Associations of Bisphenol A Exposure With Heart Rate Variability and Blood Pressure

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Abstract—Bisphenol A (BPA) is a high-volume production chemical that has been suspected to have adverse health effects. Recent studies have suggested that cardiovascular diseases are associated with the BPA exposure. The aim of present study was to investigate the associations of urinary BPA with heart rate variability and blood pressure. We recruited 560 noninstitutionalized elderly citizens from August 2008 to August 2010 in Seoul. All of the participants were ≥60 years old. The participants took medical examinations ≤5 times. Urinary BPA concentration, heart rate variability, and blood pressure were measured at each time. A total of 1511 observations from 521 participants were included in the analyses. We observed that urinary BPA was associated negatively with the root mean square of successive differences for heart rate and positively with blood pressure. The odds ratio of showing hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) was 1.27 (95% CI, 0.85–1.88) in the fourth quartile compared with the first quartile of urinary BPA concentration. When the analyses were restricted to participants who did not report previous history of hypertension (n=258), the odds ratio was increased to 2.35 (95% CI, 1.33–4.17). **(*Hypertension*. 2012;60: 786-793.)** ● **Online Data Supplement**

Key Words: bisphenol A ■ heart rate variability ■ blood pressure ■ aged ■ panel study

Bisphenol A (BPA) is produced in high volumes worldwide. It is used in the manufacture of polycarbonate plastics and epoxy resin, which are used in the linings of food or beverage cans, water bottles, and dental fillings.[1] BPA has been detected in 95% of the population of the United States.[2]

BPA is considered to be an endocrine-disrupting chemical, and it shows affinity for estrogen receptors. It was initially considered to be a weak xenoestrogen, but subsequent studies showed that BPA can have effects even at low concentrations.[3] In addition, pathways other than binding to estrogen receptors have been proposed. These include the thyroid hormone pathway, binding to glucocorticoid receptors and androgen receptors, or interfering with the central nervous system and immune system.[4–6]

Epidemiological studies have suggested that BPA could have adverse effects on human health.[7] Specifically, BPA exposure has been shown to be associated with increased production of liver enzymes,[8] recurrent miscarriages,[9] premature delivery of fetuses,[10] inflammation and oxidative stress,[11] decreased quality of semen,[12,13] and male sexual dysfunction.[14]

In 2008, Lang et al[8] conducted a study investigating the associations between past history of chronic diseases and BPA concentration by analyzing data sets from the National Health and Nutrition Examinations Survey. They reported that the concentration of urinary BPA was associated with history of diabetes mellitus and cardiovascular diseases (CVDs).[8] Later, Melzer et al[15] conducted similar analyses using larger National Health and Nutrition Examinations Survey data sets and found association between the concentration of BPA and CVDs but not with diabetes mellitus. More recently, a nested case-control study reported the association between higher BPA exposure and incident coronary artery disease with a dose-response relationship.[16] However, the knowledge on how BPA affects the cardiovascular system is still limited.

The cells of the cardiovascular system have estrogen receptors (α and β). These receptors are involved in antiatherogenic actions, vasodilation and preservation of vascular integrity, cardiomyocyte survival, and regulation of excitability of smooth muscle cells.[17,18] As a xenoestrogen, BPA may alter these functions of estrogen receptors by mimicking or blocking the action of estrogen.[19]

We hypothesized that exposure to BPA is associated with reduced heart rate variability (HRV) and hypertension, which are risk factors of CVDs. HRV is a measurement of the beat-to-beat variation of heart rate. This variation is "physiological fine tuning" of the heart rate according to the

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changing demand of blood supply. Reduced HRV is known to increase the risk of cardiac events.[20] Hypertension is a well-known risk factor for CVDs. Even people with high normal blood pressure have a >2-fold risk of CVDs.[21]

The aim of the present study was to investigate the associations of urinary concentration of BPA with blood pressure and HRV.

Methods

Study Design and Participants

The Korean Elderly Environmental Panel Study has recruited 560 noninstitutionalized elderly citizens from August 2008 to August 2010 in Seoul. All of the participants were aged ≥60 years. They were asked to participate in medical examinations ≤5 times during the study period (twice in 2008, once in 2009, and twice in 2010). A survey inquiring about demographic characteristics, past medical history, and lifestyle was conducted at the time of enrollment. Among the panel, 2 participants did not provide urine samples and were excluded from the analyses. Thirty-seven participants who answered the survey that they had a history of myocardial infarction or angina were subsequently excluded from the analyses. Among the participants, 37 (7.1%) participated in the examination 5 times, 148 (28.4%) 4 times, 131 (25.1%) three times, 136 (26.1%) twice, and 69 (13.2%) just once. A total of 1511 observations from 521 participants were included in the analyses. The study protocol was approved by the institutional review board of the College of Medicine, Seoul National University/Seoul National University Hospital (C-0704-040-205).

Measurement of Urinary BPA

The participants were asked to fast for ≥8 hours before the examination. Spot urine samples were collected in conical tubes (SPL Lifesciences, Pocheon, Gyunggi-do, Korea) from 10:00 AM to 12:00 PM. They were sent to the laboratory (NeoDin Medical Institute, Seoul, Korea) and aliquots taken. This took <90 minutes, and the samples were stored at −20°C. The laboratory personnel were blinded about any other measurements. We measured urinary concentrations of BPA using high-performance liquid chromatography tandem mass spectrometry (Agilent 6410 triple Quad LCMS; Agilent, Santa Clara, CA).[22] A detailed measurement process is described in the online-only Data Supplement. We adjusted the concentration of BPA for creatinine measured from the same urine sample and used the concentration of BPA in microgram per gram of creatinine in the analyses. This was to compare the BPA concentration that was not influenced by the different urinary excretion rates of individuals.[2]

Measurement of Blood Pressure and HRV

Blood pressure was measured by trained medical technologist using an automatic sphygmomanometer (HEM-780, Omron, Kyoto, Japan) after ≥10 minutes of rest. Participants were asked to remain in a sedentary position for an additional 10 minutes, and then another measurement of blood pressure was conducted. The value of blood pressure from the second measurement was used as the dependent variable in the analyses to ensure that the participants had been completely relaxed and familiar with the procedure. The results of the analyses using the mean of both measurements as outcomes are presented as supplemental material (Table S1 and Table S2, available in the online-only Data Supplement).

HRV was measured using an automated HRV analyzer (SA-3000P, Medicore, Seoul, Korea) with 3 limb leads. ECG was carried out for ≥5 minutes, and HRV was automatically analyzed from the ECG. Mean heart rate, SD of normal-to-normal intervals, and the root mean square of successive differences (RMSSD) were measured.

Table 1. Basic Characteristics of Participants at Enrollment

Variable	All	Men	Women
Participants, n (%)	521 (100.0)	138 (26.5)	383 (73.5)
Mean age, y±SD	70.6 (5.2)	71.3 (4.4)	70.3 (5.5)
Mean height, cm±SD	154.9 (7.7)	164.4 (5.2)	151.4 (5.1)
Mean weight, kg±SD	59.5 (8.7)	65.7 (9.5)	57.3 (7.2)
Current smoker, n (%)	27 (5.2)	26 (18.8)	1 (0.3)
Ex-smoker, n (%)	34 (6.5)	30 (21.7)	4 (1.0)
Nonsmoker, n (%)	446 (85.6)	79 (57.3)	367 (95.8)
Did not answer, n (%)	14 (2.7)	3 (2.2)	11 (2.9)
Current drinker, n (%)	116 (22.2)	75 (54.4)	41 (10.7)
Nondrinker, n (%)	388 (74.5)	58 (42.0)	330 (86.2)
Did not answer, n (%)	17 (3.3)	5 (3.6)	12 (3.1)
No history of hypertension, n (%)	258 (49.5)	63 (45.7)	195 (50.9)
Hypertension with treatment, n (%)	260 (49.5)	74 (53.6)	186 (48.5)
Hypertension without treatment, n (%)	3 (0.6)	1 (0.7)	2 (0.5)
Mean BPA, μg/g of creatinine±SD	1.2 (1.9)	1.0 (1.4)	1.3 (2.0)
Mean fast blood glucose, mg/dL±SD	96.6 (21.1)	97.6 (21.2)	96.3 (21.1)
Mean SBP, mm Hg±SD	131.2 (17.0)	130.8 (16.9)	131.3 (17.0)
Mean DBP, mm Hg±SD	74.1 (10.3)	73.9 (10.9)	74.2 (10.1)
Mean heart rate, bpm±SD	70.2 (10.1)	69.6 (10.9)	70.4 (9.9)
Mean SDNN, ms±SD	30.7 (19.4)	28.2 (17.9)	31.5 (19.9)
Mean RMSSD, ms±SD	25.9 (22.4)	24.3 (23.7)	26.5 (21.9)

SBP indicates systolic blood pressure; BPA, bisphenol A; DBP, diastolic blood pressure; HRT, mean heart rate; SDNN, SD of normal-to-normal intervals; RMSSD, square root of the mean squared difference of successive normal-to-normal intervals.

Statistical Analyses

Detailed methods for statistical analyses are presented in the online-only Data Supplement.

The number of the medical examinations varied among participants. This may lead to selection bias if the participation in the medical examinations of each participant was not random.[23] We gave weight to observations by the inverse probability of participating in the subsequent medical examination.[24]

Statistical analyses were conducted in 3 steps. First, nonparametric analyses of the associations were conducted to examine the linearity of associations graphically. Generalized additive mixed models were constructed for each outcome using the gamm4 package of R version 2.12.2 (R Foundation for Statistical Computing, Vienna, Austria). The concentration of urinary BPA was not normally distributed, so it was log transformed for the analyses. Covariates, which were selected a priori to adjust for the possible confounding, were also included in the models.

Then we constructed a linear mixed model with a compound symmetry variance-covariance matrix using PROC MIXED of SAS version 9.2 (SAS Institute, Cary, NC) to examine the association of urinary BPA concentration with HRV and blood pressure. Different models were constructed to examine confounding of covariates. SD of normal-to-normal intervals and RMSSD have been suggested to be inversely associated with blood pressure,[25] so we examined the association between blood pressure and BPA while further adjusting for RMSSD.

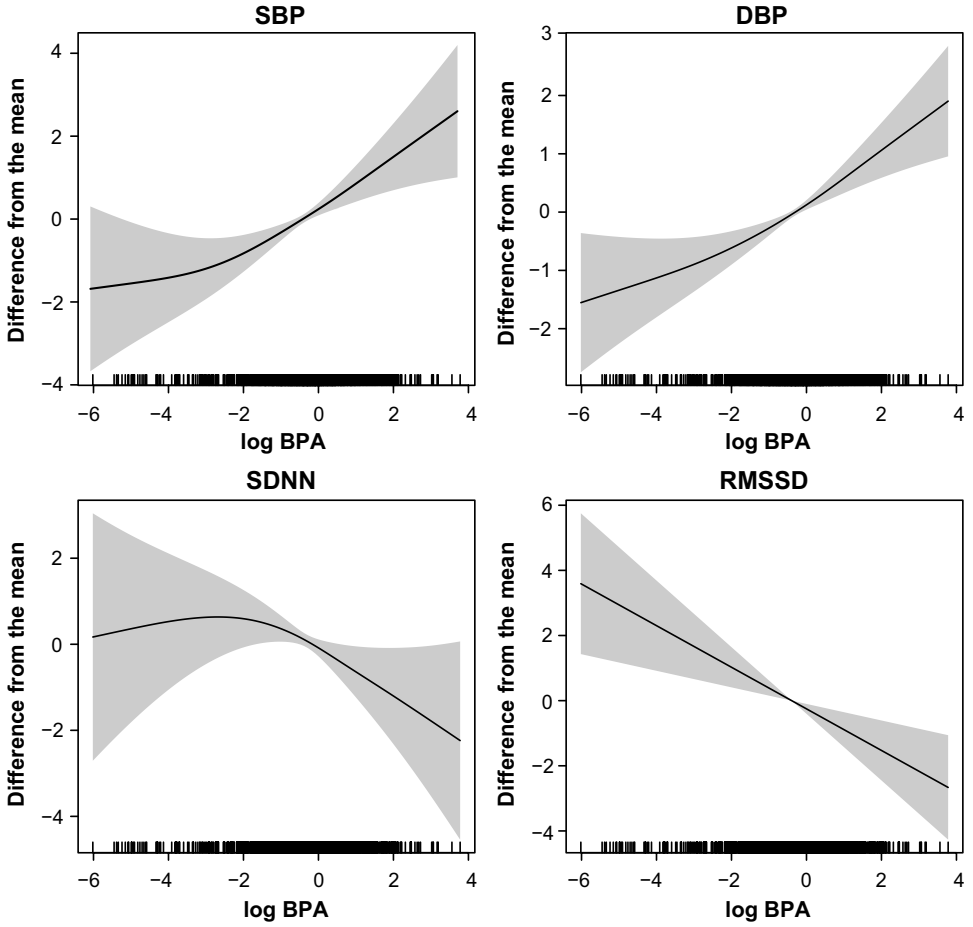

Figure. Nonparametrical associations of concentration of urinary BPA with blood pressure and heart rate variability. Data were adjusted for sex, age, date of examination, height, weight, mean fast blood glucose, smoking status, current consumption of alcohol, and previous history of hypertension. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; SDNN, SD of normal-to-normal intervals; RMSSD, square root of the mean squared difference of successive normal-to-normal intervals.

Finally, the risk of hypertension was evaluated. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg.[21] The quartiles of the concentration of urinary BPA of all of the observations were defined with the cut points of 0.37, 0.73, and 1.33 μg/g of creatinine. PROC GENMOD of the SAS was used. Odds ratios (ORs) were calculated by taking exponential values of the estimates. Subgroup analyses with participants who did not have a history of hypertension were conducted in the same manner. We also conducted additional analyses stratified by the sex of the participants using the same models.

Results

Table 1 shows the basic characteristics of the study participants at the time of enrollment. The mean age of the participants was 70.6±5.2 years. The range of the age was 60 to 87 years. Among the participants, 85.6% were self-identified as being nonsmokers, and 74.5% answered that they did not consume alcohol. A total of 49.5% of the participants answered that they did not have a history of hypertension. The mean concentration of urinary BPA was 1.2 μg/g of creatinine, and the mean blood pressure was within the normal limit.

The Figure shows the nonparametric associations of urinary BPA concentration with blood pressure and HRV. DBP, SBP, and RMSSD showed almost linear associations with BPA. SD of normal-to-normal intervals did not show linear association with the urinary concentration of BPA. DBP and SBP increased with increasing concentrations of BPA. Mean heart rate also increased with increasing BPA concentrations (Figure S4). RMSSD decreased with increasing concentrations of BPA.

The associations of HRV with the urinary concentration of BPA are shown in Table 2. In the crude model, mean heart rate and RMSSD were significantly associated with the concentration of BPA, but SD of normal-to-normal intervals was not. All of the associations that were significant in the crude model remained significant after the adjustment for the covariates in models 1 and 2. These associations were similar when we analyzed the same model among those who had not report previous history of hypertension. When we stratified the analyses with the sex of the participants, only the associations with mean heart rate in women were statistically significant.

Table 3 shows the association between urinary BPA concentration and blood pressure. In the crude model among all of the participants, SBP and DBP were significantly associated with BPA concentration. The association of DBP and BPA concentration remained significant even after fully adjusting for covariates in model 2. However, the SBP

Table 2. Associations of Urinary Concentration of BPA With Heart Rate Variability

	Crude			Model 1			Model 2		
Group and HRV Component	β	SE	*P* Value	β	SE	*P* Value	β	SE	*P* Value
All (n=521)									
Mean heart rate	0.79	0.21	<0.001	0.79	0.22	<0.001	0.78	0.22	<0.001
SDNN	−0.54	0.40	0.176	−0.46	0.40	0.251	−0.46	0.40	0.255
RMSSD	−1.04	0.40	0.008	−1.01	0.40	0.012	−1.03	0.40	0.011
Without history of HTN (n=258)									
Mean heart rate	1.08	0.31	0.001	1.04	0.32	0.001	1.03	0.32	0.001
SDNN	−0.79	0.51	0.127	−0.69	0.52	0.188	−0.72	0.52	0.170
RMSSD	−1.04	0.59	0.078	−0.99	0.60	0.099	−1.03	0.60	0.087
Men (n=138)									
Mean heart rate	0.43	0.39	0.278	0.31	0.40	0.439	0.32	0.39	0.410
SDNN	−0.79	0.78	0.311	−0.41	0.78	0.601	−0.45	0.79	0.570
RMSSD	−1.81	0.86	0.037	−1.47	0.86	0.091	−1.57	0.87	0.074
Men without history of HTN (n=63)									
Mean heart rate	0.78	0.63	0.213	0.65	0.63	0.302	0.68	0.63	0.285
SDNN	−1.16	1.16	0.321	−0.66	1.16	0.567	−0.68	1.17	0.561
RMSSD	−1.99	1.46	0.177	−1.54	1.47	0.295	−1.59	1.50	0.291
Women (n=383)									
Mean heart rate	0.89	0.25	0.001	0.93	0.25	<0.001	0.91	0.25	<0.001
SDNN	−0.54	0.46	0.248	−0.46	0.47	0.329	−0.43	0.47	0.358
RMSSD	−0.85	0.45	0.057	−0.81	0.45	0.074	−0.80	0.45	0.077
Women without history of HTN (n=159)									
Mean heart rate	1.15	0.36	0.001	1.19	0.36	0.001	1.18	0.36	0.001
SDNN	−0.71	0.58	0.219	−0.63	0.59	0.287	−0.63	0.59	0.282
RMSSD	−0.81	0.63	0.205	−0.75	0.64	0.243	−0.74	0.65	0.251

HTN indicates hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HRT, mean heart rate; SDNN, SD of normal-to-normal intervals; BPA, bisphenol A; RMSSD, square root of the mean squared difference of successive normal-to-normal intervals. Model 1 was adjusted for age, sex, height, weight, and date of examination. Model 2 was model 1+mean fast blood glucose, smoking status, current consumption of alcohol, and previous history of hypertension.

showed marginal significance when fully adjusted. When we adjusted for RMSSD in model 3, the association of DBP remained significant. When we restricted the analyses to the participants who had not reported previous history of hypertension, only the crude model showed significant association. When we stratified the analyses with the sex of the participants, men who had not reported a previous history of hypertension showed greater coefficients than women whereas it was vice versa for all of the subjects.

We calculated the OR of showing hypertension for each quartile of the BPA concentration (Table 4). No significantly increased risk was observed when we analyzed for the whole study population. However, it showed a significant OR when we restricted the analyses to those who had not reported a history of hypertension. The ORs of hypertension in this subgroup for each quartile of the concentration of urinary BPA were statistically significant in all of the quartiles. When we stratified the analyses with the sex of the participants, only the ORs in women were significant. The intraindividual variation over time is presented in the online-only Data Supplement.

Discussion

The present study showed that exposure to BPA is associated with increased blood pressure and decreased HRV, which are risk factors of cardiovascular disorders. The risk of hypertension also increased with increasing concentrations of BPA in participants who had not reported previous history of hypertension.

Little is known about the mechanism of how BPA affects the cardiovascular system. BPA is suspected to have various mechanisms of action in humans, and the estrogenic action is considered to be one of the mechanisms.[7] Estrogen affects the cardiovascular system, but whether exogenous estrogen protects or harms the cardiovascular system is controversial. Estrogen receptors (α and β) in the cardiovascular system may have important roles in repairing blood vessels and controlling blood pressure, so exogenous estrogen may have protective effects on CVDs.[26,27] Conversely, unopposed estrogens in contraceptives are known to increase blood pressure.[21]

We observed that the urinary BPA concentration was negatively associated with RMSSD. This suggests that BPA may have effects on the autonomic nervous system for regulation of the cardiac rhythm.[28] This may also be one of the estrogenic actions of BPA, because estrogen replacement has been shown to affect HRV.[29] Asano et al[30] showed in an in vitro study using animal and human cells that binding of BPA with estrogenic receptors in coronary artery smooth

Table 3. Associations of Urinary Concentration of BPA With Blood Pressure

	Crude			Model 1			Model 2			Model 3		
Group and Blood Pressure	β	SE	*P* Value	β	SE	*P* Value	β	SE	*P* Value	β	SE	*P* Value
All (n=521)												
SBP	0.82	0.30	0.006	0.56	0.30	0.060	0.57	0.30	0.054	0.53	0.30	0.073
DBP	0.61	0.18	0.001	0.40	0.18	0.031	0.42	0.18	0.022	0.38	0.18	0.038
Without history of HTN (n=258)												
SBP	1.22	0.46	0.008	0.82	0.45	0.073	0.86	0.45	0.058	0.82	0.45	0.070
DBP	0.71	0.27	0.008	0.36	0.27	0.174	0.41	0.26	0.124	0.36	0.27	0.176
Men (n=138)												
SBP	0.75	0.59	0.206	0.44	0.59	0.457	0.55	0.58	0.343	0.46	0.59	0.436
DBP	0.53	0.40	0.190	0.28	0.40	0.484	0.36	0.40	0.371	0.32	0.40	0.429
Men without history of HTN (n=63)												
SBP	1.78	0.89	0.048	1.36	0.87	0.121	1.71	0.87	0.051	1.48	0.89	0.099
DBP	0.83	0.62	0.186	0.53	0.62	0.399	0.87	0.62	0.166	0.73	0.63	0.249
Women (n=383)												
SBP	0.90	0.35	0.010	0.60	0.35	0.083	0.58	0.35	0.095	0.56	0.35	0.109
DBP	0.62	0.21	0.003	0.42	0.21	0.042	0.40	0.21	0.050	0.37	0.21	0.072
Women without history of HTN (n=159)												
SBP	1.19	0.54	0.027	0.76	0.53	0.150	0.74	0.53	0.161	0.74	0.53	0.159
DBP	0.64	0.30	0.032	0.29	0.29	0.329	0.26	0.29	0.383	0.24	0.29	0.419

HTN indicates hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HRT, mean heart rate; SDNN, SD of normal-to-normal intervals; BPA, bisphenol A; RMSSD, square root of the mean squared difference of successive normal-to-normal intervals. Model 1 was adjusted for age, sex, height, weight, and date of examination. Model 2 included model 1+mean fast blood glucose, smoking status, current consumption of alcohol, and previous history of hypertension. Model 3 included model 2+RMSSD.

muscle cells could increase the activity of large-conductance Ca^{2+}/voltage-sensitive K^+ channels, possibly affecting heart function.

However, the action of estrogen receptors in the cardiovascular system is complicated, and the action triggered by binding chemicals can vary even with chemicals with similar properties. Hiroi et al[19] showed in an in vitro study that the interaction of BPA with estrogen receptors may differ from that of estrogen, because BPA has dual effects on the receptors as an agonist and antagonist.

In the present study, we observed that the concentration of BPA affected HRV and blood pressure independently. This suggests that BPA may affect the cardiovascular system not only through the autonomic nervous system but also directly by the regulation of blood pressure. To the best of our knowledge, no further investigation on the physiological and molecular mechanisms of BPA on the cardiovascular system has been conducted so far, and the present result warrants such investigations.

A total of 263 participants reported that they have hypertension, and only 3 were not receiving any treatment. If the exposure to BPA increases blood pressure, as we observed in the present study, the participants who have a higher concentration of BPA are more likely to be medicated antihypertensives, which probably keep the blood pressure below the diagnostic criteria of hypertension. This may attenuate the magnitude of association between exposure to BPA and blood pressure. In the present study, the OR of hypertension became significant only after we restricted the analyses to those who had not reported a previous history of hypertension, and this may be because of the antihypertensive treatment that almost half the participants reported to receive.

We observed that there are differences between men and women in the magnitude and significance of associations, including mean heart rate and blood pressure. Specifically, the male participants showed smaller effect size on mean heart rate (Table 2) and greater effect size on blood pressure (Table 3). However, these differences were not clear between all of the male and female participants compared with those between men and women who did not report a previous history of hypertension. As discussed earlier, this may be because of the treatment that they receive. Women have higher baseline heart rate compared with men partly because of the presence of more estrogen in women.[31] In addition, postmenopausal women with hormonal replacement therapy showed a higher low-frequency power component compared with men, suggesting greater parasympathetic modulation.[32] This might be the reason for the greater effect size on mean heart rate in female participants. There are sex differences in the action of estrogenic receptors in the cardiovascular system, and the susceptibility of effect of interference of the estrogenic signaling pathway in the cardiovascular system seems greater among men.[33] This may be the reason for the greater effect size on blood pressure in men. On the contrary, the point estimates of the risk of hypertension seem greater in women who did not report previous history of hypertension (Table 4), but the 95% CIs overlapped, and the difference is not statistically significant. Although it is biologically plausible to assume that BPA, as a xenoestrogen, may act on the cardiovascular system by the same mechanism, no mecha-

Table 4. OR of Hypertension According to Different Levels of Urinary BPA

Group and Criteria of Blood Pressure	No. of Events	1Q, OR	2Q, OR (95% CI)	3Q, OR (95% CI)	4Q, OR (95% CI)
All (n=521)					
No. of observations		369	378	386	378
SBP ≥140 mm Hg	333	1	1.19 (0.77–1.82)	1.15 (0.77–1.70)	1.26 (0.84–1.88)
DBP ≥90 mm Hg	70	1	1.56 (0.71–3.42)	1.07 (0.48–2.40)	1.52 (0.66–3.52)
HTN*	343	1	1.21 (0.80–1.84)	1.16 (0.78–1.72)	1.27 (0.85–1.88)
Without history of HTN (n=258)					
No. of observations		187	197	203	167
SBP ≥140 mm Hg	163	1	2.16 (1.16–4.04)	1.68 (0.94–3.00)	2.25 (1.26–4.01)
DBP ≥90 mm Hg	42	1	NA†		
HTN*	170	1	2.23 (1.21–4.12)	1.79 (1.01–3.17)	2.35 (1.33–4.17)
Men (n=138)					
No. of observations		102	98	103	69
SBP ≥140 mm Hg	92	1	1.29 (0.57–2.92)	1.16 (0.51–2.64)	1.58 (0.69–3.58)
DBP ≥90 mm Hg	19	1	2.47 (0.44–13.87)	1.42 (0.23–8.78)	3.65 (0.74–17.90)
HTN*	95	1	1.21 (0.80–1.84)	1.16 (0.78–1.72)	1.27 (0.85–1.88)
Men without history of HTN (n=63)					
No. of observations		52	47	45	25
SBP ≥140 mm Hg	42	1	2.06 (0.63–6.72)	1.20 (0.34–4.22)	1.64 (0.45–5.89)
DBP ≥90 mm Hg	10	1	NA†		
HTN*	44	1	2.21 (0.68–7.17)	1.33 (0.39–4.60)	1.72 (0.49–6.03)
Women (n=383)					
No. of observations		267	280	283	309
SBP ≥140 mm Hg	241	1	1.13 (0.68–1.86)	1.13 (0.72–1.77)	1.17 (0.74–1.84)
DBP ≥90 mm Hg	51	1	NA†		
HTN*	248	1	1.14 (0.70–1.85)	1.13 (0.72–1.77)	1.16 (0.74–1.82)
Women without history of HTN (n=159)					
No. of observations		135	150	158	142
SBP ≥140 mm Hg	121	1	2.27 (1.07–4.81)	1.96 (0.99–3.91)	2.46 (1.26–4.82)
DBP ≥90 mm Hg	32	1	10.89 (1.24–95.55)	11.53 (1.40–95.16)	13.74 (1.66–113.72)
HTN*	126	1	2.30 (1.10–4.81)	2.07 (1.05–4.11)	2.59 (1.33–5.04)

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; NA, not applicable. Data were adjusted for age, sex, height, weight, date of examination, mean fast blood glucose, smoking status, and current consumption of alcohol. First quartile, <0.37 μg/g of creatinine; second quartile, 0.37–0.73 μg/g of creatinine; third quartile, 0.73–1.33 μg/g of creatinine; fourth quartile, ≥1.33 μg/g of creatinine.

*Hypertension was defined as either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

†We were unable to estimate because of the lack of the No. of events.

nism of sex difference of the effect of BPA in humans is known, and some differences observed in the present study are statistically inconclusive because of the limited sample size of each sex.

We used spot urine samples in our analyses. The half-life of BPA is thought to be as short as 4 to 6 hours.[34] Hence, the concentration of BPA may vary during a day,[35] and spot urine samples may not capture all of the variations in the day. However, the participants provided urine samples from 10:00 AM to 12:00 PM, and the objective of the study was to examine the acute effect of BPA, so analyzing a spot urine sample was adequate to evaluate the level of exposure. There has also been report of the possibility of BPA having a longer half-life than expected,[36] so that the variance during a day might not be great. In addition, if there were any misclassifications in exposure assessment because of random variations of BPA concentrations, the significance of the association would have moved toward the null.

We used 140/90 mm Hg as the cutoff point to examine the clinical significance of the association. Although the blood pressure is higher in the elderly compared with the younger population and it is unclear whether people >80 years of age should be considered as the same as people <80 years of age, the diagnostic criteria and management goal of hypertension are 140/90 mm Hg.[37] Also, 95% of participants were <80 years of age.

We used a repeated measure design, and the associations derived from the mixed models shown in the present study accounted for between- and within-person variation of exposure and outcome. By accounting for the within-person variation (which is the association between the concentration of BPA and the level of outcome according to time in the

same subject), the present study provided more powerful evidence on the adverse health effects of BPA exposure on CVDs than previous observational studies.

The present study had limitations. First, our study population was limited to the elderly (≥60 years old). The elderly are considered to be more susceptible to the adverse health effects of environmental exposures,[38] so the observed association may not be the same in the general population. Second, although covariates such as smoking and status of alcohol consumption were adjusted in the analyses, the possibility of residual confounding remained. For instance, we could not adjust the type of food containers that the study participants used.[39] This might act as a confounder because the oral intake is a major route of exposure of BPA,[40] and plastic containers are often used in Korea for storage of salt-rich foods, such as kimchi. Eating high quantity of such salt-rich food stored in plastic containers would have resulted in a high consumption of salt, which, in turn, increased the blood pressure. In such case, the exposure to BPA would also have increased, and this might confound the association between exposure of BPA and blood pressure. Third, we could not observe the dose-response relationship in the associations between the quartiles of BPA and risk of hypertension (Table 4). The effect of BPA has been reported to be nonmonotonic,[41] and the lack of a dose-response relationship in the present study might be the result of this nature. Fourth, the present study was limited by the relatively small sample size, and further stratification by the previous history of hypertension and sex made the sample size even smaller. Thus, nonsignificant results in the subgroup analyses may be the result of lack of power because of the limited sample size. Fifth, although BPA is suspected to have estrogenic effects by binding to estrogen receptors, knowledge of the molecular or physiological mechanism of action on the cardiovascular system is limited.

Perspectives

The present study, which used repeated-measure design in 521 participants, showed that exposure to BPA is associated with decreased HRV and increased blood pressure and that the increase in blood pressure was clinically relevant in those who did not have hypertension. Exposure to BPA has been reported to be associated with CVDs, and the associations reported in the present study may explain the biological mechanism. These results have important implications in public health perspectives because of the almost ubiquitous usage and exposure of BPA. However, there still exist gaps in the knowledge concerning the long-term exposure of BPA and molecular mechanisms of the action of BPA on the cardiovascular system.

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Disclosures

None.

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Novelty and Significance

What Is New?

- The urinary concentration of BPA is associated with decreased HRV and increased blood pressure.

What Is Relevant?

- Higher exposure to BPA may increase the risk of hypertension.

Summary

The present study showed that exposure to BPA is associated with decreased HRV and increased blood pressure and that the increase in blood pressure was clinically relevant in those who did not have hypertension.