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Acute Effects of Fine Particulate Air Pollution on Cardiac Electrophysiology

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1. Introduction

Numerous epidemiological studies have demonstrated a consistent link between particulate air pollution, especially fine particulate matter with aerodynamic diameter $< 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$), and increased cardiopulmonary morbidity and mortality (1-5). The mechanisms responsible for such an association have been the focus of recent environmental health studies. The most promising and frequently studied mechanism is PM related effects on cardiac autonomic modulation (6-10). In a study specifically designed to investigate the time course of PM on cardiac autonomic modulation, Cavallari et al. reported an early and a later phase response, with the early effects at 2 hours and delayed effects at 9-13 hours after exposure (11). Since cardiac autonomic modulation regulates important cardiac electrophysiological activities, other electrophysiological parameters have been proposed as important markers of electric activity disturbances associated with PM. These markers include ventricular repolarization, ischemic potential, arrhythmia, and other waveform changes. For instance, it was reported (12-14) that air pollution is associated with severe arrhythmia in patients with implantable cardioverter defibrillators (ICDs). Recently, it was reported that elevated GIS-estimated ambient $\text{PM}_{2.5}$ exposures one day prior to the ECG measurement were associated with increased odds of PVC in women enrolled in the Women's Health Initiative (WHI) clinical trials study (15). However, very little is known about PM effects on various cardiac electrophysiological parameters from a study specifically designed to examine the individual-level exposures to $\text{PM}_{2.5}$ and all ECG-based parameters.

We therefore designed the Air Pollution and Cardiac Risk and its Time Course (APACR) study to investigate the effects and time course of individual-level exposures to $\text{PM}_{2.5}$ on various cardiac electrophysiological parameters. The individual findings on each of the electrophysiological parameters have been reported elsewhere (7;16-19). This chapter summarizes those major findings and presents the overall findings indicating various time-courses from those publications.

2. Materials and methods

2.1 Population

The APACR study successfully examined 106 individuals, with a response rate of approximately 75%. The study was designed as a 24-hour continuous real-time monitoring of PM_{2.5} exposures and cardiac electrophysiological parameters, with the blood samples drawn from the beginning and end of 24 hours to obtain measures of the blood markers (7;16). Briefly, all study participants were recruited from communities in central Pennsylvania, primarily from the Harrisburg metropolitan area. The inclusion criteria for the study included nonsmoking adults ≥ 45 years old who had not been diagnosed with severe cardiac problems (defined as diagnosed valvular heart disease, congenital heart disease, acute myocardial infarction or stroke within 6 months, or congestive heart failure). Approximately 75% of the individuals who were contacted and who met our inclusion criteria were enrolled in the APACR study. Our targeted sample size was 100 individuals, and we enrolled and examined 106 individuals for the APACR study. Individual-level PM_{2.5} and Holter ECG monitoring were initiated between 0800 and 1000 hours on the first day, immediately after participants were administered a standardized questionnaire, underwent a brief physical examination, and a fasting blood draw by a trained and certified research nurse. The next morning, the participants returned to remove the monitors and had their second blood draw. The APACR study has maintained approval by the Penn State University College of Medicine institutional review board. All participants gave written informed consent prior to their participation in the study.

2.2 Personal PM_{2.5} exposures

The APACR study used a personal PM_{2.5} DataRam (pDR, model 1200, Thermo Scientific, Boston, MA) for real-time 24-hour personal PM_{2.5} exposure assessment. Details of the exposure assessment (7;16) and of the instrument's performance have been reported elsewhere (20-23). Real-time PM_{2.5} concentrations were recorded at 1-minute intervals and averaged over 30-minute segments, beginning on the hour or half hour. Therefore, we calculated, on a 30-minute basis, the corresponding time-of-the-day specific average exposure to PM_{2.5} for each participant as a time-dependent repeated measures over a 24-hour period. Thus, each participant contributed 48 exposure data points.

2.3 Electrophysiological variables

We used the high sampling rate (1000 Hz) 12-lead Hscribe Holter System (Mortara Instrument, Inc.) for 24-hour Holter beat-to-beat ECG data collection. This high sampling rate Holter system is available for research use only. The high sampling rate significantly increases the resolution and enhances the accurate capture of fiducial point and various wave form measures. The ECG data were scanned to a designated computer for offline processing, using specialized software by an experienced investigator. One experienced investigator followed established protocols to identify machine scanned errors, to verify the Holter identified, and to identify and label additional electronic artifacts and arrhythmic beats in the ECG recording. The reader adjudicated files are saved and used for the calculation of the following five ECG variable categories: the heart rate variability (HRV), ectopy, ventricular repolarization, potential ischemia, and P-wave related measures. All variables were calculated on a 30-minute basis. Thus, they were treated as time-of-the-day specific repeated measures over a 24-hour period. Each participant contributed 48 dependent variable data points.

2.4 HRV variables

We used the above mentioned “reader adjudicated” beat-to-beat ECG for HRV analysis. From the “reader adjudicated” data, we eliminated artifacts and other arrhythmic beats, and only retained normal R to R intervals. We then performed time and frequency domain HRV analysis [Fast Fourier Transformation (FFT)] using the HRV Analysis System (Department of Physics, University of Kuopio, Finland). All calculations were based on current recommendations (24). Briefly, the adjacent RR interval data were interpolated using a piecewise cubic spline approach, with a 2 Hz sampling rate. The FFT was performed on the equidistantly interpolated RR time series. We used a second order polynomial model to remove the slow non-stationary trends of the HRV signal. The following HRV indices were calculated as measures of CAM: standard deviation of all RR intervals (SDNN, ms), square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD, ms), power in the high frequency range (0.15-0.40 Hz, HF), power in the low frequency range (0.04-0.15 Hz, LF), and the LF/HF ratio.

2.5 Arrhythmia frequency

We calculated the frequency of ventricular and supraventricular ectopy. No participant had other less frequent arrhythmic beats, such as atrial fibrillation/flutter and supraventricular and ventricular tachycardia in our study period.

2.6 Ventricular repolarization

We calculated QT Prolongation Index (QTI, %) as a primary measure of ventricular repolarization. The duration of ventricular repolarization is often estimated by Bazett’s heart rate-corrected QT interval (QT_c) (25). Although QT_c and QTI (26) are strongly correlated ($r = 0.96$), QTI is less rate-sensitive (26;27) and has a higher repeatability than QT_c (28;29). We focused on QTI, but also reported other HR-corrected QT indices are also available for analysis.

2.7 P wave related measures

The following P-wave based atrial fibrillation/flutter (AF) predictors were calculated from the normal heart beats:

- P wave duration (ms), as the time between the first “onset” and last “offset” deflection from the isoelectro line.
- PR duration (ms), as the time between the first onset deflection of the P and R wave, (the latter representing the onset of ventricular depolarization), with longer PR duration the higher risk of AF.
- P wave complexity (unitless), as the average ratio of the second to the first eigenvalue, the value of which reflects the relative complexity of atrial depolarization (30), with more complexity in the atrial depolarization indicating the higher risk of AF.

2.8 ST-height

The calculated ST-height included beat-to-beat ST-height from 10 leads (inferior leads II, III, and aVF; lateral leads I, V5, and V6; septal leads V1 and V2; and anterior leads V3 and V4), defined as the distance between the J point, and 60 ms after the J point. We then calculated on a 30-minute basis the average ST-height for each lead. Therefore, the ST-height measures are treated as repeated outcome measures, and each individual contributed 48 data points for each of the 10 leads.

2.9 Other individual-level covariables

A standardized questionnaire was used to collect the following individual-level information: (a) demographic variables, including age, race, sex, and highest education level; (b) medication uses, including anti-anginal medication, anti-hypertensive medication, and anti-diabetic medication; and (c) physician diagnosed chronic disease history, including CVD (including revascularization procedures and myocardial infarction), hypertension, and diabetes. The averages of the 2nd and 3rd measures of seated systolic and diastolic blood pressures on Day-1 were used to represent a participant's blood pressure levels. Day-1 fasting glucose was measured by the GCRC central laboratory. CVD was defined by anti-anginal medication use or a history of CVD. Hypertension was defined by anti-hypertensive medication use, physician diagnosed hypertension, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mm Hg. Diabetes was defined by anti-diabetic medication use, physician diagnosed diabetes, or fasting glucose >126 mg/dl. Body mass index (BMI) was defined as the ratio of weight to height squared (BMI, kg/m²).

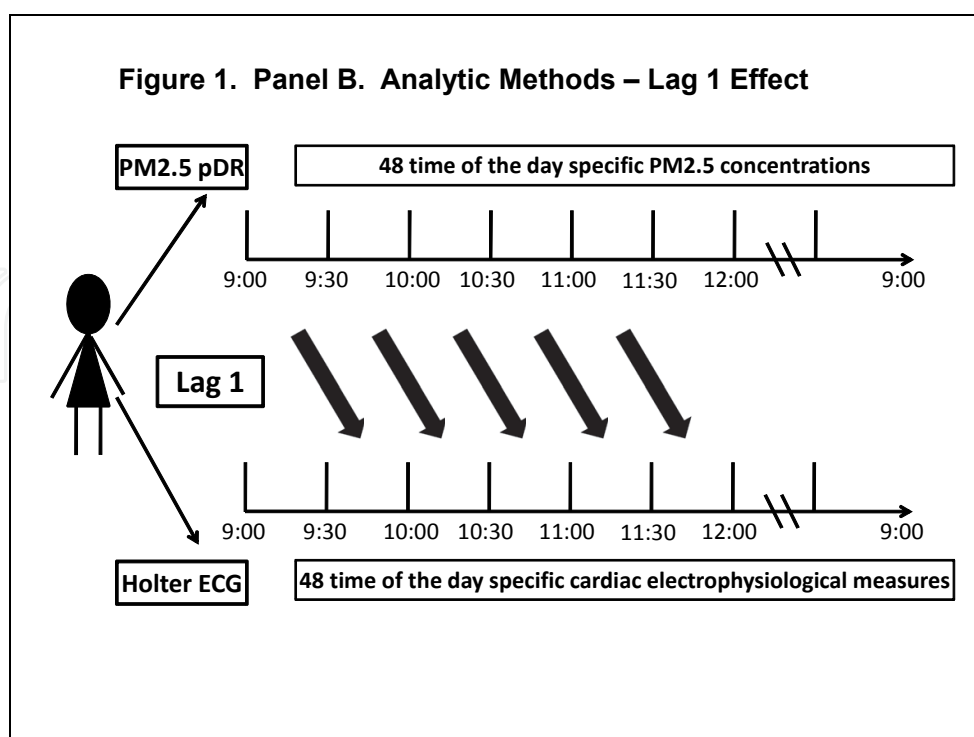
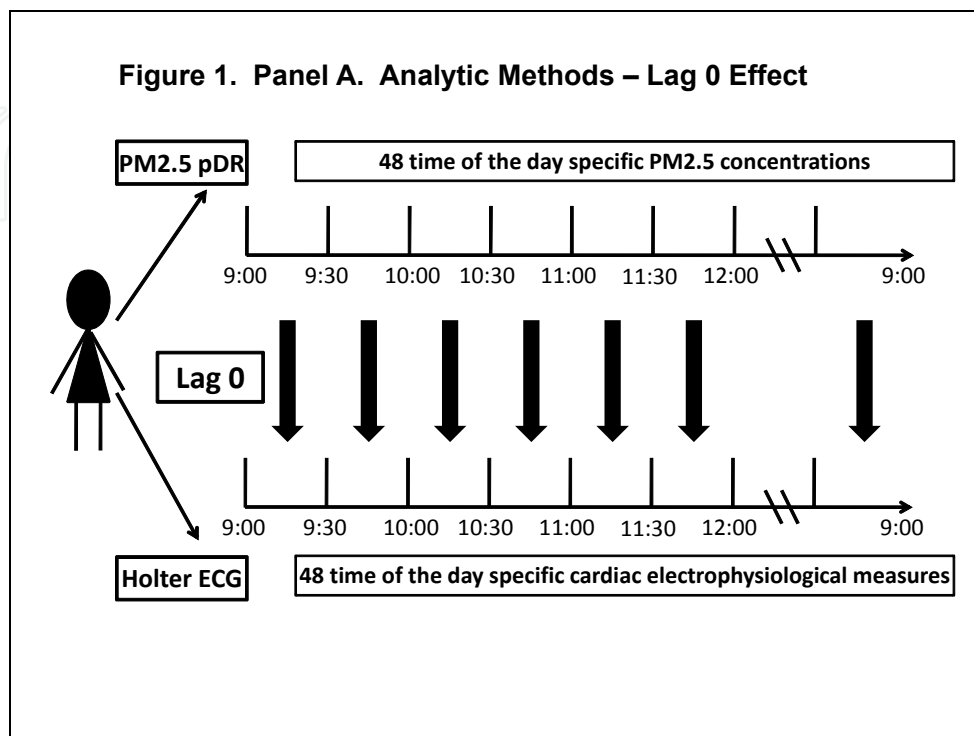
2.10 Weather variables

We obtained real-time temperature and relative humidity using the HOBO H8 logger (Onset Computer Corporation, Bourne, MA), directly fixed on top of the container housing the PM_{2.5} monitor. The real-time temperature and relative humidity were recorded at 1-minute intervals and averaged over 30-minute segments corresponding to the time segments during which PM_{2.5} and ECG variables were measured. The weather variables were treated as repeated measures, and each individual contributed 48 data points for each.

3. Statistical analysis

In the APACR study, the individual-level, real-time PM_{2.5} exposure and cardiac electrophysiology outcomes were measured over a 24 hour period. The PM_{2.5} and outcome summaries were constructed every 30 minutes for all participants, producing 48 repeated measures. We extended the distributed lag model (31-33) for statistical analyses. Specifically, we constructed polynomial distributed lag models, which enable us to provide interpretation of the cumulative effects of the lags included in the model, as well as individual lag effects. In a lag distributed model, all lags to be analyzed are entered into a single model. The coefficients from the lags are the respective effects from the individual lags. The cumulative effect of all lags is the weighted average of individual effects. In contrast, the moving average model takes the average of intended lag exposures and relates the average with the outcome measured a given total lag units ago. Since PM_{2.5} exposures and ECG outcome data were assessed in parallel over 48 lags (24 hours), we decided *a priori* to model no more than 10 lags, which allowed us to fit the distributed lag models using at least 80% of the data. For continuous outcomes (e.g., heart rate-corrected QT intervals) we used a linear mixed-effects models framework (34). For count (e.g., PVC count, total ectopy count) data we used negative binomial regression model (35) and generalized estimating equations (GEE) framework (36). Details of these models have been published (7;16-19). We systematically started from the largest number of lags (lag 0-10), and reduced the total number of individual lags by back-eliminating the longer lags (e.g., lag 10), one lag at a time until a significant cumulative effect from all the included lags ($p < 0.05$) was identified. We then used this model as our final model for a specific ECG outcome. All results are

expressed per $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$. We used SAS version 9 (SAS Institute, Inc., Cary, NC) for all analyses. **Figure 1** graphically represents the individual lag and cumulative effects from a distributed lag model.



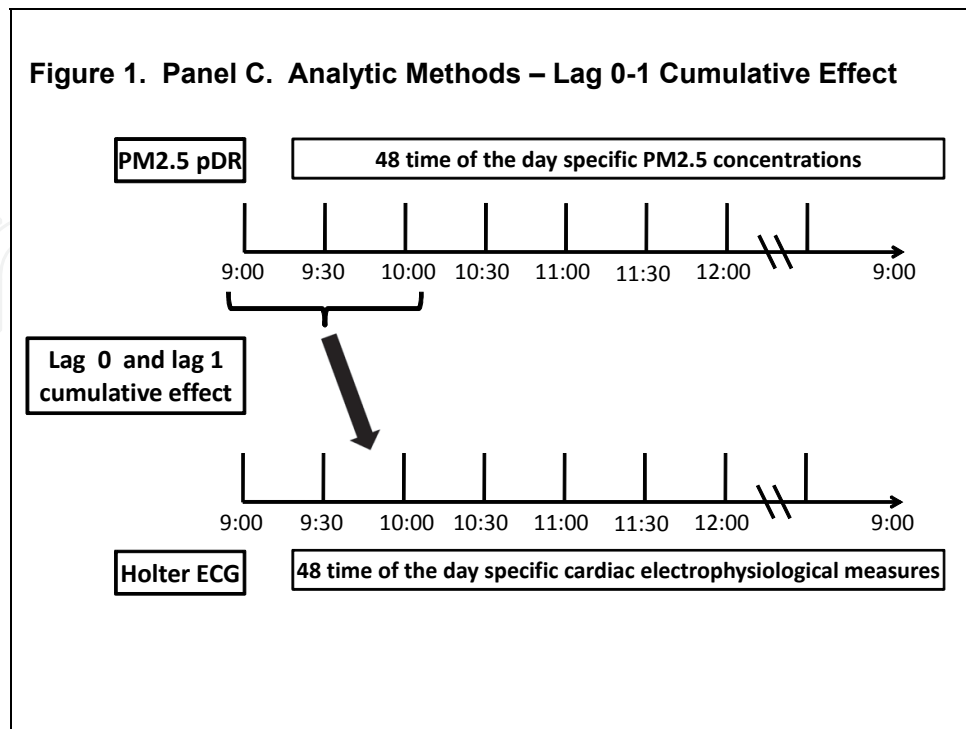


Fig. 1. Illustrations of PM_{2.5} effects from a distributed lag model

4. Results

Table 1 presents demographic and clinical characteristics in this community-based sample of 106 middle-aged healthy non-smokers. The mean age of the participants was 56 years, with 73% non-Hispanic white, 60% females, and 43% classified as having chronic disease (CVD, hypertension, or diabetes). The prevalence of CVD, hypertension, and diabetes was 7.6%, 35.2%, and 7.6%, respectively.

The average individual-level exposure to PM_{2.5} (over all 30 minute segments) was 13.49 (SD=22) $\mu\text{g}/\text{m}^3$. The medians of the within-individual interquartile ranges (IQR) for the entire study sample on lag 0, lag 0-1, lag 0-2, lag 0-3, and lag 0-4 PM_{2.5} concentration were 6.38 $\mu\text{g}/\text{m}^3$, 6.57 $\mu\text{g}/\text{m}^3$, 5.97 $\mu\text{g}/\text{m}^3$, 5.83 $\mu\text{g}/\text{m}^3$, and 6.06 $\mu\text{g}/\text{m}^3$, respectively, which indicates no substantial variation in the IQRs across the window of exposure, supporting our decision of reporting the relationship between PM_{2.5} and ECG parameters per 10 $\mu\text{g}/\text{m}^3$ increase of PM_{2.5} across all models.

According to the model selection strategy described above, the final models for each of the continuous ECG outcomes are summarized in **Table 2**, and the results from arrhythmia counts as outcome are presented in **Table 3**. All these models were adjusted for age, sex, race, temperature, relative humidity, diabetes, hypertension, and CVD. From the cumulative effects of PM_{2.5} summarized in Tables 2 and 3, the time course patterns are clearly shown as ranging from 30 minutes to several hours of elevated PM_{2.5} levels.

Characteristic	All subjects N=106	Hypertension, Diabetes, or CVD		P value ^c
		No N=60	Yes N=45	
Age	56 (7.6)	56 (8.2)	57 (6.8)	0.32
Gender (% Male)	40	40	40	1.00
Race (% non-Hispanic White)	73	72	76	0.66
Glucose (mg/dL)	89 (25)	85 (10)	94 (36)	0.10
BMI (kg/m ²)	28 (5.9)	26 (4.3)	30 (7.1)	<0.01
CVD (%)	7.6	0.00	18	<0.01
Hypertension (%)	35	0.00	85	<0.01
Diabetes (%)	7.6	0.00	18	<0.01
Systolic Blood Pressure (mm Hg)	122 (16)	117 (12)	128 (18)	<0.01
Diastolic Blood Pressure (mm Hg)	75 (9.2)	73 (8.3)	77 (9.8)	0.02
College or Higher (%)	79	73	87	0.10
Hypertensive Medicine Use (%)	19	0.00	44	<0.01
Diabetic Medicine Use (%)	6.7	0.00	16	<0.01
Arrhythmia Medicine Use (%)	1.9	0.00	4.4	0.18

a Results are presented as mean (standard deviation) for continuous variables and percentage for categorical variables

b the median of the within-individual interquartile ranges of PM_{2.5} concentration.

c p-value for comparing CVD and No CVD groups.

Table 1. Demographic and clinical characteristics of the study population^a

ECG Parameter	Lags	β (SE, p value)
HRV Log_HF (ms ²)	Lag 0	-0.003 (0.007)
	Lag 1	-0.006 (0.005)
	Lag 2	-0.007 (0.003) *
	Lag 3	-0.009 (0.004) **
	Lag 4	-0.009 (0.004) *
	Lag 5	-0.009 (0.004) *
	Lag 6	-0.008 (0.004) *
	Lag 7	-0.007 (0.003) *
	Lag 8	-0.005 (0.004)
	Lag 9	-0.002 (0.005)
	Lag 10	0.002 (0.008)
	Cumulative	-0.062 (0.022) **
SDNN (ms)	Lag 0	-0.07 (0.21)
	Lag 1	-0.09 (0.13)
	Lag 2	-0.12 (0.10)
	Lag 3	-0.13 (0.10)
	Lag 4	-0.15 (0.12)
	Lag 5	-0.16 (0.12)
	Lag 6	-0.17 (0.11)
	Lag 7	-0.18 (0.10)
	Lag 8	-0.18 (0.10)
	Lag 9	-0.18 (0.15)
	Lag 10	-0.17 (0.24)
	Cumulative	-1.59 (0.54) **

ECG Parameter	Lags	β (SE, p value)
QTI (%)	Lag 0	0.07 (0.04) *
	Lag 1	0.04 (0.02) *
	Lag 2	0.02 (0.02)
	Lag 3	0.01 (0.03)
	Lag 4	0.01 (0.03)
	Lag 5	0.02 (0.02)
	Lag 6	0.05 (0.03) *
	Lag 7	0.08 (0.04) *
	Cumulative	0.32 (0.13) **
ST-height ST-II	Lag 0	0.04 (0.08)
	Lag 1	0.14 (0.06) **
	Lag 2	0.20 (0.07) **
	Lag 3	0.21 (0.09) **
	Lag 4	0.20 (0.16)
	Cumulative	0.79 (0.23) **
ST-III	Lag 0	0.02 (0.07)
	Lag 1	0.08 (0.05)
	Lag 2	0.13 (0.06) *
	Lag 3	0.15 (0.08) *
	Lag 4	0.14 (0.14)
	Cumulative	0.52 (0.27)*
P complexity	Lag 0	0.0002 (0.0002)
	Lag 1	0.0004 (0.0002) **
	Lag 2	0.0005 (0.0002) **
	Lag 3	0.0004 (0.0004)
	Cumulative	0.0016 (0.0006) **

*: p<0.05 **: p<0.01

Table 2. Regression coefficient of continuous ECG variables associated with a 10 $\mu\text{g}/\text{m}^3$ increment of PM_{2.5}.

Ectopy Variable	Lags	Rate Ratio ^b (95% CI)
PVC (count)	Lag 0 (same time)	1.08 (1.05, 1.10) **
	Lag 0-1 (30 min. prior)	1.03 (1.00, 1.05) *
PAC (count)	Lag 0 (same time)	0.94 (0.85, 1.04)
	Lag 0-1 (30 min. prior)	0.97 (0.89, 1.05)

a The rate ratios were calculating by exponentiating the regression coefficients from distributed lag negative binomial models. A rate ratio of 1.05 indicates a 5% increase in ectopy count/30 minutes in association with a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration

b Adjusted for age, sex, race, chronic disease status, and the same lag period temperature and relative humidity.

*: P value<0.05 **: P value<0.01

Table 3. The cumulative rate ratios^a (95% CI) of ectopy counts associated with a 10 $\mu\text{g}/\text{m}^3$ increment of PM_{2.5}.

To elucidate whether PM_{2.5} affects inflammatory response as a potential mechanism that explains the associations between PM_{2.5} and ECG-based parameters, we examined the association between individual level 24-hour PM_{2.5} concentration and blood inflammatory markers in the APACR study population. In these analyses, we treated PM_{2.5} exposure as 24-hour average from the pDR measures. Two blood samples were collected from each participant, one immediately before and one immediately after the 24-hour study period. Concentrations of several inflammation markers were assessed and averaged. Linear regression models were used to assess the association between mean 24-hour PM_{2.5} exposure and the mean inflammation markers. Age, race, gender, relative humidity, temperature, and participant's chronic disease status were adjusted for in the regression models. We did not observe significant associations between 24-hour mean PM_{2.5} exposure and mean inflammation markers. The regression coefficients (SE) per 10 µg/m³ increase in PM_{2.5} were: -0.02 (0.02) g/dL for albumin, 81 (217) ng/mL for C-reactive protein (CRP), -0.56 (0.13) pg/mL for interleukin-1 α (IL-1 α), -0.28 (0.30) pg/mL for interleukin-1 β (IL-1 β), -19 (56) pg/mL for macrophage migration inhibitory factor (MIF), -1.66 (5.37) pg/mL for tumor necrosis factor-α (TNFα), 100 (73) pg/mL for tumor necrosis factor soluble receptor I (TNFsRI), and 0.02 (0.09) × 10³/mm³ for white blood cell count, respectively (all p-values > 0.05).

Similarly, we also examined the association between individual level 24-hour PM_{2.5} concentration and blood hemostatic factors--blood markers of coagulation and thrombosis potential in the APACR. We did not observe significant associations between 24-hour mean PM_{2.5} exposure and mean hemostatic factor levels. The regression coefficients (SE) per 10 µg/m³ increase in PM_{2.5} were: -0.13 (0.78) % for antithrombin III, 1.95 (2.97) % for factor VIII, -2.79 (3.88) mg/dL for fibrinogen, 0.56 (0.54) IU/mL for plasminogen activator inhibitor, 0.06 (0.19) ng/mL for tissue plasminogen activator, and -0.13 (0.15) µg/mL for D-Dimer (all p-values > 0.05).

5. Discussion

The mechanisms responsible for the consistently reported association between fine particle exposure and cardiovascular disease mortality and morbidity are not fully understood. Previous studies have suggested several possible underlying mechanisms, including cardiac autonomic impairment as measured by lower HRV (Creason et al. 2001; Gold et al. 2000; He et al. 2010; Liao et al. 1999, 2004; Pope et al. 1999) and effects on ventricular repolarization (Campen et al. 2006; Ghelfi et al. 2008; Henneberger et al. 2005; Liao et al. 2010; Lux and Pope 2009; Samet et al. 2009; Yue et al. 2007), T-wave alternans (Zanobetti et al. 2009), myocardium ischemia (Zhang et al. 2009), and arrhythmias (Berger et al. 2006; Dockery et al. 2005; Eblet et al. 2005; Liao et al. 2009; Sarnat et al. 2006). We conducted this study to systematically examine all of these cardiac electrophysiological parameters in one study population under a single standardized personal PM_{2.5} exposure. With both PM_{2.5} exposure and ECG based parameters assessed in parallel for 24 hours, and subsequently divided as 30-minute based segment specific measures, we can apply distributed lag methods to identify the suggested time-course of associations, the lagged time of any significant associations between PM_{2.5} and ECG parameters.

Since the associations we found on each of the five ECG-based parameter domains have been published (7;16-19), we selected to use 1-2 parameters from each domain to illustrate

the overall pattern of the time-courses of elevated $PM_{2.5}$ on ECG parameters. The following patterns are clearly shown in Tables 2 and 3:

1. The effects on HRV as measures of cardiac autonomic modulation were limited to within approximately 5.5 hours of the $PM_{2.5}$ exposure;
2. The effects on heart rate corrected QT as measure of ventricular repolarization were limited to within approximately 4 hours of the $PM_{2.5}$ exposure;
3. The effects on ST-height as measures of ischemic potential were limited to within approximately 2.5 hours of the $PM_{2.5}$ exposure;
4. The effects on P-wave based parameters as measures of atrial fibrillation (Afib) vulnerability were limited to within approximately 2 hours of the $PM_{2.5}$ exposure; and
5. The effects on the frequency of ventricular ectopy were limited to within approximately 60 minutes.

To our knowledge, this is the first study designed to have sufficient temporal resolution of both exposure and ECG variables, e.g. on the 30-minute basis of exposure, outcome, and covariables. Such a study design enabled us to examine the acute effect of $PM_{2.5}$ exposure on various ECG-based parameters. Another major strength of this study is that $PM_{2.5}$ exposures, the ECG outcome data, and the covariables were measured at the individual level on a real-time basis over 24 hours. With these individual-level data, we can adjust for individual-level time-varying and non-time-varying confounding factors. Overall, our data provide evidence of acute effects of $PM_{2.5}$ exposure on cardiac electrophysiological profiles. Mechanisms that would explain the associations between various ECG parameters and $PM_{2.5}$ exposure are unknown at this time. It is biologically plausible that exposures to $PM_{2.5}$ directly reduce parasympathetic modulation and increase sympathetic modulation, resulting in longer ventricular repolarization, elevated ST-height, increased Afib vulnerability, and a decreased threshold for arrhythmia. Since HRV is a reliable measure of cardiac autonomic modulation, and most published studies have suggested that PM exposure is associated with lower HRV indices, we repeated all of our analyses to include adjustment for HRV variables in the final models. In general, associations between $PM_{2.5}$ and various ECG-based parameters were attenuated but still remained statistically significant when we adjusted for HRV variables. These HRV-adjusted findings are consistent with an intermediate effect of PM exposure on autonomic modulation. However, adjustment for HRV parameters did not completely eliminate the associations between $PM_{2.5}$ and various ECG parameters suggesting that other mechanisms might also explain the associations. For the inflammatory responses to $PM_{2.5}$ pathway, our relatively low levels of 24-hour mean $PM_{2.5}$ exposure are not associated with blood inflammation markers. These null findings suggest that more studies on the chronic exposure and inflammatory responses are needed to elucidate the sub-acute and chronic effects of PM on systemic inflammation as a mechanistic link between PM and cardiac electrophysiology and cardiopulmonary disease. For the blood coagulation and thrombosis potential responses to $PM_{2.5}$ pathway, the 24-hour mean levels of $PM_{2.5}$ exposure were not associated with blood hemostatic factors. These null findings suggest that more studies on chronic PM exposure and hemostatic factors are needed to elucidate their role in the pathophysiologic effects of air pollution on deep vein thrombosis and cardiopulmonary disease. In a just published study by Zuurbier and co-workers [37], it was concluded that air pollution exposure during commuting was not consistently associated with acute changes in inflammation markers, blood cell counts or blood coagulation markers in individuals. It should be noted that individuals in this study

were exposed to higher levels of traffic-related pollutants than the APACR study participants.

The APACR study has several limitations. First, our findings may not apply to smokers or persons with a recent acute cardiac event, as such persons were excluded from the study population. Second, the majority of participants reported that they stayed indoors most of the time during the 24-hour study period, except when they had to travel by automobile, and they had limited exposure to second hand cigarette smoke. Thus, participants had relatively low levels of exposure to PM_{2.5} and we cannot determine whether exposures at higher levels would exhibit similar associations. Third, it is well known that sympathetic nervous activity increases during physical activity, which could be related to higher PM_{2.5} exposure if it occurs outdoors. Thus, it is possible that the PM_{2.5} and ECG-parameters associations in this study were confounded by physical activity. However, the vast majority of our participants reported staying indoors 97% of the 24 hour study period reduces the possibility that the consistent associations were mainly due to outdoor activity confounding. Fourth, the ECG data were not collected under a controlled, supine-position setting, and short-term variation due to other factors that may impact the ECG parameters cannot be fully accounted for in our analysis. However, it is not feasible to keep a healthy participant in a supine indoor position for 24 hours, and even if this were achieved, the results from such a study design would not be generalizable to a real-world situation.

6. Conclusions

The data from the APACR study enabled us to systematically examine the acute effects of PM_{2.5} exposures on various clinically relevant cardiac electrophysiological disturbances. In general, higher PM_{2.5} is adversely associated with all five major ECG parameters we analyzed, with the adverse effects occurring acutely (within 2-5 hours of elevated PM_{2.5}) or ultra acutely (within 0.5 hr of elevated PM_{2.5}). These adverse effects on ECG parameters may trigger the onset of acute cardiac events and cumulatively over time, may result in increased risk of cardiac disease. Thus, it is possible that PM_{2.5} exposure is associated with cardiovascular and cerebral vascular disease by first affecting the cardiac electrophysiology.

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The book describes the effects of air pollutants, from the indoor and outdoor spaces, on the human physiology. Air pollutants can influence inflammation biomarkers, can influence the pathogenesis of chronic cough, can influence reactive oxygen species (ROS) and can induce autonomic nervous system interactions that modulate cardiac oxidative stress and cardiac electrophysiological changes, can participate in the onset and exacerbation of upper respiratory and cardio-vascular diseases, can lead to the exacerbation of asthma and allergic diseases. The book also presents how the urban environment can influence and modify the impact of various pollutants on human health.

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