this study, we examined the influence of ambient $PM_{2.5}$ on myocardial substrate and cardiac autonomic function through a panel study. The study population consisted of elderly individuals from Beijing who suffered from heart disease.

MATERIALS AND METHODS

Study Subjects

The study was conducted in Beijing, China, from July 2007 to September 2008. The study protocol was approved by the Ethics Committee of Peking University Health Science Center. 90 elderly patients with heart disease (age ≥54 years were recruited as a study panel. The subjects were from a community located next to the campus of Peking University Health Science Center near the North Fourth Ring Road in Haidian district, Beijing. Before entering the study, all subjects provided written informed consent and completed a baseline questionnaire which included questions on the participant's demographics, smoking status, history of heart disease or other diseases as well as medication use. Of the 90 recruited subjects, 42 met the criteria for ECG analysis. The inclusion criteria for the panel were: 1) patients with clinically proven coronary artery disease; 2) patients with a history of clinically diagnosed angina; 3) patients with clinically confirmed myocardial ischemia symptoms for at least 1 year before recruitment, such as ST–segment abnormal elevation and depression, T-wave towering or inversion, and Q-T interval prolongation detected by treadmill, regular resting or ambulatory electrocardiographic examination. The exclusion criteria included: current smokers; patients with pacemaker, bundle-branch block or type I diabetes; patients with recent myocardial infarction, bypass surgery or balloon dilatation (less than 3 months ago); and patients on anticoagulant therapy.

Data of $PM_{2.5}$ and Weather

The study included ten monitoring periods, three in 2007 (visit 1(V1), 01-09 July 2007; V2, 15-20 August 2007; V3, 21-25 August 2007) and seven in 2008 (V4, 15-18 January 2008; V5, 18-25 April 2008; V6, 20-26 June 2008; V7, 4-11 July 2008; V8, 6-15 August 2008; V9, 16-29 August 2008; V10, 15-19 September 2008). In each monitoring period, the daily mass concentration of ambient $PM_{2.5}$ was monitored from 10 a.m. of one day to 6 a.m. of the next day (20 h) continuously using a Wuhan Tianhong TH150C Sampler and PALL Quartz filter membrane. The monitoring devices were on the sixth floor of a building located 700 m from the community. Daily air temperature and relative humidity were obtained from the China Meteorological Data Sharing Service System. Dew point temperature (DT) was computed applying the following equation[26]:

Dew point temperature=[(0.66077-EW)×237.3]/(EW-8.16077)

Where EW=0.66077+[7.5×T/(237.3+T)]+log10(RH)-2; T=air temperature (°C) and RH=relative humidity (%).

ECG Measurements

Subjects visited the Campus Hospital of Peking University Health Science Center between 8 a.m. and 10 a.m. on the last day of each air pollutant monitoring period. They completed a follow-up questionnaire and had a physical examination including height, weight and ECG measurements. The ECG monitoring protocol included 90-second 12-lead electrocardiogram and 5-min HRV, which were recorded and analyzed by an ECG comprehensive analysis system (ECGLAB 3.0, produced by Beijing MeiGaoYi Software technology Co. and the United States DM Software Company). Subjects' skin was shaved (if necessary) and carefully cleaned with 75% alcohol to ensure proper lead contact. ECGs were recorded digitally with the subject lying in the supine position. All ECG records were reviewed in order to avoid noise and artifacts. Ectopic beats were excluded in the process.

Finally, mean heart rate (HR), the QT interval duration corrected for heart rate (QTc) and the QRS complex were obtained and used as the indexes representing 12-lead electrocardiogram in the analysis. The entire process of depolarization and repolarization in the ventricle can be assessed by QTc. The increase in QTc represents an increment in asynchronism of repolarization and electrical instability in the ventricle. The QRS complex reflects the ventricular depolarization process.

Through the use of 5-min HRV measurements, time-domain, frequency-domain, and geometric HRV variables were examined. Nine indexes of HRV were obtained. Time-domain variables included: a) standard deviation of the NN interval (SDNN), estimating overall HRV; b) the square root of the mean of the sum of squares of differences between adjacent NN intervals (r-MSSD), estimating short-term components of HRV and as a sensitive indicator of vagal tone; c) standard deviation of differences between adjacent NN intervals (SDSD) reflecting parasympathetic activity. Five frequency-domain variables included total power (TP), high frequency (HF) power (0.15-0.4 Hz), low frequency (LF) power (0.04-0.15 Hz), very low frequency (VLF) power (0.01-0.04 Hz), and the ratio of LF and HF (LF/HF). TP is an indicator of overall HRV. HF components provide an index of parasympathetic activity, LF components are considered to encompass both sympathetic and parasympathetic activity, while VLF components mainly reflect sympathetic activity. LF/HF is used to reflect the balance of sympathetic activity and parasympathetic activity; increased LF/HF indicates high sympathetic activity. Geometric methods are used to analyze the sample density histogram of R-R interval durations. The triangular index (TRII) is the used geometric HRV variable, providing an estimate of overall HRV.

Statistical Analysis

Data were analyzed using SAS statistical package (version 9.2; SAS Institute Inc., Cary, NC, USA). HR, QRS complex and HRV variables were log transformed prior to analysis. We applied mixed linear regression models to estimate the effects of $PM_{2.5}$ on 12-lead ECG and HRV. A random intercept for each subject, as well as the fixed covariates such as gender, age, body mass index (BMI), day of the week and dew-point temperature (DT) were included in the models. DT was calculated with air temperature and relative humidity as an overall weather indicator, then was controlled as linear and quadratic terms as the association between weather variables and HR as well as HRV variables was reported to be nonlinear[27]. Model-fitting was based on the Akaike Information Criterion (AIC). According to minimal AIC, the autoregressive-1 (AR-1) was chosen as covariance structure in the model analysis.

We examined the impacts of lag 0, lag 1, and lag 2 $PM_{2.5}$ on the outcome variables. Lag 0 $PM_{2.5}$ was defined as the $PM_{2.5}$ concentration measured in the 20 h period prior to the ECG measurement; lag 1 $PM_{2.5}$ was defined as the 20 h of $PM_{2.5}$ monitoring prior to lag 0 measurement; similarly, lag 2 was defined as the 20 h of $PM_{2.5}$ monitoring prior to lag 1. As HRV is inversely associated with HR[28], the other model also included HR as a confounder. For effect modification, we ran separate regressions stratified by hypertension variable.

The effect estimates were given together with 95% confidence intervals (CI) based on per 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration. We considered $P<0.05$ as statistically significant and $P<0.10$ as borderline significant.

RESULTS

Table 1 presents the descriptive statistics of demographic and medical data of the subjects. Measurements were obtained from 42 participants (14 men and 28 women) with a mean age of 65 years old (range: 54~78 years) and a mean BMI of 25.11 kg/m^2 (range: 15.62~33.46 kg/m^2). Two-thirds of the participants were retired. All participants were non-smokers during the study period, but 24% of

them had experience of passive smoking. Every subject had one or more cardiac conditions. 38% of the subjects had angina, 57% had arrhythmia, 71% had cardiac insufficiency and 26% had previously diagnosed coronary disease. Additionally, 69% of the participants had hypertension and 19% had diabetes. In total, 372 observations were obtained.

Table 2 presents the descriptive statistics of ECG measurements data. Table 3 presents the $PM_{2.5}$ concentration and weather data in each motoring period. During the whole study period, the average $PM_{2.5}$ concentration was 80.6 μg/m^3, which exceeded the standard annual average concentration (35.0 μg/m^3) specified in the China Ambient Air Quality Standards issued in February 2012[29]. However, during V8-V10 period, which was within the Olympic and Paralympic air quality intervention period, the average $PM_{2.5}$ concentration was down to 47.0 μg/m^3, almost half lower than 84.9 μg/m^3 in August 2007 (V2-V3 period).

Table 4 shows the estimated effects of $PM_{2.5}$ on the 90-second 12-lead ECG indexes together with 95% CI at different lags. No statistically significant associations were found for the three indexes with per 10 μg/m^3 increase in lag 0 to lag 2 $PM_{2.5}$.

Table 5 shows the estimated effects of per 10 μg/m^3 increase in $PM_{2.5}$ on 5-min HRV at different lags. The associations between lag 1 $PM_{2.5}$ and SDNN as well as SDSD out of the three time-domain HRV variables were only borderline significant after including mean heart rate in the model. Consistent negative associations were found between $PM_{2.5}$ at all lags and all the frequency-domain HRV indexes

Table 1. The Characteristics of the 42 Participants

Items	$\bar{x} \pm s$ or *n* (%)
Age (years)	65±6
BMI (kg/m^2)	25.11±3.38
Sex	
Male	14 (33%)
Female	28 (67%)
Education	
Primary school or below	3 (7%)
Junior high school	7 (17%)
Senior high school	4 (10%)
College	8 (19%)
University or above	19 (45%)
Occupational status	
Work full time or part time	12 (28%)
Retired	28 (67%)
Unemployed	2 (5%)
Smoking	
Never-smoking	35 (83%)
Ex-smoking	7 (17%)
Passive-smoking	10 (24%)
Heart disease	
Angina	16 (38%)
Arrhythmia	24 (57%)
Cardiac insufficiency	30 (71%)
Coronary disease	11 (26%)
Other diseases	
Hypertension	29 (69%)
Diabetes	8 (19%)

Note. Mean: $\bar{x}$; Standard deviation: *s*; Number: *n*.

Table 2. Descriptive Statistics of Variables from ECG Measurements

Variable	Number of Measurements	$\bar{x} \pm s$	25th Percentile	*M*	75th Percentile
HR (bpm)	369	66.1±10.8	59	65	72
QTC (msec)	372	445.7±33.6	425	443	462
QRS (msec)	372	103.4±20.6	92	100	110
SDNN (msec)	367	97.8±317.4	22	36	62
r-MSSD (msec)	368	110.7±348.4	16	32	72
SDSD (msec)	368	97.8±317.8	22	36	62
TP (msec^2)	361	930.6±1151.6	333.9	566.5	1086
VLF (msec^2)	361	472.2±659.7	160.6	286.8	534.5
LF (msec^2)	361	198.5±276.5	52.4	96.8	183.9
HF (msec^2)	361	227.1±393.1	46.3	99.4	193.3
LF/HF	359	1.6±1.6	0.6	1.1	2.1
TRII	370	7.7±3.7	5.7	6.9	8.6

Note. Mean: $\bar{x}$; Standard deviation: *s*; Median: *M*.

Table 3. Descriptive Statistics ($\overline{x} \pm s$) of $PM_{2.5}$ and Weather Data During Each Monitoring Period (V1-V10)

Monitoring Period	$PM_{2.5}$ ($\mu g/m^3$)	Air Temperature (℃)	Relative Humidity (%)
V1	114.9±36.9	27.1±1.4	69.8±7.4
V2	103.2±19.8	27.5±0.9	72.3±6.3
V3	62.8±11.9	28.6±1.0	53.6±4.8
V4	182.6±34.0	-5.3±0.9	50.8±20.1
V5	86.6±32.9	15.2±3.2	54.4±22.4
V6	93.5±24.9	25.3±2.3	72.1±8.6
V7	89.3±28.2	26.9±1.8	73.0±8.9
V8	49.8±40.4	26.9±2.2	73.6±7.1
V9	41.8±30.5	25.1±1.8	68.3±9.7
V10	56.0±13.1	22.6±1.1	73.2±8.2

Note. V1, 01-09 July 2007; V2, 15-20 August 2007; V3, 21-25 August 2007; V4, 15-18 January 2008; V5, 18-25 April 2008; V6, 20-26 June 2008; V7, 4-11 July 2008; V8, 6-15 August 2008; V9, 16-29 August 2008; V10, 15-19 September 2008.

Table 4. Estimated Effects of per 10 $\mu g/m^3$ Increase in $PM_{2.5}$ on 90-second 12-lead ECG Indexes with 95% CI at Different Lags

	HR (%)	QRS (%)	QTc (msec)
Lag 0	0.149 (-0.16%~0.46%)	-0.217 (-0.53%~0.10%)	0.484 (-0.213~1.181)
Lag 1	-0.239 (-0.60%~0.13%)	-0.154 (-0.52%~0.22%)	0.016 (-0.814~0.847)
Lag 2	-0.195 (-0.45%~0.06%)	-0.090 (-0.35%~0.17%)	-0.032 (-0.618~0.555)

Note. This model adjusted linear covariates (age, sex, BMI, day of the week and Td) and non-linear covariate (quadric terms of DT).

except for LF/HF. However, the lag 0 $PM_{2.5}$ effects were almost all without statistical significance. The most significant and largest effects on the four frequency-domain HRV indexes were observed at lag 1 $PM_{2.5}$. Among which, HF had the largest decrease of 3.83% (95% CI, 1.36% to 6.24%), when lag 1 $PM_{2.5}$ concentration increased 10 $\mu g/m^3$. In contrast to the four aforementioned frequency-domain HRV indexes, only insignificant (one borderline significant) positive associations between $PM_{2.5}$ and LF/HF were detected. The geometric HRV variable TRII showed no significant association with $PM_{2.5}$ at all lags.

Table 5. Estimated Effects of per 10 $\mu g/m^3$ Increase in $PM_{2.5}$ on 5-min HRV with 95% CI at Different Lags

	Lag 0	Lag 1	Lag 2
SDNN(%)			
Model 1[a]	-0.74 (-2.31,0.86)	-1.54 (-3.45,0.41)	-0.95 (-2.31,0.43)
Model 2[b]	-0.69 (-2.28,0.93)	-1.79 (-3.71,0.18)*	-1.13 (-2.50,0.26)
r-MSSD(%)			
Model 1	-1.62 (-3.57,0.36)	-1.70 (-4.11,0.77)	-0.89 (-2.61,0.85)
Model 2	-1.49 (-3.46,0.52)	-1.94 (-4.36,0.53)	-1.09 (-2.81,0.67)
SDSD(%)			
Model 1	-0.85 (-2.40,0.74)	-1.60 (-3.49,0.35)	-0.96 (-2.31,0.41)
Model 2	-0.80 (-2.38,0.80)	-1.84 (-3.75,0.11)*	-1.15 (-2.51,0.23)
TP(%)			
Model 1	-1.10 (-2.48,0.29)	-3.19 (-4.84,-1.51)**	-1.90 (-3.08,-0.69)**
Model 2	-1.05 (-2.43,0.36)	-3.18 (-4.84,-1.48)#	-1.88 (-3.07,-0.67)#
VLF(%)			
Model 1	-0.40 (-2.07,1.30)	-2.68 (-4.66,-0.65)**	-1.79 (-3.21,-0.35)**
Model 2	-0.53 (-2.20,1.17)	-2.90 (-4.87,-0.90)#	-1.95 (-3.36,-0.52)#
LF(%)			
Model 1	-0.18 (-1.99,1.66)	-2.07 (-4.21,0.13)*	-1.28 (-2.81,0.28)
Model 2	-0.20 (-2.02,1.66)	-2.07 (-4.23,0.15)*	-1.26 (-2.81,0.31)
HF(%)			
Model 1	-2.65 (-4.69,-0.58)**	-3.83 (-6.24,-1.36)#	-2.13 (-3.88,-0.35)**
Model 2	-2.33 (-4.35,-0.27)**	-3.53 (-5.94,-1.06)#	-1.92 (-3.67,-0.15)**
LF/HF(%)			
Model 1	1.47 (-0.40,3.37)	1.94 (-0.33,4.26)*	1.13 (-0.47,2.75)
Model 2	1.25 (-0.60,3.14)	1.76 (-0.49,4.06)	1.01 (-0.57,2.62)
TRII(%)			
Model 1	-0.44 (-1.13,0.24)	-0.61 (-1.45,0.25)	-0.28 (-0.88,0.32)
Model 2	-0.45 (-1.14,-0.25)	-0.70 (-1.55,0.17)	-0.35 (-0.95,0.26)

Note. *$P<0.10$, **$P<0.05$, #$P<0.01$. [a]Model 1 adjusted linear covariates (age, sex, BMI, day of the week , and DT) and non-linear covariate (quadric terms of DT). [b]Model 2 adjusted linear covariates (age, sex, BMI, day of the week , logHR, and DT) and non-linear covariate (quadric terms of DT).

With or without adjusting mean heart rate in the models only slightly affected the effect estimates of $PM_{2.5}$ and the changes of the estimates were in different directions. For example, when adjusting mean heart rate, per 10 μg/m^3 increase in lag 2 $PM_{2.5}$ was associated with 1.95% decrease in VLF instead of 1.79%, and the estimate became more significant. In contrast, the effects of lag 1 and lag 2 $PM_{2.5}$ on HF were smaller by 0.30% and 0.21%, respectively, after adjusting mean heart rate in the model.

Table 6 shows the estimated effects of per 10 μg/m^3 increase in lag 1 $PM_{2.5}$ on 5-min HRV stratified by hypertension. For people with hypertension, the effects of lag 1 $PM_{2.5}$ on r-MSSD, HF and LF/HF were weaker; while the effects of $PM_{2.5}$ on other HRV indexes were stronger.

Table 6. Estimated Percentage Change with 95% CI in 5-min HRV Associated with per 10 μg/m^3 Increase in Lag 1 $PM_{2.5}$ Stratified by Hypertension

	Hypertension	
	Without (13 subjects)	With (29 subjects)
SDNN(%)	-1.65 (-4.59,1.39)	-1.92 (-4.32,0.54)
r-MSSD(%)	-2.55 (-5.69,0.99)	-1.81 (-4.86,1.34)
SDSD(%)	-1.81 (-4.65,1.13)	-1.94 (-4.33,0.52)
TP(%)	-2.44 (-5.11,-0.31)*	-3.07 (-5.16,-0.93)**
VLF(%)	-1.08 (-4.45,2.42)	-3.49 (-5.92,-1.00)**
LF(%)	-0.52 (-4.48,3.60)	-2.31 (-4.90,0.35)*
HF(%)	-3.88 (-8.01,0.44)*	-2.85 (-5.79,0.19)*
LF/HF(%)	2.46 (-1.34,6.41)	1.22 (-1.53,4.05)
TRII(%)	-0.63 (-1.79,0.54)	-0.73 (-1.83,0.39)

Note. $^*P$<0.10, $^{**}P$<0.05. This model adjusted linear covariates (age, sex, BMI, day of the week, logHR and DT) and non-linear covariate (quadric terms of DT).

DISCUSSION

This panel study showed that increased level of $PM_{2.5}$ was insignificantly associated with changes in HR, QRS, or QTc. For HRV metrics, only statistically robust negative associations between $PM_{2.5}$ and the frequency-domain indexes of HRV were observed, with the strongest effects detected at lag 1.

The QRS complex duration can provide insight into the changes in the ventricular depolarization process, which affects myocardial substrate and increases individuals' propensities toward arrhythmogenic response[10]. We found insignificant association between $PM_{2.5}$ and QRS. It is possible that $PM_{2.5}$ did not affect the myocardial depolarization or the changes induced by $PM_{2.5}$ were not large enough and thus undetectable by monitoring QRS complex in our study with a small number of subjects. QTc is clinically widely used to quantify baseline repolarization abnormalities. Prolonged repolarization is associated with cardiovascular morbidity and mortality[30]. $PM_{2.5}$ was previously found to be associated with an increase in QTc with 0-5 h exposure, which reflected its short-term influence on the myocardium, potentially operating on potassium or calcium ion channels[9]. However, our findings indicated no significant association between QTc and $PM_{2.5}$, which might be due to the longer $PM_{2.5}$ exposure of the subjects in this study. To summarize, in our study we did not find evidence about $PM_{2.5}$ affecting myocardial substrate, which was assessed by depolarization or repolarization parameters.

In our study, the effects of $PM_{2.5}$ on frequency-domain HRV indexes were observed to be more pronounced than the effects on time-domain indexes. This may support the point raised before, that the frequency-domain measurements could describe the autonomic contribution to cardiac oscillation more accurately than the time-domain analyses did in short-time HRV recordings[25,31].

Previous epidemiological studies have reported heterogeneous associations between HRV indexes and particulate air pollution in elderly subjects[19,25,27-28,31-33]. SDNN, TP and TRII are all markers of estimating overall HRV. We found no significant effect of $PM_{2.5}$ on decreased TP at lag 0; this is in agreement with a previous study in California[28]. However, increased $PM_{2.5}$ significantly decreased TP (indicating a reduction in HRV) at lag 1 and lag 2, suggesting a reduction in HRV. R-MSSD and HF are both used to reflect parasympathetic influences. Our study observed that increase in $PM_{2.5}$ led to the decrease in HF (representing decrement of parasympathetic tone); this is in agreement with some previous studies[21-23,32,34]. LF reflects modulation of sympathetic and parasympathetic tone but with stronger sympathetic influence. Our result suggested that increase in $PM_{2.5}$ was not significantly associated with decrease in LF (indicating decline in sympathetic influence) at lag 0, and just borderline significantly associated with decrease in LF at lag 1 and lag 2. In contrast, a

previous study conducted on 36 elderly individuals measuring 30-min ECG measurements reported a significantly inverse association between LF and lag 0 $PM_{2.5}$[22]. LF/HF ratio (sympathovagal tone) is used to evaluate the relative contribution of sympathetic and parasympathetic tones in modulating cardiac rhythm. Our study and several previous studies all found insignificant associations of LF/HF with lag 0 $PM_{2.5}$[31,33-34]. In contrast, Park et al.[23] examined HRV in a longitudinal study consisting of 497 elderly subjects and reported a significant increase in LF/HF with 24 h $PM_{2.5}$ exposure. VLF mainly reflects the sympathetic activity. This study observed significant inverse effects of $PM_{2.5}$ on VLF (decreased VLF reflecting decline of the sympathetic tone) at lag 1 and lag 2. In general, our results demonstrated that increased $PM_{2.5}$ concentration was associated with greater reduction in parasympathetic activity than in sympathetic tone, which leads to decreased HRV.

We found the strongest effects of $PM_{2.5}$ on all HRV indexes at lag 1. Park et al.[23] also observed that 48-h moving average $PM_{2.5}$ had the strongest effect on the decrement in HRV. In contrast, several epidemiologic studies have shown that the strongest effect of $PM_{2.5}$ occurred within a few hours before the HRV measures. Moreover, they have shown that there was no association between $PM_{2.5}$ and HRV at lags longer than 24 h[27-28,35]. Some other investigators have observed that the 24-h average PM had somewhat stronger effect on HRV when they used 24-h average PM concentration as well as 4-h or more than 24-h PM concentration as exposure terms[32,36]. The possible underlying mechanism explaining the same-day response could be the direct PM effects by stimulating the vagal receptors in the lung. While the strongest effect occurring at lag 1 (prolonged response) may be explained by the indirect pathway through systemic inflammation or oxidative stress[19].

HR is regulated by both sympathetic and parasympathetic tone. An increase in sympathetic activity speeds up the heart rate, whereas an increase in parasympathetic response slows down the heart rate. The associations between $PM_{2.5}$ and HR were unidentified. Pope et al.[32] and Gold et al.[27] reported a significant association between decreased HR and increased $PM_{2.5}$ in elderly subjects. On the other hand, Luttmann-Gibson et al.[22] found HR increased by 1.1% (95% CI: 0.2% to 2.1%) in association with a 13.4 $\mu g/m^3$ increase in 24-h $PM_{2.5}$. However, there was no significant association between HR and $PM_{2.5}$ observed in the present study.

Direct quantitative comparison between results is impossible given the differences in chosen exposure metrics and study designs. The qualitative discrepancy of the associations between $PM_{2.5}$ and HRV/HR found by different studies may be attributable to the used PM concentration terms (e.g. daily or hourly concentration), the various compositions of PM in different areas, the length of HRV recordings, and/or the different disease conditions of study populations.

When $PM_{2.5}$ level increased, we observed a larger decrease in HRV among subjects with hypertension compared to subjects without hypertension. The association between hypertension and lower baseline HRV and endothelium dysfunction may be a potential explanation. Several previous studies also reported that hypertension could modify the effects of air pollution on HRV[23,34,37].

The limitation of this study must be acknowledged. Firstly, considerable exposure misclassification might exist as we did not conduct personal exposure monitoring. The exposure evaluation was based on data only from a single monitoring station and also not made by the time-weighted model, therefore the ambient exposure conditions for the various participants may only be approximate. This could complicate the identification of the effects of $PM_{2.5}$ on ECG parameters[38]. Secondly, applying certain medication may modify the association between $PM_{2.5}$ and HRV[22]. In this study, we collected information about medication use of the subjects and put this variable in the regression models to control potential confounding. However, the missing percentage of this data was high (37.4%). So this potential confounding might not be fully controlled and may bias the analysis toward the null. Thirdly, subject selection that was from campus residents, probably including more retired academics and spouses, produced a much higher level of university educated participants (45%), which may limit the results to apply to other population. Besides, the season was not placed in the final model. Because the measures for the panel was not balanced on the sample size, where it was larger in summer and smaller in the other season. When adjusting the variable, we found model fitting got worse. Finally, we did not control other unmeasured pollutants in the statistical analysis which could be related with the observed associations.

CONCLUSION

Our study results showed that elevated $PM_{2.5}$ induced decreased HRV in elderly people with heart disease at lag 0 to lag 2. It did not affect HR, QRS complex and QTc. The effects of $PM_{2.5}$ on HRV were strengthened by hypertension.

Our findings provide additional evidence for the statements that $PM_{2.5}$ can affect cardiac autonomic function in elderly individuals with heart disease and people with hypertension appear to be more susceptive to autonomic dysfunction induced by $PM_{2.5}$. The cardiac autonomic dysfunction is a major cause of cardiac death. In contrast, our findings cannot provide evidence about the influence of $PM_{2.5}$ on myocardial substrate.

ACKNOWLEDGEMENT

The authors thank all the subjects for participating the study, and Dr. Dane Westerdahl from Cornell University, USA for his good advice about improving this manuscript.

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