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Relationship between arterial stiffness and circadian pattern of blood pressure

Jin-Sun Park, MD, PhD[a], Joon-Han Shin, MD[a,*], Jeong-Bae Park, MD, PhD[b], Dong-Ju Choi, MD, PhD[c], Ho-Joong Youn, MD, PhD[d], Chang-Gyu Park, MD, PhD[e], Jun Kwan, MD[f], Youngkeun Ahn, MD, PhD[g], Dong-Woon Kim, MD, PhD[h], Se-Joong Rim, MD, PhD[i], Seung-Woo Park, MD, PhD[j], Jidong Sung, MD[j], Jang-Ho Bae, MD, PhD[k], on behalf of the Korean Hypertension Research Network

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, RAS = renin-angiotensin, SBP = systolic blood pressure.

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

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[a] Department of Cardiology, Ajou University School of Medicine, Suwon, [b] JB Lab and Clinic, Seoul, [c] Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, [d] Cardiovascular Center and Cardiology Division, College of Medicine, The Catholic University of Korea, Seoul, [e] Cardiovascular Center, Korea University Guro Hospital, Seoul, [f] Department of Cardiology, Inha University College of Medicine, Incheon, [g] Department of Cardiology, Chonnam National University Hospital, Gwangju, [h] Division of Cardiology, Department of Internal Medicine, Chungbuk National University Hospital and Chungbuk National University College of Medicine, Cheongju, [i] Division of Cardiology, Department of Internal Medicine, Yonsei University College Medicine, Seoul, [j] Division of Cardiology, Heart Vascular and Stroke Institute, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [k] Department of Cardiology, Heart Center, College of Medicine, Konyang University, Deajeon, Republic of Korea.

[*] Correspondence: Joon-Han Shin, Department of Cardiology, Ajou University School of Medicine, 164 Worldcup-ro, Yeongtong-gu, Suwon 443-380, Republic of Korea (e-mail: shinjh@ajou.ac.kr).

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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).[11] 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 aortic 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,[14] 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%, 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 night-day ratio was different when the definition is based on SBP or DBP,[15–17] non-dipping groups were defined based on SBP, DBP or both: 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. 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).

To account for the effects of circadian patterns on arterial stiffness, multivariate logistic regression analysis was done using dummy variables classifying patients' dipping groups. A dipping group was used as a reference category. In the young, isolated diastolic non-dipping pattern was significantly related with

Table 1

Baseline characteristics according to the presence of nocturnal dipping.

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)	.174
BMI (kg/m^2)	24.7 ± 2.8	24.6 ± 3	.562
Daytime SBP (mmHg)	147 ± 93	139 ± 12	.105
Daytime DBP (mmHg)	93 ± 11	91 ± 10	.093
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 (%)	31 ± 25	32 ± 23	.557
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 (n = 225)	SND (n = 107)	DND (n = 25)	BND (n = 191)	*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/m^2)	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
Daytime DBP (mmHg)	93 ± 11	92 ± 10	91 ± 9	91 ± 11	.262
Nighttime SBP (mmHg)	120 ± 13	129 ± 12	128 ± 15	134 ± 13	<.001
Nighttime DBP (mmHg)	76 ± 10	78 ± 14	86 ± 9	87 ± 10	<.001
Central SBP (mmHg)	133 ± 20	133 ± 17	136 ± 19	133 ± 20	.272
Central DBP (mmHg)	92 ± 13	92 ± 14	93 ± 18	92 ± 12	.95
AP (mmHg)	13 ± 9	11 ± 9	15 ± 4	15 ± 8	.011
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, 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).

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 3

Baseline characteristics according to the dipping patterns in the young.

Variables	D (n = 171)	SND (n = 84)	DND (n = 14)	BND (n = 121)	*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/m^2)	24.9 ± 3	24.8 ± 3	25.7 ± 1.7	24.4 ± 3	.285
Daytime SBP (mmHg)	142 ± 14	138 ± 13	144 ± 12	141 ± 13	.059
Daytime DBP (mmHg)	94 ± 11	93 ± 10	95 ± 8	94 ± 11	.639
Nighttime SBP (mmHg)	121 ± 13	129 ± 12	128 ± 17	135 ± 13	<.001
Nighttime DBP (mmHg)	77 ± 10	78 ± 15	89 ± 8	89 ± 11	<.001
Central SBP (mmHg)	131 ± 20	132 ± 17	143 ± 18	135 ± 16	.029
Central DBP (mmHg)	93 ± 13	93 ± 14	103 ± 15	95 ± 12	.02
AP (mmHg)	11 ± 8	10 ± 9	15 ± 7	12 ± 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.

Table 4

Baseline characteristics according to the dipping patterns in the old.

Variables	D (n = 54)	SND (n = 23)	DND (n = 11)	BND (n = 70)	*P* value
Age (year-old)	63 ± 6	62 ± 6	63 ± 5	63 ± 5	.908
Men, n (%)	26 (48)	10 (46)	6 (55)	32 (46)	.953
BMI (kg/m^2)	24.1 ± 1.7	23.9 ± 2.8	24.5 ± 2	24.5 ± 3.3	.747
Daytime SBP (mmHg)	139 ± 11	140 ± 11	141 ± 7	137 ± 12	.37
Daytime DBP (mmHg)	87 ± 8	90 ± 9	86 ± 9	86 ± 8	.143
Nighttime SBP (mmHg)	117 ± 10	130 ± 10	125 ± 12	132 ± 12	<.001
Nighttime DBP (mmHg)	72 ± 8	78 ± 8	80 ± 9	83 ± 9	<.001
Central SBP (mmHg)	137 ± 17	137 ± 10	125 ± 15	136 ± 16	.157
Central DBP (mmHg)	88 ± 12	90 ± 9	79 ± 13	87 ± 11	.068
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.

Table 5

Multivariate logistic regression analysis of circadian patterns for the arterial stiffness in the young.

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

Augmentation Index @ HR 75 = augmentation index adjusted for heart rate of 75 bpm.

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.[9,10] 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.[22] The incidence of coronary disease, lacunar infarction, intracranial hemorrhage, and diabetes are higher among hypertensive with abnormal dipping patterns.[10]

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.[5,23,24] Vascular structural changes reduce the sensitivity of arterial baroreceptor. Weakening baroresponse of BP results in abnormal BP variation.[5] 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.[25] 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 6

Multivariate logistic regression analysis of circadian patterns for the arterial stiffness in the old.

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

Augmentation Index @ HR 75 = augmentation index adjusted for heart rate of 75 bpm.

Early vascular aging reinforces the cross-talk by which small artery alterations influence large artery phenotype, and conversely large artery alterations influence small artery phenotype into a vicious circle of increased peripheral vascular resistance, increased large artery stiffness, increased central BP, and ultimately target organ damage. Early vascular aging is observed in young hypertensives.[26] In the present study, the relation between arterial stiffness and abnormal circadian BP patterns was more definite in the young than in the old. Early vascular aging could explain the possible mechanism of the results.

RAS blocking agents, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, significantly reduce sympathetic activity and ameliorate the impairment of baroreceptor reflex function, which are main pathophysiologic factors of abnormal circadian BP patterns. Especially in the young hypertensives with early vascular aging, relationship between abnormal circadian BP patterns and arterial stiffness is dominant. Considering possible mechanism of this relation, RAS blocking agents might be more useful for the young hypertensives with abnormal circadian BP patterns.

This study has several limitations. First, small number of patients was categorized in the 4 different dipping groups. As relatively small numbers were enrolled in the old group, it might be not enough to evaluate the relationship between the arterial stiffness and the circadian BP patterns in this study group. As early vascular aging is usually seen in the young hypertensives,[26] the relation between arterial stiffness and abnormal circadian BP patterns was more definite in the young than in the old. As aging process is not always same in the same aging population, possibilities of relationship between the arterial stiffness and the circadian BP patterns is still present in the old group. Second, we divided these patients into 2 groups by age 55. Reference value of aging is different in many studies. In the present study, we decided age 55 for more even distribution among the 4 different dipping patterns. Third, level of vascular angiotensin 1 receptor, related with enhancement of sympathetic activity and impairment of autonomic function, was not checked in the present study. The present study logically implied that vascular angiotensin 1 receptor and related cytokines had a pathological role in the abnormal circadian BP patterns. To prove this, further studies might be needed. Finally, we could not fully evaluate the impact of abnormal circadian patterns on target organ damage. As abnormal circadian patterns seemed to correlate with arterial stiffness, target organ damage might be more frequently found in the young hypertensives with abnormal circadian BP patterns.

In summary, arterial stiffness might be closely related with the pattern of non-dipping in young patients with HTN and high normal BP. Considering possible mechanism of early vascular aging, RAS blockers should be considered in young hypertensives with abnormal circadian BP patterns.

Author contributions

Conceptualization: Joon-Han Shin, Jeong-Bae Park, Jun Kwan, Jang-Ho Bae.

Data curation: Jeong-Bae Park, Dong-Ju Choi, Ho-Joong Youn, Chang-Gyu Park, Jun Kwan, Youngkeun Ahn, Dong-Woon Kim, Se-Joong Rim, Seung-Woo Park, Jidong Sung, Jang-Ho Bae.

Formal analysis: Jidong Sung, Jang-Ho Bae.

Methodology: Chang-Gyu Park, Youngkeun Ahn, Dong-Woon Kim.

Software: Dong-Ju Choi.

Supervision: Joon-Han Shin, Jeong-Bae Park, Se-Joong Rim.
Validation: Ho-Joong Youn.
Writing – original draft: Jin-Sun Park.
Writing – review & editing: Jin-Sun Park, Joon-Han Shin.

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