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The Relationships between the Differences in the Central Blood Pressure and Brachial Blood Pressure and Other Factors in Patients with Essential Hypertension

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Abstract

Objective The management of blood pressure (BP) in hypertensive patients is the key to preventing a progression of organ damage. The brachial BP (bBP) has been used as the representative method for measuring the BP. The central BP (cBP), which is, different from the bBP due to the propagation and the reflection of the pulse wave in the arterial system, has recently received attention because it can now be estimated non-invasively. We examined the relationships between the difference in the central systolic BP (csBP) and the brachial systolic BP (bsBP) (Δ) and other factors in hypertensive patients.

Methods The bsBP and csBP were measured in patients with essential hypertension and the relationships between the bsBP, csBP, or Δ and background factors including age, the brain natriuretic peptide (BNP) level, the estimated glomerular filtration rate (eGFR), flow-mediated vasodilation (an index of vascular endothelial function), the cardio-ankle vascular index (CAVI, an index of arteriosclerosis), and the carotid intima-media thickness (an index of atherosis) were investigated.

Results The data of 191 patients were analyzed. Although there was no significant correlation between the CAVI and the bsBP; positive correlations were observed between the CAVI and the csBP (r=0.249, p=0.001). The Δ value showed significant positive correlations with age, and the BNP, eGFR, and CAVI values.

Conclusion The csBP is more strongly associated with arteriosclerosis than the bsBP. Moreover, the Δ value is more strongly associated with cardiac function, renal function, and arteriosclerosis than the bsBP or csBP. These data suggested that the Δ value may have a greater prognostic value than the bsBP or csBP and may be worth calculating in the clinical setting.

Key words: central blood pressure, atherosclerosis, age, SBP2, pulse pressure

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Introduction

The measurement of brachial blood pressure (bBP) has been used in clinical practice since the 18th century, and many studies have proven its efficacy in patient evaluation and management. An elevated systolic BP (sBP) is an independent risk factor for cardiovascular mortality (1); thus, the management of blood pressure (BP) in hypertensive patients is the key to preventing the progression of organ damage.

The measurement of the central BP (cBP) has recently received increased attention since several studies indicated its independent relationship with end-organ damage, cardiovascular events, and mortality, suggesting that the cBP is a more accurate predictor of patient outcomes than the bBP (2, 3). In the Anglo-Scandinavian Cardiac Outcomes Trial-Conduit Artery Functional (ASCOT-CAFÉ) study (2), it was suggested that different antihypertensive drugs are not equally efficient in reducing the cBP, regardless of their similar effects on the bBP, and that bBP values may not al-

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ways be a good indicator of the efficacy of antihypertensive agents. Moreover, the management of hypertension based on the cBP is thought to achieve optimal BP control, with the use of less medication and without adverse effects on the left ventricular mass, aortic stiffness, or even quality of life (4). Direct measurement by cardiac catheterization used to be the only method for determining the cBP; however, because of its invasiveness, it was not possible to measure the cBP in large-scale trials. With the recent developments in automated devices for measuring the cBP, data have been gradually collected, which has facilitated the use of the cBP in daily clinical practice. A number of commercially available devices can be used to estimate the cBP. Some of the devices apply applanation tonometry to the radial artery, and the estimation is performed without any risk or discomfort. The SphygmoCor device (AtCor Medical, Sydney, Australia) has been used for more than a decade. Several studies have reported using this device for the estimation of the cBP (2, 3). The device directly records the radial pulse waveform using applanation tonometry and applies a transfer function. With the calibration of the bBP, the cBP and pulse pressure (PP) can be derived automatically. The estimated cBP is strongly correlated with the invasively measured cBP (5); however, due to the use of the bBP in its calibration, cuff measurement errors are included in the estimation of the cBP (6). Meanwhile, a new device, the Omron HEM-9000AI can also estimate the cBP. The device also records the radial pulse waveform using a multi-tonometer sensor and estimates the cBP from the late systolic shoulder (P2) of the radial waveform. Using the close correlation between the pressure of the late systolic shoulder (SBP2) and the cBP (7), the newly developed device applies a commercial algorithm based on a linear regression model to estimate the cBP from the SBP2. Because the brachial systolic BP (bsBP), which is measured using cuff methods, is prone to underestimation in comparison to the bsBP, which is obtained by invasive measurement using the catheter (8), the regression equation is used to correct the underestimation. Examination with this device is convenient because it is fast and operator independent. However, it is still unclear whether the central systolic BP (csBP) or the SBP2, which are provided by the device, are closer to the actual cBP value and should be used in clinical practice.

As the sBP has two components, the early and late sBP, it might not be possible to determine the cBP by the measurement of the bBP alone; moreover, the cBP may differ between individuals with similar sBP values. It is well known that the bsBP is higher than the csBP due to the amplification of pressure from the aorta to the brachial artery (5), whereas the diastolic and mean arterial pressure values are almost equal. This amplification varies based on age, sex, height, and heart rate (9). In fact, age-dependent arterial stiffening will itself enlarge the reflection of the pulse wave in late systole, leading to the elevation of the csBP. In a recent multi-center, multi-device study, the typical values of the csBP and the amplification (bsBP - csBP) were investigated in a healthy population (10). It was confirmed that the amplification was influenced by a number of factors, including smoking, dyslipidemia and the blood glucose level, in addition to age, sex, and heart rate.

Although numerous studies have identified the efficacy of the measurement of the cBP, few studies have shown the relationship between the cBP and background factors, such as physiological function test data. Furthermore, the utility or superiority of measuring the difference between the csBP and bsBP remains to be established. We hypothesized that this difference would be a good predictor of factors such as arterial stiffening and sought to identify the implications of the difference by examining its relationship with other background factors.

Materials and Methods

Subjects

Patients with essential hypertension (EH) who visited our outpatient clinic from October 2011 to January 2013 were included in this study. Patients who were taking antihypertensive medications or whose office BP was above 140/90 mmHg were defined as hypertensive (1). The exclusion criteria were the presence of secondary causes of hypertension; thus, renal and endocrine sources of hypertension and physical findings were appropriately evaluated in all patients. Hypertensive patients were either untreated or were treated with antihypertensive drugs. In the total population of all 191 patients, 105 patients were untreated, 73 patients were taking calcium channel blockers and 27 patients were taking renin-angiotensin system inhibitors. Patients who had a hemorrhagic stroke or cardiac infarction in the previous 6 months, pregnant women, and those with apparent peripheral vascular or malignant disease were excluded from the present study. All of the participants were enrolled after obtaining their informed consent and the approval of the ethical committee of Tokyo Women's Medical University.

Background factors

At enrollment, the sex, age, height, body weight, and waist circumference of all of the patients were recorded. The waist circumference was measured at the umbilicus after the patient exhaled, with the patient in a standing position.

The office blood pressure and pulse rate

The office BP, pulse rate (PR), and PP were measured with a sphygmomanometer, which was attached to an HEM-9000AI device(Omron Healthcare Co., Ltd., Kyoto, Japan), which is described below. At the time in which the augmentation index (AI) and csBP were measured, the PP was calculated by subtracting the diastolic BP from the bsBP. The measurements were performed at an outpatient clinic with the patient in a sitting position after resting for at least 5 minutes.

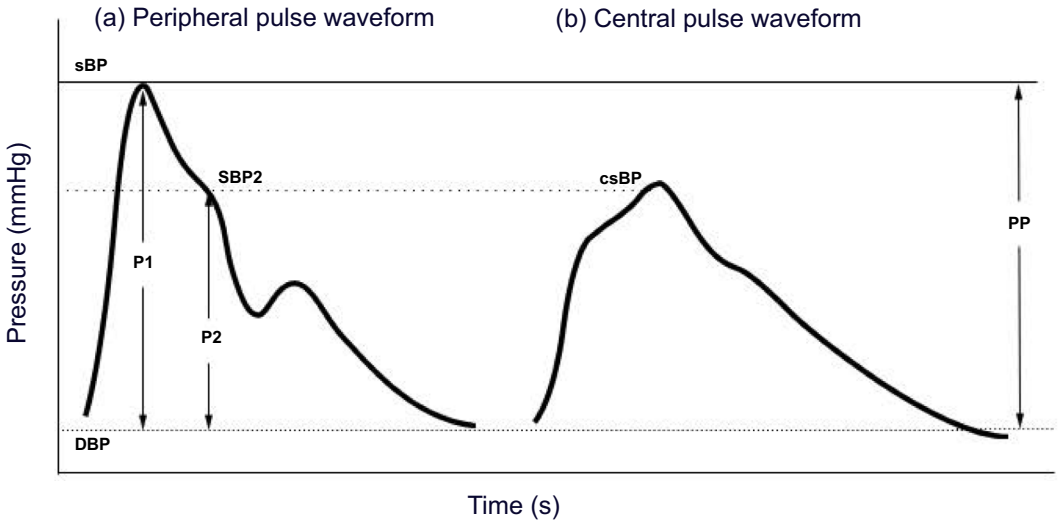

Figure 1. **The peripheral and central pulse waveform patterns. (a) The peripheral (radial) pulse waveform showing the peripheral systolic pressure (P1) and peripheral late systolic shoulder (P2, SBP2), which were used to calculate the augmentation index. The dashed line shows the SBP2, which corresponded to the central systolic blood pressure (csBP). (b) The central (aortic) waveform showing the csBP. Both waves are consistent with the description of Richardson et al. (28). sBP: systolic blood pressure, DBP: diastolic blood pressure**

The augmentation index and csBP

The AI, which is an index of arterial stiffness, and csBP were measured using an automated tonometry device (such as the HEM-9000AI). Using this device, the radial artery waveforms and bBP were recorded simultaneously, and the SBP2 and estimated csBP were automatically calculated in a linear regression analysis. As described previously (11), the radial pulse waveform patterns, which are identical to the simultaneously and invasively measured intra-arterial pulse waveform patterns (7), were recorded noninvasively by applanation tonometry. As shown in Fig. 1, the arterial blood pressure waveform patterns at the aorta are markedly different from those at the peripheral arteries, such as the brachial and radial arteries. From each waveform, the inflection points or peaks that corresponded to early and late sBP were obtained. P1 indicates the amplitude of the early systolic pressure, which is equal to the PP of the radial artery, and the P2 reflects the late systolic pressure. As the P2 is generated by the addition of the reflected pulse wave from the periphery to the incident pulse wave, it is thought to reflect the arterial stiffness. As the pressure wave proceeds to the arterial tree, the waveform will gradually change, with the P 1 going upwards and the P2 going downwards, as the reflection components decrease.

The following equation was used to determine the SBP2, which reflects the late sBP in the radial artery:

SBP2 = (P2/PP) × (sBP - diastolic BP) + diastolic BP.

Using the SBP2, csBP was estimated from a regression equation as previously described (7).

The peripheral AI was derived from the following equation using the peaks of the waveform:

AI = (P2/P1) ×100.

Ambulatory BP monitoring

Ambulatory BP monitoring (ABPM) was performed with an automatic device, TM-2431 (A&D Company, Tokyo, Japan), which recorded the BP (by the oscillometric method) and PR every 30 minutes from 6 AM to 10 PM and every 60 minutes during the rest of the day. The nighttime BP and PR were defined as the mean values of the measurements recorded from the time the patient went to bed until the time he/she got out of bed. The daytime BP and PR were defined as the mean values of the measurements recorded during the rest of the day. The morning surge in the sBP was calculated by subtracting the 2-h average sBP before waking from the 2-h average sBP after waking. The fall in the nocturnal sBP (%) was calculated as 100× [1-nighttime sBP/daytime sBP ratio].

Urinary examinations

Spot urine samples were obtained and the creatinine and albumin concentrations were quantified by standardized assessment methods at our clinical laboratory center. The excretion of albumin was evaluated by dividing the obtained values by the creatinine concentration.

Blood examinations

Blood samples were taken after at least 15 minutes of rest, while the patients were sitting. The blood glucose, hemoglobin A1c (HbA1c), low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, creatinine, uric acid, high-sensitivity C-reactive protein (hs-CRP), and brain natriuretic peptide (BNP) levels were measured by standard laboratory methods at our clinical laboratory center. The estimated glomerular filtration rate

(eGFR) was calculated using the following equation:

eGFR (mL/min per 1.73 m^2) =194 × creatinine$^{-1.094}$ × age$^{-0.287}$ (×0.739 if female). (12)

Flow-mediated vasodilation

The percent changes in the brachial artery diameter were calculated in response to the increased flow-mediated vasodilation (FMD), which is an index of the endothelial function, after the 5-min cuff occlusion of the brachial artery, as previously described (13), using a UNEX EF38 G device (UNEX Corporation, Nagoya, Aichi, Japan).

The cardio-ankle vascular and ankle-brachial indices

The cardio-ankle vascular index (CAVI), an index of arteriosclerosis, and the ankle-brachial index (ABI) were measured using a VaSera VS-1500AN device (Fukuda Denshi Co., Ltd., Tokyo, Japan), as described previously (14). The CAVI was not calculated for patients with an ABI value of <0.90.

The carotid intima-media thickness

The carotid intima-media thickness (IMT) was measured by ultrasonography scans of the common carotid artery, bulb, and internal carotid artery. Ultrasonography was performed bilaterally using a Nemio XG ultrasound system (Toshiba Cooperation, Tokyo, Japan). The carotid IMT was defined as the length from the leading edge of the first echogenic line (representing the lumen-intimal interface) to the leading edge of the second echogenic line (representing the collagen-containing upper layer of the tunica adventitia) on the scans, and the maximum IMT was detected by scanning along the vessel from the common carotid artery to the internal carotid artery, as described previously (15). The examinations were conducted while the subjects were in the supine position with their head turned 45° from the site being scanned. Both carotid arteries were scanned longitudinally in order to visualize the IMT in the far wall of the artery, and the maximum IMT, an index of atherosis, was assessed.

Study protocol

The relationships between the background factors, the BP and PR data, the urine and blood data, the FMD, the CAVI, the AI or maximum IMT and the office sBP, cBP, or Δ were examined by single or multiple regression analyses. Additionally, the patients were divided into 2 groups: patients with positive Δ values (the Δ+ group) and those with negative Δ values (the Δ- group). The relationship between the background factors, the BP and PR data, the urinary and blood data, the FMD, CAVI, and AI values, and the maximum IMT were compared between the groups.

Statistical Analysis

All of the data were expressed as mean ± standard deviation, and all of the single regression analyses were performed using the StatView 5.0 software program (SAS Institute, Cary, NC, USA). Single regression analyses were performed to investigate the correlations between background factors, the BP and PR data, the urine and blood data, and the physiological function test results and the office BP, csBP, or Δ. An a priori power analysis was performed using a G*Power of 3.1.9.2. with an assumed r value of 0.3, which suggested that at least 134 patients were required to determine the correlation between Δ and other factors with a power of 95%. Multiple regression analyses were used to identify possible determinants. An unpaired Student's *t*-test and the χ^2 test were used for the intergroup comparisons. p values of <0.05 were considered to indicate statistical significance.

Results

Characteristics of the study subjects

A total of 191 EH patients were enrolled in this study. Table 1 shows the background factors, including the office BP, PR, and PP, csBP, BP and PR data obtained by ABPM, the urine and blood data, and data from the physiological function tests. Five patients showed an ABI value of <0.9 and were excluded from the study. Taken together, these data indicated that most study subjects had essential hypertension with mild to moderate, but not severe, organ damage.

The csBP, SBP2, and Δ values

The mean csBP (145±20 mmHg) was significantly higher than the mean bsBP (141±17 mmHg) (Table 1). The mean SBP2 (129±18 mmHg) was significantly lower than both the mean csBP and bsBP. The central sBP and SBP2 were perfectly correlated (r=1.0; p<0.001). The mean Δ value was 4±9 mmHg (range, -26 to 18 mmHg). The mean Δ value was higher in women (7±7 mmHg) than in men (0±9 mmHg; p<0.001), and the mean of csBP value was higher in women (147±20 mmHg) than in men (140±18; p=0.007). Those findings are in line with those of previous reports (4). However, there was no sex difference in the bsBP or PP values.

The relationships between the background factors and the bsBP, csBP, and Δ values

There was no significant relationship between the csBP and age (Table 2). Interestingly, however, there were significant correlations between age and bsBP (Table 3), the Δ value (Table 4), and the PP value (Table 5). These results are also shown as scattergrams in Fig. 2. The brachial sBP was significantly correlated with age, the office diastolic BP, office pulse rate, csBP, SBP2, PP, 24-h sBP, 24-h diastolic BP, urinary albumin excretion rate, and the LDL-cholesterol level (Table 3). There were no significant relationships between the bsBP and any of the physiological function test data. The central sBP had significant relationships with height, the office systolic and diastolic BP, Δ, SBP2, PP, 24-h sBP, 24-h diastolic BP, urinary albumin excretion rate, and

Table 1. Characteristics of the Study Subjects.

Sex (Male/Female)	86/105	Urinary tests	
Age (y)	57±12	Albumin excretion (mg/gCre)	73.9±150.6
Body mass index (kg/m^2)	23.8±3.9		
Waist circumference (cm)	88.8±10.5	Blood tests	
Smoker (%)	16.8	Blood glucose (mg/dL)	112±38
Diabetes mellitus complication (%)	9.9	Hemoglobin A1c (%)	5.6±0.7
Dyslipidemia complication (%)	13.1	LDL-cholesterol (mg/dL)	127±30
Blood pressure and pulse rate		HDL-cholesterol (mg/dL)	65±20
Office blood pressure and pulse rate		Triglyceride (mg/dL)	121±73
Systolic blood pressure (mmHg)	141±17	Creatinine (mg/dL)	0.74±0.20
Diastolic blood pressure (mmHg)	85±12	eGFR (mL·min^{-1}·1.73m^{-2})	76.1±20.8
Pulse pressure (mmHg)	54±14	Uric acid (mg/dL)	5.5±1.6
Pulse rate (bpm)	77±11	hs CRP (ng/dL)	1,043±2,357
Central systolic blood pressure (mmHg)	145±20	BNP (pg/mL)	26.8±30.7
Δ (mmHg)	4±9		
SBP2 (mmHg)	129±18	Physiological function tests	
		FMD (%)	5.4±2.4
ABPM data		CAVI (m/s)	8.1±1.2
24 hours		ABI	1.15±0.26
Systolic blood pressure (mmHg)	141±15	AI (%)	79.1±15.1
Diastolic blood pressure (mmHg)	86±10	IMT(mm)	1.0±0.4
Pulse rate (bpm)	75±9		
Daytime			
Systolic blood pressure (mmHg)	145±15		
Diastolic blood pressure (mmHg)	89±11		
Pulse rate (bpm)	79±11		
Nighttime			
Systolic blood pressure (mmHg)	129±18		
Diastolic blood pressure (mmHg)	77±10		
Pulse rate (bpm)	65±10		
Morning surge (systolic blood pressure) (mmHg)	17±24		
Nocturnal systolic blood pressure fall (%)	10.8±9.3		

Δ: central systolic blood pressure - office systolic blood pressure, ABPM: ambulatory blood pressure monitoring, eGFR: estimated glomerular filtration rate, hs CRP: high sensitive C-reactive protein, BNP: brain natriuretic peptide, FMD: flow mediated dilation, CAVI: cardio-ankle vascular index, ABI: ankle-brachial index, AI: augmentation index, IMT: intima-media thickness

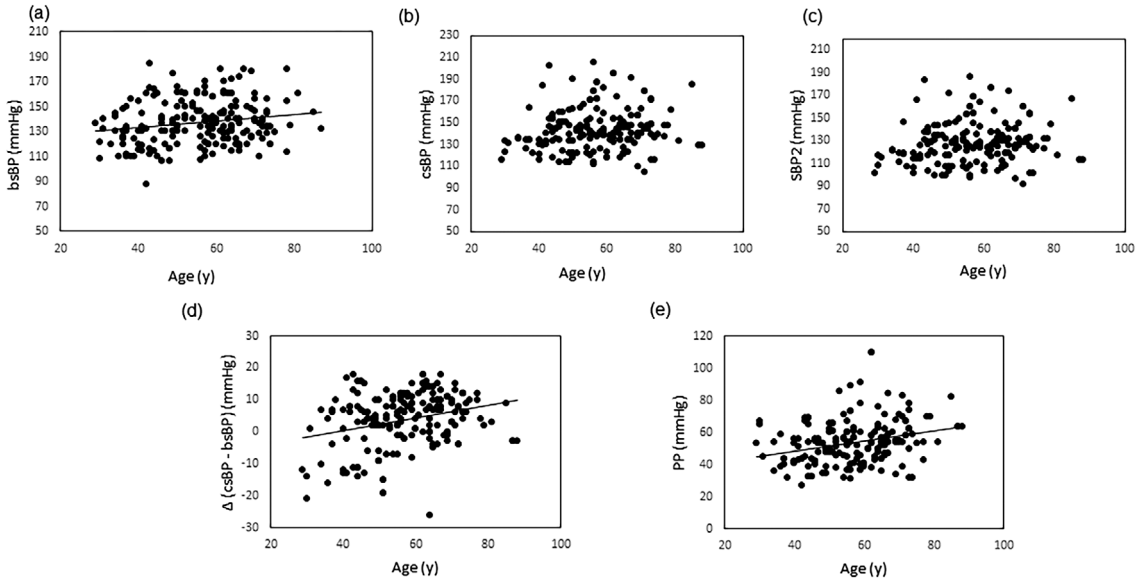

Figure 2. Scattergrams showing the relationships between age and the blood pressure data. The correlation between age and (a) the bsBP; y=0.2607x+122.56, (b) csBP, (c) SBP2, (d) Δ (csBP-bsBP); y=0.1946x-7.311, and (e) PP; y=0.3088x+36.284. bsBP: brachial systolic blood pressure, sBP: systolic blood pressure, csBP: central systolic blood pressure, Δ: central systolic blood pressure-brachial systolic blood pressure, PP: pulse pressure, SBP2: pressure of the late systolic shoulder

the triglyceride level (Table 2). The central sBP was also significantly correlated with the CAVI and AI values, suggesting an interaction between arteriosclerosis and csBP. The Δ value was significantly correlated with age, height, the of-

Table 2. Single Regression Analyses with Central Systolic Blood Pressure.

	r	p value		r	p value
Age	0.137	0.061	Urinary tests		
Body mass index	0.024	0.813	Albumin excretion	0.316	0.005
Height	-0.257	0.011	Blood tests		
Waist circumference	0.071	0.485	Hemoglobin A1c	0.152	0.097
Blood pressure and pulse rate			LDL-cholesterol	0.086	0.351
Office blood pressure and pulse rate			HDL-cholesterol	-0.025	0.783
Systolic blood pressure	0.444	<0.001	Triglyceride	0.186	0.042
Diastolic blood pressure	0.352	<0.001	Creatinine	-0.158	0.084
Pulse pressure	0.618	<0.001	eGFR	0.063	0.493
Pulse rate	0.138	0.546	Uric acid	0.031	0.743
Central systolic blood pressure			hs CRP	0.032	0.744
Δ	0.388	<0.001	BNP	0.132	0.18
SBP2	1	<0.001	Physiological function tests		
ABPM data			FMD	0.007	0.933
Systolic blood pressure	0.596	<0.001	CAVI	0.249	0.001
Diastolic blood pressure	0.367	0.001	ABI	-0.043	0.569
Pulse rate	0.198	0.083	AI	0.46	<0.001
			IMT	-0.051	0.64

Δ: central systolic blood pressure - office systolic blood pressure, ABPM: ambulatory blood pressure monitoring, eGFR: estimated glomerular filtration rate, hs CRP: high sensitive C-reactive protein, BNP: brain natriuretic peptide, FMD: flow mediated dilation, CAVI: cardio-ankle vascular index, ABI: ankle-brachial index, AI: augmentation index, IMT: intima-media thickness

Table 3. Single Regression Analyses with Brachial Systolic Blood Pressure.

	r	p value		r	p value
Age	0.183	0.011	Urinary tests		
Body mass index	-0.153	0.083	Albumin excretion	0.336	0.001
Height	-0.099	0.263			
Waist circumference	0.087	0.342	Blood tests		
Blood pressure and pulse rate			Hemoglobin A1c	-0.015	0.839
Office blood pressure and pulse rate			LDL-cholesterol	0.199	0.008
Systolic blood pressure			HDL-cholesterol	0.036	0.627
Diastolic blood pressure	0.74	<0.001	Triglyceride	0.1	0.181
Pulse pressure	0.279	0.002	Creatinine	0.106	0.149
Pulse rate	0.386	0.031	eGFR	-0.044	0.556
Central systolic blood pressure	0.444	<0.001	Uric acid	0.105	0.181
Δ	-0.055	0.547	hs CRP	-0.084	0.355
SBP2	0.442	<0.001	BNP	0.123	0.173
ABPM data					
Systolic blood pressure	0.535	<0.001	Physiological function tests		
Diastolic blood pressure	0.45	<0.001	FMD	0.053	0.573
Pulse rate	0.209	0.069	CAVI	0.099	0.243

Δ: central systolic blood pressure – office systolic blood pressure, ABPM: ambulatory blood pressure monitoring, eGFR: estimated glomerular filtration rate, hs CRP: high sensitive C-reactive protein, BNP: brain natriuretic peptide, FMD: flow mediated dilation, CAVI: cardio-ankle vascular index, ABI: ankle-brachial index, AI: augmentation index, IMT: intima-media thickness

fice PR, csBP, SBP2, PP, eGFR, uric acid, and the BNP levels (Table 4). Significant correlations between the Δ value and both the eGFR and BNP suggest interactions between the Δ value and the cardiac and renal functions. Similarly to csBP, the Δ value showed significant correlations with the CAVI and AI values, indicating that there was also an interaction between arteriosclerosis and the Δ value. The PP value showed significant correlations with age, height, the office sBP, csBP, Δ, SBP2, 24-h sBP, HbA1c, uric acid, and the BNP levels, suggesting an association with the cardiac function (Table 5). The PP value also showed a significant correlation with the CAVI value, suggesting that there was also an interaction between arteriosclerosis and the PP.

A single regression analyses showed that the eGFR was significantly negatively associated with age (r=-0.534, p< 0.0001) and the Δ value (r=-0.266, p<0.005) but not with sex, or the LDL-cholesterol, triglyceride, or HbA1c levels. A multiple regression analysis in which age and the Δ value were included as dependent variables showed that the Δ value and age were significantly negatively correlated with the eGFR (Table 6). A single regression analyses revealed that the BNP was significantly positively associated with age (r=0.342, p<0.0001) and the Δ value (r=0.255, p<0.01) and negatively associated with the eGFR (r=-0.206, p=0.021) but not with sex, or the LDL-cholesterol, triglyceride, or HbA1c levels. A multiple regression analysis in which age, the eGFR, and the Δ value were included as dependent variables showed that age and the Δ values were positively associated with the BNP (Table 7).

Differences between the Δ+ and Δ- groups

As shown in Table 8, significant differences were observed between the Δ+ and Δ- groups with regard to age, height, the office PR, csBP, Δ, SBP2, PP, and the eGFR,

Table 4. Single Regression Analyses with Δ.

	r	p value		r	p value
Age	0.294	<0.001	Urinary tests		
Body mass index	-0.044	0.668	Albumin excretion	0.125	0.281
Height	-0.477	<0.001	Blood tests		
Waist circumference	-0.138	0.173	Hemoglobin A1c	-0.062	0.503
Blood pressure and pulse rate			LDL-cholesterol	-0.096	0.298
Office blood pressure and pulse rate			HDL-cholesterol	0.107	0.247
Systolic blood pressure	-0.055	0.547	Triglyceride	-0.155	0.09
Diastolic blood pressure	0.068	0.456	Creatinine	-0.073	0.425
Pulse pressure	-0.145	0.047	eGFR	-0.243	0.007
Pulse rate	-0.503	0.016	Uric acid	-0.193	0.04
Central systolic blood pressure	0.388	<0.001	hs CRP	0.041	0.682
			BNP	0.245	0.012
SBP2	0.385	<0.001	Physiological function tests		
ABPM data			FMD	0.144	0.069
Systolic blood pressure	0.052	0.654	CAVI	0.219	0.003
Diastolic blood pressure	-0.035	0.764	ABI	0.048	0.522
Pulse rate	-0.047	0.684	AI	0.937	<0.001
			IMT	0.095	0.38

Δ: central systolic blood pressure - office systolic blood pressure, ABPM: ambulatory blood pressure monitoring, eGFR: estimated glomerular filtration rate, hs CRP: high sensitive C-reactive protein, BNP: brain natriuretic peptide, FMD: flow mediated dilation, CAVI: cardio-ankle vascular index, ABI: ankle-brachial index, AI: augmentation index, IMT: intima-media thickness

Table 5. Single Regression Analyses with Pulse Pressure.

	r	p value		r	p value
Age	0.278	<0.001	Urinary tests		
Body mass index	-0.108	0.293	Albumin excretion	-0.019	0.87
Height	-0.237	0.019	Blood tests		
Waist circumference	0.062	0.538	Hemoglobin A1c	0.199	0.029
Blood pressure and pulse rate			LDL-cholesterol	0.039	0.677
Office blood pressure and pulse rate			HDL-cholesterol	-0.05	0.592
Systolic blood pressure	0.279	0.002	Triglyceride	0.129	0.162
Diastolic blood pressure	-0.052	0.572	Creatinine	-0.071	0.438
Pulse pressure			eGFR	0.025	0.786
Pulse rate	0.352	0.109	Uric acid	0.186	0.048
Central systolic blood pressure	0.618	<0.001	hs CRP	0.046	0.641
Δ	-0.145	0.047	BNP	0.268	0.006
SBP2	0.617	<0.001	Physiological function tests		
ABPM data			FMD	-0.108	0.172
Systolic blood pressure	0.344	0.002	CAVI	0.263	0
Diastolic blood pressure	-0.089	0.439	ABI	-0.144	0.053
Pulse rate	-0.093	0.421	AI	0.07	0.341
			IMT	-0.049	0.65

Δ: central systolic blood pressure - office systolic blood pressure, ABPM: ambulatory blood pressure monitoring, eGFR: estimated glomerular filtration rate, hs CRP: high sensitive C-reactive protein, BNP: brain natriuretic peptide, FMD: flow mediated dilation, CAVI: cardio-ankle vascular index, ABI: ankle-brachial index, AI: augmentation index, IMT: intima-media thickness

Table 6. Multiple Regression Analysis with eGFR.

	β	p value
Age	-0.455	<0.0001
Δ	-0.169	0.047

eGFR: estimated glomerular filtration rat, Δ: central systolic blood pressure - office systolic blood pressure. R^2 =0.268, p <0.0001 for entire model

Table 7. Multiple Regression Analysis with BNP.

	β	p value
Age	0.342	<0.0001
eGFR	-0.206	0.021
Δ	0.255	0.01

BNP: brain natriuretic peptide, eGFR: estimated glomerular filtration rate, Δ: central systolic blood pressure - office systolic blood pressure. R^2 = 0.165, p =0.0006 for entire model

suggesting an interaction between the Δ value and the renal function. Additionally, the FMD, CAVI, and AI values were significantly higher in the Δ+ group than in the Δ- group, indicating interactions between the Δ value and endothelial dysfunction and arteriosclerosis.

Discussion

The present study showed 4 major findings regarding the csBP and the Δ value in EH patients. First, the csBP was

Table 8. Comparisons of Background Factors between Δ- and Δ+.

	Δ-	Δ+	p value		Δ-	Δ+	p value
Age (y)	53±14	58±11	0.005	Urinary tests			
Body mass index (kg/m^2)	24.9±3.6	23.5±3.9	0.141	Albumin excretion (mg/gCre)	27.1±20.3	86.2±167.0	0.164
Height (cm)	165.4±8.6	158.8±8.2	0.001	Blood tests			
Waist circumference (cm)	91.4±12.6	87.5±9.5	0.05	Hemoglobin A1c (%)	5.9±1.3	5.6±0.6	0.084
Blood pressure and pulse rate				LDL-cholesterol (mg/dL)	128±25	126±31	0.738
Office blood pressure and pulse rate				HDL-cholesterol (mg/dL)	61±19	66±20	0.24
Systolic blood pressure (mmHg)	143±15	141±17	0.554	Triglyceride (mg/dL)	139±83	117±71	0.188
Diastolic blood pressure (mmHg)	83±9	86±13	0.212	Creatinine (mg/dL)	0.75±0.20	0.74±0.20	0.846
Pulse pressure (mmHg)	60±10	52±14	0.001	eGFR (mL·min-1^{-1}.73m^{-2})	85.8±26.1	73.9±18.8	0.011
Pulse rate (bpm)	85±14	74±9	0.033	Uric acid (mg/dL)	5.7±1.6	5.4±1.5	0.503
Central systolic blood pressure (mmHg)	136±16	146±20	0.002	hsCRP (ng/mL)	1,226±1,337	1,010±2,563	0.704
Δ (mmHg)	-9±6	8±5	<0.001	BNP (pg/mL)	16.0±13.5	29.3±33.2	0.077
SBP2 (mmHg)	121±15	131±18	0.003	Physiological function tests			
ABPM data				FMD (%)	4.7±2.4	5.6±2.4	0.038
Systolic blood pressure (mmHg)	138±11	142±15	0.391	CAVI (m/s)	7.7±1.2	8.1±1.1	0.041
Diastolic blood pressure (mmHg)	84±9	87±10	0.381	ABI	1.13±0.10	1.17±0.29	0.4
Pulse rate (bpm)	74±7	75±10	0.647	AI (%)	59.8±9.9	84.8±11.2	<0.001
				IMT (mm)	0.9±0.2	1.0±0.4	0.147

Δ: central systolic blood pressure - office systolic blood pressure, ABPM: ambulatory blood pressure monitoring, eGFR: estimated glomerular filtration rate, hs CRP: high sensitive C-reactive protein, BNP: brain natriuretic peptide, FMD: flow mediated dilation, CAVI: cardio-ankle vascular index, ABI: ankle-brachial index, AI: augmentation index, IMT: intima-media thickness

significantly higher than the bsBP, while the SBP2 was significantly lower than the bsBP. Second, the csBP but not the bsBP showed a significant positive correlation with the CAVI value. Additionally, the correlation of the Δ value with the CAVI value was even stronger than the correlation between the csBP and CAVI values. Third, significant positive correlations were observed between the Δ value and age, and the BNP, CAVI, and AI values. Finally, the age and the FMD and CAVI values were significantly higher in patients with positive Δ values than in those with negative Δ values.

Our data showed that the measurement of the Δ value, which reflects the difference between the csBP and bsBP, might have additional prognostic value than the measurement of the bsBP or csBP alone. The Δ value showed significant correlations with the eGFR and BNP (Table 4), while both bsBP (Table 3) and csBP (Table 2) showed no significant relationships with those factors. Additionally, a multiple regression analyses revealed the presence of independent relationships between the eGFR (Table 6), the BNP (Table 7) and the Δ value. On dividing the patients into the Δ+ and Δ- groups, significant differences were observed in the patients' FMD, CAVI, and AI values (Table 8). An increased AI value is reported to reflect both early vascular damage and subsequent damage to the heart (16). Taken together, these data suggest the existence of interactions between the Δ value and endothelial dysfunction and arteriosclerosis, probably leading to the relationships between the Δ value and the altered cardiac and renal functions.

The cBP is the pressure that the left ventricle has to confront and reflects the direct left ventricular wall stress. In fact, the increase in the peripheral reflection wave on the left ventricle is thought to be one of the important factors that causes cardiac hypertrophy, and many other studies have proven that the cBP is more relevant than the peripheral BP in the pathogenesis of cardiovascular diseases (17). Moreover, recent trials have shown that the cBP and AI values can be used to independently predict future clinical outcomes (18). We cannot point out the reason why our data did not show a significant relationship between the BNP and csBP or the bsBP. However, from the fact that the Δ value was significantly associated with the BNP; we hypothesize that the predicted Δ values exceed those of the csBP or bsBP values. Furthermore, arterial stiffness and PP are reported to be linked with the plasma creatinine level and even microproteinuria (19). Because the kidneys have torrential blood flow, which exposes them to the pulsatility of the central pressure, the central pressure or the reflected pulse wave might be more relevant to associated risks, including the renal function, leading to the negative correlation of the Δ value with the eGFR.

Generally, the bsBP is higher than the csBP because of the pressure amplification. This central to radial amplification has been shown to be higher in men than in women (20); it is also higher in young people and decreases with age (21), and is affected by height (22) and the heart rate (23). While other articles referred to the difference between the bsBP and csBP as "bsBP - csBP", we defined our Δ value as "csBP - bsBP" because the csBP was mostly higher than the bsBP in our data. This seems like a contradiction, because the bsBP is, in general, higher than the csBP. This contradiction might be due to estimation errors by the measurement devices (we will discuss this discrepancy later). Until now, very few studies have focused on the difference between the csBP and bsBP values, which we defined as the Δ value. Sharman et al. (4) showed that the csBP values can be similar in patients with optimal or high bsBP values, due to the large variation in the difference in the brachial-aortic sBP. They also pointed out the sex differences in the brachial-aortic sBP values: men had higher brachial-aortic sBP values than women. Because tall people are likely to have long limbs, the arterial branch will be longer. Accordingly, we can speculate that the central to radial amplification is larger in taller people, leading to the

correlation. Nakamura et al. (23) showed that in women, short stature was correlated with low levels of central to peripheral sBP amplification; highlighting that the sex and stature differences were correlated with the brachial-aortic sBP difference. Herbert et al. (9) revealed that amplification was higher in males than in females. These data are in accordance with our own, which indicated that the Δ value was higher in women than in men, and that the csBP and Δ values were negatively correlated with height. On average, men are taller than women; thus, this maybe one of the reasons underlying the sex difference. Furthermore, it was previously pointed out (23) that there are differences in the arterial characteristics of men and women. This difference may have also been a factor in the sex differences observed in the Δ value.

The PP value was also found to be an independent predictor of cardiovascular and all-cause mortality (24). Like the sBP, the PP increases along the artery. The peripheral PP is higher than the central PP because of the propagation of the pressure wave with the increase in arterial stiffness and the declining diameter. Accordingly, the degradation of the amplification of the PP is caused by an increase in the csBP in relation to the increase in arterial stiffness and wave reflections. Although the PP and Δ values have a lot in common, their relationships with the other background factors have never been compared. In our data, while both the PP and Δ values were found to be significantly correlated with the BNP, only the Δ value was significantly correlated with the eGFR and AI values. As we only presented the brachial PP values and not central or carotid PP values, we cannot simply compare these values. However, we are at least able to assume that the predictive value of the Δ value is greater than that of the brachial PP.

Significantly positive associations were found between age and the bsBP, Δ, and PP values (Fig. 2). Although several studies have shown a significant positive association between age and the csBP (11), our data failed to show this relationship. The small number of patients in the present study could explain why this relationship was not shown in our data. On the other hand, a significant positive association was observed between the Δ value and age. It was previously reported that the difference between the bsBP and csBP (brachial sBP - aortic sBP) was the highest in patients under 20 years of age and that it decreased with an increase in age; however, it was also shown that the difference began to gradually increase with advancing age, mainly among patients in their 70s (9). Since the Δ value is the difference between the csBP and bsBP, it directly reflects the reflected pulse wave. Furthermore, the degree of reflection is based on the arterial anatomy and vessel functions, which are characterized by aging and the progression of vessel diseases such as arteriosclerosis. Taken together, the Δ value might be a stronger predictor of arterial stiffness than the cBP.

Studies have been conducted to compare the accuracy and availability of two devices for estimating the cBP: the SphygmoCor system and the Omron system. In fact, a systematic meta-analysis has shown device-/technique-dependent variability in the noninvasive estimation of the cBP (25). The SphygmoCor system uses a transfer function to synthesize the aortic pressure from the radial tonometry, and the Omron system uses radial tonometry to presume the central pressure from the late systolic peak using an established algorithm (26). In the measurement of the central aortic pressure, a strong correlation ($r=0.99$, $p<0.001$) was found between the 2 methods when the same methods of cuff calibration were applied (27). However, they have also shown that the Omron estimate was 18.8±4.3 mmHg higher than the SphygmoCor estimate. Richardson et al. (28) also pointed out a significant difference between the cBP values measured by the 2 devices (the Omron estimate was 12.2± 4.6 mmHg higher). They also showed that when comparing the SBP2 values identified by the Omron system with the csBP calculated by the SphygmoCor, the mean difference was only 1.8 mmHg, suggesting that the SBP2 might be closer to the true aortic pressure. Other studies have noted similar findings when the SBP2 was used for the comparison of the values estimated by the 2 devices (29). On the other hand, Ding et al. (30) showed that the csBP estimated by the Omron device was only 2 mmHg lower than the values obtained by invasive measurements, where the underestimation when measurements were made using the SphygmoCor was as high as 15 mmHg. Takazawa et al. (6) also showed the accuracy of the values estimated by the Omron device, this was evidenced by the difference between the estimated csBP and the invasively measured sBP, which was only 0.39±9.68 mmHg. Taken together, the measurement of the csBP using the Omron device might be better for predicting the "true" cBP from approximate data than the values obtained by invasive measurements. The differences in the cBP values obtained by the Omron and SphygmoCor devices are mainly caused by the underestimation of the bsBP (8, 9). Thus, measurement errors in the estimation of cBP remain an unresolved issue and require a more accurate approach.

Limitations

Considering the previous studies on device-dependent variability, the Δ values obtained in our study lack credibility as the absolute difference between the central and brachial sBP values. Although Cheng et al. proposed a cBP of 130/90 mmHg as the cutoff limit of normality (18), the threshold or standard values have never been determined for the cBP, suggesting that studies and discussions regarding the cBP are still developing. Since we only used the Omron HEM-9000AI in our study, we cannot simply compare our results to those obtained by previous studies that used other devices for measurement. In addition, nearly half of the patients in our study were taking antihypertensive drugs. As it is considered that different drugs show varying degrees of efficacy against cBP, we cannot exclude the impact of these agents. However, by calculating the Δ value, additional

prognostic values may be ensured. More accurate and precise devices are needed to perform a proper evaluation, and large-scale trials are needed to further examine the accuracy of calculating the Δ value.

Conclusion

We reconfirmed the importance of measuring the cBP by showing that it had a stronger impact on arterial stiffening than the peripheral BP in essential hypertensive patients. In addition, in comparison to the cBP, the Δ value showed even stronger relationships with endothelial dysfunction and arterial stiffening. All of these data suggest that the Δ value has additional prognostic value and that it may be worth calculating in clinical settings.

The authors state that they have no Conflict of Interest (COI).

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