Differences in Dynamic Diurnal Blood Pressure Variability Between Japanese and American Treatment-Resistant Hypertensive Populations

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Background: Dynamic diurnal changes in 24-h ambulatory systolic blood pressure (SBP) are associated with increased cardiovascular risk. We compared ambulatory BP dynamics in Japanese and American black and white populations with treatment-resistant hypertension.

Methods and Results: Both HTN-Japan (n=41) and SYMPLICITY HTN-3 (n=384 white and n=140 black patients) enrolled patients with office SBP ≥ 160 mmHg and 24-h ambulatory SBP ≥ 135 mmHg while on ≥ 3 antihypertensive medications. Indices of circadian variation in ambulatory BP, including morning and nighttime dynamic surges, were retrospectively compared. All 3 cohorts had similar baseline office SBP. The Japanese cohort had significantly lower body mass index, less obstructive sleep apnea, and less hypercholesterolemia than the black and white cohorts, but significantly greater morning SBP levels, including moving peak morning SBP (183 vs. 169 vs. 169 mmHg, $P < 0.001$), morning dynamic surge (37.9 vs. 28.6 vs. 24.2 mmHg, $P < 0.001$) and nighttime dynamic surge (24.9 vs. 8.3 vs. 7.7 mmHg, $P < 0.001$). These racial differences in SBP surge parameters persisted despite adjustment for baseline demographic population differences through multivariate regression.

Conclusions: Greater diurnal BP variability, including dynamic surges, in Japanese compared with black and white patients may indicate ethnic differences in the underlying BP regulatory mechanism of resistant hypertension. These differences may be important to take into consideration for more specific drug and device-based therapy strategies based on ethnicity.

Key Words: Americans; Ethnicity; Japanese; Morning/nighttime surge; Resistant hypertension

Upon awakening, arterial blood pressure (BP) increases abruptly (surges) because of heightened activity of the sympathetic nervous system and α -mediated vasoconstriction.^{1,2} Likewise, cardiovascular events occur most frequently in the morning awakening period, at the time of peak ambulatory BP.³ International databases of ambulatory BP over 24 h have described an increased risk of cardiovascular events and stroke associated with elevated BP variability, in particular a morning BP surge.^{4,6} For instance, the prospective HONEST (Home blood pressure measurement with Olmesartan Naïve patients to Establish Standard Target blood pressure) study of 21,591 treated hypertensive patients followed for 2 years found morning home BP to be a strong predictor of cardiovascular events, including stroke and coronary events, independent of office BP.^{4,7} Even in patients with office systolic BP (SBP) < 130 mmHg, uncontrolled morning home SBP remained a significant risk factor for stroke and cardiovascular events⁴

and is a superior predictor of events compared with simultaneous assessment of morning and evening SBP.⁸ Furthermore, morning SBP surge is directly related to 24-h SBP variability and future cardiovascular events.⁹ Prior research found morning SBP surge to be associated with stroke events independently of nocturnal BP falls and 24-h SBP in hypertensive patients.⁵ This finding could result from the link between greater arterial stiffness, as measured by carotid-femoral pulse wave velocity, and higher morning SBP.¹⁰

Basal sympathetic tone and the risk of hypertension (HTN) and related cardiovascular disease both vary with ethnicity.¹¹ African Americans have a disproportionately high prevalence and severity of HTN compared with other racial groups in the USA.^{12,13} Even after antihypertensive treatment, black hypertensive subjects are less likely to have controlled BP.^{14,15} Additionally, compared with white populations, Asian populations have higher risks of HTN

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Figure 1. Illustration of systolic blood pressure (SBP) measurements at different times.

and related cardiovascular disease, a higher risk of death from cardiovascular disease, and a greater relative risk associated with higher body mass index (BMI).^{16,17}

Racial differences in the circadian variation in BP and morning surge parameters might explain differences in the severity of HTN and associated cardiovascular risk. Hoshida and colleagues observed that morning surge was higher in Japanese compared with European patients.¹⁸ Another study also reported a significant association between stroke and the degree of morning surge in a Japanese elderly population independent of ambulatory BP⁵ that was not observed in the other racial groups analyzed.^{9,19,20} However, the specific racial differences in sympathetic tone, diurnal BP variation, and hypertensive risk remain incompletely understood.

The aim of this analysis was to explore the potential differences in ambulatory BP dynamics based on ethnicity by comparing diurnal BP variability, including morning and nighttime surge parameters, in Japanese and American black and white populations with treatment-resistant HTN.

Methods

Patient Population

The present analysis was derived from the SYMPLICITY HTN-3 and HTN-Japan prospective, multicenter studies that were conducted in the USA and Japan.^{21,22} Both studies used the same standardized inclusion and exclusion criteria to enroll patients with baseline office SBP ≥ 160 mmHg and 24-h ambulatory SBP ≥ 135 mmHg despite a stable prescribed antihypertensive drug regimen that included maximally tolerated doses of at least 3 antihypertensive medication classes, including a diuretic. The SYMPLICITY HTN-3 trial also stratified enrollment by race in order to assure a racial distribution similar to the US hypertensive population.²⁰ Patients with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m² were excluded. Both trials were approved by the Institutional Review Board for each site, and all patients gave written informed consent. Patients were defined as Japanese (from the HTN-Japan trial), black (when patient designated “of African descent” in the SYMPLICITY HTN-3 trial), or white (when the patient designated “white”

in the SYMPLICITY HTN-3 trial). Patients of other descent in the SYMPLICITY HTN-3 trial (Asian, American Indian, Alaska Native, Native Hawaiian or other Pacific Islander, or “other”) were excluded from this analysis.

Ambulatory BP Measurements

Ambulatory BP monitoring (ABPM) was performed every 30 min throughout the day (7:00 AM and 9:59 PM) and night (10:00 PM and 6:59 AM) over a 24-h period (using the Space Labs 24 Ambulatory Blood Pressure Monitoring System [Space Labs Medical, Issaquah, WA, USA] in SYMPLICITY HTN-3 and the TM-2431 Ambulatory Blood Pressure Monitoring System [A&D Company, Limited, Tokyo, Japan] in HTN-Japan). Only subjects with 24-h readings that included 21 daytime and 12 nighttime readings were included, as previously specified in the SYMPLICITY HTN-3 trial.²³

Definitions

Morning, daytime, and nighttime time periods were defined as 6:00 AM to 8:59 AM, 9:00 AM to 8:59 PM, and 1:00 AM to 5:59 AM, respectively, as previously described, and illustrated in **Figure 1**.²⁴ Maximum, minimum, moving peak, mean peak, and mean surge were also determined as defined previously.³ Average morning surge is defined as the difference between the average morning SBP minus the average nighttime SBP. Dynamic morning surge is the moving peak morning SBP minus the moving lowest nighttime SBP.²⁵ Maximum dynamic morning surge is the maximum morning SBP minus the minimum nighttime SBP, and the peri-morning surge is the difference between the maximum and minimum morning SBP. Moving peak morning SBP was defined as the highest 1 h moving average of 3 consecutive SBP readings over the morning time interval. Average peak nighttime SBP was defined as the average of the 3 highest measurements over the nighttime interval. A dipping BP pattern was defined as an average decrease in nighttime SBP $\geq 10\%$ average daytime SBP.

Statistical Analysis

Multivariate stepwise linear regression analysis was conducted to assess independent correlates of the moving peak

Table 1. Baseline Demographics of the Japanese, White, and Black Patients

	Japanese (n=41)	White (n=384)	Black (n=140)	3-way P value	P value Japanese vs. White	P value Japanese vs. Black	P value White vs. Black
Age (years)	58±12	59±11	53±10	<0.001	0.535	0.016	<0.001
Male	76 (31)	66 (254)	47.9 (67)	<0.001	0.294	0.002	<0.001
BMI (kg/m ²)	27±5	34±6	35±7	<0.001	<0.001	<0.001	0.044
Renal insufficiency (eGFR <60 mL/min/1.73 m ²)	10 (4)	11 (41)	7 (10)	0.482	>0.999	0.524	0.249
Renal artery stenosis	0 (0)	1.8 (7)	1.4 (2)	0.665	>0.999	>0.999	>0.999
Obstructive sleep apnea	10 (4)	29 (113)	22 (31)	0.011	0.006	0.114	0.121
Stroke	17 (7)	7 (28)	15 (21)	0.009	0.064	0.807	0.011
TIA	0 (0)	8 (30)	8 (11)	0.177	0.099	0.072	>0.999
Peripheral artery disease	7 (3)	4 (17)	4 (6)	0.688	0.427	0.426	>0.999
Coronary artery disease	15 (6)	29 (113)	20 (28)	0.021	0.045	0.504	0.034
MI	10 (4)	7 (28)	10.7 (15)	0.428	0.534	>0.999	0.211
Type 2 diabetes mellitus	49 (20)	47 (180)	39 (55)	0.269	0.870	0.286	0.137
Heart failure	7 (3)	10 (40)	19 (27)	0.014	0.785	0.094	0.011
Atrial fibrillation	0 (0)	10 (40)	6 (8)	0.030	0.023	0.201	0.123
Hyperlipidemia	32 (13)	69 (264)	64 (89)	<0.0001	<0.001	<0.001	0.293
Current smoker	32 (13)	10 (38)	14 (19)	<0.001	<0.001	0.011	0.267
Family history of hypertension	68 (28)	83 (315)	86 (120)	0.035	0.034	0.020	0.506
Hospitalization for hypertensive crisis	2 (1)	22 (83)	25 (35)	0.007	0.002	<0.001	0.410

Results presented as mean±standard deviation or % (n). BMI, body mass index; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; TIA, transient ischemic attack.

Table 2. Antihypertensive Medication Use by the Japanese, White, and Black Patients

	Japanese (n=41)	White (n=384)	Black (n=140)	3-way P value	P value Japanese vs. White	P value Japanese vs. Black	P value White vs. Black
No. of antihypertensive medication classes	4.9±1.6	5.0±1.3	5.5±1.6	0.005	0.637	0.050	0.004
Aldosterone antagonist	41.5 (17)	21.1 (81)	33.6 (47)	0.001	0.006	0.359	0.004
α-1 blocker	31.7 (13)	12.5 (48)	10.0 (14)	0.001	0.003	0.002	0.541
α-2 agonist	0.0 (0)	46.1 (177)	50.0 (70)	<0.001	<0.001	<0.001	0.431
Angiotensin-converting enzyme inhibitor	12.2 (5)	45.8 (176)	48.6 (68)	<0.001	<0.001	<0.001	0.621
Angiotensin-receptor blocker	97.6 (40)	54.2 (208)	43.6 (61)	<0.001	<0.001	<0.001	0.038
β-blocker	75.6 (31)	84.6 (325)	87.9 (123)	0.157	0.178	0.078	0.402
Calcium-channel blocker	95.1 (39)	69.5 (267)	75.0 (105)	0.002	<0.001	0.004	0.233
Diuretic	100.0 (41)	99.7 (383)	100.0 (140)	0.790	>0.999	>0.999	>0.999
Direct renin inhibitor	0.0 (0)	7.3 (28)	5.7 (8)	0.179	0.095	0.201	0.696
Vasodilator	0.0 (0)	34.6 (133)	50.0 (70)	<0.001	<0.001	<0.001	0.002

Results presented as mean±standard deviation or % (n).

morning SBP, dynamic morning SBP surge, and dynamic nighttime SBP surge. The following baseline characteristics were considered: age, sex, BMI, history of type II diabetes, eGFR, obstructive sleep apnea (OSA), heart failure, history of atrial fibrillation, history of hypercholesterolemia, current smoker, history of peripheral artery disease, family history of HTN, prior myocardial infarction, history of coronary artery disease, baseline SBP, and prescription of the following antihypertensive medications: aldosterone antagonists, α-1 blockers, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and diuretics, as well as the number of medication classes prescribed, and number of medications prescribed (α-2 agonists, vasodilators, and direct renin inhibitors were not prescribed in the Japanese

population and therefore were not included in the multivariate analysis). Multivariate predictors of moving peak morning SBP, dynamic morning surge SBP, and dynamic nighttime surge SBP were assessed using multiple linear regression analysis. A stepwise selection algorithm was used to select significant covariates using entry/stay significance levels of 0.1/0.05.

All analyses were based on the intent-to-treat principle. Continuous variables are presented as mean±standard deviation, and between-group differences were compared using the t test or ANOVA as appropriate. Within-group differences from baseline to follow-up were assessed using the paired t test. Categorical variables are presented as counts and percentages and compared using Fisher's exact test

Table 3. Office and Ambulatory Blood Pressures and Pulse Rates of the Japanese, White, and Black Patients

	Japanese (n=41)	White (n=384)	Black (n=140)	3-way P value	P value Japanese vs. White	P value Japanese vs. Black	P value White vs. Black
Office							
SBP (mmHg)	179.9±17.7	179.3±15.9	181.8±17.7	0.321	0.827	0.551	0.130
DBP (mmHg)	93.0±17.1	95.5±15.9	102.3±16.8	<0.0001	0.355	0.002	<0.001
Pulse rate (beats/min)	68.6±10.3	70.6±14.7	71.1±14.4	0.611	0.262	0.214	0.721
24-h							
SBP (mmHg)	164.0±17.6	158.4±13.6	161.3±14.7	0.014	0.053	0.314	0.039
DBP (mmHg)	91.0±12.2	87.3±13.8	93.6±14.1	<0.0001	0.104	0.282	<0.001
Pulse rate (beats/min)	69.3±9.2	70.7±12.7	73.7±13.3	0.034	0.374	0.019	0.020
Daytime							
SBP (mmHg)	167.7±16.4	162.9±13.9	164.8±14.4	0.072	0.040	0.279	0.170
DBP (mmHg)	93.3±12.4	90.9±14.5	96.9±14.4	<0.0001	0.305	0.146	<0.001
Pulse rate (beats/min)	72.2±10.2	73.3±13.8	75.5±13.9	0.192	0.555	0.101	0.103
Nighttime							
SBP (mmHg)	157.3±23.8	150.8±16.5	155.2±18.2	0.007	0.096	0.607	0.009
DBP (mmHg)	86.7±14.0	81.3±14.2	87.8±15.2	<0.0001	0.020	0.683	<0.001
Pulse rate (beats/min)	64.0±9.1	66.3±11.7	70.5±13.0	<0.001	0.230	<0.001	<0.001

Results presented as mean ± standard deviation. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 4. Morning and Nighttime Blood Pressure Level Indices in the Japanese, White, and Black Patients

	Japanese (n=41)	White (n=384)	Black (n=140)	3-way P value	P value Japanese vs. White	P value Japanese vs. Black	P value White vs. Black
Morning							
Average morning SBP	170.0±19.9	159.9±17.2	161.2±18.7	0.003	<0.001	0.009	0.470
Maximum morning SBP	193.0±26.6	175.9±19.4	176.7±20.8	<0.001	<0.001	<0.001	0.694
Minimum morning SBP	146.0±22.6	144.1±18.3	146.4±20.1	0.454	0.619	0.904	0.226
Moving peak morning SBP	182.5±20.9	168.9±17.9	169.0±19.2	<0.001	<0.001	<0.001	0.961
Moving lowest pre-awakening morning SBP	155.9±26.0	149.3±18.2	151.5±19.3	0.078	0.118	0.314	0.238
Nighttime							
Average nighttime SBP	157.2±25.2	149.1±17.8	153.0±19.4	0.009	0.052	0.324	0.035
Average peak nighttime SBP	175.8±30.6	161.2±18.9	164.7±20.3	<0.0001	0.004	0.033	0.068
Maximum nighttime SBP	184.6±33.6	167.1±20.1	170.3±21.9	<0.0001	0.002	0.013	0.113
Minimum nighttime SBP	133.5±22.6	132.7±18.0	137.3±20.0	0.049	0.840	0.293	0.013
Moving lowest nighttime SBP	144.5±23.6	140.3±17.9	145.1±20.4	0.028	0.274	0.886	0.011

Results presented as mean ± standard deviation. Abbreviations as in Table 3.

and the chi-square test for multilevel variables. All analyses were performed using SAS version 9.1 or higher (SAS Institute, Inc., Cary, NC, USA). $P < 0.05$ was considered statistically significant.

Results

A total of 565 patients with treatment-resistant HTN of Japanese (n=41), white (n=384), or black (n=140) ethnicity were included in the analysis; 11 patients in SYMPLICITY HTN-3 who designated themselves as Asian (n=2), American Indian (n=2), “other” (n=6), or did not provide race information (n=1) were excluded from analysis.

Table 1 shows the baseline population characteristics. The Japanese cohort had significantly lower BMI, less OSA, and less hypercholesterolemia than the black or white patients. However, Japanese patients had more comorbidities overall, including stroke, and were more likely to smoke.

The black cohort was younger and had higher BMI and a higher proportion of women than the other groups.

Antihypertensive Medications

The mean number of antihypertensive medications prescribed to patients was approximately 5 in all 3 cohorts (**Table 2**). The black cohort was prescribed the most antihypertensive classes primarily because of a higher proportion of prescribed vasodilators and despite fewer prescriptions for angiotensin-receptor blockers. Japanese patients were more likely to be prescribed an aldosterone antagonist, calcium-channel blocker, angiotensin-receptor blocker and α -1 blocker, but less likely to be prescribed an ACE inhibitor. Alpha-2 agonists, direct renin inhibitors, and vasodilators were not prescribed in the Japanese cohort.

BP

BP parameters are shown in **Tables 3–5**. All 3 cohorts had

Table 5. Morning and Nighttime Blood Pressure Surge Indices in the Japanese, White, and Black Patients

	Japanese (n=41)	White (n=384)	Black (n=140)	3-way P value	P value Japanese vs. White	P value Japanese vs. Black	P value White vs. Black
Morning surge							
Dynamic morning SBP surge	37.9±21.4	28.6±16.0	24.2±15.3	<0.001	0.009	<0.001	0.006
Maximum dynamic morning SBP surge	62.8±26.1	46.6±17.7	43.5±18.1	<0.001	<0.001	<0.001	0.087
Peri-morning SBP surge	55.0±32.8	37.0±16.5	36.0±15.9	<0.001	0.001	<0.001	0.518
Nighttime surge							
Dynamic nighttime SBP surge	24.9±20.2	8.3±5.0	7.7±4.6	<0.0001	<0.001	<0.001	0.198
Maximum dynamic nighttime SBP surge	51.1±24.8	34.3±13.2	33.0±13.2	<0.0001	<0.001	<0.001	0.302

Results presented as mean±standard deviation. Abbreviations as in Table 3.

Figure 2. Ambulatory systolic blood pressure (SBP) parameters stratified by Japanese, white, and black patients. (A) Average morning and moving peak morning SBP; (B) dynamic morning and nighttime SBP surges.

similar baseline office SBP. The 24-h ambulatory SBP differed somewhat between the cohorts, but these differences were not clinically meaningful (Table 3). The Japanese cohort had significantly higher morning SBP parameters, including average, maximum, and moving peak morning SBP, while the basal morning SBP parameters (minimum and moving lowest pre-awakening morning SBP) were comparable among the 3 groups (Table 4; Figure 2A). In addition, the Japanese group had significantly greater average peak and maximum nighttime SBP, while the average and basal nighttime SBP parameters in Japanese were comparable to those in whites and blacks (Table 4). Dynamic surge parameters were also greater in the Japanese patient population (Figure 2B), including morning dynamic surge (38±21 vs. 29±16 vs. 24±15 mmHg, $P<0.001$), and nighttime dynamic surge (25±20 vs. 8±5 vs. 8±5 mmHg, $P<0.001$) (Table 5).

Multivariate Analysis

Covariates associated with moving peak morning SBP,

dynamic morning SBP surge, and dynamic nighttime SBP surge stratified by the Japanese and white populations, and separately, the Japanese vs. black populations are shown in Table 6. The greater morning BP parameters in the Japanese population, compared with the black or white populations, persisted after adjusting for baseline characteristics. The estimates in Japanese vs. white patients and separately Japanese vs. black patients was 6.6 mmHg ($P<0.001$) and 10.2 ($P<0.001$), respectively, for moving peak morning SBP; 6.2 mmHg ($P=0.027$) and 13.4 ($P<0.001$) for dynamic morning SBP surge; and 16.6 mmHg ($P<0.001$) and 17.2 mmHg ($P<0.001$) for dynamic nighttime surge. The higher moving peak morning SBP in Japanese vs. black patients was also associated with OSA and a history of myocardial infarction, but this was not observed in the Japanese vs. white cohort model. However, baseline BMI was associated with moving peak morning and dynamic morning SBP surge in the Japanese vs. white cohort but not the Japanese vs. black model.

Table 6. Covariates Associated With Moving Peak Morning SBP, Dynamic Morning SBP Surge, and Dynamic Nighttime SBP Surge in the Japanese, White, and Black Patients

	Estimate (95% CI)	P value
Japanese vs. White		
Moving peak morning		
Japanese vs. White	6.6 (2.8, 10.4)	<0.001
Age	0.1 (0.0, 0.2)	0.044
Baseline BMI	−0.2 (−0.4, 0.0)	0.031
Baseline 24-h ambulatory SBP	1.0 (1.0, 1.1)	<0.001
Dynamic morning SBP surge		
Japanese vs. White	6.2 (0.7, 11.7)	0.027
Baseline eGFR	0.1 (0.0, 0.2)	0.024
Current smoker	5.6 (0.7, 10.4)	0.025
Baseline BMI	−0.4 (−0.6, −0.1)	0.006
Dynamic nighttime SBP surge		
Japanese vs. White	16.6 (14.1, 19.1)	<0.001
Japanese vs. Black		
Moving peak morning SBP		
Japanese vs. Black	10.2 (6.0, 14.4)	<0.001
Age	0.2 (0.0, 0.4)	0.033
MI	−10.0 (−16.6, −3.4)	0.003
Coronary artery disease	5.5 (0.1, 10.9)	0.048
Baseline calcium-channel blockers	−5.3 (−9.5, −1.0)	0.016
Obstructive sleep apnea	−5.5 (−9.9, −1.1)	0.014
Baseline 24-h ambulatory SBP	1.0 (0.9, 1.1)	<0.001
Dynamic morning SBP surge		
Japanese vs. Black	13.4 (7.6, 19.2)	<0.001
MI	−9.2 (−17.0, −1.3)	0.023
Baseline office SBP	−0.2 (−0.3, 0.0)	0.039
Dynamic nighttime SBP surge		
Japanese vs. Black	17.2 (13.6, 20.9)	<0.001

Abbreviations as in Tables 1,3.

Discussion

The main finding of this analysis was that, despite similar baseline office and 24-h ambulatory SBP levels, morning SBP parameters were higher in Japanese than in white or black hypertensive patients recruited by the same global criteria, and included moving peak morning SBP and morning dynamic SBP surge. Even after controlling for well-known confounders that affect ambulatory BP variability and have known ethnic differences, such as BMI and prevalence of OSA syndrome, the Japanese had significantly higher morning and nocturnal BP variability. In addition, nocturnal BP surge parameters were also highest in the Japanese hypertensive patients. These racial differences in BP surge parameters persisted despite adjustment for baseline demographic population differences through multivariate regression, and may indicate important differences in the underlying autonomic mechanism of resistant HTN within these populations.

Previous post-hoc subgroup analyses of HTN-3 examined the effects of ethnicity and medication regimens on BP measurements with and without adjunctive renal denervation therapy.^{13,26} Kandzari et al found that African American patients in the sham group of HTN-3 who were prescribed vasodilators at baseline had a larger decline in SBP compared with non-African American patients in the sham group, as well as African Americans in the sham

group not prescribed vasodilators.²⁶ Additional post-hoc multivariate analysis of the sham group in HTN-3 found that the interaction between African American race and being prescribed at least one antihypertensive medication three times per day was associated with a larger change in office SBP at 6 months, whereas in the renal denervation treatment group, the interaction between African American race and baseline office SBP ≥ 180 mmHg was associated with a greater reduction in 6-month office SBP.¹³ Future clinical studies could be designed to further examine the interaction between drug and device therapies for different ethnic groups. For instance, there is evidence that calcium-channel blockers²⁷ and renal denervation²⁸ can both individually reduce BP variability. Calcium-channel blockers can decrease SBP but have a lesser effect on diastolic BP. The role of renal denervation with or without antihypertensive medication is the subject of ongoing investigation.

Morning BP Levels

In the present study, the average morning SBP and moving peak morning SBP were higher in Japanese than in white or black patients with treatment-resistant HTN by approximately 10 mmHg. The pre-awakening morning period is associated with lowest plasma levels of antihypertensive medications, and morning SBP is a strong predictor of cardiovascular events independent of office BP.^{4,7} In a prior analysis, a 10-mmHg difference in average morning systolic

BP in hypertensive patients was associated with a 44% increased risk of stroke.⁴ In HONEST, the largest real-world prospective study examining home BP levels and the risk of stroke and coronary events, even in patients with well-controlled office BP, uncontrolled morning SBP remains a significant potential risk factor for cardiovascular events.⁷

Morning BP Surge Parameters

All 3 ambulatory measures of morning BP surge (dynamic morning BP surge, maximum dynamic morning surge, and peri-morning surge) were all significantly higher in Japanese compared with white and black resistant hypertensive patients by approximately 15 mmHg. This difference may partially explain the greater risk of stroke with elevated BP in Eastern Asian patients.^{4,25} In addition, Hoshida et al previously reported higher morning BP surge measured by ABPM in Japanese compared with Western European hypertensive patients matched for age and office BP.¹⁸ Likewise, McCausland et al demonstrated that black race was associated with lower morning surge compared with non-blacks, after controlling for other factors.²⁹ Our results showing significantly lower dynamic morning surge in black vs. white patients confirm and extend these findings by further differentiating the Japanese population from US white and black hypertensive cohorts.

We cannot explain why ethnic differences exist in the degree of morning BP surge found in the hypertensive patients,¹⁸ including severely drug-resistant hypertensive patients, in the present study. Environmental factors such as temperature, culture, salt intake, and sleep quality may affect the balance of the autonomic nervous system. Morning dynamic surge is associated with a heightened activity of the sympathetic nervous system and α -mediated vasoconstriction, as well as adverse consequences on left ventricular remodeling.^{1,2,30} Therefore, differences in sympathetic activity by race may have caused the observed differences in surge parameters. Recently, Okada et al analyzed muscle sympathetic nerve activity during cold pressor stimulus in elderly black and white hypertensive patients, and found blacks to have smaller sympathetic and cardiac output responses, but a greater response for a given sympathetic activation.³¹ The reason for racial differences in sympathetic tone is unclear, but may be caused by augmented sympathetic vascular transduction, greater sympathetic activation to other vascular beds, or enhanced non-adrenergically mediated vasoconstriction in elderly blacks. Similarly, earlier observations by Calhoun and colleagues showed increased basal sympathetic tone in normotensive black subjects.³² However, to date no prospective study of the ethnic differences in sympathetic tone between Asian and white subjects has been performed.

Nocturnal BP Surge Parameters

Both dynamic nighttime surge and maximum dynamic nighttime surge were significantly higher in the Japanese than in the white or black patients. OSA is often associated with a nocturnal surge in BP because of high BP peaks, and these patients are at increased cardiovascular risk.³³ However, in our analysis, Japanese patients were less likely to have OSA, and only Japanese race was significantly associated with dynamic nighttime SBP surge, suggesting that this difference is caused by racial differences that are not well understood.

Antihypertensive Medications

Although protocol requirements for antihypertensive medications were identical for HTN-3 and HTN-Japan, there were differences in prescribed drugs between the trials. In HTN-Japan, 100% of treatment patients and 94.7% of control patients were on maximally tolerated doses of angiotensin-receptor blockers,²² whereas only 50.0% of treatment patients and 53.2% of control patients were prescribed such drugs in HTN-3.²³ Between randomization and 6 months, 7.3% of patients had a change in antihypertensive medication dosage or class in HTN-Japan,²² whereas 39% of patients in HTN-3 during that time period had medication changes.²⁶ Patients in both studies were asked to self-report daily doses of antihypertensive medications in a diary, but medication adherence was not objectively assessed. Patients' difficulties in maintaining compliance with their antihypertensive medication regimens has been well documented.^{34–39} Two clinical studies reported approximately half of their patients had incomplete adherence to prescribed antihypertensive medications.^{34,37}

Study Limitations

Our retrospective analysis was conducted by comparing baseline characteristics and BP parameters from 2 separate clinical trials. However, both trials used the same inclusion and exclusion criteria. The Japanese trial included only 41 patients, but still demonstrated significant ethnic differences in circadian variability compared with the white and black patients treated in the USA. These studies did not include any objective measure of antihypertensive medication adherence, and thus no assessment of the effect of adherence to medication on BP variability could be made. Population demographics differed at baseline because African Americans were younger. This concurs with previous analyses that blacks develop HTN at a younger age compared with whites.^{40,41} Additionally, salt intake was not recorded and therefore not taken into account. However, differences in surge parameters were still observed after multivariate analysis to account for differences in baseline demographics.

Conclusions

Greater circadian variability, including dynamic surge parameters, in Japanese compared with black and white patients may indicate ethnic differences in the underlying autonomic mechanism of resistant HTN in these populations and a clinical need for more specific drug- and device-based therapy strategies based on ethnicity. In light of the recent SPRINT trial,⁴² identifying possible ethnicity-related differences in BP parameters, and in particular morning surge parameters, may be an important component in determining risk stratification for treatment strategies and prevention of BP-related cardiovascular events.

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