Journal of Electrocardiology 52 (2019) 112–116

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

Diurnal cardiac sympathetic hyperactivity after exposure to acute particulate matter 2.5 air pollution

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ARTICLE INFO

Keywords:
Arrhythmia
Autonomic
Diurnal
Heart rate variability
PM2.5

ABSTRACT

Background: Ambient fine particulate matter (PM2.5) exposure is associated with increased cardiovascular and cardiac arrhythmias events, but the detailed mechanism remains unclear.
Objective: We aimed to investigate the effect of PM2.5 (particulate matter < 2.5 μm in aerodynamic diameter) on the cardiac autonomics through a heart rate variability (HRV) analysis.
Method: Among 6912 patients who had underwent 24-hour Holter ECG recordings between Oct 1st 2015 and Oct 31st 2016, 46 (25 males, 69.3 ± 12.1 years old) were enrolled with confirmation of living in an environment with a reported PM2.5 level and were classified as elevated (Group 1, >36 μg/m^3, 50.73 ± 8.50) or low (Group 2, <11 μg/m^3, 6.06 ± 1.00) PM2.5 group. The Holter recordings and HRV parameters were evaluated.
Result: The baseline characteristics including the comorbidities and medications were similar between the 2 groups. The Holter ECG parameters were also similar. There were no significant HRV differences between the two groups for the 24-hour interval analysis. However, the LF/HF ratio was significantly higher in Group 1 than Group 2 in the 9 am to 9 pm ($p = 0.028$), 8 am to 4 pm ($p = 0.024$), and 4 pm to 12 pm ($p = 0.025$) periods, respectively, but not for the nocturnal HRV parameters.
Conclusion: Our study demonstrated that an elevated PM2.5 exposure had a significant association with an increased daytime LF/HF ratio suggesting a diurnal difference in the response to PM2.5 exposure.

Introduction

Air pollution is the single largest environmental risk factor, and accounts for over 3 million deaths worldwide [1]. Among the numerous air pollutants, the health effect of PM2.5 exposure (particulate matter < 2.5 μm in aerodynamic diameter) has been most rigorously studied and is commonly used as an air pollution indicator. In epidemiologic studies, a significant association between increased cardiovascular, pulmonary, and all cause mortalities with a high PM2.5 exposure has been established [2–4]. The association between an increased risk of arrhythmia admissions and a PM2.5 exposure has also been established [5,6]. The mechanisms behind these associations remain unclear but it is known that PM2.5 particles can travel deep into alveolar and enter systemic circulation [7]. The particles can then exert systemic effects via 3 main pathways: (1) increasing systemic inflammation and vasculoactive mediators, (2) directly affecting local vasoconstriction and/or platelet aggregation through translocation, and (3) altering the systemic and cardiac autonomic nervous tone [8]. The heart rate variability (HRV) is the marker of cardiac autonomic balance [9]. A reduced HRV, which has been associated with higher cardiovascular events and arrhythmias, is a marker of autonomic dysfunction and sympathetic hyperactivity [10,11]. There have been a great number of literatures evaluating the association between short term air pollution and HRV. However, those clinical studies have varied substantially in their study design, study population, and statistical methods, and thus their results have been inconsistent [12]. A previous meta-analysis of 18,667 patients from 29 studies has demonstrated a significant decrease in the HRV parameters after exposure to an elevated PM2.5 level [13]. However, most (75%) of the included studies derived the HRV from short-term ECGs and the relationship between the PM2.5 exposure and different time periods of the day were not evaluated. In this study, we aimed to investigate the association between a PM2.5 exposure and the HRV, namely how a daily average of PM2.5 exposure would affect the HRV in a community dwelling population during different time periods.

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https://doi.org/10.1016/j.jelectrocard.2018.11.012
0022-0736/

Methods

Study design

We analyzed the consecutive Holter ECG database of Taipei Veteran General Hospital. A total of 6912 patients who had undergone 24-hour Holter ECG recordings between October 1st 2015 and October 31st 2016 were reviewed. The PM2.5 exposure data were provided by the PM2.5 database of the environmental protection administration of Taiwan, which was derived from the hourly PM2.5 concertation from 7 fixed-site monitoring stations located in Taipei city. All the clinical data were extracted under the approval of the Institutional Review Board committee of Taipei Veteran General Hospital (IRB No: 2017-07-007BC).

Study population

Patients who were between 20 and 85 years old, had a registered address in Taipei city, and who had a higher PM2.5 exposure (Group 1, defined as >36 μg/m^3, index band 4 on the Daily Air Quality Index [DAQI]) or lower PM2.5 exposure (Group 2, defined as <11 μg/m^3, index band 1 on the DAQI) were recruited. Those who were taking beta-blockers and who had an established diagnosis of sick sinus syndrome or neurogenic orthostatic hypotension defined by a positive tilt table test were excluded. We also excluded patients whose Holter recordings were conducted during admission to the hospital and those whose baseline rhythm was not sinus rhythm. The baseline characteristics, including the sex, age, and smoking status, their co-morbidities including hypertension, coronary artery disease (CAD), heart failure, dyslipidemia, thyroid disorders, chronic obstructive lung disease (COPD), sleep apnea, and a medication history were reviewed in each patient. The echocardiographic records within the study period were reviewed.

Holter ECG analysis

The patients' baseline Holter ECG parameters were evaluated including the mean heart rate, maximal heart rate, minimal heart rate, and corrected QT interval (QTc). The HRV parameters were analyzed from the Holter recordings on a high precision Holter analysis system (Oxford Excel 2, Oxford Instrument Abingdon). The RR intervals were interpreted as premature beats and thus were not calculated as normal-normal intervals if they deviated from the previous qualified interval value by more than a given tolerance (e.g., 30%), which was a programmable parameter depending on the prematurity index of ectopic beats in each patient. Abrupt temporary changes in the RR interval sequence, representing ectopic beats, were removed and more stationary data were achieved for the analysis with this filtering technique. Only the RR intervals related to normal sinus beats in a stationary state were included in the analysis. In this study, reliable measurements of the spectral components of the HRV had been achieved by this technique (<5% error) if <15% of the impulses were excluded from the analysis. In calculating the HRV variables, only the normal-to-normal QRS complex intervals were included. We defined the normal-to-normal beats as beats that were from sinus impulses and not premature beats or of a ventricular origin. The HRV parameters, including the mean normal to normal intervals (NN intervals), standard deviation (SD) of the NN intervals (SDNN), high frequency (HF) and low frequency (LF) powers of the HRV, and low frequency/high frequency ratio (L/H ratio) of the 2 groups were evaluated and compared based on the different time slots (24-hour, 12-hour [9 am to 9 pm and 9 pm to 9 am], and 8-hour periods [8 am to 4 pm, 4 pm to 12 pm, and 12 pm to 8 am]).

The beat-to-beat fluctuations were transformed to the frequency domain using a fast Fourier transformation to generate the HRV spectral power. The HRV spectral power (ms^2) was defined as the low-frequency component (LF) from 0.04 Hz to 0.15 Hz and high-frequency component (HF) from 0.15 Hz to 0.40 Hz. The low- and high-frequency components were calculated as the area under the frequency bands. The low/high frequency component ratio (L/H ratio) was calculated as an index of the autonomic balance of the heart. The mean RR cycle length was derived from the mean of all normal RR intervals.

Statistical analysis

The data were expressed as mean ± standard deviation for normally distributed continuous variables and mean ± 95% confidence interval for categorical variables. The characteristics of the distribution between the 2 groups were analyzed with Chi-square test and two-tailed *t*-test as appropriate. The echocardiography data were analyzed with two-tailed *t*-test. The 24-hour Holter ECG parameters were analyzed with two-tailed *t*-test and Mann-Whitney's non-parametric test when appropriate. The HRV parameters of the 2 groups were compared with Mann-Whitney's non-parametric test while the mean and standard deviations of each parameter were calculated separately. The statistical significance was set as a $P < 0.05$. All statistical analyses were carried out using SPSS 20.0 software (IBM, Inc. Chicago, USA).

Results

Baseline characteristics

A total of 46 patients (25 males, mean age 69.3 ± 12.1 years old) were enrolled. Twenty-one patients were assigned to Group 1 and 25 to Group 2. The PM2.5 exposure in Group 1 and Group 2 was 50.73 ± 8.50, and 6.06 ± 1.00 μg/m^3, respectively. The baseline characteristics, including the comorbidities and medications were similar between the 2 groups (Table 1). The echocardiography data were available for 15 of 21 Group 1 and 21 of 25 Group 2 patients (Table 2). The echocardiographic parameters were also similar between the 2 groups.

General Holter monitoring data

The baseline parameters of the 24-hour Holter recordings were analyzed and compared between the 2 groups (Table 3). The mean heart

Table 1
Baseline characteristics, comorbidities, and medications between the two groups.

Parameters	High group (n = 21)	Low group (n = 25)	p value
PM2.5 (μg/m^3)	50.73 ± 8.50	6.06 ± 1.00	<0.001
Female gender (n, %)	8 (38.1%)	13 (52.0%)	0.346
Age (y/o)	67.0 ± 13.8	71.2 ± 10.68	0.257
Smoking (n, %)	4 (19.0%)	9 (36.0%)	0.078
Dyslipidemia (n, %)	12 (57.1%)	8 (32.0%)	0.087
Thyroid disease (n, %)	2 (9.5%)	0 (0.0%)	0.203
Type 2 diabetes (n, %)	5 (23.8%)	7 (28.0%)	0.747
CAD (n, %)	10 (47.6%)	7 (28.0%)	0.170
CHF (n, %)	2 (9.5%)	0 (0.0%)	0.203
Hypertension (n, %)	10 (47.6%)	16 (64.0%)	0.264
COPD	2 (9.5%)	2 (8.0%)	1.000
Sleep apnea	1 (4.8%)	0 (0.0%)	0.457
CCB (n, %)	4 (19.0%)	5 (20.0%)	1.000
ACEI/ARB (n, %)	7 (33.3%)	6 (24.0%)	0.484
Statin (n, %)	10 (47.6%)	8 (32.0%)	0.280
Mexitil (n, %)	1 (4.8%)	1 (4.0%)	1.000
Propafenone (n, %)	0 (0.0%)	3 (12.0%)	0.239
Flecanide (n, %)	1 (4.8%)	1 (4.0%)	1.000
Digoxin (n, %)	2 (9.8%)	0 (0.0%)	0.203
Dronadarone (n, %)	0 (0.0%)	1 (4.0%)	1.000
Soltalol (n, %)	0 (0.0%)	0 (0.0%)	1.000
Amiodarone (n, %)	1 (4.8%)	1 (4.0%)	1.000

ACEI = angiotensin converting enzyme inhibitors. ARB = angiotensin II receptor blockers. CAD = coronary artery disease. CCB = calcium channel blockers. CHF = congestive heart failure. COPD = chronic obstructive lung disease.

Table 2
Echocardiography characteristics.

Parameters	Group 1 (n = 15)	Group 2 (n = 21)	p value
LVEF (%)	60.13% ± 4.44%	61.10% ± 4.41%	0.525
LVIDd (mm)	46.80 ± 4.96	44.19 ± 5.89	0.171
LVIDs (mm)	29.13 ± 4.53	26.52 ± 4.70	0.104
LAD (mm)	37.53 ± 8.32	36.14 ± 5.15	0.572
E/E′	12.23 ± 3.86	12.69 ± 6.11	0.897
RVSP (mm Hg)	32.07 ± 6.93	29.15 ± 7.80	0.254

E/E′ = the ratio of the early transmitral flow velocity and early mitral annular velocity. LAD = left atrial dimension. LVEF = left ventricular ejection fraction. LVIDd = left ventricular internal diameter end diastole. LVIDs = left ventricular internal diameter end systole. RVSP = right ventricular systolic pressure.

rate, maximal heart rate, minimal heart rate, and QTc were similar between the 2 groups.

HRV analysis

There were no significant HRV differences between the two groups in the 24-hour time slot. There were significantly higher LF/HF ratios in Group 1 than Group 2 in the 9 am to 9 pm (p = 0.028), 8 am to 4 pm (p = 0.024), and 4 pm to 12 pm (p = 0.025) periods, respectively (Table 4). There were no differences in the HRV parameters among the different nocturnal time slots (9 pm–9 am, and 12 pm–8 am). To exam the diurnal variations in the HRV and PM2.5, we then compared the HRV parameters of the different time slots within Group 1. There was a significantly higher mean SDNN during 12 pm to 8 am (145.48 ± 60.65 ms) when compared to the 8 am to 4 pm (96.66 ± 57.13 ms p = 0.003) and 4 pm to 12 pm (107.07 ± 50.85 ms p = 0.0017) periods in Group 1. To investigate the effect of PM2.5 variation on the HRV, we also analyzed the relationship between the difference in the PM2.5 exposure on the study day and one day before the study day. The result showed that an alteration in the PM2.5 exposure had a weak correlation with the HF for the 8 am to 4 pm and 12 pm to 8 am time periods and with the LF for the 12 pm to 8 am time period (Supplement Table 1). To further investigate the delayed effect of previous PM2.5 exposures, we evaluated the correlation between the HRV parameters and PM2.5 exposure with: 1. On the day of the Holter recording; 2. The previous day; 3. Two days prior, and 4. An average of 3 days (Supplement Table 2). The results showed that the PM2.5 exposure during those 4 time-frames have no correlations with any HRV parameters.

Discussion

Main findings

The results of this study showed that the LF/HF ratios of the HRV were associated with a diurnal PM2.5 exposure in a community dwelling population. This pattern demonstrated that a PM2.5 exposure may have a stronger impact on the cardiac autonomics with a reduced HRV and sympathetic hyperactivity during the daytime. Our findings are compatible with a diurnal change in the PM2.5 exposure and diurnal change in the HRV. This effect may explain the higher cardiovascular events and arrhythmogenecity during the daytime with serious air pollution [14].

Table 3
24-hour Holter ECG characteristics between the two groups.

Parameters	Group 1 (n = 21)	Group 2 (n = 25)	p value
Mean HR (beats/min)	72.14 ± 12.35	74.60 ± 9.37	0.447
Maximal HR (beats/min)	127.29 ± 24.87	130.72 ± 26.60	0.938
Minimal HR (beats/min)	50.71 ± 10.16	50.76 ± 7.28	0.986
QTc (ms)	390.33 ± 37.30	393.68 ± 55.30	0.815

HR = heart rate. QTc = corrected QT interval.

Table 4
Comparisons of the HRV parameters between groups 1 and 2.

Time periods	Parameters	Group 1 (n = 21)	Group 2 (n = 25)	p value
24 h	LF/HF ratio	5.30 ± 13.00	1.77 ± 1.15	0.072
	HF (ms^2)	517.23 ± 1490.52	1080.66 ± 4359.06	0.716
	LF (ms^2)	1510.28 ± 3583.57	3076.89 ± 13,561.93	0.337
	R-R interval (ms)	841.41 ± 133.59	806.88 ± 98.70	0.305
	SDNN (ms)	123.42 ± 43.24	118.81 ± 38.00	0.716
9 am to 9 pm	LF/HF ratio	2.68 ± 1.46	1.93 ± 1.44	0.028
	HF (ms^2)	684.41 ± 1645.83	1021.74 ± 4424.43	0.574
	LF (ms^2)	1197.62 ± 2651.90	2734.40 ± 12,358.63	0.051
	R-R interval (ms)	813.25 ± 130.25	768.51 ± 98.42	0.175
	SDNN (ms)	107.71 ± 59.68	87.35 ± 37.92	0.087
9 pm to 9 am	LF/HF ratio	2.36 ± 1.62	2.90 ± 6.95	0.217
	HF (ms^2)	1458.18 ± 4311.83	345.77 ± 447.91	0.974
	LF (ms^2)	3638.41 ± 12,798.44	537.58 ± 724.86	0.716
	R-R interval (ms)	914.46 ± 170.47	855.90 ± 105.60	0.265
	SDNN (ms)	129.81 ± 47.85	126.08 ± 46.68	0.991
8 am to 4 pm	LF/HF ratio	2.78 ± 1.71	1.77 ± 1.39	0.012
	HF (ms^2)	762.05 ± 1841.22	258.42 ± 586.90	0.691
	LF (ms^2)	1202.93 ± 2661.49	469.16 ± 1311.15	0.030
	R-R interval (ms)	795.18 ± 124.00	762.06 ± 95.50	0.265
	SDNN (ms)	96.66 ± 57.13	86.7540.98	0.414
4 pm to 12 pm	LF/HF ratio	2.59 ± 1.25	1.77 ± 1.25	0.025
	HF (ms^2)	586.61 ± 1638.75	350.83 ± 727.89	0.869
	LF (ms^2)	956.57 ± 2171.69	514.78 ± 908.60	0.149
	R-R interval (ms)	883.83 ± 162.73	820.91 ± 122.18	0.120
	SDNN (ms)	107.07 ± 50.85	99.21 ± 32.01	0.956
12 pm to 8 am	LF/HF ratio	234 ± 1.74	1.54 ± 0.88	0.137
	HF (ms^2)	886.22 ± 2046.41	324.08 ± 415.72	0.716
	LF (ms^2)	1188.24 ± 2589.13	435.97 ± 546.95	0.415
	R-R interval (ms)	866.06 ± 145.84	837.52 ± 92.79	0.589
	SDNN (ms)	145.48 ± 60.65	132.83 ± 50.50	0.604

LF/HF ratio = the ratio between the low- (LF) and high-frequency bands (HF) in the heart rate variability (HRV). SDNN = standard deviation of NN-intervals.

Relationship between the HRV and PM2.5

There has been a substantial number of publications investigating the association between PM2.5 exposure and the HRV. However, these studies were conducted on different populations, in different climate zones under different time frames. As a result, those studies often draw different conclusions. Paceli et al. demonstrated that high PM2.5 levels in the outdoor environment have the greatest effect on the autonomic imbalances in young and healthy individuals [16]. Pope et al. demonstrated a decreased SDNN, root mean square of the successive differences (r-MSSD), and increased C-reactive protein (CRP) in elderly individuals in response to an elevated PM2.5 exposure [17]. He et al. reported increases in the mean 6 hour PM2.5 level were significantly associated with a lower HF and SDNN in a study of 106 non-smoking community dwellers [18]. While some other studies aiming at young and healthy individuals or patients with COPD have shown contradictory results in which a PM2.5 level was associated with elevated HRV parameters [19–21]. In a meta-analysis of 29 studies, Pieters et al. demonstrated that an increase in the PM2.5 level was associated with a decrease in the SDNN, rMSSD, LF, and HF. [13]. However, in a more recent systemic review, Buteau et al. reported that they were unable to draw any conclusion due to pronounced differences in the design characteristics and methodologies between the studies [12]. In our study, we excluded the confounding effect of beta-blockers and focused on a relatively healthy community dwelling Asian population. Unlike previous studies, our population was exposed to a relatively low PM2.5 level but still demonstrated altered HRV parameters. We also demonstrated a significant diurnal interaction between a PM2.5 exposure and the HRV parameters. To the best of our knowledge, these associations have not been previously reported. In addition, we have shown and a weak correlation between alteration in the PM2.5 exposure and the HRV. This result may imply that a change in the PM2.5 exposure may be associated with an alteration in the autonomic tone, especially

the parasympathetic component. However, our patients did not receive a Holter ECG on the previous day thus we cannot obtain the alteration in the HRV parameters for a frim correlation analysis. Our results are in line with the current expert consensus that a PM2.5 exposure is associated with a reduction in the HRV among older or susceptible individuals [22].

The diurnal change of PM2.5 effect on the HRV

The concentration of PM2.5 has a strong temporal and geographical distribution [23]. The pattern of the PM2.5 level fluctuations could differ significantly at different locations, indicating a difference in the local geographic features and human activities [24]. In a previous study that was also conducted in Taipei city [25], the PM2.5 level follows a unimodal curve that is highest in the morning and lowest at midnight. The result is in line with the recent data reported by the environmental protection administration of Taiwan. The HRV is a surrogate marker for the autonomic tone, which also fluctuates in a diurnal pattern [26]. Kim et al. demonstrated that the heart rate and LF/HF ratio also had a unimodal pattern with a minimum value during nocturnal sleep, sharp increase upon waking in the morning, and maximum value during the afternoon in 61 healthy volunteers [27]. We observed that the PM2.5 exposure and LF/HF ratio had a diurnal correlation. This could have been the result of a higher PM2.5 exposure in the morning, higher sympathetic tone in the waking hours, or a combined effect of both. Thus, it may be important to avoid a PM2.5 exposure in the morning when the environmental level is higher and the patients are more susceptible to arrhythmias. However, prospective trials are required to confirm this implication.

Study limitations

We were not able to obtain longer (>24 h) continuous ECG data, which thus limited our ability to assess the association between the acute alteration in the PM2.5 exposure and acute alteration in the HRV parameters. There have been many non-invasive monitoring ECG devices approved and implemented in randomized control trials [28]. Thus, we will need future studies to evaluate whether the acute alterations in the PM2.5 exposure are associated with altered HRV parameters.

Conclusion

Our study demonstrated that an elevated PM2.5 exposure may be associated with sympathetic hyperactivity, as measured by an increased LF/HF ratio, in an urban community dwelling population. We also demonstrated a diurnal correlation between the PM2.5 level and HRV parameters. This effect may help explain the higher cardiovascular events and arrhythmogenecity during the daytime in serious air pollution conditions.

Author contributions

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Concept/design[1],
Data analysis/interpretation[2],
Drafting article[3],
Critical revision of article[4],
Approval of article[5],
Statistics[6],
Data collection[7],
Other (logistic)[8].

Funding

This work was supported by the Research Foundation of Cardiovascular Medicine [Grant number: MOST104-2314-B-075-089-MY3, MOST106-2314-B-075-073-MY3] and Szu-Yuan Research Foundation of Internal Medicine [Grant number: V107C-054].

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2018.11.012.

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