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Associations of urinary polycyclic aromatic hydrocarbon metabolites with fractional exhaled nitric oxide and exhaled carbon monoxide: A cross-sectional study

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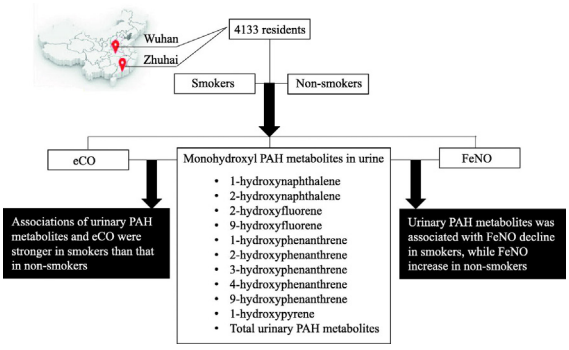
HIGHLIGHTS

- Estimating associations of urinary PAH metabolites (OH-PAHs) with FeNO and eCO levels
- Urinary PAH metabolites were significantly associated with levels of eCO and FeNO.
- Associations of urinary PAH metabolites and eCO were stronger in smokers than that in non-smokers.
- PAH metabolites were associated with FeNO decline in smokers, while FeNO increase in non-smokers.

GRAPHICAL ABSTRACT



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ABSTRACT

Exposure to Polycyclic aromatic hydrocarbons (PAHs) has been associated with inflammatory responses. Fractional exhaled nitric oxide (FeNO) and exhaled carbon monoxide (eCO) are both important inflammatory mediators especially in airways. However, few studies have investigated associations of PAH exposures with FeNO or eCO. Therefore, we aimed to quantify the associations of urinary PAH metabolites with FeNO and eCO levels, and investigate their potential effect modifiers by linear mixed models among 4133 participants from the Wuhan-Zhuhai cohort in China. We further performed stratified analyses to estimate effect modification. We found significant associations of increased urinary PAH metabolites with elevated eCO and FeNO. Among all participants, each 1% increase of 1-hydroxynaphthalene, 2-hydroxynaphthalene, 2-hydroxyfluorene, 4-hydroxyphenanthrene, 3-hydroxyphenanthrene, and total PAH metabolites was significantly associated with a 12.6% (95% confidence interval: 9.3%, 15.9%), 9.7% (6.5%, 12.9%), 7.5% (4.1%, 10.9%), 3.2% (0.2%, 6.2%), 2.7% (0.1%, 5.3%), and 6.5% (2.7%, 10.4%) increased eCO level, respectively; while each 1% increase of urinary 1-hydroxynaphthalene, 9-hydroxyphenanthrene, 3-hydroxyphenanthrene, and 2-hydroxyphenanthrene was associated with a −3.0% (−5.8%, −0.2%), 2.9% (0.3%, 5.6%), 3.2% (1.0%, 5.4%), and 4.5% (2.2%, 6.9%) change of FeNO level, respectively. Positive associations between certain urinary PAH metabolites and eCO were observed among both ever-smokers and non-smokers, and the associations were stronger among ever-smokers than that among non-smokers. Increased

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urinary PAH metabolites were associated with decreased FeNO among ever-smokers and elevated FeNO levels among non-smokers. Our findings suggest that PAH exposures may impair airway through inducing inflammatory response, especially among ever-smokers.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are considered as one kind of the most widespread organic environmental pollutants. The US Environmental Protection Agency (EPA) has classified seven PAH compounds as probable human carcinogens, including benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz(a,h)anthracene, and indeno(1,2,3-cd)pyrene (U.S. EPA, 1993; ATSDR, 2011). Exposure to PAHs is associated with increased risk of malignant tumors in skin, lung, bladder, liver, and stomach (Mastrangelo et al., 1996; Boffetta et al., 1997; Liao et al., 2014; White et al., 2016). Recent studies reported that inhalation or dietary intake of PAHs can impair respiratory system, leading to lung function decline and respiratory diseases (i.e. COPD and asthma) (Burstyn et al., 2003; Al-Daghri et al., 2013; Zhou et al., 2016b). However, the mechanism for PAHs causing respiratory damages is unclear. Oxidative stress and inflammatory response have been implicated in the pathogenesis of lung diseases (MacNee, 2001; Gerritsen et al., 2005). Although certain classical markers of oxidative stress and inflammation such as reactive oxygen species (ROS) and C-reactive protein (CRP) are increased after exposure to PAHs (Park et al., 2008; Farzan et al., 2016), they mainly reflect the levels of systemic inflammation and are nonspecific to lung or airway injury.

Endogenous nitric oxide (NO) is an important inflammatory mediator. Accumulated experimental evidence suggest that inflammation can induce inducible nitric oxide synthase (iNOS), which are expressed in resident and inflammatory cells and activated by inflammatory cytokines (Tatsumi et al., 2000; Kwon et al., 2001). iNOS can produce NO and lead to elevated NO level in exhaled breath (Fractional exhaled nitric oxide, FeNO). Therefore, FeNO originates in the airway epithelium, and acts as an important marker of airway inflammation (Martini et al., 2012; Haccuria et al., 2014). Similar to NO, CO is another important biological mediator reflecting the inflammation Exhaled CO (eCO) from humans is recently related with endogenous levels of CO, which is induced by inducible heme oxygenase (HO-1), and increased after oxidant injuries and inflammation (Choi and Alam, 1996; Slebos et al., 2003; Barnes et al., 2006). Both FeNO and eCO are also important biological inflammatory mediators, and can be used as specific and easy-to-measure clinical markers of some respiratory system diseases (Zayasu et al., 1997; Van Muylem et al., 2007; Zhang et al., 2013). The levels of eCO and FeNO can be affected by air pollutants such as cigarette smoke, cooking fuel or traffic exhaust, which are important sources of PAHs (McSharry et al., 2005; Sundy et al., 2007; Alshaarawy et al., 2013; Zhang et al., 2013; Berhane et al., 2014; Obaseki et al., 2014). However, the association of PAH exposures with eCO or FeNO is still unclear.

In the present study, we used urinary monohydroxyl metabolites of naphthalene, fluorene, phenanthrene, and pyrene to assess human exposures to PAHs from all sources. We also measured the levels of eCO and FeNO for 4133 adults from the Wuhan-Zhuhai Cohort in China. Our aim was to investigate the associations of urinary PAH metabolites with eCO and FeNO among adult residents in Wuhan and Zhuhai, China, as well as their potential effect modifiers.

2. Materials and methods

2.1. Study population

This cross-section study is a sub-study of a community-based and prospective cohort, the Wuhan-Zhuhai cohort study, which has been described elsewhere (Song et al., 2014). In brief, the study was established between 2011 and 2012, and enrolled 4812 participants aged 18 to 81 who lived in Wuhan (N = 3053) or Zhuhai City (N = 1759) for more than five years. All the residents were informed by community committees and invited for examinations voluntarily. Residents who had severe illnesses or unable to attend clinic visits were excluded from the study. A face-to-face interview was conducted for each participant by trained investigators. Health and lifestyle questionnaires covered information on demographic characteristics, occupational hazards exposure, smoking history, passive smoking history, alcohol consumption, regular physical activity, cooking and disease history. Smoking amount (pack-years) for each smoker was calculated as packs of cigarettes per day multiplied by years of smoking. Passive smoking amount was calculated as hours of cigarettes per week multiplied by years of passive smoking. With exclusion of 679 participants who failed to complete collection of urine, or measurements for eCO or FeNO, there were 4133 participants enrolled in the final analysis. All participants in this study have given written informed consent for participation. The research protocol was approved by the Ethics and Human Subject Committee of Tongji Medical College, Huazhong University of Science and Technology.

2.2. Urinary PAH metabolite and urinary Creatinine determination

We extracted 3 ml of the urine sample to measure the concentrations of twelve PAH metabolites, including 1-hydroxynaphthalene (1-OHNa), 2-hydroxynaphthalene (2-OHNa), 2-hydroxyfluorene (2-OHFlu), 9-hydroxyfluorene (9-OHFlu), 1-hydroxyphenanthrene (1-OHPh), 2-hydroxyphenanthrene (2-OHPh), 3-hydroxyphenanthrene (3-OHPh), 4-hydroxyphenanthrene (4-OHPh), 9-hydroxyphenanthrene (9-OHPh), 1-hydroxypyrene (1-OHP), 6-hydroxychrysene (6-OHChr), and 3-hydroxybenzo[*a*]pyrene (3-OHBaP). The samples were buffered with sodium acetate (0.5 M, pH 5.0), spiked with diluted internal standards. Deuterated1-hydroxypyrene, deuterated 1-hydroxynaphthalene (Toronto Research Chemicals, Toronto, Canada and C/D/N isotopes Inc. Beijing, China, respectively), and hydrolyzed enzymatically by β-Glucuronidase with sulphatase activity (Sigma-Aldrich, Milan, Italy) at 37 °C overnight. After hydrolysis, samples were extracted by n-hexane, and the extracts were evaporated under a gentle stream of nitrogen (N-EVAP 112, Organomation Associates Inc., MA, USA). BSTFA [N,O-Bis (trimethylsilyl) trifluoroacetammide with 1% trimethylchlorosilane, Regis Technologies, Inc. Morton Grove] was added to the residue and the mixture was incubated at 90 °C for 45 min. After derivatization, 1 μl of each sample was injected on the gas chromatography–mass spectrometry (Agilent 5975B/6890 N GC/MS System, Santa Clara, CA, USA). The identification and quantification of urinary PAH metabolites were based on the retention time, mass-to-charge ratio, and peak area using a linear regression curve obtained from separate internal standard solutions (Campo et al., 2008; Li et al., 2012). For quality control, we fitted a standard curve for each 100 samples and calculated R square (R^2 > 0.996). Reproducibility was also assessed with repeated measurements from 10% samples with coefficient of variation below 10%. The recoveries of 12 OH-PAHs were in the range of 54–92%. The concentrations of both 6-OHCHR and 3-OHBAP in urine were below the limits of detection (LOD), and we therefore did not include the two urinary PAH metabolites in the final analysis. The LOD for the urinary PAH metabolites ranged from 0.1 to 0.9 μg/l, and the concentrations of those samples below the LOD were replaced by 50% of the LOD value. We measured the levels of