

# Association of Morning Hypertension Subtype With Vascular Target Organ Damage and Central Hemodynamics

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**Background**—A recent study reported that morning hypertension is associated with poor cardiovascular outcomes in hypertensive patients. However, it is unclear whether morning hypertension associated with sustained nocturnal hypertension and that associated with morning blood pressure (BP) surge differ in terms of their effects on cardiovascular target organ damage and clinical outcomes. The present study aimed to determine the association of morning hypertension with/without nocturnal hypertension with vascular target organ damage and central hemodynamics in patients at high risk for cardiovascular disease.

**Methods and Results**—Ambulatory BP monitoring was performed and central BP was measured in 1070 consecutive patients with high cardiovascular risk. We grouped morning hypertension into the following 3 subtypes: (I) morning normotension; (II) morning hypertension without nocturnal hypertension; and (III) morning hypertension with nocturnal hypertension. Morning hypertension was noted in 469 (43.8%) patients and morning hypertension with nocturnal hypertension was noted in 374 (34.9%) patients. The central systolic/diastolic BP and carotid to femoral pulse wave velocity were significantly higher in the subtype III group than in the subtype I and II groups (all  $P < 0.001$ ). Subtype III (versus subtype I) was an independent predictor of central hypertension and high-risk arterial stiffness ( $P < 0.001$  and  $P = 0.018$ , respectively) but not vascular damage in a fully adjusted model (model Y).

**Conclusions**—Morning hypertension, especially that associated with nocturnal hypertension, is related to high central BP and increased arterial stiffness. Further studies on whether morning hypertension with or without nocturnal hypertension is related to clinical outcomes should be performed.

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**Key Words:** ambulatory blood pressure monitoring • arterial stiffness • hypertension • morning hypertension • nocturnal hypertension

During the past decade, mounting evidence has indicated that ambulatory blood pressure (BP) monitoring (ABPM) provides various details on BP profiles, including the average 24-hour BP, daytime and nighttime BP, and circadian variability, which is superior to clinical BP for the diagnosis and prognostic evaluation of hypertensive individuals.<sup>1–4</sup> As such, current guidelines recommend the use of ABPM in routine clinical practice.<sup>5</sup>

Recent studies have demonstrated that morning hypertension is associated with target organ damage and adverse cardiovascular outcomes in patients with hypertension.<sup>6–9</sup> The Japan Morning Surge Home Blood Pressure (J-HOP) study reported that morning systolic BP (SBP) was closely related to subclinical target organ damage indicators, such as urine albumin/creatinine ratio and pulse wave velocity (PWV).<sup>7</sup> In the Home Blood Pressure Measurement With Olmesartan

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Naive Patients to Establish Standard Target Blood Pressure (HONEST) registry, in a cohort of 21 591 patients with essential hypertension, morning hypertension (morning home BP  $\geq 145$  mm Hg) was associated with adverse cardiovascular outcomes, even among patients with well-controlled clinical BP.<sup>8,9</sup>

Patients with morning hypertension could be categorized as either those with nocturnal hypertension who have sustained hypertension upon awakening or those without nocturnal hypertension who have morning hypertension upon awakening. Previous studies have shown that both nocturnal hypertension and early morning BP surge are associated with a higher risk of target organ damage and cardiovascular disease (CVD).<sup>6,8</sup> However, it is unclear whether morning hypertension associated with sustained nocturnal hypertension and that associated with morning BP surge differ in terms of their effects on cardiovascular target organ damage and clinical outcomes. In the present study, we aimed to determine the association of morning hypertension with or without nocturnal hypertension with vascular target organ damage and central hemodynamics in a prospective cohort of patients at high risk for CVD.

## Methods

### Study Participants

The participants were enrolled in a South Korean government-sponsored prospective cohort study (Cardiovascular and Metabolic Disease Etiology Research Center-High Risk Cohort [CMERC-HI]; clinicaltrials.gov: NCT02003781). The institutional review board at Yonsei University College of Medicine approved the study (2013-0752-027), and all participants provided informed consent. The inclusion criteria were as follows: patients with high-risk hypertension, diabetes mellitus with albuminuria, anuric end-stage renal disease, and use of dialysis (urine output  $< 200$  mL/d); relatives of acute myocardial infarction patients who were younger than 55 years (for men) or 65 years (for women); patients with asymptomatic atherosclerotic CVD (abdominal aorta diameter  $\geq 3$  cm or ankle-brachial index  $< 0.9$ , carotid plaque or carotid intima-media thickness  $\geq 0.9$  mm, asymptomatic old cerebrovascular accident, or  $> 30\%$  stenosis in at least 1 major coronary artery); rheumatic arthritis patients aged older than 40 years taking methotrexate and steroids; atrial fibrillation patients with a CHA2DS<sub>2</sub>-VASc score  $\geq 1$ ; and kidney transplant recipients who underwent transplantation more than 3 months previously. The exclusion criteria were histories of acute coronary syndrome, symptomatic coronary artery disease, symptomatic peripheral artery disease, and heart failure; desired life expectancy less than 6 months because of non-CVD; pregnancy or breastfeeding; and histories of

contrast allergy and related side effects. The present study included 1070 consecutive patients from the CMERC-HI cohort in whom ABPM was performed, and markers for vascular damage and central hemodynamics were assessed between December 2013 and February 2016. Patients with end-stage renal disease and those who underwent kidney transplantation were excluded in this study.

### Clinical and Anthropometric Measurements

All participants underwent baseline evaluations, including an initial standardized questionnaire. Height, weight, body mass index, anthropometric data, and sitting brachial BP were measured (HEM 7080-IC, Omron, Japan). Sitting brachial BP was measured after 5 minutes of rest in the right arm 3 times at 2-minute intervals. The mean of the 3 values was used for analysis. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose levels were measured in blood samples obtained after a 12-hour fast. A resting 12-lead ECG was obtained using the GE Marquette MUSE system (GE Medical Systems, Milwaukee, WI). Participants were considered to be smokers if they were current or former smokers. Participants were considered to have dyslipidemia if they had high total cholesterol ( $> 200$  mg/dL), high low-density lipoprotein cholesterol ( $> 160$  mg/dL), low high-density lipoprotein cholesterol ( $< 40$  mg/dL for men,  $< 50$  mg/dL for women), or high triglyceride ( $> 150$  mg/dL) levels, or if they were currently using lipid-lowering drugs. Participants were considered to have diabetes mellitus if they had a history of diabetes mellitus, were receiving antidiabetic treatment, or had fasting plasma glucose levels of  $> 126$  mg/dL. Participants were considered to have hypertension if they had a self-reported history of hypertension, a history of antihypertensive medication use, or a BP of  $\geq 140/90$  mm Hg at the visit time.

### Ambulatory BP Monitoring

Twenty-four-hour ABPM was performed using the Takeda TM-2430 instrument (A&D Medical, Tokyo, Japan), with readings taken every 30 minutes. Daytime and nighttime periods were defined according to information provided by the patient. Ambulatory BP readings were averaged for 24-hour, daytime, and nighttime values. Patients were classified according to dipping pattern as follows: dippers (nighttime BP decrease  $> 10\%$ ), nondippers (nighttime BP decrease  $< 10\%$  and  $> 0\%$ ), and reverse dippers (nighttime BP  $>$  daytime BP). Morning BP was defined as the average BP of 4 measurements taken after awakening. Morning hypertension was defined as a morning BP  $> 135/85$  mm Hg. Nocturnal hypertension was defined as an average nighttime BP  $> 120/70$  mm Hg, as previously defined.<sup>5</sup> The study participants were grouped according to

the morning BP as follows: subtype I group, patients with normal morning BP; subtype II group, patients with morning hypertension and normal nocturnal BP; and subtype III group, patients with morning hypertension and nocturnal hypertension.

## Measurement of Vascular Target Organ Damage and Central Hemodynamics

All study patients underwent pulse wave measurement, ankle-brachial index assessment, coronary calcium scan, carotid to femoral PWV (cfPWV), and central BP measurement in the morning. The brachial to ankle PWV (baPWV) and ankle-brachial index were determined using a validated oscillometric device (VP-1000 plus/VP-2000, Omron, Japan), as previously described.<sup>10,11</sup> Briefly, after an overnight fast and 5 minutes of rest, the cfPWV was measured in the supine position in a quiet, temperature-controlled room using a SphygmoCor device (AtCor Medical, West Ryde, Australia), as previously described.<sup>10</sup> Central hemodynamics were evaluated in the sitting position after 10 minutes of rest using a commercially available radial artery tonometry device (SphygmoCor), as previously described.<sup>10,12</sup> Briefly, using a high-fidelity micro-manometer (Millar Instruments, Houston, TX), peripheral pressure waveforms were recorded from the radial artery at the wrist, as previously reported. Central SBP, diastolic BP (DBP), pulse pressure, augmentation pressure, forward wave amplitude, and the augmentation index (Alx) were acquired from pulse waveform analysis. Pulse pressure was calculated as the difference between systolic and diastolic pressure. Augmentation pressure was defined as the difference between the second and first systolic peak pressures, and the Alx was defined as the ratio of augmentation pressure to aortic pulse pressure. The Alx was normalized for a heart rate of 75 beats per minute (Alx at 75/min), as this measurement is influenced by heart rate.

## Coronary Artery Calcium Scan

All examinations were performed using a 320-row computed tomographic system (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan) with patients in the supine position on a table, and images were acquired during a single breath hold, which allows image reconstruction in a single cardiac phase. Dual scanograms were used for planning the examination and determining the anatomical range to be covered. A nonenhanced prospective ECG-gated scan was performed to measure the coronary artery calcium score (CACS) with the following parameters: rotation time, 275 ms; slice collimation, 0.5 mm; slice width, 3.0 mm; tube voltage, 100 kV; and automatic tube current modulation (SURE Exposure 3D standard, Toshiba Medical Systems Corporation, Otawara, Japan). Images were analyzed in a core workstation using

dedicated software (TeraRecon version 4.4.11.82.3430.Beta, Foster City, CA). Agatston calcium scores were calculated to quantify the extent of coronary artery calcification.<sup>13,14</sup>

## Statistical Analysis

Continuous variables are summarized as mean±SD, and categorical variables are summarized as a percentage of the group total. Non-normally distributed variables were log transformed for statistical analyses. Continuous variables were compared using independent *t* tests or the Mann–Whitney *U* test for non-normally distributed variables if needed. Multivariate logistic regression analysis was performed in a model using known cardiovascular risk factors and confounding variables. A 2-tailed *P*<0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 software (IBM Corp, Armonk, NY).

## Results

### Clinical Characteristics and Laboratory Findings

Among the 1070 patients, 601 (56.2%), 95 (8.9%), and 374 (34.9%) were included in the subtype I, subtype II, and subtype III groups, respectively. Among 469 patients with morning hypertension, 79.7% showed an association with nocturnal hypertension. In 222 uncontrolled hypertensive patients, according to the clinical BP target, 64.0% showed morning hypertension and 55.4% showed morning hypertension with nocturnal hypertension (subtype III). Baseline characteristics of the study patients are summarized in Table 1. The mean age of patients was greater in the subtype II group than in the subtype I group; however, there were no significant differences in male prevalence among the 3 groups. Waist circumference and body mass index were significantly higher in the subtype II and III groups than in the subtype I group. Office brachial BP was significantly higher in the subtype III group than in the subtype I and II groups. In addition, the prevalence of diabetes mellitus and chronic kidney disease was higher in the subtype III group than in the subtype I and II groups. Moreover,  $\beta$ -blockers and calcium channel blockers were more commonly used and serum blood urea nitrogen levels, creatinine levels, and albumin/creatinine ratio were significantly higher in the subtype III group than in the subtype I and II groups.

### ABPM Data

The 24-hour average SBP/DBP, daytime average SBP/DBP, and nighttime average SBP/DBP were significantly higher in the subtype III group than in the subtype I and II groups (Table 2). As expected, considering the definition of the

**Table 1.** Baseline Characteristics of the Study Participants

	Subtype I (n=601)	Subtype II (n=95)	Subtype III (n=374)	P Value
Age, y	60±11	63±11*	62±10	0.003
Men, No. (%)	342 (56.9)	45 (47.4)	210 (56.1)	0.217
Waist conference, cm	86±9	89±9*	89±9*	<0.001
Body mass index, kg/m <sup>2</sup>	25.0±3.5	26.0±3.5*	25.9±3.4*	<0.001
SBP, mm Hg	123±13	126±15	134±17*†	<0.001
DBP, mm Hg	75±9	72±8*	77±11*†	<0.001
Heart rate, beat per min	69±11	66±11	67±12	0.047
Smoker, No. (%)	267 (44.4)	40 (42.1)	180 (48.1)	0.414
Hypertension, No. (%)	499 (83.0)	81 (85.3)	330 (88.2)	0.085
Diabetes mellitus, No. (%)	188 (31.3)	27 (28.4)	158 (42.2)	0.001
Hypercholesterolemia, No. (%)	347 (57.7)	59 (62.1)	215 (57.5)	0.700
Cerebrovascular accident, No. (%)	25 (3.5)	3 (2.8)	13 (2.5)	0.593
Chronic kidney disease, No. (%)	132 (22.0)	12 (12.6)	94 (25.1)	0.032
CVD family history, No. (%)	176 (29.3)	25 (26.3)	83 (22.2)	0.051
ACEI/ARB, No. (%)	251 (41.8)	46 (48.4)	156 (41.7)	0.454
β-Blocker, No. (%)	119 (19.8)	20 (21.1)	115 (30.7)	<0.001
Calcium channel blocker, No. (%)	205 (34.1)	40 (42.1)	176 (47.1)	<0.001
Diuretics, No. (%)	81 (13.5)	22 (23.2)	60 (16.0)	0.044
Aspirin, No. (%)	160 (26.6)	35 (36.8)	113 (30.2)	0.093
Statin, No. (%)	250 (41.6)	47 (49.5)	149 (39.8)	0.235
Glucose, mg/dL	109±28	108±21	113±30	0.040
Total cholesterol, mg/dL	174±38	171±32	171±32	0.439
Blood urea nitrogen, mg/dL	19.5±9.3	18.0±8.6	20.7±10.3*†	0.033
Creatinine, mg/dL	1.1±0.6	1.0±0.6	1.2±0.7†	0.005
eGFR, mL/min per 1.73 m <sup>2</sup>	77±30	84±31	72±29*†	<0.001
ACR, mg/g (n=753)	32±81	15±33	52±98*†	0.001

Data are presented as mean±SD or number (percentage). ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ACR, albumin/creatinine ratio; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

\* $P<0.05$  by  $t$  test (subtype II or III vs I).

† $P<0.05$  by  $t$  test (subtype III vs II).

morning hypertension subtypes, the subtype II group had a significantly higher proportion of patients with extreme dippers and dippers, whereas the subtype III group had a significantly higher proportion of patients with nondippers and reverse dippers. In addition, nocturnal trough SBP was higher in the subtype III group than in the subtype I and II groups, whereas the prevalence and degree of morning BP surge were higher in the subtype II group than in the subtype I group.

### Indices of PWV and Central Hemodynamics

The proportion of patients with high-risk cfPWV, defined as a value  $>10$  m/s, recommended by the current guidelines,<sup>5</sup> was significantly higher in the subtype III group than in the

subtype I and II groups. In addition, the heart to carotid PWV, heart to femoral PWV, femoral to ankle PWV, baPWV, and central SBP and DBP were significantly higher in the subtype III group than in the subtype I and II groups. The AIx was higher in the subtype III group than in the subtype I group. The central SBP and cfPWV were higher in the subtype II group than in the subtype I group; however, there were no significant differences in the PWV indices between the 2 groups (Figure and Table 3).

### Coronary Artery Calcium Score

The CACS was higher in patients in the subtype III group than in the subtype I and II groups; however, there was no

**Table 2.** Ambulatory BP Monitoring Data in Terms of Morning Hypertension Subtypes

	Subtype I	Subtype II	Subtype III	P Value
Total SBP, mm Hg	122±10	125±14	141±11*†	<0.001
Total DBP, mm Hg	75±7	74±5	82±10*†	<0.001
Day SBP, mm Hg	127±101	135±10*	145±12*†	<0.001
Day DBP, mm Hg	78±7	80±7	85±9*†	<0.001
Night SBP, mm Hg	113±12	111±8	133±13*†	<0.001
Night DBP, mm Hg	69±8	65±3*	77±7*†	<0.001
Extreme dipper	74 (12.3)	33 (34.7)	15 (4.0)	<0.001
Dipper	249 (41.1)	49 (51.6)	139 (37.2)	0.035
Nondipper	234 (38.9)	13 (13.7)	167 (44.7)	<0.001
Reverse dipper	44 (7.3)	0 (0)	53 (14.2)	<0.001
Morning peak SBP, mm Hg	135±15	169±20*	165±19*	<0.001
Morning mean SBP, mm Hg	122±10	144±7*	150±12*†	<0.001
Nocturnal trough SBP, mm Hg	104±14	101±12	123±15*†	<0.001
Morning BP surge, mm Hg	18±14	43±14*	28±16*†	<0.001
Morning BP surge, No. (%)	214 (35.6)	87 (91.6)	224 (59.9)	<0.001

Data are presented as mean±SD or number (percentage). BP indicates blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

\* $P<0.05$  by  $t$  test (subtype II or III vs I).

† $P<0.05$  by  $t$  test (subtype III vs II).

significant difference in the CACS between the patients in the subtype I and II groups (Table S1). We defined a high-risk CACS using different CACS cutoffs (300, 400, and 1000 AU); however, we did not note any significant difference in the prevalence of high-risk CACS when considering any of the CACS cutoffs among the subtypes.

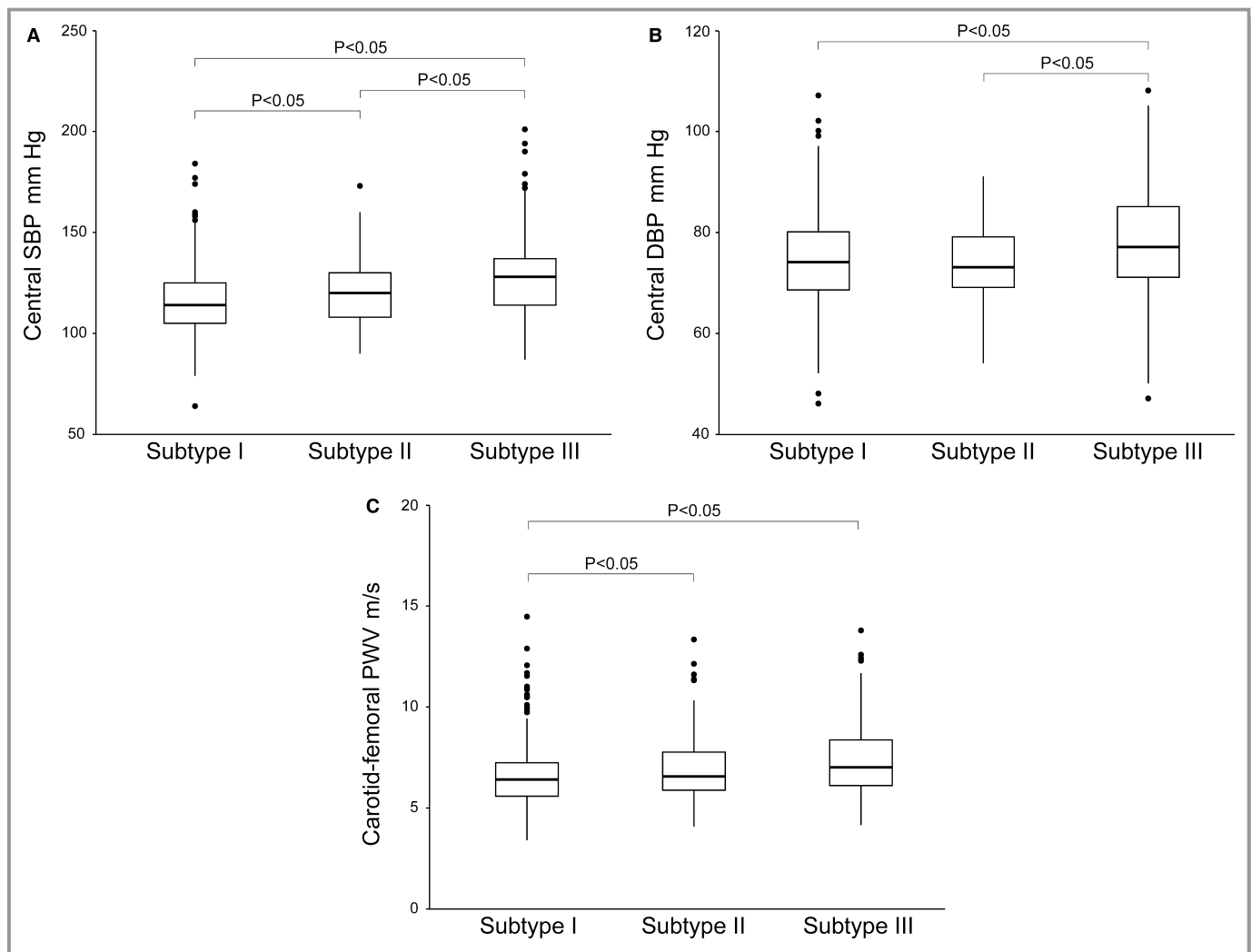
### Adjusted Logistic Regression Analysis

As demonstrated in Tables 1 through 3, there were significant differences in the baseline characteristics and measurements among the subtypes. As such, we adjusted for confounding factors to determine the independent role of the morning hypertension subtype in a multivariate regression model. First, for predicting central hypertension, defined as central SBP >130 mm Hg or DBP >90 mm Hg, suggested by a recent study,<sup>15</sup> subtype III (versus subtype I) was an independent predictor in the fully adjusted model ( $P<0.001$ , model Y; Table 4). This independence remained significant even after further adjusting with daytime average SBP ( $P=0.013$ , model Y+day SBP; Table 4) and cfPWV level ( $P<0.001$ , model Y+cfPWV; Table S2). Second, we adjusted the regression analysis for predicting high-risk cfPWV (>10 m/s), as defined by a recent guideline.<sup>5</sup> In the same model (model Y), subtype III was an independent predictor for high-risk cfPWV ( $P=0.018$ , Table 5). There was a tendency towards significant association after further adjusting with daytime average SBP ( $P=0.104$ , model Y+day SBP, Table 5). However, when we

divided the patients into two groups according to median heart rate (high,  $\leq 65$  beats per minute or low,  $>65$  beats per minute), morning hypertension subtype III (versus subtype I) was associated with high-risk cfPWV in only the high heart rate group ( $P=0.045$  for high heart rate versus  $P=0.932$  for low heart rate,  $P$  for interaction=0.023, model Y+day SBP; Table S3). When we selected a different cutoff of high-risk cfPWV (eg, >12 m/s), the independent association of subtype III remained significant ( $P=0.026$ , Table S4). We then analyzed the prediction of each vascular damage marker (CACS >300 AU, ankle-brachial index <0.9, and baPWV >1800 cm/s). However, we could not find any independent associations of subtype III (versus subtype I or II) after adjustment (Table S5). In summary, there were independent associations of subtype III with the parameters of central hemodynamics and aortic cfPWV. However, there were no significant associations of morning hypertension subtypes with the coronary calcium score and baPWV after adjustment.

### Discussion

The present study made some important findings. First, in the cohort of patients at high risk for CVD, nearly 50% had morning hypertension, with 80% having nocturnal hypertension with morning hypertension. Second, morning hypertension with elevated nocturnal hypertension was associated with significant increases in the indices of central hemodynamics and vascular organ damage. Third, morning



**Figure.** Central hemodynamic parameters according to morning hypertension subtypes. A, Central systolic blood pressure (SBP), (B) central diastolic blood pressure (DBP), (C) carotid-femoral pulse wave velocity (PWV). Subtype I indicates morning normotension; subtype II, morning hypertension without nocturnal hypertension; subtype III, morning hypertension with nocturnal hypertension.

hypertension subtype III was independently associated with central hypertension and increased arterial stiffness.

The fact that nearly half of the study patients had morning hypertension has clinical significance in that despite control of office BP, elevated morning BP has been shown to be an adverse prognostic factor for both target organ damage and adverse cardiovascular outcomes.<sup>6–9,16</sup> The reason for the higher prevalence of morning hypertension in this study (47.5%) compared with that reported in the HONEST study (16.5%)<sup>8,9</sup> may be related to the different definitions of morning hypertension (home morning SBP  $\geq 145$  mm Hg in the HONEST study), the difference in the use of ABPM, and the high cardiovascular risk of this cohort. The high prevalence of morning hypertension can also be explained by the fact that nocturnal hypertension and the nondipping pattern of nocturnal BP are highly prevalent in patients with diabetes mellitus or chronic kidney disease.<sup>17–20</sup> In a cross-sectional

analysis from the African American Study of Kidney Disease, the nondipping pattern was observed in 80% of the study participants, and 70% of 377 participants with well-controlled office BP had masked hypertension. The results from this cohort support this finding as well.<sup>17</sup> As such, the assessment of ambulatory BP to evaluate nocturnal hypertension and morning hypertension should be part of the routine management in patients at high risk for CVD.

Another key finding of this study was that sustained elevation of morning BP that extended from elevated nocturnal hypertension and not morning hypertension due to early morning surge was significantly associated with markers of aortic target organ damage. Previous studies also reported that target organ damage was more prevalent in patients with nocturnal hypertension.<sup>17</sup> In addition, the J-HOP study showed that morning hypertension was related to target organ damage indicators, such as urine albumin/creatinine ratio.<sup>7</sup>

**Table 3.** PWV and Indices of Central Hemodynamics According to Morning Hypertension Subtypes

	Subtype I	Subtype II	Subtype III	P Value
<b>PWV and ABI</b>				
hcPWV, cm/s	920±400	891±310	989±346*	0.008
hfPWV, cm/s	1020±298	1032±354	1123±357*†	<0.001
Mean faPWV, cm/s	1054±281	1016±176	1087±220†	0.028
Mean baPWV, cm/s	1461±267	1500±277	1603±304*†	<0.001
baPWV >1800 cm/s, No. (%)	64 (10.8)	12 (12.6)	72 (19.5)	0.001
ABI	1.13±0.08	1.13±0.09	1.14±0.09*	0.046
ABI <0.9, No. (%)	8 (1.3)	4 (4.2)	10 (2.7)	0.110
<b>Central hemodynamics</b>				
SBP, mm Hg	115±15	120±17*	127±18*†	<0.001
DBP, mm Hg	75±9	74±8	78±11*†	<0.001
Alx	27.4±13.2	30.3±12.8	30.2±10.7*	0.002
cfPWV, m/s	8.8±1.9	9.4±2.3*	10.0±2.4*	<0.001
cfPWV >10 m/s, No. (%)	112 (20.7)	27 (30.3)	127 (39.6)	<0.001
cfPWV >12 m/s, No. (%)	34 (6.3)	9 (10.1)	62 (19.3)	<0.001
Central hypertension, No. (%)	97 (17.9)	24 (27.0)	148 (46.1)	<0.001

Data are presented as mean±SD or number (percentage). ABI indicates ankle-brachial index; Alx, augmentation index; baPWV, brachial to ankle pulse wave velocity; cfPWV, carotid to femoral pulse wave velocity; DBP, diastolic blood pressure; faPWV, femoral to ankle pulse wave velocity; hfPWV, heart to femoral pulse wave velocity; PWV, pulse wave velocity; SBP, systolic blood pressure.

\* $P<0.05$  by  $t$  test (subtype II or III vs I).

† $P<0.05$  by  $t$  test (subtype III vs II).

Recent studies have shown that arterial stiffness and central hemodynamic load are independent prognostic predictors of adverse cardiovascular outcomes.<sup>21,22</sup> Growing evidence suggests that central BP may be more relevant than brachial BP for predicting target organ damage and cardiovascular outcomes.<sup>15,23–25</sup> Arterial stiffness is one of the earliest manifestations of adverse structural and functional changes within the arterial wall. It results in augmentation of the central aortic pressure in central hemodynamics.<sup>22</sup> The significance of this study is that it is the first report to show the interrelationship of central hemodynamics and arterial stiffness with morning hypertension, especially the morning hypertension subtype associated with nocturnal hypertension.

There has been some controversy with regard to the clinical implications of morning hypertension, especially morning hypertension associated with morning BP surge. In the study by Verdecchia et al,<sup>26</sup> which was a cohort study of 3012 patients followed up for a mean period of 8.44 years, blunted morning surge, rather than excessive morning surge, was associated with adverse cardiovascular events. In addition, a study by Bombelli et al<sup>27</sup> reported that morning BP surge was not associated with cardiovascular death, all-cause death, or target organ damage in a cohort of 2051 patients followed up for 16 years. In contrast, nocturnal hypertension has been consistently shown to be associated with adverse cardiovascular events and cardiovascular target

organ damage.<sup>2,28</sup> As such, we can suggest that morning hypertension associated with elevated nocturnal BP may be a subtype with a higher risk of cardiovascular end organ damage and adverse events. It will be interesting to further reanalyze the negative results from the aforementioned study to determine the difference in clinical outcomes according to the morning hypertension subtypes.

Interestingly, subtype II patients did not show any significant difference in regional PWV using the Omron device but showed higher central SBP and cfPWV when compared with the findings in subtype I patients (Table 3). As there was a graded increase in central aortic stiffness from morning normotension to morning hypertension due to morning surge when compared with morning hypertension with nocturnal hypertension, our data may shed light on the different reports with regard to the prognostic significance of morning surge for cardiovascular outcomes. As the aortic PWV is higher for morning hypertension associated with nocturnal hypertension than for morning hypertension associated with morning surge, efforts to determine the subtypes of morning hypertension may be needed. This has important prognostic implications since chronotherapy to target both nocturnal hypertension and morning hypertension may reduce aortic stiffness and central aortic pressure.<sup>29</sup>

The explanation for the different interaction of morning hypertension subtype with aortic stiffness is unclear. Previous

**Table 4.** Multivariate Logistic Regression Analysis for Central Hypertension

	OR (95% CI)	P Value
<b>Model Y</b>		
Age, y	1.024 (1.004–1.044)	0.019
Brachial SBP, mm Hg	1.104 (1.086–1.123)	<0.001
Heart rate, beats per min	0.975 (0.957–0.992)	0.005
ACEI/ARB	1.687 (1.115–2.552)	0.013
Subtype II vs I	1.253 (0.662–2.369)	0.489
Subtype III vs I	2.249 (1.523–3.322)	<0.001
<b>Model Y+day SBP</b>		
Age, y	1.024 (1.004–1.044)	0.017
Brachial SBP, mm Hg	1.101 (1.082–1.119)	<0.001
Heart rate, beats per min	0.976 (0.958–0.994)	0.008
ACEI/ARB	1.728 (1.141–2.619)	0.010
Subtype II vs I	1.134 (0.594–2.167)	0.703
Subtype III vs I	1.806 (1.133–2.881)	0.013

Model Y includes age, sex, body mass index, brachial systolic blood pressure (SBP), heart rate, hypertension, hypercholesterolemia, diabetes mellitus, family history of cardiovascular disease, smoking, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ACE) use, calcium channel blocker use,  $\beta$ -blocker use, diuretic use, statin use, aspirin use, blood urea nitrogen, creatinine, glucose, and cholesterol. Central hypertension is defined as central SBP  $\geq$ 130 mm Hg or central diastolic blood pressure  $\geq$ 90 mm Hg. OR indicates odds ratio.

studies have demonstrated a significant association of increased heart rate with PWV.<sup>30,31</sup> Although the mechanism behind this phenomenon has yet to be firmly established, passive decrease in arterial compliance due to reduced time for elastic recoil has been suggested to be an explanation for this phenomenon.<sup>31,32</sup> We postulate that the effect of nocturnal hypertension and morning hypertension on arterial stiffening is accentuated in arteries passively stiffened by increased baseline heart rate. With regard to the significant association of morning hypertension related to nocturnal hypertension with central aortic BP and aortic PWV, we postulate that the increased hemodynamic stress that is related to nocturnal/morning hypertension over time will result in increased aortic stiffness, which, in turn, will increase central aortic BP and vice versa.<sup>29</sup> However, as this was a cross-sectional analysis, we cannot rule out the possibility that increased aortic stiffness and central hemodynamic loads are responsible for elevated nocturnal hypertension and morning hypertension in these patients. According to previous trials such as the Conduit Artery Function Evaluation (CAFE) study,<sup>33</sup>  $\beta$ -blocker use may be related to impaired central hemodynamics in hypertensive patients.<sup>34</sup> In our study, although more  $\beta$ -blockers were used in patients with morning hypertension subtype III,  $\beta$ -blocker administration was not an independent predictor for central hypertension in our adjusted

**Table 5.** Multivariate Logistic Regression Analysis for High-Risk cfPWV (10 m/s)

	OR (95% CI)	P Value
<b>Model Y</b>		
Age, y	1.099 (1.075–1.123)	<0.001
Body mass index, kg/m <sup>2</sup>	1.058 (1.004–1.114)	0.034
Brachial SBP, mm Hg	1.044 (1.031–1.057)	<0.001
Heart rate, beats per min	1.044 (1.027–1.062)	<0.001
Diabetes mellitus	1.651 (1.097–2.487)	0.016
locker	1.600 (1.019–2.514)	0.041
Creatinine, mg/dL	2.273 (1.292–3.997)	0.004
Subtype II vs I	1.186 (0.642–2.192)	0.585
Subtype III vs I	1.586 (1.082–2.325)	0.018
<b>Model Y+day SBP</b>		
Age, y	1.099 (1.076–1.123)	<0.001
Body mass index, kg/m <sup>2</sup>	1.057 (1.004–1.114)	0.036
Brachial SBP, mm Hg	1.043 (1.029–1.056)	<0.001
Heart rate, beats per min	1.044 (1.027–1.062)	<0.001
Diabetes mellitus	1.632 (1.081–2.462)	0.020
locker	1.613 (1.026–2.535)	0.038
Creatinine, mg/dL	2.258 (1.285–3.969)	0.005
Subtype II vs I	1.143 (0.611–2.139)	0.676
Subtype III vs I	1.469 (0.924–2.335)	0.104

Model Y as in Table 4. High-risk carotid to femoral pulse wave velocity (cfPWV) is defined as aortic cfPWV  $>$ 10 m/s. OR indicates odds ratio; SBP, systolic blood pressure.

model. Further, prospective analyses on the association between morning hypertension subtypes and progression of aortic stiffness are needed.

### Study Strengths

The strength of this study is that comprehensive assessment of markers of target organ damage and determination of their association with morning hypertension with or without nocturnal hypertension were performed in a relatively large cohort at high risk for CVD. However, our study had some limitations. First, owing to the cross-sectional design of the study, we could not distinguish the cause-effect relationship. Second, we could not evaluate the prognostic significance of the different morning hypertension subtypes. However, as this is an ongoing prospective longitudinal study, we will be able to address these issues in the future. Third, because this study was performed in a population with relatively high cardiovascular risk, the results of this study should be generalized with caution. A further study in patients with relatively low to moderate cardiovascular risk who are assumed to have morning hypertension subtype II (morning surge) will be



interesting. Fourth, drug adherence and the administration timing of hypertensive medication could be important confounders. However, we were not able to analyze for drug adherence and thus could not control for it in the analysis. Finally, this study included only Korean individuals. A recent study reported ethnic differences in the degree of morning BP surge between Japanese and European hypertensive patients.<sup>35</sup> Therefore, a further study to confirm our findings is warranted in Western populations.

## Conclusions

We propose, for the first time, that morning hypertension, especially that associated with nocturnal hypertension, is related to an increased risk of cardiovascular target organ damage, especially central hemodynamics, such as higher central BP and increased arterial stiffness.

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## Disclosures

None.

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Indices of the coronary artery calcium score according to morning hypertension subtypes**

	Subtype I	Subtype II	Subtype III	P value
CACS, AU	168±415	185±346	230±482	0.145
Log CACS	1.11±1.13	1.24±1.18	1.37±1.15*	0.007
CACS > 300AU, n(%)	102 (16.7)	19 (21.3)	85 (19.8)	0.328
CACS > 400AU, n(%)	82 (13.4)	14 (15.7)	71 (16.6)	0.369
CACS > 1000AU, n(%)	28 (4.6)	4 (4.5)	34 (7.9)	0.067

Data are presented as mean ± standard deviation or number (percentage).

\*p-value <0.05 in the *t*-test (subtype II or III vs. I), #p-value <0.05 in the *t*-test (subtype III vs. II)

CACS, coronary artery calcium score

**Table S2. Multivariate logistic regression analysis for central hypertension**

<b>Model Y+ cfPWV</b>	<b>OR (95% CI)</b>	<b>p-value</b>
Brachial SBP, mmHg	1.097 (1.078–1.116)	< 0.001
Heart rate, /min	0.966 (0.948–0.985)	< 0.001
ACEI/ARB	1.726 (1.133–2.622)	0.011
Chronic kidney disease	1.910 (1.039–3.510)	0.037
cfPWV, m/sec	1.216 (1.096–1.349)	< 0.001
Subtype II vs. I	1.186 (0.622–2.260)	0.605
Subtype III vs. I	1.806 (1.133–2.881)	0.013

Model Y as in Table 4

Central hypertension is defined as central SBP  $\geq$  130 mmHg or central DBP  $\geq$  90 mmHg.

SBP, systolic blood pressure; cfPWV, carotid to femoral PWV; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker

**Table S3. Multivariate logistic regression analysis for high-risk cfPWV (10 m/s) according to heart rate**

<b>Heart rate &gt;65/min (Model Y + Day SBP)</b>	<b>OR (95% CI)</b>	<b>p-value</b>
Age, years old	1.095 (1.065–1.125)	< 0.001
Brachial SBP, mmHg	1.050 (1.031–1.070)	< 0.001
Heart rate, /min	1.034 (1.005–1.063)	0.020
Diabetes	1.822 (1.040–3.194)	0.036
Subtype II vs. I	1.492 (0.634–3.511)	0.359
Subtype III vs. I	1.920 (1.014–3.634)	0.045
<b>Heart rate ≤65/min (Model Y + Day SBP)</b>	<b>OR (95% CI)</b>	<b>p-value</b>
Age, years old	1.119 (1.076–1.164)	< 0.001
Brachial SBP, mmHg	1.040 (1.019–1.061)	< 0.001
Heart rate, /min	1.100 (1.038–1.167)	0.001
Chronic kidney disease	0.308 (0.110–0.860)	0.025
Beta blocker	2.732 (1.407–5.305)	0.003
Creatinine, mg/dL	2.450 (1.061–5.657)	0.036
Subtype II vs. I	0.970 (0.357–2.634)	0.953
Subtype III vs. I	1.032 (0.497–2.145)	0.932

Model Y as in Table 4.

High-risk cfPWV is defined as aortic cfPWV > 10 m/s.

SBP, systolic blood pressure; cfPWV, carotid to femoral PWV

**Table S4. Multivariate logistic regression analysis for high-risk cfPWV (12 m/s)**

<b>Model Y</b>	<b>OR (95% CI)</b>	<b>p-value</b>
Age, years old	1.104 (1.068–1.141)	< 0.001
Brachial SBP, mmHg	1.059 (1.041–1.077)	< 0.001
Heart rate, /min	1.041 (1.018–1.065)	0.001
Diabetes	2.442 (1.360–4.386)	0.003
Glucose, mg/dL	1.011 (1.002–1.019)	0.011
Subtype II vs. I	0.826 (0.326–2.092)	0.686
Subtype III vs. I	1.863 (1.077–3.221)	0.026

Model Y as in Table 4

SBP, systolic blood pressure; cfPWV, carotid to femoral PWV

**Table S5. Multivariate logistic regression analysis for vascular damage marker**

<b>Model Y</b>	<b>OR (95% CI)</b>	<b>p-value</b>
CACS > 300AU		
Subtype III vs. I	0.947 (0.611–1.469)	0.809
ABI < 0.9		
Subtype III vs. I	2.250 (0.792–6.390)	0.128
baPWV > 1800cm/s		
Subtype III vs. I	1.044 (0.655–1.666)	0.856

Model Y as in Table 4

CACS, coronary artery calcium score; baPWV, brachial to ankle PWV; ABI, ankle-brachial index