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The impact of decreases in air temperature and increases in ozone on markers of endothelial function in individuals having type-2 diabetes

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ABSTRACT

Several studies have reported an association between air pollution and endothelial dysfunction, especially in individuals having diabetes. However, very few studies have examined the impact of air temperature on endothelial function. The objective of this analysis was to investigate short-term effects of temperature and ozone on endothelial function in individuals having diabetes. Moreover, we investigated interactive effects between air temperature and air pollution on markers of endothelial function. Between November 2004 and December 2005 flow-mediated dilatation (FMD), nitroglycerin-mediated dilatation (NTGMD) and several blood markers representing endothelial function were measured using brachial artery ultrasound on four consecutive days in 22 individuals with type-2 diabetes mellitus in Chapel Hill, North Carolina (USA). Daily measurements of meteorological parameters, ozone and particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) were obtained from fixed monitoring sites. We used additive mixed-models adjusting for time trend, day of the week, relative humidity and barometric pressure to assess temperature and ozone associations with endothelial function. A 1 °C decrease in the 24-h temperature average was associated with a decrease in mean FMD on the same day (−2.2% (95%-confidence interval:[−4.7;0.3%])) and with a delay of one and four days. A temperature decrement also led to an immediate (−1.7%[−3.3;−0.04]) decrease in NTGMD. Moreover, we observed an immediate (−14.6%[−26.3;−2.9%]) and a one day delayed (−13.5% [−27.0; 0.04%]) decrease in FMD in association with a 0.01 ppm increase in the maximum 8-h moving average of ozone. Temperature effects on FMD strengthened when $PM_{2.5}$ and ozone concentrations were high. The associations were similar during winter and summer. We detected an association between temperature decreases and ozone increases on endothelial dysfunction in individuals having diabetes. We conclude that endothelial dysfunction might be a possible mechanism explaining cardiovascular events in association with environmental stimuli.

1. Introduction

Air pollution and air temperature have been shown to be associated with cardiovascular events (Brook et al., 2010, 2011; Henrotin et al., 2010; Rückerl et al., 2011; Wolf et al., 2009). Individuals with diabetes are especially susceptible to environmental stimuli (Schwartz, 2005; Stafoggia et al., 2010; Zanobetti and Schwartz, 2001) due to vascular abnormalities such as an impaired function of the vascular endothelium (Calles-Escandon and Cipolla, 2001). Observational studies have shown that endothelial dysfunction is associated with the occurrence of

Abbreviations: AIC, Akaike's Information Criterion; BMI, body mass index; CI, confidence interval; ELISA, enzyme-linked immunosorbent assays; EPA, Environmental Protection Agency; EPHD, Environmental Public Health Division; E-Selectin, soluble endothelial-leukocyte adhesion molecule; FMD, flow-mediated dilatation; IQR, interquartile range; NO, nitric oxide; NTGMD, nitroglycerin-mediated dilatation; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; P-splines, penalized splines; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; T2D, type-2 diabetes; UNC, University of North Carolina; vWF, von Willebrand factor.

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cardiovascular events (Deanfield et al., 2007; Lerman and Zeiher, 2005; Vita and Keaney, 2002; Widlansky et al., 2007). Moreover, it has been suggested that endothelial dysfunction might be one of the biological mechanisms explaining cardiovascular events in association with environmental changes (Nawrot et al., 2005; Widlansky et al., 2007). Several studies have reported an association between air pollution and endothelial dysfunction (Briet et al., 2007; Brook, 2002; Hashemi et al., 2012; O'Neill et al., 2005; Schneider et al., 2008). However, only a few studies have examined the impact of air temperature on endothelial function (Nawrot et al., 2005; Widlansky et al., 2007; Zanobetti et al., 2014), and little is known about the interaction between air temperature and air pollution (Burkart et al., 2013; Roberts, 2004; Stafoggia et al., 2008).

Flow-mediated dilatation (FMD) of the brachial artery – quantified as the percent change in diameter induced by reactive hyperemia – is a marker of endothelial function. FMD occurs predominantly through the release of nitric oxide (NO) by endothelial cells and reflects the bioavailability of NO (Corretti et al., 2002; Deanfield et al., 2007; Faulx et al., 2003; Gokce et al., 2003). Soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble endothelial-leukocyte adhesion molecule (E-Selectin) are specific markers for endothelial cell activation, and von Willebrand factor (vWF) is a largely endothelium derived blood glycoprotein involved in platelet adhesion (Deanfield et al., 2007). Increased levels of sICAM-1 and sVCAM-1 have been shown to be associated with cardiovascular events (Ballantyne and Entman, 2002; Deanfield et al., 2007).

The objective of this analysis was to investigate the short-term effects of air temperature and ozone on FMD, nitroglycerin-mediated dilatation (NTGMD), sICAM-1, sVCAM-1, E-Selectin and vWF in type-2 diabetes (T2D). Moreover, we aimed to evaluate interactive effects between air temperature and air pollution on markers of endothelial function. In this context, we examined interactive effects between air temperature and ozone as well as air temperature and particulate matter with an aerodynamic diameter $\leq 2.5\ \mu m$ ($PM_{2.5}$).

Studies so far reported an immediate (same day) decrease in FMD in association with changes in air pollution and air temperature (Nawrot et al., 2005; Schneider et al., 2008). Therefore, we also expected an immediate effect of air temperature decreases and ozone increases on endothelial function. Moreover, the association between air temperature and endothelial function is assumed to be similar during winter and summer as it was shown for the association between air temperature and myocardial infarction (Wolf et al., 2009). Nawrot et al. reported a linear relationship between air temperature and endothelial function (Nawrot et al., 2005). Moreover, a study conducted by Halonen et al. showed a linear relationship between air temperature and blood markers of endothelial function (Halonen et al., 2010). Therefore, we expected a linear response relationship between decreases in air temperature and changes in endothelial function.

2. Methods

2.1. Study design and study population

Between November 2004 and December 2005, a prospective panel study was conducted in individuals with T2D in Chapel Hill, North Carolina (USA). Persons with T2D aged 48 to 78 years were identified through the University of North Carolina (UNC) Diabetes Care Center as well as newspaper advertisements. The following inclusion criteria had to be fulfilled for each participant: 1) T2D, but without insulin treatment; 2) a stable medication regimen throughout their participation in the study; and 3) normal sinus rhythm. Individuals with the following characteristics were excluded from the study: 1) smoking or recent past-smoking, defined as more than one pack of cigarettes within the year before enrollment; 2) hematocrit $< 36\%$; 3) medical history or health problems precluding participation, decided by the study physician, like pacemaker or implanted cardioverter defibrillator, history of atrial fibrillation, history of solid organ transplant, dialysis therapy, cancer or history of cancer within the last five years, hepatitis B or C, unstable angina, hypersensibility to nitroglycerin/nitrates/nitrites, or respiratory tract infection within the preceding four weeks; 4) a recent vascular event or intervention less than six months or a year ago, depending on the intervention, (e.g. coronary artery graft bypass surgery or percutaneous coronary intervention); or 5) pregnancy. Participants were asked to refrain from vigorous exercise on study mornings as well as to refrain from taking antioxidants (e.g. vitamins C and E), fish oil, niacin, arginine, over-the-counter vasoactive agents (e.g. decongestants), anti-inflammatory agents (e.g. ibuprofen or aspirin) unless it was prescribed as a daily medication (in which case it was continued), for the week before and the week of the study. Moreover, participants were asked to refrain from the usage of phosphodiesterase enzyme inhibitors during the week of study.

The study was conducted at the U.S. Environmental Protection Agency's (EPA) National Health and Environmental Effects Research Laboratory, Environmental Public Health Division (EPHD) in Chapel Hill, North Carolina. Data on demographics, medication, health and smoking status were obtained at baseline as well as at follow-up visits via questionnaires. All participants gave written informed consent. The University of North Carolina Human Studies Biomedical Institutional Review Board and the U.S. EPA approved the study protocol.

2.2. Clinical measurements

Participants visited the study site on five consecutive weekdays starting on Monday morning of each examination week. On the first day, the participants completed a baseline questionnaire. On each of the next four consecutive mornings, the participants came to the study site having fasted since midnight and without having taken diabetes medication. FMD and NTGMD of the brachial artery were measured using ultrasound (HDI 5000 ATL ultrasound machine equipped with a 12.5 MHz transducer (Philips, Bothell, WA, USA)) based on the guidelines published by Corretti et al. (2002). Moreover, blood pressure was measured at rest. FMD measures the endothelium-dependent increase in blood vessel diameter in response to reactive hyperemia, as previously described by Schneider et al. (2008). After baseline images of the artery were recorded, reactive hyperemia was induced through inflation of a pneumatic tourniquet positioned proximal to the antecubital fossa to 50 mmHg above systolic blood pressure for 5 min. After abrupt deflation of the tourniquet images of the brachial artery were recorded once more for 90 s. FMD was quantified as the percent change in brachial artery diameter. NTGMD, an endothelium-independent index of vascular reactivity, was then measured. A second baseline image was acquired after a rest of 15 min. Five minutes after administration of 400 μg sublingual nitroglycerin spray, a final image of the artery was acquired. NTGMD was calculated as the percent change in blood vessel diameter in response to nitroglycerin.

At each visit blood was collected in citrated tubes, and plasma isolated and stored at $-80\ ^{\circ}C$ until the end of the study. sICAM-1, sVCAM-1, E-Selectin, and vWF were measured in blood. Moreover, sICAM-1, sVCAM-1 and E-Selectin were quantified using commercially available enzyme-linked immunosorbent assays (ELISA) kits purchased from Lincoplex (Linco Research, Inc., St. Charles, MO) and run on a Luminex 100 Multiplex system. ELISA assays were developed using paired antibodies for vWF purchased from Diagnostica Stago (Asnieres-Sur-Seine, France) as described by Schneider et al. (2010).

2.3. Meteorological and air pollution measurements

Continuous 2-min measurements of air temperature, relative humidity, and barometric pressure were obtained from the EPHD rooftop approximately 30 m above ground level. We calculated 24-h averages for the meteorological parameters if at least 66% of the 2-min measurements were available on a day. Daily 24-h concentrations (midnight to midnight) of $PM_{2.5}$ network data were obtained from a monitoring site located approximately 44 km (27 miles) east of the EPHD. In addition, 9 a.m. to 9 a.m. concentrations of $PM_{2.5}$ measured at the EPHD rooftop were available. The Spearman correlation between both measurements was 0.85 and rooftop $PM_{2.5}$ data was used to impute 3 days of missing network data based on a linear regression model. Rooftop data for meteorological data was complete. Hourly means of ozone concentration were measured at monitoring sites in Wake and Durham Counties, NC, located 42 km (26 miles) and 20 km (12 miles) away from the EPHD. The Spearman correlation between the two sites in Wake County and Durham County was 0.90. Ozone data obtained from Durham County were used to impute missing data in Wake County based on a linear regression model. We calculated maximum 8-h moving averages to analyze effects of ozone concentration. Furthermore, we considered the following time lags for meteorological and air pollution parameters in order to assess immediate, delayed or cumulative effects: 24-h averages of the examination day (lag 0), averages of 24–47 h (lag 1), 48–71 h (lag 2), 72–95 h (lag 3), 96-119 h (lag 4) before the visits and a 5-day average (lag 04).