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The Clinical Association of the Blood Pressure Variability with the Target Organ Damage in Hypertensive Patients with Chronic Kidney Disease

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It is known that blood pressure variability (BPV) can independently affect target organ damage (TOD), even with normal blood pressure. There have been few studieson chronic kidney disease (CKD) patients. We evaluated the relationship between BPV and TOD in a cross-sectional, multicenter study on hypertensive CKD patients. We evaluated 1,173 patients using 24-hr ambulatory blood pressure monitoring. BPV was defined as the average real variability, with a mean value of the absolute differences between consecutive readings of systolic blood pressure. TOD was defined as left ventricular hypertrophy (LVH) (by the Romhilt-Estes score ≥ 4 in electrocardiography) and kidney injury (as determined from an estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 and proteinuria). The mean BPV of the subjects was 15.9 ± 4.63 mmHg. BPV displayed a positive relationship with LVH in a univariate analysis and after adjustment for multi-variables (odds ratio per 1 mmHg increase in BPV: 1.053, $P = 0.006$). In contrast, BPV had no relationship with kidney injury. These data suggest that BPV may be positively associated with LVH in hypertensive CKD patients.

Keywords: Blood Pressure Variability; Kidney Failure, Chronic; Hypertension; Hypertrophy, Left Ventricular; Target Organ Damage

INTRODUCTION

The regulation of blood pressure (BP) is an important factor in the prevention of target organ damage (TOD). Independent of the blood pressure level, blood pressure variability (BPV) is as important as BP in TOD occurrence (1, 2). This effect of BPV might be important in chronic kidney disease (CKD) patients, who tend to be at high risk of mortality and morbidity. However, most studies about BPV and TOD have focused on the general population, whereas reports on CKD patients are rare.

There are several methods available for measuring BPV, from BP measurement when a patient visits in-office (visit-to-visit BPV); 24-hr ambulatory blood pressure (24-hr BPV) (2-4). Many studies have used visit-to-visit BPV, including some studies on CKD patients, for the association with cardiovascular mortality (5-8). The 24-hr BPV was also significantly associated with TOD in several studies; however, the effect of 24-hr BPV on complications in CKD patients has not been investigated (9-12).

We previously performed a cross-sectional multicenter study on hypertensive CKD patients in Korea (the Assessment of blood Pressure control and target Organ Damage In patients with chronic kidney disease and hyperTEnsion [APrODiTe] study) (13). Using these data, we evaluated whether 24-hr BPV is associated with TOD, as indicated by left ventricular hypertrophy (LVH) and kidney injury in CKD patients.

MATERIALS AND METHODS

Study design

The APrODiTe study assessed BP regulation and TOD in patients with hypertension

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and CKD. This study was designed as a nationwide, prospective, cross-sectional study and included 21 centers. The study was conducted from October 2009 to May 2011. Here, we used data from the APrODiTe study that included demographic information; office BP; 24-hr ambulatory BP (24-hr ABP); prescribed drugs; laboratory data including serum creatinine; estimated glomerular filtration rate (eGFR, calculated using the Modification of Diet in Renal Disease equation [MDRD] with the Korean coefficient value), urine protein/creatinine ratio; and electrocardiography (ECG) (14, 15).

Study population

We included patients who met the following criteria: 1) provided informed consent, 2) aged 20 to 75 yr, 3) diagnosed with hypertension for > 6 months (or in ≥ 3 clinic visits) prior to participation and had taken anti-hypertensive drugs for > 3 months, 4) had an eGFR level between 15 and 89 mL/min/1.73 m^2, and 5) displayed good medication compliance and no change in prescription in the 2 weeks prior to participation. Exclusion criteria included the following: 1) prescription change according to 24-hr ABP, 2) acute kidney injury or hospitalization, 3) proteinuria > 6 g/day (protein/creatinine ratio > 6.0), 4) end-stage of renal disease (ESRD) with dialysis or kidney transplantation, 5) diseases such as uncontrolled arrhythmia, uncontrolled bronchial asthma/chronic obstructive pulmonary disease, and primary endocrine diseases except diabetes mellitus, 6) pregnancy or lactation, 7) night-shift workers, 8) enrollment in other clinical studies within the previous two months, and 9) participation judged inappropriate by the study physicians. Added to these criteria, we excluded patients with missing BP data during more than 3 consecutive time-points of 24-hr ABP monitoring. Among the 1,317 patients, 1,173 were considered eligible to be evaluated for BPV.

BP measurement and BPV

All of the participants were asked to remain in a seated rest position for 5 min and to not drink coffee or smoke for at least 30 min before the BP measurement. Experienced staff measured each patient's BP using an OMRON IA-2 automatic BP device (IntelliSense™, Omron Corporation, Kyoto, Japan) in triplicate at intervals of 1 to 2 min and recorded the mean of the last 2 readings. The ABP monitoring was performed on the first day of enrollment in this study using a TM-2430 (A&D Co., Ltd., Seoul, Korea) over the course of 24 hr. The device was programmed to measure BP every 30 min. The ABP readings were considered adequate if the monitor had been worn for 24 hr and if there were ≥ 16 acceptable readings between 8 a.m. and 10 p.m. (daytime) and ≥ 12 acceptable readings between 10 p.m. and 8 a.m. (night-time), as based on the recommendation of Fagard et al. (16).

We used only systolic BPV for this study because it presents a more predictable value than diastolic BPV (9). In this study, BPV was defined as the average real variability weighted for the time interval between consecutive readings of 24-hr ABP recordings: this BPV averages the absolute differences of consecutive measurements and accounts for the order in which the blood pressure measurements are obtained (4). The formula for the calculation of BPV is as follows:

$$\mathrm{BPV} = \frac{1}{\mathrm{n\text{-}1}} \sum_{i=0}^{n-1} |SBP(\mathrm{i+1}) - SBP(i)|$$

Target organ evaluation

LVH was defined as 4 points or higher, using the Romhilt-Estes criteria based on ECG (17). Kidney injury included proteinuria and low eGFR; proteinuria was defined as 300 mg/g or higher for a spot urine protein/creatinine ratio and low eGFR was defined as less than 30 mL/min/1.73 m^2 (18, 19).

Statistical methods

The 24-hr SBP and BPV were analyzed as continuous variables using Student's *t*-test, correlation analysis, and linear regression. Because the protein/creatinine ratio was skewed, these values were log-transformed for all of the analyses. Categorical variables were examined using chi-square tests. All of the variables that could potentially affect LVH or renal parameters were analyzed individually using univariate regression and were adjusted for in multivariable analysis. The patients were stratified into several subgroups for a more detailed analysis. In addition, we used *P*-interaction (*P-int*) for the evaluation of interactions in subgroups. If the *P-int* was not significant, it was interpreted as being attenuated for the analyzed difference in each subgroup. A two-sided $P \leq 0.05$ was adopted to indicate statistical significance. The statistical analysis was conducted using SPSS 19 (SPSS, Inc., Chicago, IL, USA) and R i386 version 3.0.0.

Ethical statement

The protocol was approved by the institutional review board of the participating centers (IRB number: B-0909/084-401 of Seoul National University Bundang Hospital). A full verbal explanation of the study was given to all participants, and the patients who consented to participate in this study on a voluntary basis were subjected.

RESULTS

The characteristics of the 1,173 patients are listed in Table 1. The mean age was 56 ± 11.9 yr old. The proportion of males was 63%, and approximately 81% of the patients had LVH. The overall mean BPVs was 15.9 ± 4.60 mmHg in non-LVH group and 16.8 ± 5.07 mmHg in the LVH group. The 24-hr mean SBP was 131 ± 16.3 mmHg and the office mean SBP was 138 ± 19.0 mmHg. The to-

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Table 1. Baseline characteristics according to the presence of left ventricular hypertrophy (LVH)

Variables*	Total (n = 1,173)	LVH (-) (n = 995)	LVH (+) (n = 178)	*P* value†
Age (yr)	56.6 ± 11.9	56.6 ± 11.9	56.9 ± 12.6	0.745
Male (%)	739 (63)	595 (59.8)	144 (80.9)	< 0.001
Systolic blood pressure variability (mmHg)	15.9 ± 4.60	15.7 ± 4.50	16.8 ± 5.07	0.011
24-hour systolic blood pressure (mmHg)	131 ± 16.3	130 ± 15.8	136 ± 17.8	< 0.001
Office mean systolic blood pressure (mmHg)	138 ± 19.0	137 ± 18.8	141 ± 19.7	0.030
eGFR (mL/min/1.73 m^2)	48.9 ± 19.2	48.8 ± 19.0	49.2 ± 20.2	0.074
Proteinuria (%)	663 (56.5)	567 (57.3)	96 (54.2)	0.453
Causes of chronic kidney disease				0.018
Hypertension (%)	437 (37.3)	356 (35.8)	81 (45.5)	
Diabetes (%)	273 (23.3)	237 (23.8)	36 (20.2)	
Others*(%)	463 (39.4)	402 (40.4)	61 (34.3)	
Body mass index (kg/m^2)	25.3 ± 3.40	25.3 ± 3.40	25.2 ± 3.30	0.785
Duration of hypertension (months)	99.0 ± 89.5	97.0 ± 88.8	110 ± 93.2	0.078
Current Smoking (%)	172 (14.7)	141 (14.2)	31 (17.4)	0.012
Current alcohol consumption (%)	410 (35.0)	335 (33.7)	75 (42.1)	0.015
ACEI/ARB (%)	1,042 (88.8)	889 (89.3)	153 (86.0)	0.186

*eGFR, estimated glomerular filtration rate calculated by MDRD; proteinuria, urine protein/creatinine ratio (≥ 300 mg/g); *others, chronic glomerulonephritis, polycystic kidney disease, lupus nephritis, and unknown origin; ACEI/ARB, patients using angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; †*P* value indicates a significant differences between the LVH and non-LVH groups by Student's *t*-test.

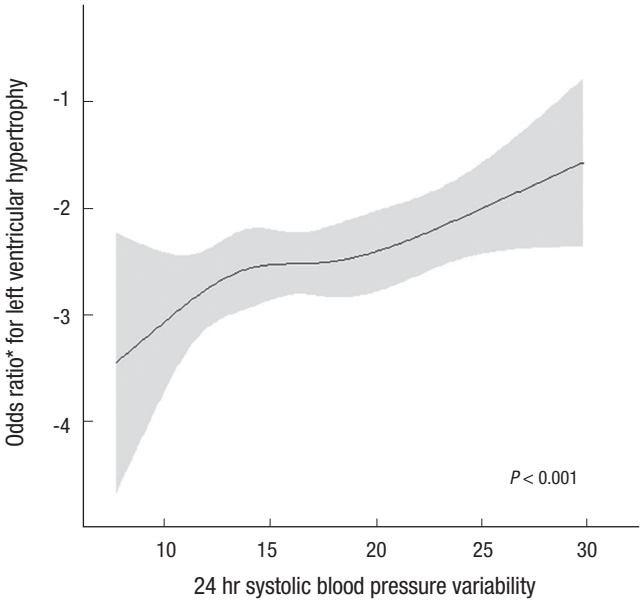

Fig. 1. Odds ratio for left ventricular hypertrophy (LVH) by systolic blood pressure variability (BPV). *Logarithm of odds ratio.

tal mean eGFR was 48.9 ± 19.2 mL/min/1.73 m^2 and approximately 56% of patients had proteinuria.

The relationship between BPV and LVH

For LVH, BPV had a tendency toward a positive relationship in the univariate analysis. Fig. 1 shows the odds ratio (OR) for LVH with regard to BPV ($P < 0.001$). In addition to BPV, several factors were associated with LVH in the univariate analysis: male, 24-hr mean SBP, current smoking, and current alcohol consumption (Table 2). After adjustments for age and sex, BPV was positively associated with LVH (OR per 1 mmHg increase in BPV, 1.061; 95% confidence interval [CI],1.025-1.099; $P = 0.001$). Then, after adjustment for all factors, BPV had a consistently positive relationship with LVH (OR per 1 mmHg increase in BPV, 1.053; 95% CI, 1.0 15-1.093; $P = 0.006$).

The patients were classified into subgroups by sex, diabetes, dipper phenomenon, proteinuria, eGFR (divided by 45 mL/min/1.73 m^2), angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) usage, and degree of BP control (Fig. 2 and 3). BPV was positively associated with LVH in males and in the diabetes, dipper phenomenon, without proteinuria, with eGFR ≥ 45 mL/min/1.73 m^2, and with ACEI/ARB groups (Fig. 2). However, after the evaluation of interactions in subgroups, only the difference between the groups with eGFR ≥ 45 mL/min/1.73 m^2 and eGFR < 45 mL/min/1.73 m^2, was statistically significant (*P-int* = 0.038). This difference indicated that the group with eGFR ≥ 45 mL/min/1.73 m^2 exhibited a statistically positive relationship between BPV and LVH but the group with eGFR < 45 mL/min/1.73 m^2 did not. In the subgroup of proteinuria, the difference between the groups with and without proteinuria, was border line significant (*P-int* = 0.062). Four groups were classified according to the status of BP control: those that represented true controlled BP, white-coat effect, masked hypertension, and sustained hypertension (20). Patients in the true controlled BP, white-coat effect, and sustained hypertension groups displayed a tendency toward a positive relationship with LVH according to their higher BPV (Fig. 3). However, in the multivariate regression analysis, the relationship between BPV and LVH was only significant for the white-coat effect group ($P = 0.006$).

The relationship between BPV and kidney injury

There were no relationships between BPV and proteinuria in the univariate and multivariate analyses (OR, 0.999, $P = 0.952$; OR, 0.977, $P = 0.147$, respectively). In the univariate analysis, the

Table 2. Relationship between systolic blood pressure variability (BPV) and left ventricular hypertrophy (LVH)

Variables*	Univariate†		Age, gender-adjusted‡		All adjusted§	
	P value	OR‖ (95% CI¶)	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Age (1-yr increment)	0.745	1.002 (0.989-1.016)	0.788	0.998 (0.984-1.012)	0.372	0.993 (0.979-1.008)
Male (vs. female)	< 0.001	2.847 (1.919-4.225)	< 0.001	3.039 (2.039-4.53)	< 0.001	2.859 (1.806-4.525)
BPV (1-mmHg increment)	0.006	1.048 (1.014-1.083)	0.001	1.061 (1.025-1.099)	0.006	1.053 (1.015-1.093)
24 hr mean SBP (1-mmHg increment)	< 0.001	1.022 (1.012-1.032)			< 0.001	1.020 (1.009-1.032)
Body mass index (1 kg/m^2 increment)	0.785	0.994 (0.948-1.041)			0.554	0.985 (0.937-1.036)
Diabetes (yes vs. no)	0.063	1.367 (0.983-1.900)			0.023	1.492 (1.056-2.108)
Current smoking (yes vs. no)	0.021	1.473 (1.060-2.046)			0.639	0.913 (0.624-1.336)
Current Alcohol consumption (yes vs. no)	0.030	1.435 (1.036-1.986)			0.944	1.013 (0.704-1.457)
Regular exercise (yes vs. no)	0.118	0.77 (0.555-1.068)			0.167	0.783 (0.553-1.108)
ACEI/ARB (yes vs. no)	0.187	0.73 (0.457-1.166)			0.302	0.768 (0.466-1.267)
eGFR (1 mL/min/1.73 m^2 increment)	0.786	1.001 (0.993-1.009)			0.939	1 (0.991-1.010)
Proteinuria (yes vs. no)	0.453	0.884 (0.641-1.219)			0.156	0.765 (0.528-1.108)

*SBP, systolic blood pressure; ACEI/ARB; patients using angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; eGFR, estimated glomerular filtration rate calculated by MDRD; proteinuria, spot urine protein/creatinine ratio (≥ 300 mg/g). †Univariate logistic regression; ‡Logistic regression: adjusted for age, sex; §Multivariable logistic regression: adjusted for age, sex, smoking, anti-hypertension medication use, 24-hr mean systolic blood pressure, diabetes, exercise, eGFR, and proteinuria (urine protein/creatinine ratio [≥ 300 mg/g]); ‖Odds ratio; ¶95% confidence interval.

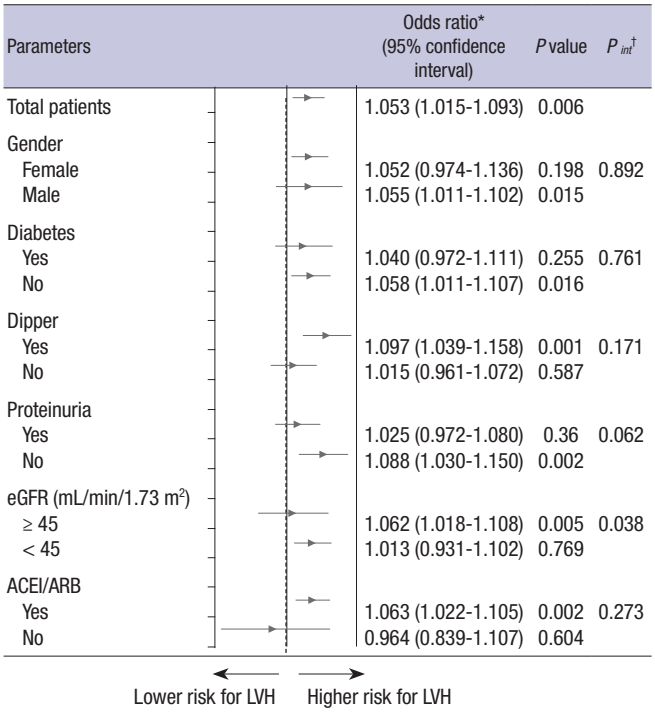

Fig. 2. The association* of blood pressure variability (BPV) and left ventricular hypertrophy (LVH) by subgroup. †ACEI/ARB, patients receiving an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. *Logistic regression analysis: adjusted for age, sex, smoking, anti-hypertension medication use, 24-hr mean systolic blood pressure, diabetes, exercise, eGFR, and proteinuria (spot urine protein/creatininerratio [≥ 300 mg/g]). ‡Odds ratio; §95% confidence interval; ‖*P* value for the interaction between corresponding subgroups, as determined by logistic regression in the multivariable analysis.

factors associated with proteinuria were age, male, 24-hr mean SBP, diabetes, current smoking, current alcohol consumption, and eGFR; however, BPV was not associated with proteinuria. With regard to the relationship with low eGFR (< 30 mL/min/1.73 m^2), BPV displayed no relationships in the univariate and multivariate analyses (OR, 0.979, *P* = 0.177; OR, 0.995, *P* = 0.792, respectively). There was no relationship between BPV and composite outcome (proteinuria and low eGFR) (data not shown).

DISCUSSION

This study revealed that BPV may be positively associated with LVH in hypertensive CKD patients. To date, studies about BPV and TOD in CKD patients have been rare. Even the studies on CKD patients by McMullan et al. and Di Iorio et al. suggesting a higher BPV associated with cardiovascular mortality did not demonstrated how that relationship changed according to subgroups such as sex, diabetes, dipper phenomenon, proteinuria, eGFR, and ACEI/ARB medication (7, 8). A strength of our study is that we show the relationship could vary with subgroups, especially in terms of eGFR value and proteinuria. Through our subgroup analysis, we found that BPV tended to be more associated with LVH in patients with eGFR values higher than 45 mL/min/1.73 m^2, without proteinuria, and with relatively controlled BP. In addition, as this study recruited nationwide participants from 21 centers, our results could be generalized to Korean CKD patients.

Although there are arguments that visit-to-visit BPV has more significance in prognosis, we used 24-hr BPV as the definition of BPV based on following studies: Parati et al. and Hansen et al. suggested that 24-hr BPV has a significant relationship with TOD and mortality, and several studies showed that 24-hr BPV can affect endothelial damage and arterial stiffness (6, 11, 12, 21-25). Schillaci et al. (11) suggested that a higher 24-hr BPV showed a direct positive relationship with large artery stiffness, as assessed by pulse wave velocity in the carotid and femoral arteries. Diaz et al. compared the influence on endothelial function of visit-to-visit BPV and 24-hr BPV, by measuring changes in brachial artery diameter using vasodilator response in response to hyperthermia and nitroglycerin, and showed that 24-

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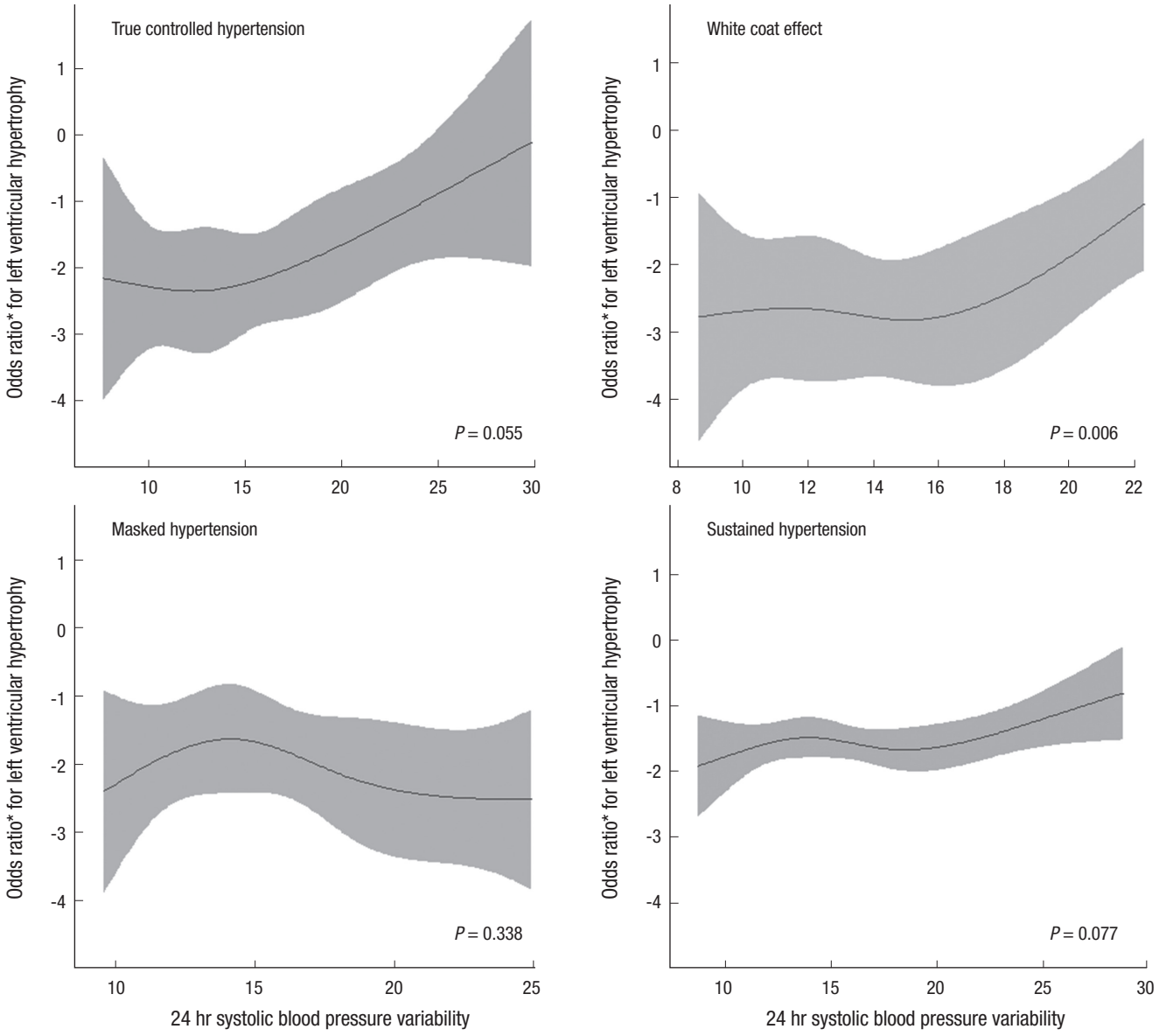

Fig. 3. Odds ratio for left ventricular hypertrophy by systolic blood pressure variability (BPV) by the status of hypertension group. *Logarithm of odds ratio; †Hypertension groups by degree of controlled blood pressure (BP) (mmHg): True controlled group: Office BP (mmHg) < 140/80 and 24-hr BP < 135/85 (day) and 120/70 (night). White-coat effect group: Office BP (mmHg) ≥ 140/80 and 24-hr BP < 135/85 (day) and 120/70 (night). Masked hypertension group: Office BP (mmHg) < 140/80 and 24-hr BP ≥ 135/85 (day) or 120/70 (night). Sustained hypertension group: Office BP (mmHg) ≥ 140/80 and 24-hr BP ≥ 135/85 (day) and 120/70 (night). *P* value in each group: True controlled group, *P* = 0.055; White-coat effect group, *P* = 0.006; Masked hypertension group, *P* = 0.338; Sustained hypertension group, *P* = 0.077.

hr BPV was more negatively associated with endothelial function than visit-to-visit BPV (12). Moreover, other studies have shown that 24-hr BPV is positively associated with higher inflammatory markers of vascular damage, such as C-reactive protein, soluble E-selectin, tumor necrotic factor alpha, and interleukin-6 (24-26). These studies support our rationale for using 24-hr BPV, and not visit-to-visit BPV, but they also could support our result that 24-hr BPV was positively associated with LVH. BPV can induce vascular inflammation and decrease endothelial function, consequentially resulting in increases in pulse wave velocity, left-ventricular mass index, and plaque score (11, 21, 27, 28).

We defined LVH with ECG as a score of 4 points using the Romhilt-Estes criteria (29). Essentially, a score of 4 points indicates the possibility of LVH and a score of 5 points indicates a diagnosis of LVH using the Romhilt-Estes criteria (15). However, Park et al. (17) suggested that 4 points is a good criterion for Koreans; thus, we used 4 points as the cut-off for the diagnosis of LVH. We did not evaluate LVH by echocardiography, and did not add other criteria, such as the Cornell Voltage criteria or the Sokolw Lyons voltage criteria. Thus, young patients with high ECG-voltage could not be evaluated as to whether they truly

had LVH. We recognize that this point could be a limitation in our study. Nonetheless, several studies indicated that ECG can be as good an indicator of left ventricular mass as echo, supporting our method (30, 31). Despite the support of these studies, further investigation using echocardiography to evaluate LVH is needed.

The previous and present studies on CKD patients reveal that BPV is not associated with kidney injury. However, there are indications that vascular damage due to BPV could also affect the kidneys. In rats, higher BPV with normal BP induced glomerular and vascular sclerosis (32). Additionally, some studies have shown that a higher BPV and pulse pressure were correlated with arterial stiffness and a higher resistive index through endothelial dysfunction and that they could be predictive of the development of ESRD (33, 34). Despite this evidence that BPV has an effect on kidney injury through vascular inflammation, the present study found no relationship between BPV and kidney injury. Based on our results, we postulate that kidney injury may not be the result of BPV. It is possible that BPV, proteinuria and a decline in eGFR are merely simultaneous phenomenon via the same process because they share common mechanisms, possibly endothelial dysfunction, arterial stiffness, and vascular inflammation (7). However, this study is cross-sectional design, which allowed us to assess the relationship between BPV and kidney injury; but not to clarify the cause-effect relationship. It would be expected that a well-conducted prospective cohort study on this relationship could reveal the true cause-effect relationship.

Through our subgroup analysis, we attempted to verify the relationship between BPV and LVH. Only the group with eGFR ≥ 45 mL/min/1.73 m^2 displayed statistically clear relationship between BPV and LVH after interaction adjustment. These results indicates that BPV in the group with eGFR < 45 mL/min/1.73 m^2 has no relationship with LVH. It is possible that these results were derived from the differences in age and sex between the subgroups. The patients in the eGFR ≥ 45 mL/min/1.73 m^2 group were younger in age (55 ± 12.1 yr old vs. 58 ± 11.3; P < 0.001) and more of them were; male (57.8% vs. 42.2%; P < 0.001) than in the other group. In the baseline characteristics, male patients already exhibited a significant association between BPV and LVH; thus, the greater proportion of males in the eGFR ≥ 45 mL/ min/1.73 m^2 group might have influenced the association. Due to lack of a relationship between BPV and LVH in the group with eGFR < 45 mL/min/1.73 m^2 and proteinuria, we postulate that progressed kidney injury could be a confounding factor between BPV and LVH. From these results, it is possible that BPV could be a more significant influence on LVH in patients with less kidney injury.

We established the cut-off for eGFR as 45 mL/min/1.73 m^2 because the value of 45 was the median value in the patients' distribution. When the groups were classified around the eGFR value of 45, the different directional nature in the relationship between BPV and LVH was apparent. As recent CKD stages in Kidney Disease Improving Global Outcomes guideline were subdivided according to the eGFR category, the value of 45 could be considered as a detailed CKD stage (35).

In the hypertension groups, with the exception of the masked hypertension group, the groups tended to show borderline relationships between BPV and LVH (the P-values were close to 0.05), and the patients in the sustained and masked hypertension groups showed lesser significance for the relationship compared to the true-controlled groups. Thus, we propose that the effect of BPV may be attenuated in patients with uncontrolled BP and could be strengthened in well-controlled patients. This proposition could also be extended to the concept that it would be important to check for and treat BPV in patients with well-controlled BP compared to those with uncontrolled BP.

This study has some limitations. It is a cross-sectional study, as mentioned earlier, and we used only ECG as an indicator of LVH. We also enrolled all hypertensive patients, even including those with secondary hypertension. But, this could be significant that the effect of BPV itself for target organ was evaluated. And, we did not check the urine albumin/creatinine ratio. There is evidence that the protein/creatinine ratio could reveal similar information as the albumin/creatinine ratio for CKD patients, besides protein/creatinine ratio could be a better indicator than the albumin/creatinine ratio (36, 37).

In conclusion, we demonstrated that BPV is independently associated with LVH, in addition to the BP level, in hypertensive CKD patients. The association with LVH was particularly manifested in patients with eGFR leves ≥ 45 mL/min/1.73 m^2, with well-controlled BP, and without proteinuria. Further prospective studies are needed to assess the real predictive relationship between BPV and organ damage.

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DISCLOSURE

The authors have no conflicts of interest to disclose.

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