Received: 30 September 2020 | Revised: 22 October 2020 | Accepted: 3 November 2020

DOI: 10.1111/jch.14108

ORIGINAL PAPER

WILEY

# 24-h ambulatory blood pressure variability and hypertensive nephropathy in Han Chinese hypertensive patients

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**Funding information**
This work was supported by research grants V101B-004, V102B-024, V103C-019, V104C-025, V106C-120, V108C-151, VGHUST108-G1-3-2, and VTA108-V1-7-2 from Taipei Veterans General Hospital, Taipei, Taiwan, ROC, and research grant MOST 108-2314-B-075-062-MY3 from the Ministry of Science and Technology, Taiwan, ROC The funders had no role in data collection or preparation of the manuscript.

## Abstract

Blood pressure (BP) is characterized by spontaneous oscillation over time, which is described as BP variability (BPV). The current study aimed to investigate whether short-term BPV was correlated with hypertensive nephropathy in Han Chinese individuals with hypertension. A single-center prospective cohort study of 300 Han Chinese participants with hypertension was conducted in Taiwan. Five different BPV parameters were derived from ambulatory BP monitoring (ABPM), including standard deviation (SD), weighted SD (wSD), coefficient of variation (CoV), successive variation (SV), and average real variability (ARV). Renal event was defined as > 50% reduction in baseline estimated glomerular filtration rate (eGFR). The average age of the participants was 63.5 years. The baseline eGFR was 84.5 mL/min/1.73 $m^2$. The participants were divided into two groups according to the wSD of systolic BP (SBP). Survival was assessed via a Kaplan-Meier analysis. During the 4.2-year follow-up, the participants with the highest SBP wSD tertile had a greater number of renal events (6.0%) than their counterparts (0.5%) (log-rank test, $p$ = .007). The Cox proportional hazard regression model was used to assess the independent effects of BPV, and results showed that 24-h SBP (HR = 1.105; 95% CI = 1.020–1.197, $p$ = .015) and 24-h DBP (HR = 1.162; 95% CI = 1.004–1.344, $p$ = .044) were independently associated with renal events. However, BPV parameters were only associated with renal events univariately, but not after adjusting for baseline characteristics, 24-h mean BP, and office BP. Therefore, the risk of hypertensive nephropathy was independently associated with 24-h mean BP, but not with ambulatory BPV, in Han Chinese participants with hypertension.

## 1 | INTRODUCTION

Hypertension is a major global health risk, affecting 1.13 billion people worldwide.[1] It is well-known that hypertension can be complicated by hypertension-mediated organ damage (HMOD), which is defined as the presence of hypertensive retinopathy with exudates and hemorrhages, left ventricular hypertrophy (LVH), or vascular or renal injury.[2]

Blood pressure (BP) is characterized by continuous dynamic fluctuations over time. Such BP spontaneous oscillation is described as BP variability (BPV). In recent studies, BPV was found to have predictive value for major cardiovascular (CV) events and mortality, independent of mean BP.[3,4] Although a relationship has been observed between BPV and CV events in hypertensive patients, its association with renal injury or hypertensive nephropathy has not been fully elucidated. Hypertension is one of the most important contributors to chronic kidney disease (CKD) and end-stage renal disease (ESRD).[5,6] Therefore, the effects of BP and BPV on the development of hypertensive nephropathy should be further validated.

Blood pressure variability can be observed in very short-term (beat-by-beat), short-term (within a 24-h period), mid-term (day-by-day), and long-term (visit-to-visit) periods.[7] Short-term BPV can be measured by ambulatory BP monitoring (ABPM). Compared with long-term BPV measured by office BP, previous studies have shown that HMOD is more closely correlated with ambulatory BP.[8] Thus, the current study aimed to investigate whether short-term BPV derived from 24-h ABPM was correlated with hypertensive nephropathy in Han Chinese individuals with hypertension in Taiwan.

## 2 | METHODS

### 2.1 | Participants

Han Chinese participants with hypertension were included in our study conducted from February 2012 to April 2019. The inclusion criteria were as follows: participants aged ≥ 20 years; those from the Han Chinese population; residents officially registered in Taiwan; and those meeting one of the following hypertension criteria: (a) systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥ 90 mmHg in at least two consecutive visits within 2 months, (b) use of one or more antihypertensive medications for 2 months; and without medical history of severe diseases, including liver or renal failure, carcinoma, and cardiac or pulmonary failure, and acute disease within 2 weeks.

The exclusion criteria were as follows: participants with secondary hypertension, those who cannot understand or provide informed consent, and those who had one or more foreign parents. The study protocol was approved by the ethics committee of Taipei Veterans General Hospital. This study was conducted in accordance with the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

### 2.2 | Study design

The study included a comprehensive examination of each participant's medical history and a physical examination conducted by a cardiologist (2nd author, Huang) at the hypertension clinic of the hospital. The participants' office BP, including SBP and DBP, and body mass index (BMI) were evaluated. Diabetes mellitus (DM) was defined as hemoglobin A1c ≥ 6.5%, fasting plasma glucose level ≥ 126 mg/dl, or 2-h plasma glucose level ≥ 200 mg/dl based on an oral glucose tolerance test. If available, data on antihypertensive drug prescriptions were also recorded.

### 2.3 | Office BP measurement

According to a standardized protocol, office BP was assessed by a highly trained nurse using an electronic BP monitor. The BP was obtained in the morning hours after the participants were instructed to sit for 10 min in a quiet room. During each measurement, both SBP and DBP were recorded. Three consecutive BP measurements were obtained in the same upper arm. The interval of each measurement was 30 s. The average value of the last two measurements was considered the BP record.

### 2.4 | Ambulatory measurement

The participants were connected to the ABPM device between 08:00 and 10:00 h. The device was an oscillometric ABPM device (Microlife Corp., WatchBP O3 Ambulatory blood pressure monitor; NeiHu, Taipei, Taiwan, ROC). The device was programmed to record BP every 15 min between 06:00 and 22:00 h (daytime BP) and every 60 min from 22:00 to 06:00 h (nighttime BP). To analyze short-term BPV, five variables were calculated for both SBP and DBP, which were as follows: standard deviation $(SD) = \sqrt{(1/n-1)\sum_{(i=1)}^{(n)}(BP_i - BP_{mean})^2}$; weighted $SD$ $(wSD) = (\text{daytime } SD \times 16 + \text{nighttime } SD \times 8)/24$, namely, the mean daytime and nighttime SD values weighted for the number of hours covered in these two periods [9]; coefficient of variation $(\text{CoV}) = SD/BP_{mean}$, defined as the ratio of SD to the mean; successive variation $(\text{SV}) = \sqrt{(1/n-1)\sum_{(i=1)}^{(n-1)}(BP_{i+1} - BP_i)2}$; and average real variability $\text{ARV} = (1/n-1)\sum_{(i=1)}^{(n-1)}|BP_{i+1} - BP_i|$, representing the average absolute difference between successive readings.[10]

### 2.5 | Laboratory measurements

In the morning, typically between 07:30 and 09:00 h, the fasting whole blood samples of the participants were collected via venipuncture after the participants rested for 10 min while in supine position. The participants were instructed to take all routine medications as they normally would. The blood samples were centrifuged, and the

serum was frozen and was then thawed at the time of analysis. The baseline estimated glomerular filtration rate (eGFR) was calculated using the four-variable equation proposed by the Modification of Diet in Renal Disease Study.[11]

### 2.6 | Renal outcomes

The development of hypertensive nephropathy was defined as >50% decline in eGFR, according to the previously proposed criteria. These criteria were also used to indicate renal dysfunction during the follow-up period.[12]

### 2.7 | Power calculation

The power calculation was based on 300 participants using the two-sample t test for the difference in the mean between the renal outcome group ($n$ = 10) and non-renal outcome group ($n$ = 290). With an SD ranging from 3 to 4 for BPV and a significance level of 0.05, the range of power was from 0.812 to 0.966.

### 2.8 | Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 18.0, SPSS Inc, Chicago, Illinois, USA). All data were expressed as mean ± SD or frequency (percentage). Survival analysis was assessed via a Kaplan-Meier analysis, with the significance based on the log-rank test. To assess the independent effects of BPV and renal outcomes, we conducted a Cox proportional hazard regression analysis. In addition to crude hazard ratios (HRs) (model 1), the adjusted HRs were assessed after adjusting for potential confounding factors. In model 2, the HRs of BPV for renal outcomes were adjusted for age, gender, BMI, DM, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), β-blocker, calcium channel blocker (CCB), thiazide, and baseline eGFR. In model 3, the HRs of BPV for renal outcomes were adjusted for age, gender, BMI, DM, ACEI/ARB, β-blocker, CCB, thiazide, baseline eGFR, and 24-h SBP or DBP. In model 4, the HRs of BPV for renal outcomes were adjusted for age, gender, BMI, DM, ACEI/ARB, β-blocker, CCB, thiazide, baseline eGFR, and office SBP or DBP. A two-sided $p$-value < .05 was considered statistically significant.

## 3 | RESULTS

### 3.1 | Baseline characteristics of the study cohort

In total, 300 Han Chinese hypertensive participants in Taiwan with a mean age of 63.5 ± 13.6 years were eligible for enrollment in the current study. Approximately 59.3% of the study cohort was men and 16.7% presented with DM. The antihypertensive drugs used included ACEI or ARB (65.7%), β-blocker (23.7%), CCB (72.0%), and thiazide diuretics (19.3%). The baseline eGFR was 84.5 ml/min/1.73 $m^2$ (Table 1).

**TABLE 1** Baseline characteristics

| | All ($n$ = 300) |
|---|---|
| Age, years | 63.5 (13.6) |
| Gender, $n$ (%) men | 178 (59.3%) |
| BMI, kg/$m^2$ | 26.0 (3.6) |
| Office SBP, mmHg | 134.2 (17.5) |
| Office DBP, mmHg | 82.3 (10.3) |
| Office heart rate, bpm | 71.0 (11.1) |
| Diabetes mellitus, $n$ (%) | 50 (16.7%) |
| ACEI/ARB, $n$ (%) | 197 (65.7%) |
| β-blocker, $n$ (%) | 71 (23.7%) |
| CCB, $n$ (%) | 216 (72.0%) |
| Thiazide, $n$ (%) | 58 (19.3%) |
| Creatinine, mg/dL | 0.9 (0.2) |
| eGFR, mL/min/1.73 $m^2$ | 84.5 (18.3) |
| Mean follow up duration, years | 4.2 (2.4) |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beat per minute; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

The ambulatory BP parameters were as follows: 24-h mean SBP: 123.0 ± 11.7 mmHg, 24-h mean DBP: 73.4 ± 8.1 mmHg, daytime SBP: 123.9 ± 11.9 mmHg, daytime DBP: 74.0 ± 8.3 mmHg, nighttime SBP: 117.6 ± 13.4 mmHg, and nighttime DBP: 69.1 ± 9.2 mmHg. The five different BPV parameters, namely SD, wSD, CoV, SV, and ARV, are presented in Table 2.

### 3.2 | Baseline characteristics of the study cohort according to SBP wSD tertile

To understand the relationship between BPV and other baseline characteristics, all the participants were further divided into two groups according to SBP wSD (the group with the SBP wSD in the highest tertile and the group with SBP wSD in other tertiles). The participants with the highest SBP wSD were older ($p$ = .005) and had lower BMI ($p$ = .001), higher office SBP ($p$ = .011), and longer follow-up duration ($p$ = .029) than their counterparts (Table S1). The ambulatory BP parameters showed that the group with the highest SBP wSD had a higher 24-h mean SBP ($p$ < .001), daytime SBP ($p$ < .001), and nighttime SBP ($p$ = .013) than the counterpart. Moreover, the other BPV parameters were consistently higher in the group with the highest SBP wSD than the counterpart (Table S2).

**TABLE 2** Twenty-four-hour ambulatory blood pressure parameters

| SBP | All (*n* = 300) | DBP | All (*n* = 300) |
|---|---|---|---|
| 24-h SBP, mmHg | 123.0 (11.7) | 24-h DBP, mmHg | 73.4 (8.1) |
| Daytime SBP, mmHg | 123.9 (11.9) | Daytime DBP, mmHg | 74.0 (8.3) |
| Nighttime SBP, mmHg | 117.6 (13.4) | Nighttime DBP, mmHg | 69.1 (9.2) |
| 24-h SBP SD | 13.1 (3.3) | 24-h DBP SD | 9.6 (2.9) |
| Daytime SBP SD | 12.9 (3.5) | Daytime DBP SD | 9.5 (3.1) |
| Nighttime SBP SD | 10.5 (4.3) | Nighttime DBP SD | 7.7 (3.3) |
| 24-h SBP wSD | 12.1 (3.0) | 24-h DBP wSD | 8.9 (2.6) |
| 24-h SBP CoV | 10.7 (2.8) | 24-h DBP CoV | 13.3 (4.2) |
| Daytime SBP CoV | 10.4 (2.9) | Daytime DBP CoV | 13.0 (4.5) |
| Nighttime SBP CoV | 9.0 (3.5) | Nighttime DBP CoV | 11.2 (4.7) |
| 24-h SBP SV | 13.1 (3.2) | 24-h DBP SV | 9.7 (3.2) |
| Daytime SBP SV | 13.0 (3.4) | Daytime DBP SV | 9.5 (3.5) |
| Nighttime SBP SV | 13.8 (5.5) | Nighttime DBP SV | 10.4 (4.6) |
| 24-h SBP ARV | 10.0 (2.2) | 24-h DBP ARV | 7.1 (1.9) |
| Daytime SBP ARV | 9.8 (2.3) | Daytime DBP ARV | 7.0 (2.1) |
| Nighttime SBP ARV | 10.6 (4.3) | Nighttime DBP ARV | 7.9 (3.4) |

Abbreviations: ARV, average real variability; CoV, coefficient of variation; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; SV, successive variation; wSD, weighted standard deviation.

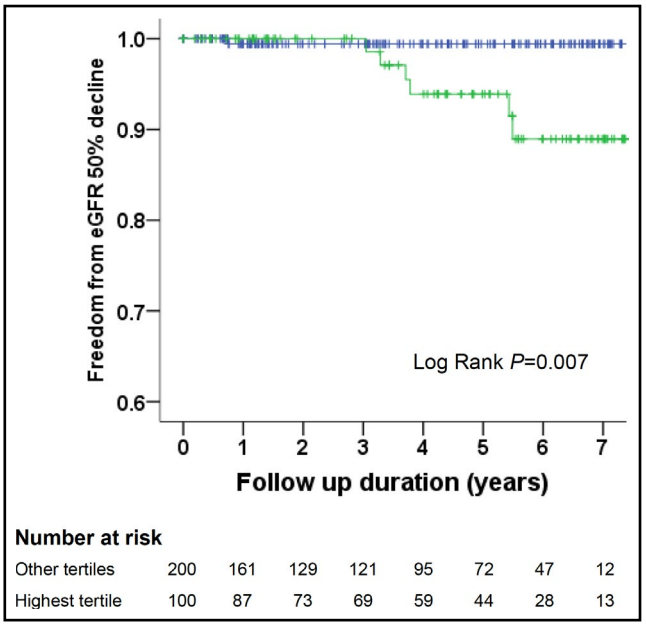


**FIGURE 1** Kaplan-Meier survival curves showing freedom from renal events according to baseline 24-h ambulatory blood pressure variability (BPV) in patients with hypertension. Then, 24-h ambulatory BPV was represented as the weighted standard deviation (wSD) of systolic blood pressure (SBP). The participants were divided into two groups according to SBP wSD (the group with the SBP wSD in the highest tertile and the group with SBP wSD in other tertiles). Renal event was defined as a significant decline in estimated glomerular filtration rate (>50%). The green line represents the group with the SBP wSD in the highest tertile. The blue line represents the group with SBP wSD in other tertiles. Differences were compared using the log-rank test ($p$ = .007)

### 3.3 | Association between BPV and renal events

During a 4.2-year follow-up period, seven renal events occurred. Regarding SBP wSD and renal events, six (6.0%) occurred in participants with the highest tertile and one (0.5%) occurred in other tertiles. Survival was assessed via a Kaplan-Meier analysis. The participants with the highest SBP wSD tertile had a greater number of renal events than their counterparts (log-rank test, $p$ = .007) (Figure 1).

The Cox proportional hazard regression model was used to examine the independent effects of 24-h mean SBP and BPV on renal events. In model 1, 24-h SBP (HR = 1.071; 95% confidence interval [CI]=1.025–1.119, $p$ = .002), daytime SBP (HR = 1.077; 95% CI = 1.028–1.128, $p$ = .002), nighttime SBP (HR = 1.037; 95% CI = 1.003–1.071, $p$ = .031), 24-h SBP SD (HR = 1.236; 95% CI = 1.036–1.476, $p$ = .019), daytime SBP SD (HR = 1.201; 95% CI = 1.022–1.411, $p$ = .026), nighttime SBP SD (HR = 1.182; 95% CI = 1.021–1.369, $p$ = .025), SBP wSD (HR = 1.275; 95% CI = 1.067–1.524, $p$ = .008), 24-h SBP SV (HR = 1.130; 95% CI = 1.002–1.275, $p$ = .046), 24-h SBP ARV (HR = 1.270; 95% CI = 1.006–1.604, $p$ = .044), and daytime SBP ARV (HR = 1.234; 95% CI = 1.004–1.517, $p$ = .046) were associated with the risk of renal events. In model 2, 24-h SBP (HR = 1.108; 95% CI = 1.027–1.197, $p$ = .009) and daytime SBP (HR = 1.127; 95% CI = 1.032–1.230, $p$ = .008), but not BPV parameters, were associated with renal events. In model 3, none of the systolic BPV parameters were associated with the risk of renal events (Table 3). In model 4, only 24-h SBP (HR = 1.105; 95% CI = 1.020–1.197, $p$ = .015) and daytime SBP (HR = 1.124; 95% CI = 1.026–1.231, $p$ = .012), instead of systolic BPV parameters, were associated with renal events (Table S3).

The Cox proportional hazard regression model was also used to assess the independent effects of 24-h mean DBP and BPV on renal events. Only daytime DBP (HR = 1.165; 95% CI = 1.012–1.341, $p$ = .034) was associated with the risk of renal events in model 2. None of the diastolic BPV parameters were associated with renal events in models 1, 2, and 3 (Table 4). In model 4, only 24-h DBP (HR = 1.162; 95% CI = 1.004–1.344, $p$ = .044) and daytime DBP (HR = 1.205; 95% CI = 1.024–1.419, $p$ = .025), instead of diastolic BPV parameters, were associated with renal events (Table S4).

**TABLE 3** Univariate and multivariate analyses of the association between systolic blood pressure variability and renal events

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| SBP | | | | | | |
| 24-h | 1.071 (1.025–1.119) | .002 | 1.108 (1.027–1.197) | .009 | | |
| Daytime | 1.077 (1.028–1.128) | .002 | 1.127 (1.032–1.230) | .008 | | |
| Nighttime | 1.037 (1.003–1.071) | .031 | 1.040 (0.990–1.092) | .120 | | |
| SD | | | | | | |
| 24-h | 1.236 (1.036–1.476) | .019 | 1.141 (0.922–1.411) | .224 | 1.032 (0.803–1.325) | .807 |
| Daytime | 1.201 (1.022–1.411) | .026 | 1.107 (0.909–1.348) | .314 | 1.014 (0.799–1.287) | .909 |
| Nighttime | 1.182 (1.021–1.369) | .025 | 1.134 (0.937–1.373) | .198 | 1.058 (0.833–1.343) | .644 |
| wSD | 1.275 (1.067–1.524) | .008 | 1.173 (0.924–1.491) | .190 | 1.039 (0.785–1.375) | .789 |
| CoV | | | | | | |
| 24-h | 1.130 (0.893–1.429) | .308 | 1.011 (0.775–1.319) | .936 | 1.031 (0.738–1.441) | .858 |
| Daytime | 1.102 (0.882–1.377) | .392 | 0.985 (0.763–1.273) | .909 | 0.991 (0.717–1.371) | .956 |
| Nighttime | 1.172 (0.968–1.419) | .105 | 1.106 (0.875–1.397) | .400 | 1.170 (0.870–1.574) | .300 |
| SV | | | | | | |
| 24-h | 1.130 (1.002–1.275) | .046 | 1.080 (0.876–1.332) | .472 | 0.978 (0.757–1.262) | .862 |
| Daytime | 1.110 (0.997–1.236) | .057 | 1.070 (0.877–1.305) | .505 | 0.962 (0.752–1.232) | .759 |
| Nighttime | 1.084 (0.974–1.207) | .139 | 1.032 (0.910–1.170) | .624 | 0.995 (0.842–1.176) | .955 |
| ARV | | | | | | |
| 24-h | 1.270 (1.006–1.604) | .044 | 1.120 (0.832–1.509) | .454 | 0.938 (0.655–1.344) | .728 |
| Daytime | 1.234 (1.004–1.517) | .046 | 1.111 (0.845–1.460) | .451 | 0.933 (0.668–1.303) | .685 |
| Nighttime | 1.065 (0.913–1.242) | .421 | 1.008 (0.844–1.205) | .927 | 0.959 (0.749–1.228) | .741 |

*Note:* Model 1: Unadjusted. Model 2: Adjusted for age, gender, BMI, DM, ACEI/ARB, β-blocker, CCB, thiazide, and baseline eGFR. Model 3: Adjusted for age, gender, BMI, DM, ACEI/ARB, β-blocker, CCB, thiazide, baseline eGFR, and 24-h SBP.

Abbreviations: ARV, average reading variability; CI, confidence interval; CoV, coefficient of variation; HR, hazard ratio;SBP, systolic blood pressure; SD, standard deviation; SV, successive variation; wSD, weighted standard deviation.

### 3.4 | Renal events of the study cohort according to SBP wSD tertile

The Cox proportional hazard regression model was further used to assess the independent effects of SBP wSD on renal events. In model 1, SBP wSD (highest tertile vs. other tertiles) (HR = 10.296; 95% CI = 1.239–85.546, $p$ = .031) was associated with the risk of renal events. However, it became insignificant in models 2, 3, and 4 (Table S5).

## 4 | DISCUSSION

The main finding of this prospective cohort study was that 24-h mean BP, but not 24-h ambulatory BPV, was correlated with the development of hypertensive nephropathy in Han Chinese hypertensive patients. Although short-term BPV parameters were associated with hypertensive nephropathy in the univariate analysis, the parameters became insignificant in the multivariate analysis after adjusting for baseline characteristics, 24-h mean BP, and office BP.

The relationship between BPV and CV diseases has been shown in previous studies[13–15]; however, the findings are not consistent. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial of 13,803 hypertensive middle aged and elderly participants, a 15% increase in the risk of CV events was noted for every 5 mmHg increase in SD of within-visit systolic BPV.[13] Palatini and colleagues reported that a higher short-term systolic BPV was associated with a higher number of fatal and nonfatal CV events in young patients with stage 1 hypertension.[14] Moreover, de Havenon and colleagues revealed that long-term systolic BPV was correlated with the risk of recurrent stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial.[15] By contrast, Tara I Chang and colleagues reported that visit-to-visit BPV had no significant associations with the composite end point of fatal and nonfatal cardiovascular events nor with heart failure or stroke hospitalizations in post hoc analysis of SPRINT (Systolic Blood Pressure Intervention Trial).[16]

Although a growing number of clinical and observational studies have investigated the association between both short- and long-term BPV and CV diseases, evidence on the relationship between BPV and renal injury has not been fully elucidated. It was found that

**TABLE 4** Univariate and multivariate analyses of the association between diastolic blood pressure variability and renal events

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| DBP | | | | | | |
| 24-h | 1.037 (0.952–1.130) | .401 | 1.133 (0.998–1.286) | .053 | | |
| Daytime | 1.045 (0.960−−1.138) | .311 | 1.165 (1.012–1.341) | .034 | | |
| Nighttime | 0.999 (0.927–1.077) | .983 | 1.037 (0.950–1.131) | .418 | | |
| SD | | | | | | |
| 24-h | 1.029 (0.825–1.282) | .800 | 0.880 (0.678–1.142) | .337 | 0.882 (0.651–1.193) | .414 |
| Daytime | 1.015 (0.824–1.250) | .886 | 0.874 (0.685–1.115) | .278 | 0.878 (0.665–1.159) | .360 |
| Nighttime | 1.031 (0.858–1.239) | .746 | 0.991 (0.799–1.230) | .938 | 0.977 (0.775–1.232) | .845 |
| wSD | 1.032 (0.806–1.322) | .801 | 0.861 (0.632–1.172) | .341 | 0.844 (0.581–1.227) | .375 |
| CoV | | | | | | |
| 24-h | 0.993 (0.842–1.170) | .929 | 0.865 (0.698–1.074) | .189 | 0.906 (0.724–1.134) | .387 |
| Daytime | 0.984 (0.839–1.155) | .847 | 0.862 (0.702–1.059) | .158 | 0.897 (0.725–1.111) | .319 |
| Nighttime | 1.014 (0.884–1.163) | .841 | 0.968 (0.830–1.129) | .678 | 0.994 (0.851–1.161) | .941 |
| SV | | | | | | |
| 24-h | 1.078 (0.926–1.255) | .332 | 0.943 (0.770–1.154) | .570 | 0.980 (0.785–1.224) | .859 |
| Daytime | 1.082 (0.952–1.230) | .227 | 0.963 (0.811–1.143) | .666 | 0.998 (0.828–1.204) | .984 |
| Nighttime | 0.976 (0.830–1.149) | .772 | 0.948 (0.797–1.128) | .546 | 0.961 (0.810–1.140) | .650 |
| ARV | | | | | | |
| 24-h | 1.186 (0.887–1.586) | .249 | 0.955 (0.688–1.326) | .785 | 1.011 (0.704–1.454) | .951 |
| Daytime | 1.203 (0.932–1.552) | .155 | 0.974 (0.737–1.288) | .856 | 1.028 (0.757–1.398) | .858 |
| Nighttime | 0.952 (0.754–1.202) | .680 | 0.942 (0.730–1.214) | .643 | 0.946 (0.735–1.217) | .664 |

*Note:* Model 1: Unadjusted. Model 2: Adjusted for age, gender, BMI, DM, ACEI/ARB, β-blocker, CCB, thiazide, and baseline eGFR. Model 3: Adjusted for age, gender, BMI, DM, ACEI/ARB, β-blocker, CCB, thiazide, baseline eGFR, and 24-h DBP.

Abbreviations: ARV, average reading variability; CI, confidence interval; CoV, coefficient of variation; DBP, diastolic blood pressure; HR, hazard ratio; SD, standard deviation; SV, successive variation; wSD, weighted standard deviation.

long-term BPV was independently associated with a higher risk of developing both CKD and ESRD.[17,18] As for short-term BPV, Farrag and colleagues showed that 24-h SBP ARV was associated with microalbuminuria in nondiabetic hypertensive patients with controlled BP and normal eGFR.[19] Mulè and colleagues revealed that 24-h SBP ARV was associated with urinary albumin excretion rate in patients with untreated essential hypertension with normal eGFR.[20] Wang and colleagues reported that wSD was associated with the risk of dialysis initiation and/or transplantation in patients with CKD.[21] However, in the telehealth-based Vascular health Assessment of the hypertensive (VASOTENS) Registry, 24-h SBP ARV was not associated with neither decreased eGFR nor increased urine albumin excretion in hypertensive patients.[22] Due to conflicting data, more evidence is still needed to comprehensively investigate the impact of mean BP and various BPV parameters on renal function decline in hypertensive patients.

To the best of our knowledge, the current study first conducted a prospective evaluation of the relationship between five different short-term BPV parameters derived from ABPM and hypertensive nephropathy in Han Chinese hypertensive patients. The current study showed that 24-h mean BP was more important than short-term BPV in the prevention of hypertensive nephropathy. Our findings were supported by previous studies.[22–26] Madden and colleagues revealed that microalbuminuria was associated with a significantly higher 24-h SBP ARV, SD, and wSD in the univariate analysis. However, there was no association between any of these parameters after adjusting for mean BP.[23] Data from the VASOTENS Registry study also indicated that either a decreased eGFR or increased urine albumin excretion was not associated with a significantly increased 24-h systolic BPV after adjusting for mean BP.[22] Recently, results from ONTARGET and TRANSCEND trials revealed that visit-to-visit systolic BPV was not a predictor of renal outcomes, which, in contrast, was sensitively predicted by mean SBP.[24] In addition, similar results were obtained in CKD patients that short-term BPV did not predict CKD progression [25]; the association between CKD and BPV was primarily explained by higher mean BP among those with CKD.[26]

Instead of subclinical renal injury,[19,20,23] the current study defined renal event as >50% reduction in eGFR. Unlike microalbuminuria, which is caused by the loss of glomerular filter selectivity, the reduction in eGFR occurs subsequent to the thinning of the media and hyalinosis of the afferent arteriole. This leads to the shrinkage of the glomerular tuft and podocyte loss.[27] The validity of surrogate

end points for kidney disease progression was stronger in reduction in eGFR than in changes in albuminuria.[28]

Furthermore, we found that participants with the highest SBP wSD were older and had lower BMI and higher 24-h mean SBP than their counterparts. Such results could be explained by a previous finding showing that ambulatory BPV increased parallel with mean BP.[29] This finding was also supported by another study showing that short-term BPV was strongly associated with 24-h, daytime, and nighttime BP.[25] Accordingly, a reduction in mean BP led to a proportional reduction in BPV. Therefore, tight control of 24-h mean SBP will reduce not only BPV but also hypertensive nephropathy.

When considering antihypertensive drugs and BPV, some studies showed that CCB is more effective in decreasing BPV than other antihypertensive drugs, including ACEI/ARB.[30] However, ACEI/ARB has better renoprotective effect than CCB.[31,32] These prior findings further strengthened the notion that tight control of mean BP per se is more important than that of BPV.

### 4.1 | Limitations

The current study had several limitations that must be considered. First, this study had a small sample size. Although our power calculation obtained acceptable results, further studies with a larger sample size must be conducted to validate our results. Second, we only measured short-term BPV, and long-term BPV, which was represented as visit-to-visit office BP, was not considered. Therefore, we could not compare the findings between short- and long-term BPV. Third, the use of antihypertensive medication could be a confounder for ambulatory BP parameters and renal events. However, we had adjusted all the antihypertensive drugs, including ACEI/ARB, β-blocker, CCB, and thiazide. Since this was only an observational study, not an interventional trial, further studies must be conducted to investigate whether medical interventions attenuate the effect of BPV on renal outcomes. Fourth, we only focused on hypertensive nephropathy, even though other extrarenal HMOD, such as myocardial infarction and stroke, may be correlated with BPV or changes in renal function overtime. Thus, further studies adjusting for other HMOD should be confirmed. Fifth, we did not exclude hypertensive patients with DM due to small sample size. Although the proportion of DM was small (16.7%) and we had adjusted it in multivariate analysis, further studies with a larger sample size of nondiabetic hypertensive patients must be conducted to validate our results. Finally, the definition of adverse renal event used was anthropic, which might vary in each study. The non-standardized definition of adverse renal event limits the use when comparing results between studies.

## 5 | CONCLUSIONS

In conclusion, 24-h mean BP, but not ambulatory BPV, is independently associated with the risk of hypertensive nephropathy in Han Chinese participants with hypertension. A well-controlled 24-h mean BP, rather than ambulatory BPV, should be prioritized in the management of hypertension.

## CONFLICT OF INTEREST

The authors declared no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Hung M-H, Huang C-C, Chung C-M, Chen J-W. 24-h ambulatory blood pressure variability and hypertensive nephropathy in Han Chinese hypertensive patients. *J Clin Hypertens*. 2021;23:281–288. https://doi.org/10.1111/jch.14108