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Circulating levels of persistent organic pollutants (POPs) are associated with left ventricular systolic and diastolic dysfunction in the elderly

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ABSTRACT

Background and objective: Major risk factors for congestive heart failure (CHF) are myocardial infarction, hypertension, diabetes, atrial fibrillation, smoking, left ventricular hypertrophy (LVH) and obesity. However, since these risk factors only explain part of the risk of CHF, we investigated whether persistent organic pollutants (POPs) might also play a role.

Methods: In the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, left ventricular ejection fraction, (EF), E/A-ratio and isovolumic relaxation time (IVRT), were determined by echocardiography and serum samples of 21 POPs were analyzed in serum measured by high-resolution chromatography coupled to high-resolution mass spectrometry (HRGC/HRMS) in 998 subjects all aged 70 years.

Results: In this cross-sectional analysis, high levels of several of the polychlorinated biphenyls (PCB congeners 99, 118, 105, 138, 153, and 180) and octachlorodibenzo-*p*-dioxin (OCDD) were significantly related to a decreased EF. Some POPs were also related to a decreased E/A-ratio (PCBs 206 and 209). All the results were adjusted for gender, hypertension, diabetes, smoking, LVH and BMI, and subjects with myocardial infarction or atrial fibrillation were excluded from the analysis.

Conclusions: Circulating levels of POPs were related to impairments in both left ventricular systolic and diastolic function independently of major congestive heart failure risk factors, suggesting a possible role of POPs in heart failure.

1. Introduction

Congestive heart failure (CHF) is a major cardiovascular disease associated with poor long-term prognosis, decreased life quality and high risk of hospitalization.

Hypertension and ischemic heart disease are the most powerful known risk factors for CHF in elderly patients (Levy et al., 1996). Atrial fibrillation is also an independent risk factor for congestive heart failure (Maisel and Stevenson, 2003), as well as diabetes, smoking, left ventricular hypertrophy (LVH) and obesity (Eriksson et al., 1989; Ho et al., 1993). However, as these established risk factors can only explain part of the risk of CHF, other factors might be of importance.

Measurable levels of persistent organic pollutants (POP) have been reported in humans for several decades. In recent years, data on associations between elevated circulating levels of POPs and a number of CHF risk factors, such as hypertension, obesity, and diabetes, as well as metabolic syndrome have been established (Everett et al., 2011; Lee et al., 2007, 2012, 2011; Ronn et al., 2011). Furthermore, prevalent myocardial infarction has also been found to associate with elevated levels of certain POPs including dioxins and PCBs (Dalton et al., 2001; Flesch-Janys et al., 1995; Ha et al., 2007; Sergeev and Carpenter, 2005).

Animal studies indicate that environmental pollutants, such as dioxins, hexachlorobenzene (HCB) and polychlorinated biphenyls (PCB 126) increase heart weight and induce hypertension (Arnold et al., 1986; Kopf et al., 2008; Lind et al., 2004). We hypothesize that certain POPs influence the left ventricular (LV) systolic and diastolic function. To test this hypothesis, we used the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (Lind et al., 2005), in which echocardiographic

Abbreviations: AHR, Acryl hydrocarbon receptor; BDE, Bromated diphenyl ether; *p,p'*–DDE, 1,1-dichloro-2,2-bis(4-dichlordiphenyl) ethylene, a metabolite to DDT.; EA-ratio, E-wave/A-wave; EF, Ejection fraction (left ventricle); HCB, Hexachlorobenzene; IVRT, Isovolumic relaxation time; OCDD, Octachlorodibenzo-*p*-dioxin; LV, Left ventricular; LVH, Left ventricular hypertrophy; LVMI, Left ventricular mass index; PCBs, Polychlorinated biphenyls; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; POPs, Persistent organic pollutants; RWT, Relative wall thickness of the left ventricle; TCDD, Tetrachlorodibenzo-*p*-dioxin; TEF, Toxic equivalency factors; TEQ, Toxic equivalents; TNC, *Trans*-nonachlordane

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data on LV systolic and diastolic function and circulating POP levels in almost 1,000 subjects have been measured.

2. Material and methods

2.1. Subjects

Eligible for the study were all subjects aged 70 living in the community of Uppsala, Sweden. The subjects were chosen from the register of community residents in a randomized order, and were invited in a randomized order April 2001 to June 2004 (Lind et al., 2005). The subjects received an invitation by letter within two months of their 70th birthday. The PIVUS study aimed to investigate an elderly population standardized to the age of 70, since age is such an important characteristic, especially in the elderly. Of the 2025 subjects invited, 1016 subjects participated, yielding a participation rate of 50.1%. The study was approved by the Ethics Committee of the Uppsala University, and the participants gave their informed consent.

Subjects with myocardial infarction that had been treated in hospital were excluded. So, too, were those with atrial fibrillation.

Approximately 10% of the cohort reported a history of coronary heart disease; 4% reported stroke, 3.8% congestive heart failure, and 9% diabetes mellitus. Almost half the cohort reported any cardiovascular medication (45%), with antihypertensive medication being the most prevalent (32%). Fifteen percent reported use of statins, while insulin and oral antiglycemic drugs were reported in 2 and 6%, respectively.

As the participation rate in this cohort was only 50%, we carried out an evaluation of cardiovascular disorders and medications in 100 consecutive non-participants. The prevalences of cardiovascular drug intake, history of myocardial infarction, coronary revascularization, antihypertensive medication, statin use and insulin treatment were similar to those in the investigated sample, while the prevalences of diabetes (17%), congestive heart failure (6.9%) and stroke (6.7%) tended to be higher among the non-participants.

2.2. Basic investigation

Before the examination the participants were asked to fill in a questionnaire about their medical history, smoking habits, and regular medication. All subjects were investigated in the morning after fasting since midnight, thus with a fasting period of at least eight hours. No medication or smoking was allowed after midnight. Blood pressure was measured by a calibrated mercury sphygmomanometer to nearest mm Hg after at least 30 min of rest, and the average of three recordings was used. Lipid variables and fasting blood glucose were measured by standard laboratory techniques. Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/l or antidiabetic treatment. Smoking was defined as current smoking; all basic characteristics are given in Table 1.

2.3. Echocardiography

A comprehensive two-dimensional and Doppler echocardiography was performed with an Acuson XP124 cardiac ultrasound unit (Acuson, California, USA) A 2.5 MHz transducer was used for the majority of the examinations. Presence of stenosis or regurgitations in the mitral and aortic valves was recorded by use of color and continuous Doppler.

LV ejection fraction (EF) was visually assessed from examinations from the parasternal and apical projections. The transmitral Dopper amplitudes of the *E* and *A* waves were assessed in the apical projection and the E/A-ratio was calculated. The isovolumetric relaxation time (IVRT) was measured by Doppler in the apical view as the time between the closure of the aortic valve (end of blood flow through the valve) and the opening of the mitral valve. LV mass was determined from M-mode recordings from the parasternal view using the Penn convention and was indexed for height$^{2.7}$. The cut-off limit for LVH was 51 g/m$^{2.7}$ (Mureddu et al., 2001).

Subjects with valvular disease or cardiomyopathies were excluded from the investigated sample ($n=23$). Also subjects with signs of a possible restrictive transmitral filling pattern (E/A-ratio >1.5 and IVRT <75 ms) were excluded from the analysis ($n=7$) regarding diastolic function.

2.4. POPs analyses

POPs were measured in stored serum samples collected at baseline. Analyses of POPs were preformed using a Micromass Autospec Ultima (Waters, Milford, MA, USA) high-resolution chromatography coupled to high-resolution mass spectrometry (HRGC/HRMS). All details on POP analyses have been reported elsewhere (Salihovic et al., 2012). A total of 23 POPs were measured: 16 polychlorinated biphenyls (PCBs), five organochlorine (OC) pesticides, one octachlorodibenzo-*p*-dioxin (OCDD), and one brominated biphenyl ether (BDE). Among the 23 POPs measured, two OC pesticides (*trans*-chlordane and *cis*-chlordane) with detection rates $<10\%$ were not included in the final results/statistical analyses. An established summation formula based on serum cholesterol and serum triglyceride concentrations was used to calculate the total amount of lipids in each plasma sample (Rylander et al., 2006). Thereafter the wet-weight concentrations of the POPs were divided by this estimation of lipids to obtain lipid-normalized values. See Table 2 for details.

Table 1
Basic characteristics and major cardiovascular risk factors in the total PIVUS cohort. Means are given ± SD. BMI=body mass index. SBP=systolic blood pressure. DBP=diastolic blood pressure.

	Mean PIVUS cohort
N	998
Female (%)	50.2
Height (cm)	169 ± 9.1
Waist circumferences (cm)	91 ± 12
BMI (kg/m^2)	27.0 ± 4.3
Waist/hip ratio	0.9 ± 0.075
SBP (mmHg)	150 ± 23
DBP (mmHg)	79 ± 10
Heart rate (beats/min)	62 ± 8.7
Serum cholesterol (mmol/l)	5.4 ± 1.0
LDL-cholesterol (mmol/l)	3.3 ± 0.88
HDL-cholesterol (mmol/l)	1.5 ± 0.42
Serum triglycerides (mmol/l)	1.3 ± 0.60
Fasting blood glucose (mmol/l)	5.3 ± 1.6
Current smoking (%)	11
Diabetes (%)	11
Myocardial infarction (%)	7
Congestive heart failure (%)	4
Atrial fibrillation (%)	3
Left ventricular hypertrophy (%)	36
Ejection fraction (%)	65 ± 10
E/A ratio	0.96 ± 0.28
Isovolumic relaxation time (ms)	121 ± 21

Table 2
Distribution of serum concentrations (ng/g lipid) by median and 25th and 75th percentile of individual persistent organic pollutants. ($n=988$).

Variable	Median (25th and 75th percentile)
PCB 74	13.9 (10; 18.8)
PCB 99	13.8 (9.5; 19.4)
PCB 105	4.9 (3.3; 7.0)
PCB 118	30 (21.6; 41.7)
PCB 126	6.2 (3.3; 10.8)
PCB 138	124.9 (95.3; 168.2)
PCB 153	217 (166.8; 279.8)
PCB 156	23.6 (18.2; 29.9)
PCB 157	4.3 (3.2; 5.5)
PCB 169	26 (20.1; 34.2)
PCB 170	74.8 (59.6; 96.3)
PCB 180	176.3 (139.3; 229)
PCB 189	2.9 (2.2; 3.9)
PCB 194	18.4 (13.6; 24.3)
PCB 206	4.2 (3.1; 5.4)
PCB 209	4.1 (3; 5.3)
OCDD	0.4 (0.2; 0.6)
HCB	38 (29; 50.2)
TNC	20.8 (14.1; 31.6)
p,p'–DDE	290.6 (158.1; 538.4)
BDE 47	1.9 (1.5; 2.9)

PCB=polychlorinated biphenyls, OCDD=octachlorodibenzo-*p*-dioxin, HCB=hexachlorobenzene, TNC=*trans*-nonachlor, *p,p'*-DDE=2,2-bis(4-chlorophenyl)-1,1-dichloroethene, BDE=bromodiphenyl ether.

2.5. Statistics

All POPs levels and E/A ratios were log-transformed, to achieve normal distributions. Since POP levels tend to differ between men and women, the first set of linear regression models between LV variables and POPs were adjusted for gender only. Since no interactions between gender and POPs were found, no

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