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Is High Central BP but Normal Office Brachial BP a risk? —The ABC-J II Study—

Kazuo Eguchi[1], Hiroshi Miyashita[2], Kazuyuki Shimada[3] and ABC-J II investigators

Abstract:

Background: Clinical significance of central blood pressure (BP) in treated hypertensives has not been established. We tested the hypothesis that subjects with high central systolic BP (CBP) but normal office brachial BP (OBP) have high cardiovascular risk profile. **Methods:** All of the subjects were participants enrolled in the Antihypertensives and Blood pressure of Central artery study in Japan (ABC-J) II study. Radial applanation tonometry (Omron 9000AI) was performed in 4077 subjects, and they were classified as; Group 1: high OBP (>140/90 mmHg) and high CBP (>130 mmHg); Group 2: high OBP and normal CBP; Group 3: normal OBP and high CBP; and Group 4 as both normal. Plasma brain natriuretic peptide (BNP) was used as a measure of cardiovascular load. **Results:** The mean age was 65.9 ± 11.2 yrs, 49.2% were females, and 25.7% had diabetes. In both genders, subjects with Group 3 were oldest, and beta-blocker was most frequently used, but body mass index (BMI), rate of diabetes, and heart rate were lowest among the four groups. In ANOVA, Group 3 tended to have higher BNP levels in both genders. In multivariate analysis after adjusting for significant covariates, BNP in Group 3 tended to be high level in females, but not in males. **Conclusion:** In treated hypertensives, higher central SBP was associated with higher BNP levels regardless of office brachial BP levels, especially in females. The results imply that high central SBP (>130 mmHg) can be used to detect high risk hypertensives with cardiovascular overload.

Key words:

Central blood pressure, Applanation tonometry, Brachial blood pressure, Brain natriuretic peptide, Cardiovascular load, Antihypertensives and Blood pressure of Central artery study in Japan (ABC-J) II study

Introduction

It has been shown that central blood pressure (BP) rather than peripheral BP was more useful to predict cardiovascular events. The Conduit Artery Function Evaluation (CAFE) sub-study of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) reported that central BP was more closely associated with cardiovascular prognosis than brachial BP[1]. In the Strong Heart study, central pulse pressure (PP) > or = 50 mmHg predicted adverse cardiovascular disease (CVD) outcomes[2]. In the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, the combination of calcium channel blockers (CCB) plus angiotensin-converting enzyme (ACE) inhibitor (ACE-I) was more effective than diuretics plus ACE-I combination because the reduction of central BP was larger in the former.

The Antihypertensives and Blood pressure of Central artery study in Japan (ABC-J) study consisting of 4000 treated hypertensive subjects started since 2007, and first report was published in 2010[3]. In this cross-sectional observation study, it was shown that vasodilatory antihypertensive agents lowered central BP independently of peripheral BP levels without evident class-specific differences, whereas non-vasodilators raised central BP. At present, the clinical application of central BP combined with brachial BP in treated

1) Department of Internal Medicine, Hanyu General Hospital, Saitama, Japan
2) Jichi Medical University Health Care Center, Tochigi, Japan
3) Division of Cardiovascular Medicine, Shin-Oyama City Hospital, Tochigi, Japan
Corresponding author: Kazuo Eguchi, ke2126@pb3.so-net.ne.jp
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hypertensives has not been established yet. In the present study, we sought to explore the clinical application of central BP, especially, focusing on treated hypertensives with normal office brachial BP but high central systolic BP (SBP).

Methods

Study design and subjects

This is a cross-sectional study, and subanalysis of the ABC-J II study, an expanded version of the original ABC-J study. Briefly, the ABC-J II study is a prospective observational study being conducted to evaluate the predictive values of central BP for cardiovascular events in Japanese treated hypertensive subjects. The protocol of the ABC-J II study has been registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) website under the trial number UMIN000002966. All of the subjects in this study were treated hypertensive subjects enrolled in the ABC-J II study[3]. The hypertensive subjects had been under stable antihypertensive treatment for at least 3 months. The institutional review board of the Jichi Medical University School of Medicine and each participating institute approved this study, and written informed consent was obtained from all participants. Between January 2007 and May 2013, a total of 4,310 subjects were enrolled by 29 doctors at 27 institutions (13 primary practices, 3 hospital-based outpatient clinics, and 11 specialized university hospitals) throughout Japan.

The inclusion criteria were treated Japanese essential hypertensive subjects who met all the 3 criteria as 1) receiving a stable dosage of antihypertensive medication for at least 3 months; 2) subjects who have a data of radial tonometry data such as radial augmentation index (rAI) or central BP data; and the age 35 yrs or more. All the data were obtained from the medical records. Exclusion criteria were: (1) subjects with extremely abnormal BP [i.e., SBP 40 mmHg or diastolic BP (DBP) 20 mmHg higher or lower, respectively] compared to usual office BP or home BP during the examination; and (2) subjects with arrhythmia.

Hypertension was defined as office SBP >140 mmHg and/or diastolic BP (DBP) >90 mmHg, or the subjects being on antihypertensive medication[4]. Impaired fasting glucose was defined as fasting glucose levels ≥110 mg/dL, and impaired glucose tolerance was defined as glucose levels of ≥ 140 mg/dL at 2 h after a 75-g oral glucose tolerance test (OGTT)[5]. In the present study, diabetes mellitus (DM) was defined as one or more of the followings: self-report, the use of diabetes medication, fasting plasma glucose ≥126 mg/dL, or hemoglobin A1c (HbA1c) (NGSP) ≥6.5%[5,6]. The diagnosis of type 2 DM was based on current American Diabetes Association's criteria[5]. Dyslipidemia was defined as one or more of the following: self-report, total cholesterol level ≥ 240 mg/dL, triglycerides (TG) ≥150, high-density lipoprotein (HDL) <40 mg/dL, or a treatment for hyperlipidemia[7]. Heart failure (HF) was diagnosed by the Framingham criteria[8] as is widely accepted. Chronic kidney disease (CKD) was defined as the presence of overt proteinuria or estimated glomerular filtration rate (eGFR)<60 ml/min/1.73 m^2, or existing renal disease.

Blood pressure measurements

Office BP

Office BP was measured by physicians or nurses using sphygmomanometers in each institution based on the hypertension guideline. Arm circumference was measured and the appropriate cuff size was selected. We advised the subjects to take their morning medication as usual even on the days when they were visiting the clinics.

Blood and urine samples

Blood samples were drawn from the antecubital vein of the subjects. Blood and urine samples were collected in the morning in a fasting state during the study. Plasma/serum samples after separation and urine samples were stored at 4℃ in refrigerated containers and sent to a commercial laboratory (SRL Inc., Tokyo, Japan) within 24 hr. Plasma brain natriuretic peptide (BNP) was measured using high-sensitivity, noncompetitive radioimmunoassay (SHIONORIA® BNP, a radioimmunoassay (RIA) kit).

The estimated GFR (eGFR) was calculated using a validated equation based on the modified version of the Modification of Diet in Renal Disease (MDRD) study: eGFR (ml/min/1.73 m^2) = 194 × $Age^{-0.287}$ × $S\text{-}Cr^{-1.094}$ (if female × 0.739)[9]. Renal dysfunction was defined as eGFR<60 ml/min/1.73 m^2.

Assessments of the measures of target organ damage

Arterial wave reflection was assessed by rAI. The rAI was measured with a semi-automatic tonometry device (HEM-9000AI; Omron Healthcare Inc., Kyoto, Japan). The detailed method is described in a previous publication[10]. The HEM-9000AI was used to calculate the peripheral augmentation index as (P2-DBP)/(P1-DBP), taking P1 and P2 as the first and second inflection points on the radial pulse waveform[10]. In the present study, rAI was also expressed as rAI adjusted for heart rate 75 bpm. Central SBP (late systolic blood pressure in the radial artery, i.e. SBP2) was calculated by the equation described previously[10]. SBP2 measured by the HEM-9000AI was almost identical to central SBP measured by the SphygmoCor system[11]. The reproducibility of this device was confirmed in previous study[12]. In the present study, high central SBP was defined as >130 mmHg based on previous outcome study[13].

M-mode echocardiography, guided by a two-dimensional echocardiography, was performed based on the American Society of Echocardiography recommendations. End-diastolic left ventricular (LV) dimensions were used to calculate LV mass using an anatomically validated formula[14]. The LV mass index (LVMI) was calculated for each patient

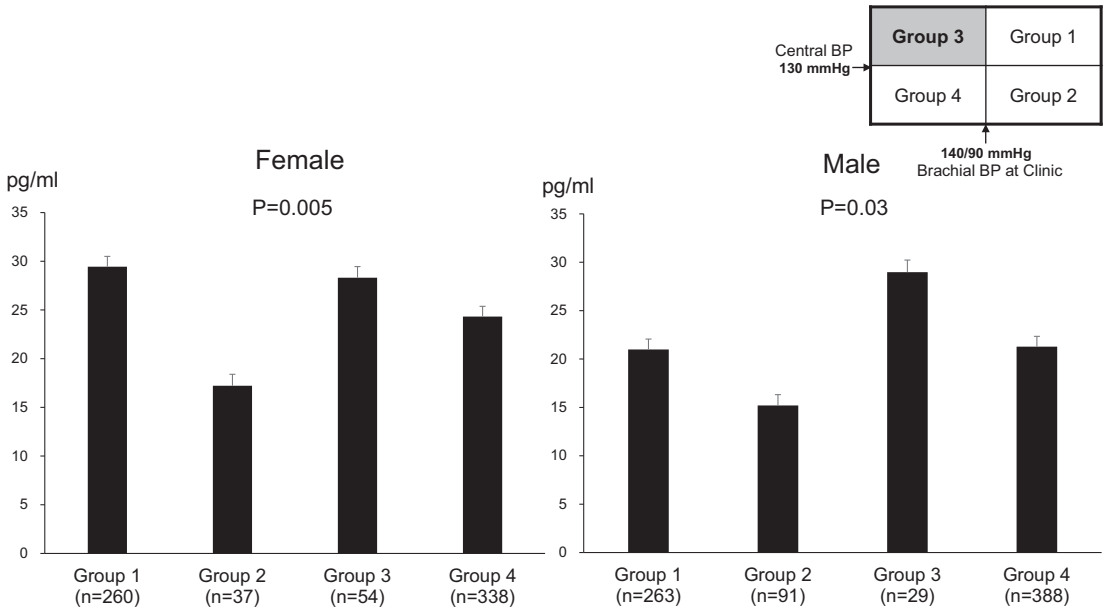

Figure 1. Comparisons of BNP in each group by ANOVA. Error bars shows standard errors. The definitions of each group are the same as Table 1.

by dividing LV mass by body surface area. The presence of LV hypertrophy (LVH) was defined by sex-specific criteria (LVMI ≥110 g/m^2 in women and ≥134 g/m^2 in men)[15].

Statistical analysis

All statistical analyses were carried out with the SPSS software package, version 19.0 (IBM-SPSS Inc., Armonk, NY). In the present study, all analyses were performed using the final dataset of the ABC-J II study. The analyses were performed separately by genders. The subjects were classified as; Group 1: high office BP (>140/90 mmHg) and high central SBP (>130 mmHg); Group 2: high office BP and normal central SBP; Group 3: normal office BP and high central SBP; and Group 4 as both normal BP. Because BNP data had a skewed distribution, and we transformed the data using the base-10 logarithm function. Data are shown as the mean ± standard deviation (SD) (continuous variables) or as percentages (categorical variables). Multivariate linear regression analysis was performed to analyze factors associated with central SBP. Factors associated with central SBP in the bivariate analysis or confirmed associating factors were entered as independent variables in this model. BNP levels among the four groups were compared using one way analysis of variance (ANOVA, **Figure 1**), and the general linear model adjusting for age, BMI, smoking, diabetes, CKD, HF history, and beta-blockers (**Figure 2**). Values of $p < 0.05$ were considered significant.

Results

There were 2007 females (67.1±10.8 years) and 2070 males (64.7±11.5 years); and 1046 (25.7%) subjects had diabetes.

Table 1 shows the characteristics of the subjects. In both males and females, the age tended to be higher in the Group 3 followed by the Group 1. BMI and the rate of diabetes tended to be higher in the Group 2 followed by Groups 1 and 4. Otherwise, there were no differences in clinical characteristics among the groups in both genders.

Table 2 shows the laboratory data among the four groups. In females, HbA1c was highest in the Group 2 among the 4 groups, and there were differences in total cholesterol and HDL-cholesterol levels. In males, AST, ALT, γ-GTP and LVH by echocardiography tended to be higher in the Group 2 than the others, however, there were no significant differences in the other items.

Table 3 shows the medications used in each group. In females, diuretics were more frequently used in the Group 4, and nitrates tended to be used more in the group 2, but no other differences were seen. In males, ARBs were more frequently used in the Groups 1 and 2, and beta-blockers were most frequently used in the Group 3 among the four groups.

Figure 1 shows the BNP levels among the four groups by ANOVA. In females, the Groups 1 and 3 had higher values of BNP followed by the Group 4 and 2. In males, Group 3 had highest value of BNP than the other three groups. When the age, BMI, smoking, DM, CKD, HF history, and the use of beta-blockers were further adjusted, the trend remained significant in women, whereas that of men became insignificant although the Group 3 had still relatively higher BNP value (**Figure 2**). When the analyses by using the cutoff value of BNP 40 pg/ml as the measure of high BNP level was performed with logistic regression analyses adjusting for age, BMI, smoking, diabetes, CKD, HF history and the use of beta-blockers, the trend was also significant in female, but not in men. However, the Group 3 had still relatively higher BNP value (**Suppl. Figure. 1**).

Table 4 shows the hemodynamic parameters by office

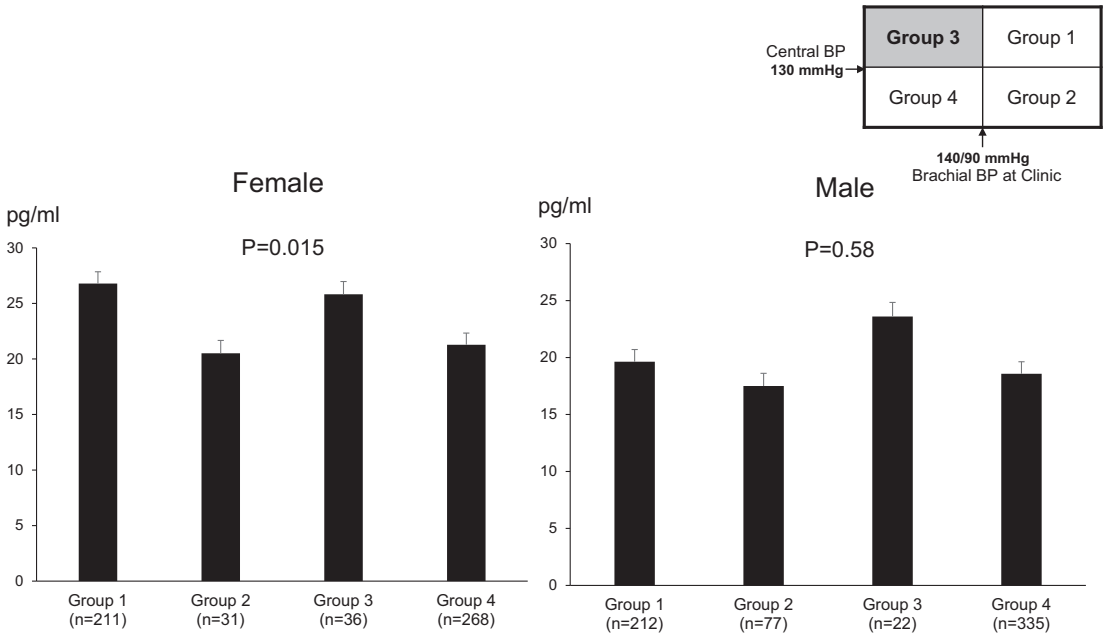

Figure 2. Comparisons of BNP in each group by the general linear model. BNP levels among the four groups adjusting for age, BMI, smoking, diabetes, CKD, history of HF and the use of beta-blockers. The definitions of each group are the same as Table 1.

Table 1. Characteristics of subjects

	Female					Male				
	Group 1	Group 2	Group 3	Group 4	P-value	Group 1	Group 2	Group 3	Group 4	P-value
N	782	76	160	989		692	201	84	1093	
Age, years	68±11.3	65.7±11.8	68.1±10.8	66.4±10.2	0.009	65.3±11.4	62.8±12.9	67.4±9.5	64.4±11.3	0.005
Body mass index, kg/m^2	24.1±3.9	25.7±4.7	23.5±3.5	24.2±3.9	0.001	24.5±3.1	25.3±3.7	24.1±2.9	24.5±3.3	0.006
†Smoking, %	5.4	3.4	7.8	5.0	0.61	27.8	28.7	15.3	22.3	0.02
‡Drinking, %	17.2	10.7	11.9	18.4	0.19	61.7	59	55.2	58.1	0.56
History of hypertension, yrs	2.9±1.0	3.1±1.0	2.9±1.1	3.0±1.0	0.50	2.9±1.1	3.0±1.1	3.0±1.0	3.0±1.0	0.32
Diabetes mellitus, %	21.7	39.5	18.8	26.2	0.001	27.0	35.5	17.3	27.9	0.01
Dyslipidemia, %	50.6	51.3	53.2	52.6	0.84	44.0	45.2	40.7	43.1	0.90
Hyperuricemia, %	7.3	6.6	7.1	8.6	0.73	19.4	21.8	28.4	23.1	0.14
Chronic kidney disease, %	5.6	3.9	3.9	5.0	0.76	7.5	7.1	7.4	7.8	0.99
Peripheral artery disease, %	4.7	6.6	3.2	4.3	0.70	4.4	7.1	4.9	4.4	0.45
Angina pectoris, %	8.8	11.8	9.1	8.6	0.83	12.1	15.7	11.1	14.4	0.39
Heart failure, %	2.2	1.3	1.9	3.1	0.52	1.3	2.5	3.7	3.1	0.10
Myocardial infarction, %	2.0	0	0.6	1.7	0.24	5.8	3.0	6.2	7.0	0.13
Cerebral infarction, %	3.3	6.6	1.3	2.8	0.19	3.7	4.1	3.7	4.5	0.85
Cerebral hemorrhage, %	0.1	0	0.6	0.4	0.53	0.4	0	0	0.4	0.55

Group1: high office brachial BP (>140/90mmHg) and high central SBP (>130mmHg); Group2: high office brachial BP and normal central SBP; Group3: normal office brachial BP and high central SBP; Group 4 as both normal BP.

Data are shown as the mean±standard deviation (SD) (continuous variables) or as percentages (categorical variables).

†smoking data was available 1533 in female and 1567 in male. ‡Drinking data was available 1507 in female and 1518 in male.

and central BP cutoff values. By definition, central BP was highest in the Group 1 followed by Group 3, but rAI, a marker of wave reflection, was highest, and HR was lowest in the Group 3 in both genders. Of note, PP amplification was also lowest in the Group 3 among the four groups.

Factors associated with central SBP by multiple linear regression analyses are shown in **Table 5**. Brachial SBP, BMI, diabetes, nitrate use, and beta-blockers were commonly associated factors with central SBP in both genders. BNP and alpha-blockers were associated with central BP only in females. When the hemodynamic parameters were analyzed by the presence of DM, central BP was significantly lower in the DM group than in the non-DM group (**Suppl Table 1**). When the subjects were further divided by DM plus genders, lower central BP was seen only in females but not in males (**Suppl Table 2**).

Discussion

In the present study, in treated hypertensives, high central

Table 2. Laboratory data in each group

	Female					Male				
	Group 1	Group 2	Group 3	Group 4	P-value	Group 1	Group 2	Group 3	Group 4	P-value
N	782	76	160	989		692	201	84	1093	
BUN, mg/dL	16.2±8.0	16.7±13.4	15.5±4.3	16.7±9.0	0.44	17.8±10.4	17.0±10.8	17.5±8.5	17.6±9.7	0.86
Serum creatinine, mg/dL	0.9±1.3	1.0±1.6	0.8±1.3	0.8±0.9	0.48	1.1±1.6	1.2±1.6	1.2±1.5	1.2±1.5	0.90
Uric acid, mg/dL	5.1±1.5	5.2±1.4	4.9±1.2	5.2±1.5	0.15	6.2±1.4	6.4±1.8	6.2±2.2	6.2±1.5	0.25
AST, U/L	24.6±19.1	23.1±7.9	24.3±9.5	23.5±9.8	0.62	25.3±11.4	29.6±18.5	23.1±6.6	25.2±13.4	0.002
ALT, U/L	21.2±17.3	22.5±15.0	22.0±13.9	21.2±13.4	0.90	26.4±17.9	35.7±31.0	21.7±9.6	26.3±18.5	<0.001
γ-GTP, U/L	28.4±25.5	35.4±41.2	28.2±26.5	30.1±30.3	0.53	57.8±68.4	69.1±66.9	38.9±23.6	53.2±52.7	0.02
Hemoglobin A1c (NGSP) %	5.6±0.8	6.1±1.3	5.5±0.6	5.6±0.9	<0.001	5.6±0.9	5.7±0.9	5.6±0.8	5.6±0.9	0.47
Total cholesterol, mg/dL	206±31	206±31	205±32	201±33	0.03	194±33	192±34	192±29	190±31	0.03
Triglycerides, mg/dL	121±101	127±68	118±51	116±61	0.49	141±94	145±80	137±102	141±91	0.90
HDL cholesterol, mg/dL	63±16	59±15	60±16	60±16	0.006	54±15	55±15	55±15	52±14	0.02
LDL cholesterol, mg/dL	121±32	123±34	119±29	118±30	0.31	114±30	114±34	110±27	113±29	0.67
LVH by UCG[1)], %	28.3	45.5	35.5	25.7	0.36	34.3	45.5	33.3	22.7	0.004
LVMI[2)], g/m^2	111±32	103±25	109±27	106±36	0.75	125±32	141±66	118±35	112±22	<0.001

BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyltranspeptidase; NGSP, National Glycohemoglobin Standardization Program; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; UCG, echocardiography; LVMI, left ventricular mass index. Data are shown as mean±standard deviation (SD) (continuous variables) or as percentages (categorical variables) N=462 in females, 474 in males; 2) N=327 in females, 339 in males

Table 3. Cardiovascular medications in each group

	Female					Male				
	Group 1	Group 2	Group 3	Group 4	P-value	Group 1	Group 2	Group 3	Group 4	P-value
N	782	76	160	989		692	201	84	1093	
ARB, %	66.6	59.2	66.3	63.4	0.37	70.5	70.6	61.9	65	0.044
Diuretics, %	21.5	27.6	24.4	29.3	0.002	21.1	22.9	21.4	25.2	0.25
Calcium channel blockers, %	64.2	75	68.1	68.9	0.086	67.2	71.1	66.7	68.9	0.71
ACE inhibitors, %	7.5	7.9	5.0	8.2	0.57	8.8	7.5	11.9	10.8	0.31
Alpha-blockers, %	13.7	18.4	13.8	16.8	0.25	17.1	14.4	11.9	16.8	0.54
Beta-blockers, %	17.9	14.5	21.9	17.7	0.51	20.1	13.9	27.4	22.4	0.02
Nitrates, %	2.4	6.6	0.6	2.2	0.044	5.5	7.5	2.4	5.9	0.40
Other drugs, %	3.7	6.6	3.8	4.0	0.68	4.9	5.0	7.1	4.7	0.79

ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme

Table 4. Hemodynamic parameters in each group

	Female					Male				
	Group 1	Group 2	Group 3	Group 4	P-value	Group 1	Group 2	Group 3	Group 4	P-value
Brachial SBP, mmHg	155±12	144±9	137±2	123±10	<0.001	156±13	143±7	137±2	125±10	<0.001
Brachial DBP, mmHg	84±12	79±12	76±9	70±9	<0.001	88±13	83±11	78±8	72±10	<0.001
Brachial PP, mmHg	72±15	66±18	61±10	53±10	<0.001	68±14	60±15	59±8	53±10	<0.001
Central SBP, mmHg	149±13	125±6	133±2	114±11	<0.001	146±14	123±6	133±2	112±11	<0.001
Central PP, mmHg	65±15	47±13	57±10	44±10	<0.001	59±15	40±12	55±8	40±10	<0.001
PP amplification	1.12±0.11	1.43±0.3	1.07±0.05	1.22±0.17	<0.001	1.18±0.15	1.63±1.12	1.07±0.04	1.37±0.29	<0.001
AI, %	93.9±11	74.9±15.2	99.8±9.6	85.7±12.3	<0.001	87.5±12.1	67.2±12.1	97.3±7.6	76±13.3	<0.001
AI adjusted by HR 75, %	92.1±9.2	77.3±12.4	95.3±9.6	84.1±11	<0.001	84.5±10	68.9±11.5	91.2±7.5	73.8±11.6	<0.001
HR, bpm	71±11	81±14	65±9	71±11	<0.001	68±11	79±12	61±9	70±12	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; AI, augmentation index; HR, heart rate

BP was associated with higher level of BNP regardless of office BP levels in females. To the best of our knowledge, this is the first study to investigate the clinical relevance of the combination of high central BP and normal office BP in treated hypertensive subjects.

Central BP and cardiac overload

In the present study, central BP evaluated by radial appla-

Table 5. Factors associated with central SBP

	Female		Male	
	Beta	P-value	Beta	P-value
Brachial SBP, mmHg	0.934	<0.001	0.913	<0.001
Body mass index, kg/m^2	–0.047	<0.001	–0.063	<0.001
Diabetes	–0.08	<0.001	–0.031	0.047
log BNP	0.035	0.009	0.007	0.674
Nitrates use	–0.046	<0.001	–0.051	0.001
Beta-blockers use	0.052	<0.001	0.073	<0.001
Alpha-blockers use	–0.054	<0.001	–0.017	0.361

Multiple linear regression analyses

SBP, systolic blood pressure; BNP, brain natriuretic peptide

nation tonometry was associated with cardiac overload in treated hypertensive subjects. Central BP stands for cardiac afterload and has been shown to be associated with left ventricular hypertrophy (LVH)[16]. However, in the present study, the rate of LVH by echocardiography was not predominantly higher in the Group 3 than the others in both genders. Because the subjects in this study are all treated at least 3 months, subjects with inappropriately high BP (i.e. SBP> 180 mmHg) were rare.

We used BNP as a measure of cardiac overload. BNP has been shown to be important in identifying cardiovascular risk in hypertensives[17] and general populations[18,19]. BNP and NT-proBNP have been shown to be useful in identifying subjects with residual risk. The independent association between central BP and BNP would be important for risk stratification of subjects with cardiovascular risk factors, because the measurement of radial applanation tonometry takes only a few minutes and the result of this test can be obtained immediately. Multivariable adjustment including CKD and history of HF diminished the significant relationship between central BP and BNP in males (**Figure 2** and **suppl. Figure 1**), but did not change the results of females. However, it would be of value to measure central BP because complete assessment of cardiovascular risk factors is not always possible in clinical practice even in treated subjects, and the assessment of central BP in addition to brachial BP could be the clue for the further assessment of cardiovascular load.

Factors associated with high central BP

In the present study, factors associated with central BP were brachial SBP, BMI, DM, nitrate use, and beta-blockers in both genders, whereas, BNP and alpha-blockers in females. Brachial SBP, BNP and the use of beta-blockers were positively associated with central SBP, but the others were negatively associated with central SBP. Besides brachial SBP, which is predominantly associated with central SBP, obesity and DM have been reported to be negatively associated with central BP[20,21]. However, the other factors were positively associated with central SBP. Those subjects who are prescribed beta-blockers, alpha-blockers, and nitrates could have had some cardiovascular disease, which raise the levels of central SBP. Beta-blockers are shown to raise BNP levels in a population-based study[22]. Nevertheless, in our multivariate analyses, the use of beta-blockers was independently associated with central BP levels, which indicates that beta-blockers can raise BNP via the increased central hemodynamics.

Diabetes and central BP

In accordance with previous reports[21,23,24], when the hemodynamic parameters were analyzed by the presence of DM, central BP was significantly lower in the diabetes group than in the non-diabetes group. The lower central BP in diabetes was seen only in females but not in males (**Suppl Table 2**). This is in line with our recent study which showed that patients with diabetes had lower reflection wave than those without diabetes[25]. Increased proximal aortic stiffening in type 2 diabetes patients with less stiffened peripheral arteries, which is so-called "impedance mismatch", may both promote more penetration of pulsatile energy into the microcirculation of the brain and kidneys and reduce the reflections at systemic reflection sites. The reason for the gender difference is not clear, but it could be speculated that women tend to have less cardiovascular risk factors than males, and the effect of impedance mismatch in males could become more evident than in females.

Study limitations

There are some limitations in this study. First, the central BP was measured by radial applanation tonometry and there are some possibilities that inaccurate measurement results are contained. However, the device is semiautomatic and the method of this measurement was rigorously standardized in advance. Second, because the subjects in this study are all treated, it is revealed that some medications affect central BP levels, but it cannot be separated whether the association is purely the effect of medication or background cardiovascular disease. Third, in multivariable analyses, the significant relationship was seen only in females (**Figure 2** and **suppl. Figure 1**), but not in men. The exact reason cannot be clarified from this study, but it can be speculated that the weight of each covariates is relatively higher than high central BP in males. Insignificantly highest BNP levels in Group 3 in men may be due to the small number of subjects in this group (n=22). Finally, because of the cross-sectional nature of this study, the effects of beta-blockers on central hemodynamics and BNP levels are not clear. Beta-blockers may fail to reduce central BP in some individuals. This topic is somewhat complicated because the effect of beta-blockers on central hemodynamics and BNP levels depends on the generation of beta-blockers and comorbidity[26].

Perspectives

With regard to central BP, although a number of important findings that clarified the physiological mechanisms of arterial stiffness have been reported, the clinical applications

of these methods are still under way. Several studies have reported normal values or reference values of central BP[13,27,28], but even brachial BP values differ by age and gender[29]. In the present study, we tentatively set the normal value of central SBP as 130 mmHg based on data from Asia[13], we combined this with the normal office brachial BP value 140/90 mmHg, and then classified the subjects into four groups. As a result, the groups with high central SBP had higher values of BNP, a marker of higher cardiovascular burden. In light of the economic burden for patients, applanation tonometry is desirable because it takes only a few minutes to carry out, and there is no need to draw blood or perform expensive and time-consuming echocardiography. A prospective study is needed to confirm the clinical significance of this technique.

Conclusions

In treated hypertensives, higher central SBP was associated with higher BNP levels in women regardless of brachial BP levels at clinic. The results imply that high central SBP (>130 mmHg) can be used to detect high risk hypertensives with cardiovascular overload. Further prospective studies are needed to determine the clinical significance of central BP compared to brachial BP levels using hard outcomes.

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Contributors and details of the study investigators of the ABC-J II study are described also in the supplemental file (appendices).

Conflicts of Interest

The authors state that there are no conflicts of interest regarding this study.

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