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Particulate and gaseous pollutants on inflammation, thrombosis, and autonomic imbalance in subjects at risk for cardiovascular disease☆

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ABSTRACT

This study examined effects of short-term urban air pollution exposures on inflammation, thrombosis, and autonomic imbalance in subjects at risk for cardiovascular disease (CVD). We enrolled 61 patients with multiple CVD risk factors and measured high sensitive C-reactive protein (hs-CRP), fibrinogen, D-dimer, and heart rate variability (HRV) indices. Two health examinations for each participant were performed during December 2002 through September 2003. Changes in inflammation and thrombotic markers and HRV indices with exposures to $PM_{2.5}$, organic carbon (OC), elemental carbon (EC), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and carbon monoxide (CO) at 1- to 3-day lags were analyzed using mixed models. The results showed inflammatory and thrombotic markers increased with 1- to 3-day lagged $PM_{2.5}$ components and gaseous pollutants exposures. hs-CRP maximally increased 0.19 [95% confidence interval (CI): 0.07–0.31] and 0.15 (95% CI: 0.05–0.24) mg/L for an interquartile range (IQR) of 1-day lagged SO_2 (2.3 ppb) and CO (0.5 ppm), respectively. D-dimer maximally increased 1.05 (95% CI: 0.13–1.75), 0.72 (95% CI: 0.09–1.21), 0.92 (95% CI: 0.13–1.50), and 0.90 (95% CI: 0.07–1.61) mg/dL for an IQR of 1-day lagged OC (3.9 μg/m^3), EC (2.0 μg/m^3), SO_2, and NO_2 (13.4 ppb), respectively. The HRV indices, including low frequency, very low frequency, and the ratio of low frequency to high frequency decreased 19.8 (95% CI: 4.4–32.7), 12.9 (95% CI: 0.8–23.4), and 17.6 (95% CI: 5.4–28.2)% for an IQR of 1-day lagged $PM_{2.5}$ (20.2 μg/m^3), respectively. Our findings demonstrated $PM_{2.5}$ components and gaseous pollutants exert prolonged inflammatory and thrombotic reactions, while $PM_{2.5}$ exert an immediate autonomic imbalance.

1. Introduction

A large body of epidemiological evidence has demonstrated the causal relationship between exposures to ambient particulate matter (PM_{10}) and cardiovascular disease (CVD) (Brook et al., 2010). The PM_{10}-related cardiovascular effects have been postulated in association with several potential biological pathways, including systemic inflammation, thrombotic reaction, and autonomic nervous system imbalance (Brook et al., 2010; Franchini and Mannucci, 2011; Franchini et al., 2012; Nelin et al., 2012). However, the effects of fine particulate matter ($PM_{2.5}$) and chemical constituents as well as gaseous pollutants on these hypothesized biomechanisms were less addressed and the results were inconsistent in previous studies. Several studies reported the positive associations between $PM_{2.5}$ and systemic inflammation markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), especially in the elderly subjects or subjects at risk of CVD (Chuang et al., 2007; Dabass et al., 2015; Delfino et al., 2008; Pope et al., 2004; Dubowsky et al., 2006); whereas other studies failed to demonstrate such relationships (Sullivan et al., 2007; Diez-Roux et al., 2006; Folino et al., 2009; Liu et al., 2007; Pope et al., 2004; Ruckerl et al., 2007; Sullivan et al., 2007; Zeka et al., 2006). Regarding air pollution-related thrombotic relation, associations between $PM_{2.5}$ and chemical compositions, including black carbon, nitrate, and sulfate with increased fibrinogen level were observed across several studies (Chuang et al., 2007; Ruckerl et al., 2007; Zeka et al., 2006); however, other

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studies did not observe the associations of $PM_{2.5}$ with fibrinogen, D-dimer, or prothrombin time, in individuals with comorbid diseases (Delfino et al., 2008; Steinvil et al., 2008; Sullivan et al., 2007). Although many studies reported short-term $PM_{2.5}$ exposures were associated with decreases in either in time-domain or frequency-domain heart rate variability (HRV) indices (Adar et al., 2007; Chuang et al., 2005, 2007; de Hartog et al., 2009; Ebelt et al., 2005; Park et al., 2005; Pope et al., 2004; Schwartz et al., 2005). However, other studies still failed to observe such relationships (Dales, 2004) or even reported increased standard deviation of normal-to-normal intervals (SDNN), root mean square of successive differences (rMSSD), and high frequency (HF) power with PM exposures (Riediker et al., 2004; Wheeler et al., 2006). The heterogeneity of $PM_{2.5}$ components and the susceptibility of study subjects may result in the diverse findings between studies. Besides, the publication bias must be considered to inflate the reported inflammation, thrombosis, and decreased HRV. Therefore, we conducted a sub-cohort study to examine the effects of short-term exposures to $PM_{2.5}$ and chemical constituents as well as gaseous pollutants on inflammation, thrombosis, and autonomic dysfunction in the elder subjects at risk for CVD.

2. Methods

2.1. Study population

The study subjects were selected from 267 subjects who had past history of physician-diagnosed coronary artery disease (CAD) or at least two of CVD comorbid diseases, such as hypertension, diabetes mellitus (DM), or hyperlipidemia, and participated in a cardiovascular promotion program in 2002. Two health examinations for each participant, first was performed during December, 2002 and February, 2003 and follow-up was completed during April–September, 2003. Here, hypertension was defined as measured systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg, and/or history of physician-diagnosed hypertension and use of anti-hypertensive agents. DM was defined as fasting glucose over 126 mg/dL and/or history of DM with management. Hyperlipidemia was defined as total cholesterol over 240 mg/dL or triglyceride over 200 mg/dL or use of lipid-lowering agents. After excluding the subjects who did not reside in Taipei City, a total of 61 subjects were finally recruited in this study. This study was approved by the Institutional Review Board of National Taiwan University Hospital. All participants provided informed consent upon recruitment into the study.

2.2. Health data

All of study subjects received two repeated assessments about one year apart during the study period, including clinical interview, self-reported questionnaire, venous blood sampling, and HRV measurement. The participants' age, sex, body mass index (BMI), and smoking status were obtained from the clinician interview and self-reported questionnaire. Blood biochemistry data, including blood sugar, total cholesterol, and triglyceride levels, were collected following a 10-h overnight fast. Biochemistry data were analyzed in the central laboratory of the National Taiwan University Hospital by enzymatic methods using an automatic multi-channel chemical analyzer (Hitachi 7450, Hitachi Corp., Tokyo, Japan). Serum high sensitive-CRP (hs-CRP) was measured by the chemiluminescent enzyme-labeled immunometric assay (Immulite C-Reactive Protein, Diagnostic Products Co., Los Angeles). Fibrinogen was measured by the clotting method of Clauss, using STA®-Fibrinogen Kits (Diagnostica, Stago). Plasma D-dimer was measured by INNOVANCE* D-Dimer (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany), a particle-enhanced, immunoturbidimetric assay.

After blood sample collection and a 15-min rest for each participant, we immediately performed the resting electrocardiogram (ECG) examination, in the sitting position, during daytime (8:00 a.m. to 12:00 p.m.) using a PacerCorder three-channel device (model 461A; Del Mar Medical Systems LLC, Irvine, CA) with a sampling rate of 250 Hz (4 ms). ECG tapes were processed using a Delmar Avionics model Strata Scan 563 (Irvine, CA). A complete 5-min segment of N-N interval was taken for HRV analysis. The time-domain measurements of HRV included SDNN and rMSSD between adjacent normal-to-normal intervals. The frequency-domain measurements of HRV included very low frequency (VLF: 0.003–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), high frequency (HF: 0.15–0.40 Hz), and LF: HF ratio, which were calculated by Welch's averaged periodogram of the normal-to-normal intervals. The details of translating ECG wave complexes to HRV indices is given in the previous study (Chuang et al., 2005).

2.3. Environmental data

The data of particulate pollutants, including $PM_{2.5}$ and chemical constituents (organic carbon (OC) and elemental carbon (EC)) and gaseous pollutants, including sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and carbon monoxide (CO), were collected from a fixed-site air quality monitoring station, Sinjhuang Supersite, which is part of the Taiwan Environmental Protection Agency (EPA) air quality monitoring network. The Sinjhuang Supersite Station is located in Sinjhuang Sports Park. Toward north of the monitoring station is the main road and the southwestern side is the green boulevard and Sinjhuang Baseball Field. The pollution around the station is primarily due to vehicles on workdays and normal activities on holidays, which are representative of typical pattern of city life. $PM_{2.5}$ were measured by the tapered element oscillating microbalance (TEOM) 1400a monitor (R&P, Albany, NY, USA), equipped a sample equilibrium system Nafion dryer. OC was measured by the Rupprecht & Patashnick 5400 (R&P, Albany, NY, USA) at 340 °C. EC measurements were obtained by subtracting the OC amount from that of total carbon. The instruments used for gaseous pollutants were an ultraviolet fluorescence analyzer (Ecotech 9850, Blackburn, Victoria, Australia) for SO_2, a chemiluminescence analyzer (Ecotech 9841, Blackburn, Victoria, Australia) for NO_2, and a non-dispersed infrared absorption analyzer (APMA-360 CE, Irvine, CA, USA) for CO. The scheduled quality control procedures included daily zero and span checks, biweekly precision checks, quarterly multi-point calibration, and data validation. The 24-h average concentrations of $PM_{2.5}$, OC, EC, SO_2, and NO_2 and 1-h daily maximum concentration of CO 1- to 7-days preceding the health examination was matched to each participant. To account for meteorological factors on the outcome variables, we also collected the data of ambient temperature and relative humidity from the Sinjhuang Supersite Station.

2.4. Statistical analysis

Because there were two repeated measures for each of study subject, we used generalized linear mixed-effect models with a random intercept for study subject and a constant correlation for each subject's two measurements to estimate the changes in inflammation marker (hs-CRP), coagulation factors (D-dimer and fibrinogen), and HRV indices (SDNN, rMSSD, VLF, LF, HF, and LF: HF ratio) in response to each particulate and gaseous pollutants at 1- to 7-day lags. We applied the variable selection technique, 10% change-in-estimate criterion, to select the potential confounding factors. Covariates including age, sex, BMI, smoking, history of