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Air pollution and diastolic function in elderly women – Results from the SALIA study cohort

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ABSTRACT

Background: Studies linking particulate matter (PM) with heart failure (HF) show inconsistent results. However, the association of air pollution with diastolic function, an important determinant of heart failure, has not been studied yet and is addressed in the presented study.
Methods: 402 women (69–79 years) of the clinical follow-up (2007–2010) of the ongoing population-based prospective SALIA (Study on the influence of Air pollution on Lung function, Inflammation and Ageing) cohort were examined using Doppler echocardiography: Of the 291 women with preserved ejection fraction, the ratio of peak early diastolic filling velocity and peak early diastolic mitral annulus velocity (E/E') was collected in 264 and left atrial volume index (LAVI) in 262 women.

Residential long-term air pollution exposure (nitrogen oxides, size-fractioned PM) was modeled at baseline and at follow-up, applying land use regression models. We used linear regression to model the cross-sectional associations of air pollutants per interquartile range (IQR) with different measures of diastolic function, adjusting for personal risk factors.
Results: Median concentrations of annual NO_x, NO_2, $PM_{2.5}$, and PM_{10} at follow-up were 37.7, 25.9, 17.4 and 26.4 $\mu g/m^3$, respectively. In the fully adjusted models, LAVI was associated with an IQR increase in $PM_{2.5}$ (1.05 [0.99; 1.12]) and NO_x (1.04 [1.00; 1.09]) at follow-up, and with NO_x and NO_2 (both 1.05 [1.00; 1.11]) at baseline. None of the pollutants were clearly associated with E/E'.
Conclusions: In this analysis of elderly women, we found suggestive evidence for an association of air pollution with impaired diastolic function.

1. Introduction

Cardiovascular diseases are the leading cause of death worldwide: In 2012, 17.5 million people died of them, representing a third of all global death cases (WHO, 2015). Among cardiovascular disease, heart failure (HF) is a growing health burden as a chronic and severe cardiovascular entity: 23 million people are estimated to suffer from HF globally. Whereas incidence remains stable, prevalence has been increasing during the last decades mainly due to demographic aging of the (western) populations (Bui et al., 2012).

Several studies suggest an association between air pollution and outcomes related to HF. Epidemiological studies showed that short-term (Dominici et al., 2006; Symons et al., 2006; Wellenius et al., 2006) and long-term (Pope et al., 2004) exposure to particulate matter (PM) was related to increased hospitalization rates for HF. Moreover, mortality due to HF was associated with different long-term air pollutant concentrations in the Netherlands (Hoek et al., 2001). In a study following HF patients for 5 years,

Abbreviations: ATC, Anatomical Therapeutic Chemical classification; BMI, Body Mass Index; BNP, plasma B-type (brain) natriuretic peptide; HF, heart failure; HDL, high density lipoprotein-cholesterol; IQR, interquartile range; LAVI, left atrial volume index; LUR, land use regression; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LDL, low density lipoprotein-cholesterol; MESA, North-American Multi-Ethnic Study of Atherosclerosis; PM, particulate matter; SALIA, Study on the Influence of Air Pollution on Lung, Inflammation and Ageing.

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exposure to residential air pollution increased the mortality risk (Medina-Ramón et al., 2008). No studies so far have investigated, whether air pollution contributes to the development of the disease.

HF with diastolic dysfunction and preserved ejection fraction represents about half of all HF cases. Predictors and comorbid conditions that are associated with diastolic dysfunction and HF with preserved ejection fraction are older age, hypertension, diabetes, angina pectoris, myocardial infarction, overweight, obesity (Abhayaratna et al., 2006), left ventricular (LV) hypertrophy (Fischer, 2003), lower hemoglobin levels and atrial fibrillation (Owan et al., 2006). Several air pollution-related pathomechanisms have been identified that could also promote the air pollution-related development of HF, including the induction of hypertension, arrhythmias, autonomic nervous system imbalance, subclinical inflammation, atherosclerosis and vascular dysfunction (Atkinson et al., 2013; Brook et al., 2010; Franchini and Mannucci, 2009; Fuks et al., 2011; Gill et al., 2011; Hoffmann et al., 2007; Mills et al., 2009).

Up to now, only toxicological studies (Tankersley et al., 2008; Wold et al., 2012) investigated explicitly the effect of exposure to air pollution on diastolic function. This is the first epidemiological study investigating the association of long-term PM air pollution exposure with indicators of diastolic function. We make use of cross-sectional data from the population-based SALIA (Study on the Influence of Air Pollution on Lung) cohort in the Ruhr Area of Western Germany with detailed residential exposure assessment for long-term air pollution exposure and information on echocardiographic indicators of diastolic function.

2. Methods

2.1. Study population

The ongoing SALIA cohort study (see Fig. 1) is based on baseline examinations that were performed between 1985 and 1994 as part of the Environmental Health Surveys in North-Rhine Westphalia (West Germany). Five different study areas from the highly industrialized Ruhr Area [Dortmund, Duisburg, Essen, Gelsenkirchen, and Herne] were chosen to represent a range of polluted areas with high-traffic load as well as high emissions from steel and coal industry. Additionally, two nearby non-industrialized towns [Borken and Dülmen] were chosen as areas with low air pollution. All women aged 54–55 years living in the above mentioned areas were invited to participate in the study. In the study area, approximately 7000 women were eligible, leading to a response rate of 70%. Many men living in the Ruhr area in the 1985s had worked in mines or heavy industry and thus were highly exposed occupationally to PM there. Therefore, in this study focusing environmental exposures, only women were recruited.

Out of those women who had received a lung function test at baseline and who had at the same time expressed their willingness to participate in a follow-up examination, 834 women were invited to take part in the clinical follow-up examination (2007–2010). The first 402 women additionally participated in an ancillary cardiovascular study from April 2007 to November 2008 (Krämer et al., 2010; Schikowski et al., 2007, 2005; Vossoughi et al., 2014). The ancillary cardiovascular examination consisted of an assessment of the medical history, physical examination, measurement of B-type natriuretic peptide (BNP), electrocardiography, and echocardiography.

The protocol of the study was approved by the Medical Ethic Committee of the Ruhr University Bochum.

2.2. Assessment of covariates

According to the standardized study protocol, each participant of the SALIA follow-up study was interviewed for a detailed medical history, including diabetes mellitus, lung diseases, cardiometabolic risk factors, cardiovascular diseases, medication and life-style variables. Physical examination comprised echocardiography, blood pressure measurement, anthropometry, spirometry, and comprehensive serological analyses. Blood pressure at rest was measured with a sphygmomanometer at the right upper arm. Hypertension was diagnosed by medical history, medication and blood pressure measurement. Arterial hypertension was defined as systolic pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg and/or antihypertensive medication which were based on the Anatomical Therapeutic Chemical (ATC) classification system using the ATC-codes C02, C03, C07, C08 and C09. High density lipoprotein (HDL) and low density lipoprotein (LDL) in pg/ml were collected from blood samples; statins were defined by means of ATC-code C10. Socioeconomic status was stratified into three categories by the maximum period of education (8 years, 10 years and $\geq$12 years) achieved by either the participating woman or her husband. Additionally, the area level mean income (Euro net income) per capita in 2008 at the postcode of the participants' addresses was used as covariate. Women were grouped according to their smoking habits as never smokers, past smokers, or current smokers. Passive smoking (at residence or at work) was included in the questionnaire as yes or no. Alcohol consumption was self-classified as never, seldom, weekly or daily consumption. Physical activity was included as total hours of physical activity per week and as statement concerning regular physical activity during lifetime.

2.3. Assessment of outcomes

The supplementary cardiovascular examinations included measurements of BNP levels at the same day as electrocardiography and echocardiography. The blood samples were collected in EDTA-containing tubes. After prompt centrifugation, BNP was measured using a chemiluminescent immunoassay kit (Biosite Triage, San Diego, CA, USA). Electrocardiography was analyzed for arrhythmias.

Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography (Lang et al., 2005) using a digital ultrasound scanner (Vivid 7, General Electrics, Horton, Norway). Left atrial volume was measured by manual tracing of end-systolic endocardial borders using the apical 4-chamber view. LV myocardial mass was calculated according to the Devereux formula, the Quinones formula was used for measurement of the LVEF and values were averaged for each patient (Germing et al., 2011). Peak velocities of early (E) and late (A) diastolic filling and deceleration time were derived from the transmitral Doppler profile (Zile et al., 2004). Tissue Doppler imaging was taken from the medial mitral annulus and analyzed for early (E') diastolic peak velocities (Ommen et al., 2000). Mitral E/E', ratio of peak early diastolic filling velocity and peak early diastolic mitral annulus velocity was subsequently calculated. The ratio E/E' as an indicator of diastolic function (Paulus et al., 2007) was used as primary outcome measure. Additionally, LAVI as an indicator for diastolic function severity and predictor for CV disease risk and burden (Tsang et al., 2003) was used as continuous outcome measure. Higher values for E/E' and LAVI indicate a decrease in diastolic function. According to the diagnostic flowchart of Paulus et al. (2007), E/E' values of <8 indicate normal diastolic function. Diagnosis of diastolic dysfunction was defined as an E/E' ratio exceeding 15. If measurements showed E/E' ratios of 8–15, other indicators were included: LAVI (left atrial volume index) >40 ml/m^2 body surface, or LVMI (left ventricular mass index) >122 g/m^2 body surface, or transmitral E/A ratio <0.5 plus deceleration time >280 ms, or blood

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