Cross-Sectional Characterization of all Classes of Antihypertensives in Terms of Central Blood Pressure in Japanese Hypertensive Patients

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BACKGROUND
Central blood pressure (CBP) has been reported to be superior to brachial blood pressure (BP) as a cardiovascular risk predictor in hypertensive patients; however, the effects of antihypertensives on CBP have not been fully examined. This cross-sectional hypothesis-generating study aimed to tentatively characterize all classes of antihypertensives in relation to CBP.

METHODS
Calibrated tonometric radial artery pressure waveforms were recorded using an automated device in 1,727 treated hypertensive patients and 848 nonhypertensive (non-HT) participants. Radial artery late systolic BP (SBP) has been reported to reflect central SBP. The difference between late and peak SBPs (ΔSBP2) was assessed with linear regression model-based adjustments. Separate regression models for ΔSBP2 were constructed for both participant groups as well as specified sub-populations.

RESULTS
ΔSBP2 was 3.3 mm Hg lower in patients treated with any single-vasodilating (VD) antihypertensive agent without significant interclass difference than with non-VD agents, and was 2.0 mm Hg lower than estimated in nonhypertensive subjects. Combinations of two vasodilators were 6.6 and 2.9 mm Hg lower in ΔSBP2 than nonvasodilator combinations and nonhypertensive subjects, respectively (P < 0.001 for all comparisons). Nonvasodilators and their combination showed high ΔSBP2, 1.1 and 3.7 mm Hg higher than in nonhypertensive subjects (P < 0.001 for both). Additional adjustment of the pulse rate reduced high ΔSBP2 with β-blockers (βBLs).

CONCLUSIONS
This cross-sectional observation suggests that vasodilatory antihypertensives lower CBP independently of peripheral BP levels without evident class-specific differences, whereas nonvasodilators may raise CBP.

Keywords: angiotensin receptor blockers; angiotensin-converting enzyme inhibitors; antihypertensive agents; blood pressure; calcium channel blockers; central blood pressure; diuretics; hypertension; late systolic blood pressure; nonvasodilating antihypertensive agents; pulse waveform; radial artery tonometry; vasodilating antihypertensive agents; a-blockers; β-blockers

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drug; however, it is practically difficult to directly compare all classes of antihypertensive agents at the same time in a single intervention trial. This cross-sectional observation therefore aimed to tentatively characterize all classes of antihypertensive agents commonly used in Japan in terms of CBP.

**METHODS**

*Study design.* This study was a cross-sectional observation, designed as an exploratory (or data-mining) study to generate rather than to test hypotheses.

*Subjects.* We enrolled 1,727 Japanese patients with essential hypertension (HT), who had been on stable antihypertensive medication for at least 3 months, and with medical data, including radial artery tonometry-derived parameters relating to CBP, from seven major centers and their related medical facilities participating in the Antihypertensives and Blood pressure of Central artery study in Japan (ABC-J). The subjects also included 1,094 participants receiving no antihypertensive therapy. From the untreated population, 848 nonhypertensive (non-HT) subjects were extracted based on BP (systolic BP <140 mm Hg and diastolic BP (DBP) <90 mm Hg) measured to CBP , from seven major centers and their related medical facilities participating in the Antihypertensives and Blood pressure of Central artery study in Japan (ABC-J). The subjects also included 1,094 participants receiving no antihypertensive therapy. From the untreated population, 848 nonhypertensive (non-HT) subjects were extracted based on BP (systolic BP <140 mm Hg and diastolic BP (DBP) <90 mm Hg) measured when the radial arterial pulse wave was recorded (Table 1).

The study protocol was approved by the institutional review board of each ABC-J center. Data were obtained from archived medical records of participants in whom the radial arterial pulse wave had been recorded in accordance with the method described below. All participants were informed of this study procedure and gave consent to providing their data. The data were collected from January to December in 2007.

**Radial artery pulse wave measurement and evaluation of CBP.**

Radial artery pressure pulse waveform was recorded with an automated tonometric system, HEM-9000AI (Omron Healthcare, Kyoto, Japan) in a sitting position after at least 5 min of rest. The waveform was calibrated automatically using built-in oscillometric brachial sphygmomanometry. The peak and bottom of the radial pressure wave were adjusted to brachial SBP and DBP, respectively. The HEM-9000AI algorithm automatically performed online detection of the second peak (late systolic inflection) based on the second maxima of the fourth derivative of the radial pressure waveform to determine the radial augmentation index as well as the late or second SBP (SBP2), as shown in Figure 1. The outline of the built-in algorithm of this device has been reported elsewhere.

In order to assess CBP-lowering effects selectively, we focused on central SBP levels relative to brachial SBP because absolute CBP levels largely depend on the mean BP level, which is nearly identical for both central and peripheral sites. Figure 1 shows the parameters derived from radial pulse waveform analysis. The height of the second peak corresponds to SBP2, which is reported by an alternative method18 to or is closely related to directly measured central aortic SBP. SBP2 obtained by the same device as in this study has also been reported to be comparable to central SBP estimated using a generalized aorto-radial transfer function.19,20 We created an index, ΔSBP2, defined as “SBP2 − SBP” (Figure 1), to assess peak SBP reduction between peripheral and central sites.

**Therapeutic drugs.** Antihypertensive drugs being administered at the time of measurement were obtained from medical records together with coadministered antidyslipidemia and anti-diabetic drugs, nitrates and/or nicorandil. All class names and antihypertensive abbreviations are in the footnote of Table 2.

**Data analysis.** All data are expressed as the mean ± s.d. unless otherwise specified. Intergroup comparisons of mean values and ratios of subjects’ characteristics were tested by unpaired Student’s *t*-test and Fisher’s exact test, respectively. Multiple regression analysis (forced entry method) was employed to compare all classes of, as well as broadly grouped (vasodilating (VD) and non-VD), antihypertensive drugs in terms of the association with ΔSBP2, where VD included angiotensin receptor blockers (ARB), ACEI, CCB, and a-blocker; and non-VD included Diur and βBL. Categorical data, such as gender and drugs, were assessed as dummy variables (“0” or “1”) in regression models. For VD and non-VD, we made a dummy variable, “Drug group,” which was coded “1” if the patient took any one or several non-VD drugs without VD drugs in combination whereas code “0” indicated any other drugs, including any one or several VD drugs and mixed combinations of VD plus non-VD drugs. In Model 1 in Table 3, where patients with mixed combination were excluded from the subject population, code “0” implied that a patient took...
any one or several VD drugs only. Multiple regression models were used for adjusted comparisons of individual classes or broadly divided groups of antihypertensive drugs and their combinations, in which determinants of ΔSBP2 other than a specified antihypertensive drug or a drug combination were adjusted. Because pulse rate is largely attributable to the drug effect itself, it was not adjusted unless otherwise specified. The adjusted comparisons were as follows:

1. A multiple regression model was constructed for ΔSBP2 forcing all possible independent variables, including all antihypertensive drugs either broadly grouped (VD vs. non-VD) or grouped by drug class, to enter the models. Interactive terms relating to drug combinations were examined and significant interactive terms were considered to be included in the model.

2. For the non-HT population, a separate model without the drug variable was constructed. Based on this model, ΔSBP2 was modified by adjusting common confounders (age, gender, height, BMI, DBP) to the mean value of HT. This provided the estimated physiological reference value of ΔSBP2 when the DBP level was comparable with treated HT.

3. We collected adjusted ΔSBP2 data for an individual group or class of antihypertensive agents by extracting cases given a specified type of drugs irrespective of monotherapy or combination. Likewise, data for each combination of two specified antihypertensive classes were collected, including combinations of ≥3 drugs.

4. In addition to adjusting for all common confounders and the use of nitrates (="0"), further adjustments of ΔSBP2 were made for each specified group or class of drugs or their combination. For interdrug group or interclass comparisons, variables for irrelevant classes coadministered and interactive terms were set as "0" (i.e., not used). Similarly, for intercombination therapy comparisons, variables for coadministered drugs not included in the specified combination as well as interactive terms (unless applicable) were set as "0."

5. Interdrug group, interclass or intercombination therapy comparisons of CBP indexed by ΔSBP2 were made using the adjusted data, as described above. Adjusted ΔSBP2 was also compared between each drug group and non-HT. Two-group comparisons, including VD only vs. non-VD only and each drug group vs. non-HT, were tested by the Mann–Whitney U-test, whereas interclass and intercombination therapy as well as intertreatment group (i.e., VD vs. non-VD vs. Mixed) comparisons were tested by the Kruskal–Wallis test with multiple comparisons by the Games–Howell method.

All statistical analyses were performed with a commercially available statistical package (SPSS, version 11.0; SPSS, Chicago, IL) and spreadsheet calculation (Excel 2007; Microsoft, Washington, DC). P values <0.05 were regarded as significant.

RESULTS
Subjects’ characteristics and details of antihypertensive therapy are shown in Tables 1 and 2. Overall, ≥60% patients were treated with CCB or ARB. Only one third of participants was treated with monotherapy (Table 1), and monotherapy with some classes of drugs was very rare (Table 2), which made it difficult to compare all individual antihypertensive classes directly. We therefore first examined broadly divided drug groups, i.e., VD and non-VD. As shown in Table 3, partial regression coefficient (B) estimates of “Drug group” in Models 1 and 2 consistently indicated that ΔSBP2 was 2.7 mm Hg higher with non-VD than with VD when all included founders were adjusted.

In 510 participants who provided a detailed clinical data set, including laboratory data and comorbidities, none showed significant associations with ΔSBP2 by multiple regression

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**Figure 1** | Definitions of ΔSBP2 and radial augmentation index (rAI), and relationship between each parameter derived from calibrated tonometric radial pressure waveform (Pra = solid line; right) and corresponding putative aortic pressure waveform (PaAo = dotted line; left). These definitions are expressed as formulas inside the figure. cPP, central pulse pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; PP, radial pulse pressure; PP1, ejection peak amplitude of Pra; PP2, second peak amplitude of Pra; SBP, central blood pressure; SBP1, radial artery pressure at the ejection peak, which is not necessarily identical to the systolic peak of Pra; SBP2, radial artery pressure at the second peak.
analysis (Supplementary Table S1a online). We further examined the multiple regression models individually, including each clinical variable available in this study. Although the total cholesterol level (N = 784; B = 0.02 mm Hg·dl/mg; P = 0.01), serum creatinine (N = 1,374; B = −0.27 mm Hg·dl/mg; P = 0.04), and hemoglobin (N = 868; B = 0.27 mm Hg·dl/g; P = 0.03) reached a significant level, only modest influences on the B estimates of “Drug group” were observed (Supplementary Table S1b online).

ΔSBP2 data adjusted using Model 1 were compared between VD only and non-VD only as well as with non-HT, in which adjusted ΔSBP2 was estimated based on Model 3 (area A in Figure 2). Although the difference between VD and non-VD was evident, N with actual non-VD only was far fewer than with VD only, which resulted in larger variance in this group. We then estimated ΔSBP2 with VD only or non-VD only in patients with mixed combination therapy based on Model 2, which increased the number of data compared. The results are shown with adjusted data of actual mixed combination within area B in Figure 2. Estimated ΔSBP2 with VD alone (−10.1 mm Hg) was lower than with non-VD alone (−6.6 mm Hg), and even lower than in non-HT (−7.7 mm Hg).

### Table 2 | Details of antihypertensive therapy

| Class of antihypertensivesa | ARB | ACEI | CCB | oBL | Diur | βBL | Nitro |
|-----------------------------|-----|------|-----|-----|------|-----|-------|
| N (pts (%))                 | 1,019 (59.0) | 207 (12.0) | 1,178 (68.2) | 161 (9.3) | 422 (24.4) | 373 (21.6) | 121 (7.0) |
| Male/female (pts)           | 537/482 | 125/82 | 601/577 | 87/74 | 190/232 | 189/184 | 84/37 |
| Age (years)                 | 66.7 ± 11.7 | 64.8 ± 13.2 | 67.4 ± 10.7 | 65.7 ± 10.9 | 66.6 ± 11.4 | 66.5 ± 11.0 | 73.3 ± 8.2 |
| Height (cm)                 | 157.7 ± 9.5 | 158.7 ± 9.7 | 157.1 ± 9.3 | 157.7 ± 8.0 | 157.0 ± 9.4 | 158.4 ± 9.0 | 157.5 ± 8.4 |
| Weight (kg)                 | 60.6 ± 11.8 | 60.3 ± 11.5 | 60.1 ± 11.5 | 61.9 ± 11.2 | 61.7 ± 11.6 | 61.5 ± 11.4 | 57.8 ± 9.2 |
| BMI (kg/m²)                 | 24.2 ± 3.5 | 23.8 ± 3.2 | 24.2 ± 3.4 | 24.8 ± 3.7 | 25.0 ± 3.6 | 24.4 ± 3.5 | 23.2 ± 2.7 |
| PR (bpm)                    | 69.1 ± 11.8 | 70.9 ± 13.1 | 69.1 ± 12.2 | 68.1 ± 12.9 | 68.2 ± 12.2 | 63.7 ± 11.2 | 69.0 ± 13.0 |

Calibrated radial artery tonometry

| | SBP (mm Hg) | SBP2 (mm Hg) | DBP (mm Hg) | rAI (%) |
|-----------------------------|-------------|--------------|-------------|--------|
| ARB+CCB                    | 138.5 ± 17.3 | 137.4 ± 17.1 | 138.2 ± 16.9 | 138.9 ± 17.3 | 134.4 ± 18.1 | 134.5 ± 17.6 | 139.2 ± 16.4 |
| ARB+Diur                   | 128.1 ± 18.7 | 126.3 ± 18.1 | 127.7 ± 18.0 | 126.8 ± 18.0 | 124.8 ± 18.1 | 126.2 ± 18.9 | 125.3 ± 18.1 |
| ARB+oBL                    | 74.9 ± 12.0  | 75.0 ± 11.5  | 74.6 ± 11.6  | 73.7 ± 12.3  | 71.7 ± 12.6  | 73.2 ± 11.8  | 72.2 ± 10.9  |
| ARB+βBL                    | 85.0 ± 13.9  | 83.8 ± 13.9  | 85.3 ± 14.0  | 83.6 ± 15.5  | 85.5 ± 13.1  | 88.2 ± 14.5  | 80.9 ± 14.8  |
| ARB+Nitro                  | 69.0 ± 12.1  | 68.2 ± 12.1  | 63.0 ± 11.0  | 71.9 ± 13.9  | 67.4 ± 11.9  | 63.4 ± 11.1  | 62.8 ± 10.7  |

Number of drugs prescribed:

| | 1 (pts) | 2 (pts) | ≥3 (pts) |
|-----------------------------|---------|---------|---------|
| N (pts (%))                 | 345/288 | 309/268 | 324/208 |
| Male/female (pts)           | 123/105 | 106/95  | 102/78  |
| Age (years)                 | 67.7     | 67.6     | 67.7     |
| Height (cm)                 | 157.4    | 156.5    | 157.4    |
| Weight (kg)                 | 61.0     | 61.7     | 61.7     |
| BMI (kg/m²)                 | 24.5     | 25.1     | 25.3     |
| PR (bpm)                    | 69.0     | 68.2     | 68.2     |

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; DBP, diastolic blood pressure; Diur, diuretics; Nitro, nitrates or nico antidil; pts, number of patients; αBL, α-blockers; βBL, β-blockers.

*Because of its vasoactive action, Nitro is included although drugs in this class are not classified as antihypertensives. The number for each specified drug combination includes patients taking three or more antihypertensives other than the specified drugs.
In contrast, with non-VD alone, it was even higher than in non-HT.

To enable the characterization of each individual class, we constructed a model including all classes of antihypertensive agents and a significant interactive term as independent variables (Table 4). Only “CCB × Diur” was significant among all interactive terms that could have been assessed previously (Supplementary Table S2a–d online). Among antihypertensive classes, ARB, CCB, and α-blockers had significant associations with lower ΔSBP2.

Using this model, we performed adjusted interclass comparisons of antihypertensive drugs to characterize each individual class in terms of ΔSBP2 (Figure 3a). Treatments with VD antihypertensive classes showed a lower ΔSBP2 than nonvasodilators comparably to VD and non-VD in Figure 2. Most importantly, no significant difference in ΔSBP2 was detected among any VD classes. The mean level of ΔSBP2 (−9.7 mm Hg) was 3.3 and 2.0 mm Hg lower than with nonvasodilators and in non-HT. In contrast, with βBL was reduced, which abolished the significant difference from ACEI.

Adjusted comparisons of ΔSBP2 among treatments with frequently used combinations of antihypertensives were also performed (Figure 4) based on the model (Table 4). The combination of two different VD antihypertensive classes, such as CCB plus ARB or ACEI, showed the lowest level of ΔSBP2 (−10.5 mm Hg; Figure 4a), which was lower than in any single VD antihypertensive class shown in Figure 3a. When the drug combined with ARB or CCB was a diuretic or βBL, the ΔSBP2 value increased in this order. The combination of diuretics and βBL-blockers showed the highest ΔSBP2 (−3.9 mm Hg). Additional pulse rate adjustment tended to reduce ΔSBP2 with βBL-including combinations, whereas its influence varied for Diur-including combinations. Differences between the combination of CCB plus ARB or ACEI and that of diuretics plus βBL remained significant even after pulse rate adjustment.

DISCUSSION

In the present study, all individual classes of antihypertensive agents commonly used in Japan and combinations of two different classes were tentatively characterized in terms of central

### Table 3 | Multiple regression models of ΔSBP2 in specified populations

| Model 1 | Model 2 | Model 3 |
|---------|---------|---------|
| N       | 1,094   | 1,711   | 848     |
| Adjust R²| 0.366   | 0.366   | 0.553   |

| Independent variables | B    | 95% CI   | β    | P    | B    | 95% CI   | β    | P    | B    | 95% CI   | β    | P    |
|-----------------------|------|----------|------|------|------|----------|------|------|------|----------|------|------|
| Physical variables    |      |          |      |      |      |          |      |      |      |          |      |      |
| Gender                | −2.808 | −3.963 to −1.654 | −0.170 | <0.001 | −2.687 | −3.571 to −1.803 | −0.169 | <0.001 | −4.539 | −5.645 to −3.422 | −0.292 | <0.001 |
| Age                   | −0.002 | −0.040 to 0.036 | −0.003 | 0.921 | −0.005 | −0.035 to 0.026 | −0.007 | 0.764 | 0.176 | 0.151 to 0.378 | 0.378 | <0.001 |
| Height                | −0.186 | −0.251 to −0.120 | −0.212 | <0.001 | −0.170 | −0.221 to −0.119 | −0.199 | <0.001 | −0.119 | −0.181 to −0.057 | −0.147 | <0.001 |
| BMI                   | −0.293 | −0.410 to −0.175 | −0.120 | <0.001 | −0.210 | −0.301 to −0.120 | −0.090 | <0.001 | −0.469 | −0.598 to −0.340 | −0.174 | <0.001 |
| Hemodynamic variables |      |          |      |      |      |          |      |      |      |          |      |      |
| PR                    | −0.342 | −0.375 to −0.308 | −0.492 | <0.001 | −0.336 | −0.362 to −0.310 | −0.508 | <0.001 | −0.238 | −0.273 to −0.203 | −0.318 | <0.001 |
| DBP                   | 0.149  | 0.114 to 0.184 | 0.212 | <0.001 | 0.141  | 0.114 to 0.168 | 0.210  | <0.001 | 0.257  | 0.214 to 0.300 | 0.295  | <0.001 |
| Nitro                 | −3.393 | −5.058 to −1.728 | −0.098 | <0.001 | −3.631 | −4.913 to −2.350 | −0.109 | <0.001 |        |          |        |      |
| Drug group            | 2.678  | 0.984 to 4.372 | 0.075 | <0.001 | 2.709  | 1.073 to 4.345 | 0.064  | 0.001 |        |          |        |      |
| Mixed                 | 0.448  | −0.209 to 1.105 | 0.027 | 0.181 |        |          |        |        |        |          |        |      |

Drug group: code “1” = treated with non-VD only; code “0” = other treatments with VD only and mixed combination with VD and non-VD. Mixed: code “1” = mixed combination with VD and non-VD; code “0” = all other treatments (with VD only or non-VD only). VD (vasodilating antihypertensive drugs) includes angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and α-blockers; non-VD (nonvasodilating antihypertensive drugs) includes diuretics and β-blockers. Subject populations for Models 1 through 3 were hypertensives (HT) without mixed (VD + non-VD) combination, HT including mixed combination except Nitro only and non-HT, respectively. Sixteen HT patients taking Nitro alone were excluded from Models 1 and 2. ΔSBP2 is defined in Figure 1. 95% CI, 95% confidence interval of B, β, nonstandardized partial regression coefficient; BMI, body mass index; DBP, diastolic blood pressure; PR, pulse rate; β, standardized partial regression coefficient.
Table 4 | Multiple regression models of ΔSBP2 in treated hypertensives

| N   | Adjusted R² | B   | 95% C.I. | β   | P   |
|-----|-------------|-----|----------|-----|-----|
|     |             |     |          |     |     |
| Physical variables |     |     |          |     |     |
| Gender | -2.358 | -3.236 to -1.480 | -0.148 | <0.001 |
| Age   | -0.004 | -0.034 to 0.027  | -0.005 | 0.813 |
| Height| -0.185 | -0.235 to -0.134  | -0.215 | <0.001 |
| BMI   | -0.200 | -0.290 to -0.109  | -0.085 | <0.001 |
| Hemodynamic variables |     |     |          |     |     |
| PR    | -0.336 | -0.362 to -0.310  | -0.508 | <0.001 |
| DBP   | 0.140  | 0.113 to 0.167    | 0.207  | <0.001 |
| Class of drugs |     |     |          |     |     |
| ARB   | -1.012 | -1.682 to -0.343  | -0.620 | 0.003 |
| ACEI  | -0.516 | -1.512 to 0.479   | -0.021 | 0.309 |
| CCB   | -0.837 | -1.619 to -0.056  | -0.049 | 0.036 |
| αBL   | -2.122 | -3.158 to -1.087  | -0.077 | <0.001 |
| Diur  | 1.890  | 0.690 to 3.090    | 0.102  | 0.002 |
| βBL   | 0.537  | -0.218 to 1.292   | 0.028  | 0.163 |
| Nitro | -3.675 | -4.882 to -2.468  | -0.118 | <0.001 |
| Interactive term |     |     |          |     |     |
| CCB × Diur | -1.953 | -3.414 to -0.493  | -0.089 | 0.009 |

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CCB, calcium channel blockers; DBP, diastolic blood pressure; Diur, diuretics; Nitro, nitrates or nicorandil; PR, pulse rate; αBL, α-blockers; βBL, β-blockers.

Figure 2 | Adjusted comparisons of ΔSBP2 between vasodilating (VD) and non-VD antihypertensive drugs. VD group includes angiotensin receptor blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and α-blockers, and non-VD group includes β-blockers and diuretics. Data are shown as the mean level (horizontal line) and the 95% confidence interval (box height) as well as the range of ±1 SD by a vertical error bar. P value in the lower part of the figure indicates the result of the Mann–Whitney U-test of each specified intergroup comparison unless specified in the figure (K-W, Kruskal–Wallis test; G-H, Games–Howell multiple comparison test). The number in each box indicates the difference (mm Hg) of mean ΔSBP2 between compared groups. Gray area A shows the comparison between actual VD and non-VD only regimes irrespective of the number of drugs. ΔSBP2 data were adjusted for confounding factors (age, gender, height, BMI, DBP, and the use of nitrates = “0”) based on Model 1 in Table 3. Cases with mixed combination (VD + non-VD) regimes were excluded. Gray area B shows the comparison among VD(est), non-VD(est) and mixed combinations of VD and non-VD. “(est)” indicates including data derived from mixed combination, for which the effects of VD or non-VD alone on ΔSBP2 were estimated using Model 2 in Table 3. Data in the nonhypertensive (non-HT) population indicate the physiological reference value of ΔSBP2 estimated by adjusting confounding factors to the mean value of treated HT using Model 3 in Table 3.

Central effects of antihypertensive classes. The lower level of CBP, even lower than in non-HT, with VD antihypertensives administered alone (area B in Figures 2 and 3a) might lead to more effective unloading of pulsatile mechanical stress on the cardiovascular system than nonvasodilatory agents. The observed reduction of ΔSBP2 with βBL by additional pulse rate adjustment (Figure 3b) suggested that the CBP-raising feature of βBL might be attributable to its negative chronotropic effect.

effects indexed by ΔSBP2. We found that treatment with any VD antihypertensive class showed lower CBP than any nonvasodilatory class when peripheral BP was lowered to the same level. CBP assessment was highly objective using a validated semiautomatic radial artery tonometry system,15,19 which could minimize variance and errors related to observer or operator skill.

Feature of ΔSBP2 and its cross-sectional determinants
The augmentation index reportedly depends on age,21 gender,22 height,23 heart rate,24,25 and BP levels.26 ΔSBP2 relates to radial augmentation index by definition as radial augmentation index is the ratio of (PP+ΔSBP2) to PP1 (Figure 1). The ΔSBP2 value is always negative and reflects the actual reduction in SBP and pulse pressure from peripheral to central sites. Comparing Models 2 and 3 (Table 3), significant associations between these variables and ΔSBP2 observed in the non-HT population were partially preserved even in treated HT except for age.

Interpretation of the results
In addition to adjustment for common confounders, model-based estimation of ΔSBP2 compensating for coadministered drug effects enabled interclass comparisons of central effects of antihypertensives that were impossible to make directly with raw data, and played a “data-mining” role in this study.
Central effects of major combinations of antihypertensive drugs. Figure 4a suggested some additive CBP-lowering effects of two different vasodilatory classes. In contrast, along with higher ΔSBP2 above the physiological level with non-VD (Figure 2), the findings with non-VD-including combinations suggested that the central effects of non-VD antihypertensives were CBP-raising rather than less potent CBP-lowering.

The negative $B$ estimate of the significant interactive term, “CCB × Diur”, suggested some synergistic CBP-lowering effect.

Comparison with other studies

The results of this study are consistent with reported studies, such as the CAFE study, and other small-scale studies. More recently, other small-scale treatment trials dealing with the effects on CBP of a newer class of antihypertensives, ARB, compared with βBL, have been reported. The results of these studies can be summarized as the superiority of vasodilatory antihypertensives, including CCB, ARB, and ACEI, to nonvasodilatory agents, such as diuretics and βBL. Similar to the CAFE study, the higher CBP level with βBL-including treatments was evident in this study; however, these studies used only limited antihypertensive regimens. This cross-sectional observation, including a data-mining model-based estimation process, enabled tentative but simultaneous comparisons of all commonly used antihypertensive agents specifically in terms of central effects by individual class as well as by common combination regimens. Additionally, this study reported ΔSBP2 levels in HT compared with an adjusted physiological reference level.

Limitations

Issues relating to the observational study design. This study was designed as an exploratory study to generate rather than to test hypotheses; therefore, the results cannot confirm the causal effects of each drug class on CBP but provide hypotheses to be assessed. Because of the cross-sectional and observational design, in which the selection of antihypertensive drugs was left to the clinician, and might have been related to patients’ clinical characteristics, an indication bias was inevitable. Although we examined available clinical variables in some participants (Supplementary Tables S1a and S1b online), they included only some of the population studied and all data could not be adjusted for clinical confounders. The influence of indication bias could therefore not be avoided and should be taken into consideration when interpreting the results of this study.

Issues relating to model-based adjustment. In addition, the results should be interpreted with caution for the following reasons. Data adjustments were based on linear regression models. The influences of adjusted variables are not necessarily linear. Also, the doses and duration of specified antihypertensive medications were not taken into consideration due...
to the limited study design. Although the findings obtained from such analysis are not conclusive, we believe that they can provide information to develop hypotheses.

Interpretation of nitrates. As nitrates are not classified as antihypertensive agents, data were compared adjusting for the use of this type of drugs. Only a minority of subjects was given nitrates (Table 2), but significantly lower ΔSBP2 was observed. This may be attributable to, at least in part, cardiac dysfunction,30,31 because nitrates are usually prescribed for cardiac patients. We could not adjust for cardiac function because of the absence of required information. It is well-known that nitrates markedly reduce aortic wave reflections or late systolic BP augmentation.3,4,32,33 In this study, to compare each class of antihypertensives in terms of central effects, the DBP level was adjusted, indicating that the mean pressure-lowering effect was ignored, which was likely to exaggerate the effect of nitrates as a central antihypertensive. Although a small-scale uncontrolled trial using extended-release isosorbide mononitrate has already been reported,7 randomized intervention trials are necessary to elucidate whether significant associations with lower ΔSBP2 are from pharmacological effects or cardiac dysfunction, as well as its clinical benefit for HT without cardiac dysfunction.

In summary, among all classes of antihypertensive drugs, any single VD antihypertensive agent (CCB, ARB, ACEI, or α-blockers) might lower CBP without interclass difference, whereas nonvasodilators (Diur and βBL) might raise CBP above the physiological level when peripheral BP is adjusted to the same level. The other novel findings obtained in this study are that (i) among assessable combinations, only CCB+Diur showed synergistic interaction; (ii) otherwise, coadministered VD antihypertensives did not affect the CBP-raising features of nonvasodilators; (iii) the CBP-raising effect of βBL is chiefly attributable to negative chronotropism; and (iv) total cholesterol level, serum creatinine, and hemoglobin showed modest but significant associations with ΔSBP2.

Finally, the hypothetical feature of each antihypertensive class in terms of CBP and its prognostic predictive value should be assessed by large-scale randomized intervention trials.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ajh

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