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Short-term exposure to high ambient air pollution increases airway inflammation and respiratory symptoms in chronic obstructive pulmonary disease patients in Beijing, China

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ABSTRACT

Background: Few studies have investigated the short-term respiratory effects of ambient air pollution in chronic obstructive pulmonary disease (COPD) patients in the context of high pollution levels in Asian cities.
Methods: A panel of 23 stable COPD patients was repeatedly measured for biomarkers of airway inflammation including exhaled nitric oxide (FeNO) and exhaled hydrogen sulfide (FeH_2S) (215 measurements) and recorded for daily respiratory symptoms (794 person-days) in two study periods in Beijing, China in January–September 2014. Daily ambient air pollution data were obtained from nearby central air-monitoring stations. Mixed-effects models were used to estimate the associations between exposures and health measurements with adjustment for potential confounders including temperature and relative humidity.
Results: Increasing levels of air pollutants were associated with significant increases in both FeNO and FeH_2S. Interquartile range (IQR) increases in $PM_{2.5}$ (76.5 μg/m^3, 5-day), PM_{10} (75.0 μg/m^3, 5-day) and SO_2 (45.7 μg/m^3, 6-day) were associated with maximum increases in FeNO of 13.6% (95% CI: 4.8%, 23.2%), 9.2% (95% CI: 2.1%, 16.8%) and 34.2% (95% CI: 17.3%, 53.4%), respectively; and the same IQR increases in $PM_{2.5}$ (6-day), PM_{10} (6-day) and SO_2 (7-day) were associated with maximum increases in FeH_2S of 11.4% (95% CI: 4.6%, 18.6%), 7.8% (95% CI: 2.3%, 13.7%) and 18.1% (95% CI: 5.5%, 32.2%), respectively. Increasing levels of air pollutants were also associated with increased odds ratios of sore throat, cough, sputum, wheeze and dyspnea.
Conclusions: FeH_2S may serve as a novel biomarker to detect adverse respiratory effects of air pollution. Our results provide potential important public health implications that ambient air pollution may pose risk to respiratory health in the context of high pollution levels in densely-populated cities in the developing world.

1. Introduction

Chronic obstructive pulmonary disease (COPD), characterized by persistent progressive airway obstruction and chronic inflammation (Chung and Adcock, 2008), has high prevalence worldwide and in China (Buist et al., 2007; Zhong et al., 2007) and will become the third leading cause of death worldwide by 2020 (Vestbo et al., 2013). Ambient air pollution is among the leading risk factors of COPD morbidity and mortality (Bentayeb et al., 2012; Viegi et al., 2006). A number of studies have used respiratory symptoms as the indicators to examine the respiratory effects of ambient air pollution in COPD (Viegi et al., 2006; Ko and Hui, 2012). However, most of these studies have been conducted in developed countries where air pollution levels are relatively low (Peacock et al., 2011).

Exhaled nitric oxide (FeNO) is a noninvasive measurement of airway inflammation that reflects eosinophilic airway inflammation among COPD patients (Barnes et al., 2010; Dweik et al., 2011). FeNO has been frequently used to assess the adverse respiratory effects associated with air pollution exposure (Scarpa et al., 2014), but only a few studies have used this marker to investigate air pollution effects in COPD patients (Adamkiewicz et al., 2004; Jansen et al., 2005; Chen et al., 2015). Along with FeNO, exhaled hydrogen sulfide (FeH_2S) is another noninvasive biomarker that is involved in the pathogenesis of airway obstruction and may be used to estimate the neutrophilic airway inflammation in COPD (Wang, 2002; Chen et al., 2005; Calvert et al.,

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2010; Saito et al., 2014; Zhang et al., 2015). Specifically, a recent study found that COPD patients without eosinophilia had significantly higher levels of FeH_2S than those with eosinophilia, suggesting that increased levels of FeH_2S predicted a non-eosinophilic phenotype of COPD in the study population (Zhang et al., 2015). However, no study has ever used FeH_2S as a surrogate to investigate the airway inflammation associated with air pollution exposure in COPD patients.

Ambient air pollution levels are high in Asian countries, especially in some Chinese megacities (Chan, 2008). For example, the annual average $PM_{2.5}$ and PM_{10} concentrations in Beijing, China were 85.9 μg/m^3 and 115.8 μg/m^3 in 2014, respectively (Bureau, 2014). These levels are >5 to 8 folds higher than the annual guidelines (10 μg/m^3 for $PM_{2.5}$ and 20 μg/m^3 for PM_{10}) recommended by World Health Organization. However, to our knowledge, no study has ever investigated the short-term effects of ambient air pollution on the airway inflammation and respiratory symptoms simultaneously in COPD patients in China or other Asian countries.

In the present study, we conducted a panel study to examine the associations between short-term exposure to high ambient air pollution and airway inflammation measured by FeNO and FeH_2S and occurrence of respiratory symptoms in COPD patients during two study periods in Beijing, China.

2. Methods

2.1. Study participants and design

We used a panel study design to investigate the potential effects of short-term ambient air pollution exposures on the airway inflammation and respiratory symptoms in a group of COPD patients in the context of high pollution levels in Beijing, China. A total of 25 physician-diagnosed stable COPD patients were recruited from Peking University Third Hospital in Beijing during September to December 2013. Details on inclusion and exclusion criteria and data collection on demographics could be found in the Appendix. The exhaled breath samples were collected and measured by trained study personnel over the following two periods with varying levels of air pollution: Period 1 from January 2nd to April 9th 2014 (cold season) and Period 2 from August 11th to September 27th 2014 (warm season). During Period 1, we collected repeated exhaled breath samples every 5–7 days for 3 to 13 times for 22 participants (totally 138 samples). During Period 2, we conducted repeated exhaled breath samples collection for 2 to 8 times for 11 participants (totally 77 samples). Two participants dropped out during the study (one of them left the study area and the other had non-respiratory system surgery). The remaining participants included 21 males and 2 females, among whom 10 participated in both study periods, 12 participated in Period 1 and 1 participated in Period 2. The average number of exhaled breath samples was 9.3 (ranged from 3 to 21) for the 23 participants over the study. During the study period, the participants also recorded diary cards for respiratory symptoms every night for an average of 34.5 days (ranged from 11 to 81 days) to indicate whether they had respiratory symptoms during the last 24 h or not. The study was approved by the Institutional Review Board of Peking University Health Science Center, and the written informed consent was obtained from each participant before the study began.

2.2. Exhaled breath measurements

The exhaled breath samples were collected at participant's residence according to the ATS/ERS guidelines by asking the participant to inhale orally to full lung capacity and then immediately perform a slow vital capacity maneuver against an expiratory resistance into the reservoir bags (3L) without a breath hold (American Thoracic and European, 2005). A nose clip was used to avoid nasal inspiration (Liu et al., 2014) and the participants were asked to refrain from eating, drinking and taking drugs for at least 2 h before the collection of the exhaled breath samples (Yoda et al., 2012). The collection was repeated twice for each participant. The reservoir bags were sealed immediately at the end of the maneuver and stored at the room temperature until analysis. The FeNO and FeH_2S were analyzed using the portable NO gas detector (4540-1999b, Interscan Corporation, USA) and portable H_2S gas detector (4170-1999b, Interscan Corporation, USA) in the laboratory within 4 h after collection, respectively. The detectors were zero calibrated using a filter type C-12 before each measurement. Then the exhaled breath sample was directed to the sampling ports of the detectors and absorbed into the detectors with the concentrations of the FeNO or FeH_2S converted out. The sample pump flow rate of the detectors was controlled and set at approximately 1 L/min. For each participant, FeNO and FeH_2S concentrations were analyzed twice separately, and the average concentration was used in data analysis.

2.3. Environmental measurements

During the study period, the hourly average concentrations of ambient air pollutants particulate matter with aerodynamic diameter ≤2 .5 μm ($PM_{2.5}$), particulate matter with aerodynamic diameter ≤10 μm (PM_{10}), sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) from the nearest city central air-monitoring stations (distances ranged between 1.6 and 8.8 km) were obtained from Beijing Municipal Environmental Monitoring Center (http://zx.bjmemc.com.cn/). Hourly meteorological (including temperature and relative humidity) data measured by national environmental monitoring stations near the participant's residence was downloaded from China Meteorological Administration (http://www.weather.com.cn). Average exposure concentrations were calculated from hourly air pollutant concentrations during 1 day to 7 days before the measurements of exhaled breath samples and symptom records for each participant.

2.4. Statistical analysis

We used linear mixed-effect models to estimate the associations between air pollutants and FeNO and FeH_2S. Because the FeNO and FeH_2S levels were log-normally distributed, the logarithms of the measurements were used for analysis (Yoda et al., 2012). We used generalized linear mixed models with binary distribution to estimate the associations between air pollutants and occurrence of respiratory symptoms, including sore throat, cough, sputum, wheeze and dyspnea (Sarnat et al., 2012; Mar et al., 2004). All mixed models included a random intercept for each study participant. The respiratory health indicators were regressed on moving average concentrations of exposure variables from 1 day to 7 days before the measurements to estimate the potential cumulative effects of the exposures. Results were reported as estimated percent changes in FeNO and FeH_2S and odd ratios (OR) of respiratory symptoms per interquartile range (IQR) increases in exposures. The estimated percent changes were calculated as $[10^{(\beta \times IQR)} - 1] \times 100\%$, with 95% confidence intervals (CIs) $\{10^{[IQR \times (\beta \pm 1.96 \times SE)]} - 1\} \times 100\%$, where β and SE are the effect estimate and its standard error (Wu et al., 2008). Both single-pollutant and two-pollutant models were performed to examine the consistency the exposure effects.

The multivariable-adjusted models controlled for an array of potential confounding variables. To control for the variability between participants, we adjusted for the personal characteristics age, gender and body mass index (BMI) in the models. A day-of-study variable was included in the models as a fixed-effect term to control for the long-term time trend (Penttinen et al., 2001) and a day-of-week variable was also included in the models as a fixed-effect term to control for the weekly temporal variation. A binary variable for daily timing (morning/afternoon) of the exhaled breath measurement was included in models for FeNO and FeH_2S to control for diurnal variation. Meteorological variables (including temperature and relative humidity) at the same exposure metrics as of the air pollutants were included to control for other environmental effects. An autoregressive-1 covariance structure