Relationship between arterial stiffness and circadian pattern of blood pressure

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Abstract
Arterial stiffness is a risk factor for cardiovascular morbidity and mortality. The relationship between the arterial stiffness and the circadian pattern of blood pressure (BP) has been controversial. The objective of the present study was to investigate the relationship between arterial stiffness by pulse wave analysis (PWA) and variables of 24-hour ambulatory BP monitoring (ABPM) in patients with high normal BP or hypertension (HTN).

Five hundred forty-eight patients (304 males, 48 ± 12-year-old) with high normal BP or HTN were enrolled. BP was measured at the outpatient clinic and 24-hour ABPM was performed. Using radial applanation tonometry, PWA was performed for evaluation of systemic arterial stiffness. Patients were classified into four groups according to the dipping patterns: a nocturnal dipping group, an isolated systolic non-dipping group, an isolated diastolic non-dipping group and a both systolic and diastolic non-dipping group. For adjustment of age, population was divided to 2 groups: old group ≥55 year-old (n = 158, 75 males), young group <55 year-old (n = 390, 229 males).

According to the dipping patterns, augmentation pressure (AP), augmentation index (AI) and heart rate (75 bpm) adjusted AI (AI@HR75) showed statistically significant difference (P = .011, .009, and .018, respectively). Multivariate analysis showed that isolated diastolic non-dipping was correlated with arterial stiffness expressed as AI and AI@HR 75, only in young group (β-coefficient = 12.6, P = .04 and β-coefficient = 7.503, P = .028, respectively).

Arterial stiffness might be closely related with the pattern of non-dipping in young patients with HTN and high normal BP.

Abbreviations: ABPM = 24-hour ambulatory blood pressure monitoring, ACE = angiotensin-converting enzyme, AI = augmentation index, AI@HR75 = heart rate (75 bpm) adjusted augmentation index, AP = augmentation pressure, ARBs = angiotensin receptor blockers, BP = blood pressure, DBP = diastolic blood pressure, HTN = hypertension, PWA = pulse wave analysis

Keywords: arterial stiffness, blood pressure, circadian pattern, hypertension, pulse wave analysis

1. Introduction
Arterial stiffness is one of the well-known risk factors for cardiovascular morbidity and mortality.[1-3] The changes in aortic wall structure and related reduction in aortic dispensability might be related to blood pressure (BP) variation.[4] Reduced large arterial compliance could compromise the sensitivity of arterial baroreceptor, resulting in abnormal BP variation.[5] Although central hemodynamics might affect the diurnal variation of BP, the relationship between the arterial stiffness and the circadian pattern of BP has been controversial.[6-8] There have been several reports demonstrating that the circadian pattern of blood pressure (BP) is related to target organ damage and cardiovascular prognosis.[9,10]

The objective of the present study was to investigate the relationship between arterial stiffness by pulse wave analysis (PWA) and variables of 24-hour ambulatory BP monitoring (ABPM) in patients with high normal BP or hypertension (HTN).

2. Materials and methods
The study included 773 patients (442 males, 48 ± 12-year-old) with high normal BP or HTN, who were consecutively recruited in 11 university hospitals in Korea. Among the study population, 548 patients (304 males, 48 ± 12-year-old), who underwent both 24-hour ambulatory BP monitoring (ABPM) and pulse wave analysis (PWA), were finally enrolled in the present study. The
study protocol and informed consent were reviewed and approved by the Institutional Review Board of each participating hospital.

Office BP measurements were taken from both arms three times by the study nurse using a validated oscillometric device (Omron HEM 747 ICN BP, Omron Healthcare Co., Kyoto, Japan) after 5 minutes of seated rest and at 2-minute intervals. Using office BP, high normal BP and HTN were defined according to 2018 ESH/ESC practice guidelines (High normal BP as systolic BP (SBP) 130 to 139 mmHg and/or diastolic BP (DBP) 85 to 89 mmHg and HTN as SBP ≥140 mmHg and/or DBP ≥90 mmHg). All studied patients underwent 24-hour ABPM. The device was set to obtain BP readings at 30-minute intervals during the day (between 6:00 AM and 11:59 PM) and at 60-minute intervals during the night (between 12:00 AM and 5:59 AM). Participants were instructed to continue with their normal daily activities during the day. A valid measurement was defined as valid readings for more than 70% of the total measurement attempts, and at least 14 measurements during the daytime and at least 7 measurements during the nighttime.

Central hemodynamics and parameters of arterial stiffness were assessed with PWA of the radial artery using commercially available applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia). After 20 sequential waveforms had been acquired, a validated generalized transfer function was used to generate the corresponding central arterial pressure waveform.[12,13] Central systolic BP, diastolic BP, augmentation pressure (AP) and augmentation index (AI) were derived using the technique of PWA. Augmentation pressure is the difference between the second and the first systolic peaks, and the AI is the ratio of AP to aortic pulse pressure calculated as the difference between respective systolic and diastolic pressure. As AI is influenced by heart rate, an index adjusted for heart rate of 75 bpm (AI@HR75) was also calculated.

All patients were divided into 2 groups according to the presence of nocturnal dipping: a dipping group and a non-dipping group. Nocturnal dipping was defined as a reduction of >10% in the day-night ratio, when compared with the daytime values, in the SBP and DBP levels at night. Patients were reclassified into 4 groups according to the dipping patterns. As the prognostic impact of circadian patterns on arterial stiffness could not be accounted for the effects of circadian patterns on arterial stiffness, multivariate logistic regression analysis was used for dummy variables classifying patients’ dipping groups. A dipping group was used as a reference category. Dipping group was as isolated systolic non-dipping, an isolated diastolic non-dipping and a both systolic and diastolic non-dipping group. When compared with the daytime values, reduction of <10% in the SBP was defined as isolated systolic non-dipping, reduction of <10% in the DBP as isolated diastolic non-dipping and reduction of <10% in both SBP and DBP as both systolic and diastolic non- dipping. As aging is major determinant of arterial stiffness,[18,19] population was divided into 2 groups for controlling the patients’ age: old group ≥55-year-old (n = 158, 75 males), young group <55-year-old (n = 390, 229 males). SPSS 18.0 statistical software package (SPSS, Chicago, IL) was used for all calculations. Data are shown as the mean± standard deviation for continuous variables and as numbers and percentages for categorical variables. Comparisons were conducted by unpaired Student t test and ANOVA for continuous variables and Pearson chi-square test for categorical variables. In each aging group, multivariate analyses were performed using linear regression for independent dipping patterns that were related to the arterial stiffness. To account for the effects of dipping patterns on arterial stiffness, dummy variables classifying patients’ dipping groups were created. Three of the groups (an isolated systolic non-dipping group, an isolated diastolic non-dipping group and a both systolic and diastolic non-dipping group) were entered in the model. A nocturnal dipping group was used as a reference category, as high cardiovascular risk is associated with non-dipping compared with dipping.[20,21] Null hypotheses of no difference were rejected if P values were <.05.

### 3. Results

Baseline clinical characteristics according to the presence of nocturnal dipping are summarized in Table 1. Among 548 patients, 225 patients (41%) were included in the dipping group and 323 patients (59%) were included in the non-dipping group. There was no significant statistical difference in central hemodynamics between the groups.

Patients in the non-dipping group were reclassified into 3 groups according to the non-dipping patterns: the isolated systolic non-dipping group, the isolated diastolic non-dipping group and the both systolic and diastolic non-dipping group. Baseline characteristic according to the reclassified groups are presented in Table 2. Among these groups, age was significantly different (48 ± 12, 45 ± 12, 54 ± 10 and 50 ± 12 years, respectively, P < .001). The parameters of arterial stiffness, AP, AI and AI@HR75, were also significantly different. As age was powerful factor affecting arterial stiffness in the analysis, effect of dipping and non-dipping patterns on arterial stiffness could not be analyzed. For controlling the patients’ age, the population was dividing into 2 groups: young group <55-year-old (n = 390, 229 males), old group ≥55-year-old (n = 158, 75 males).

In the young, the isolated diastolic non-dipping group had highest central systolic & diastolic BP among the group (Table 3). The parameters of arterial stiffness, AI and AI@HR75, were also highest in the isolated diastolic non-dipping group. Although central hemodynamics were statistically different according to the circadian patterns in the young, there was no statistical significance in the old (Table 4).

### Table 1

| Variables | Dipping group (n = 225) | Non-dipping group (n = 323) | P value |
|-----------|------------------------|-----------------------------|---------|
| Age (year-old) | 48 ± 12 | 49 ± 12 | .299 |
| Men, n (%) | 133 (59) | 172 (53) | .74 |
| BMI (kg/m²) | 24.7 ± 2.8 | 24.6 ± 3 | .562 |
| Daytime SBP (mmHg) | 147 ± 93 | 139 ± 12 | .005 |
| Daytime DBP (mmHg) | 93 ± 11 | 91 ± 10 | .903 |
| Nighttime SBP (mmHg) | 120 ± 13 | 132 ± 13 | <.001 |
| Nighttime DBP (mmHg) | 76 ± 10 | 84 ± 13 | <.001 |
| Central SBP (mmHg) | 133 ± 20 | 135 ± 16 | .134 |
| Central DBP (mmHg) | 92 ± 13 | 92 ± 13 | .707 |
| AP (mmHg) | 13 ± 9 | 14 ± 8 | .408 |
| AI (%) | 51 ± 25 | 52 ± 23 | .567 |
| AI@HR75 (%) | 26 ± 13 | 27 ± 11 | .433 |

AI@HR75=AI adjusted for heart rate of 75 bpm, AI = augmentation index, AP = augmentation pressure, BMI = body mass index, BSA = body surface area, DBP = diastolic BP, SBP = systolic blood pressure.
Table 2
Baseline characteristics according to the dipping patterns in all subjects.

| Variables               | D     | SND    | DND    | BND    | P value |
|-------------------------|-------|--------|--------|--------|---------|
| Age (year-old)          | 48 ± 12 | 45 ± 12 | 54 ± 10 | 50 ± 12 | <.001   |
| Men, n (%)              | 133 (59) | 61 (57) | 14 (56) | 97 (51) | .393    |
| BMI (kg/m²)             | 24.7 ± 2.8 | 24.7 ± 3 | 25.1 ± 1.9 | 24.4 ± 3.1 | .59     |
| Daytime SBP (mmHg)      | 142 ± 13 | 138 ± 12 | 142 ± 10 | 139 ± 12 | .055    |
| Nighttime SBP (mmHg)    | 93 ± 11  | 92 ± 10  | 91 ± 9  | 91 ± 11 | .262    |
| Central SBP (mmHg)      | 76 ± 10  | 76 ± 14  | 86 ± 9  | 87 ± 10 | >.001   |
| Central DBP (mmHg)      | 133 ± 20 | 133 ± 17 | 136 ± 19 | 133 ± 20 | .272    |
| AP (mmHg)               | 9 ± 13   | 9 ± 14   | 93 ± 18 | 92 ± 12 | .95     |
| AI (%)                  | 31 ± 25  | 26 ± 14  | 38 ± 21 | 35 ± 26 | .009    |
| AI@HR75 (%)             | 26 ± 13  | 24 ± 13  | 31 ± 9  | 28 ± 11 | .017    |

AI@HR75 = AI adjusted for heart rate of 75 bpm, AI = augmentation index, BMI = body mass index, BND = both systolic and diastolic non-dipping group, BSA = body surface area, D = dipping group, DBP = diastolic BP, DND = isolated diastolic non-dipping group, SBP = systolic blood pressure, SND = isolated systolic non-dipping group.

Table 3
Baseline characteristics according to the dipping patterns in the young.

| Variables               | D     | SND    | DND    | BND    | P value |
|-------------------------|-------|--------|--------|--------|---------|
| Age (year-old)          | 43 ± 9  | 41 ± 9  | 47 ± 6  | 43 ± 9  | .064    |
| Men, n (%)              | 107 (63) | 50 (60) | 8 (57)  | 65 (54) | .51     |
| BMI (kg/m²)             | 24.9 ± 3 | 24.8 ± 3 | 25.7 ± 1.7 | 24.4 ± 3 | .085    |
| Daytime SBP (mmHg)      | 142 ± 14 | 139 ± 13 | 144 ± 12 | 141 ± 13 | .059    |
| Nighttime SBP (mmHg)    | 94 ± 11  | 90 ± 10  | 95 ± 8  | 94 ± 11 | .639    |
| Central SBP (mmHg)      | 121 ± 13 | 129 ± 12 | 128 ± 17 | 135 ± 13 | <.001   |
| Central DBP (mmHg)      | 77 ± 10  | 78 ± 15  | 89 ± 8  | 89 ± 11 | <.001   |
| AP (mmHg)               | 11 ± 8   | 10 ± 9   | 15 ± 7  | 14 ± 8  | .128    |
| AI (%)                  | 27 ± 23  | 25 ± 15  | 40 ± 27 | 31 ± 23 | .05     |
| AI@HR75 (%)             | 24 ± 12  | 23 ± 14  | 31 ± 8  | 26 ± 12 | .043    |

AI@HR75 = AI adjusted for heart rate of 75 bpm, AI = augmentation index, AP = augmentation pressure, BMI = body mass index, BND = both systolic and diastolic non-dipping group, BSA = body surface area, D = dipping group, DBP = diastolic BP, DND = isolated diastolic non-dipping group, SBP = systolic blood pressure, SND = isolated systolic non-dipping group.

4. Discussion and conclusions
The present study demonstrated that the relationship between circadian patterns of BP and arterial stiffness was present in the young patients with high normal BP or HTN.

Table 4
Baseline characteristics according to the dipping patterns in the old.

| Variables               | D     | SND    | DND    | BND    | P value |
|-------------------------|-------|--------|--------|--------|---------|
| Age (year-old)          | 63 ± 6  | 62 ± 6  | 63 ± 5  | 63 ± 5  | .908    |
| Men, n (%)              | 26 (48) | 10 (46) | 6 (65)  | 32 (46) | .953    |
| BMI (kg/m²)             | 24.1 ± 17 | 23.9 ± 2.8 | 24.5 ± 2 | 24.5 ± 3.3 | .747    |
| Daytime SBP (mmHg)      | 139 ± 11 | 140 ± 11 | 141 ± 7  | 137 ± 12 | .37     |
| Nighttime SBP (mmHg)    | 87 ± 8   | 90 ± 9   | 86 ± 9  | 86 ± 8  | .143    |
| Central SBP (mmHg)      | 117 ± 10 | 130 ± 10 | 125 ± 12 | 132 ± 12 | <.001   |
| Central DBP (mmHg)      | 72 ± 8   | 78 ± 8   | 80 ± 9  | 83 ± 9  | <.001   |
| AP (mmHg)               | 19 ± 8   | 16 ± 6   | 15 ± 7  | 19 ± 7  | .158    |
| AI (%)                  | 43 ± 28  | 33 ± 9   | 35 ± 9  | 43 ± 29 | .328    |
| AI@HR75 (%)             | 33 ± 11  | 29 ± 6   | 31 ± 10 | 31 ± 8  | .287    |

AI@HR75 = AI adjusted for heart rate of 75 bpm, AI = augmentation index, AP = augmentation pressure, BMI = body mass index, BND = both systolic and diastolic non-dipping group, BSA = body surface area, D = dipping group, DBP = diastolic BP, DND = isolated diastolic non-dipping group, SBP = systolic blood pressure, SND = isolated systolic non-dipping group.

Arterial stiffness (Table 5, AI, β-coefficient = 12.6, P = .04 and AI@HR75, β-coefficient = 7.503, P = .028). In the old, the circadian patterns of BP had no relationship with arterial stiffness (Table 6).
BP has a reproducible circadian pattern characterized by a low period during sleep; an early morning, post-awakening rise and a high plateau period during awake. Abnormal BP circadian pattern is one of emerging index for target organ damage and cardiovascular risk and prognosis. The circadian profile of BP has been connected to subclinical target organ damage in heart, brain, and kidney, such as LV hypertrophy, ventricular arrhythmias, microvascular damage in the brain, white matter lesions, microalbuminuria and decrement in the estimated glomerular filtration. The incidence of coronary disease, lacunar infarction, intracranial hemorrhage, and diabetes are higher among hypertensive with abnormal dipping patterns.

The baroreflex control of the cardiovascular system, sympathetic nerve activity, the renin-angiotensin (RAS) system and vascular endothelial function contribute to circadian patterns in BP. Vascular structural changes reduce the sensitivity of arterial baroreceptor. Weakening baroresponse of BP results in abnormal BP variation. Vascular aging leads to increment of vascular angiotensin 1 receptor levels, which is related with enhancement of sympathetic activity and impairment of autonomic function, resulting in abnormal circadian BP patterns. Vascular endothelium-dependent relaxation by acetylcholine is impaired in stiff artery. Also, vascular endothelial dysfunction is a factor for abnormal circadian BP patterns.

Normal aging exerts opposing effects on proximal large elastic arteries and distal small-sized muscular arteries. Age-induced arterial stiffening predominates on proximal elastic arteries, with no effect on distal medium-sized arteries, attenuating the stiffness gradient throughout the arterial tree. Optimal aging can be considered as a balance between the damaging effects of mechanical, metabolic, and chemical stresses and the repair mechanisms. Contrary to optimal aging, early vascular aging is rather a defect of repair mechanisms in face of various stresses.

Table 5
| Variables | β-coefficient | P value |
|-----------|--------------|---------|
| Augmentation Index | | |
| Isolated systolic non-dipping | −2.763 | .353 |
| Isolated diastolic non-dipping | 12.6 | .04 |
| Both systolic & diastolic non-dipping | 3.179 | .23 |
| Augmentation Index @ HR 75 | | |
| Isolated systolic non-dipping | −0.734 | .658 |
| Isolated diastolic non-dipping | 7.503 | .028 |
| Both systolic & diastolic non-dipping | 2.326 | .115 |

Table 6
| Variables | β-coefficient | P value |
|-----------|--------------|---------|
| Augmentation Index | | |
| Isolated systolic non-dipping | −10.76 | .119 |
| Isolated diastolic non-dipping | −7.96 | .377 |
| Both systolic & diastolic non-dipping | −0.66 | .989 |
| Augmentation Index @ HR 75 | | |
| Isolated systolic non-dipping | −4.03 | .095 |
| Isolated diastolic non-dipping | −2.68 | .395 |
| Both systolic & diastolic non-dipping | −2.634 | .122 |

Author contributions

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