Nocturnal blood pressure rather than night-to-day blood pressure ratio is related to arterial stiffening in untreated young and middle-aged adults with non-dipper hypertension

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Abstract
Little is known about nocturnal blood pressure (BP) or night-to-day BP ratio, which is a more specific determinant of arterial stiffness in subjects with non-dipper hypertension? This study aims to investigate the correlation of nocturnal BP and brachial-ankle pulse wave velocity (ba PWV), an index of arterial stiffness in untreated young and middle-aged adults with non-dipper hypertension.

A cross-sectional analysis of baseline parameters of the NARRAS trial was performed. Twenty-four hour ambulatory BP measurements, ba PWV and routine clinical data collection were performed in all patients. The relationship of 24-h ambulatory BP profiles, biochemical measures as well as demographic parameters and ba PWV were analyzed using Pearson’s correlation and multiple stepwise regression analysis.

A total of 77 patients (mean age 47.0 ± 11.7 years) with non-dipper hypertension were included. Age, height, weight and nocturnal systolic BP were related to ba PWV in Pearson’s correlation analysis. In stepwise regression analysis, age (β = 10.57, 95% confidence interval (CI): 6.099–15.042, p < 0.001) and weight (β = -3.835, 95% CI: -7.658–-0.013, p = 0.049) are related to ba PWV. Nocturnal systolic BP (β = 8.662, 95% CI: 2.511–14.814, p = 0.006) was the independent predictors of ba PWV, even after night-to-day systolic BP ratio or 24-h ambulatory BP profile were taken into account.

Nocturnal systolic BP rather than night-to-day systolic BP ratio appears to be a more specific determinant for arterial stiffness, as assessed by ba PWV in young and middle-aged adults with non-dipper hypertension. 24-h ambulatory BP measurements are essential for cardiovascular risk evaluation.

KEYWORDS
arterial stiffness, circadian pattern, nocturnal blood pressure, non-dipping, pulse wave velocity
1 | INTRODUCTION

Blood pressure (BP) fluctuates day and night under the regulation of circadian clock. Most healthy individuals exhibit a nocturnal BP decline about 10–20% of the diurnal values, which is so called “dippers.” Hypertensive patients with a blunted nighttime BP drop (non-dippers: night-to-day BP ratio > 0.9) had a significantly worse cardiovascular (CV) outcome than those with normal BP circadian pattern (dippers).

An elevated nighttime BP > 120/70 mmHg is defined as nocturnal hypertension according to the European and Chinese hypertension guidelines. People with nocturnal hypertension are also at higher CV risks, as compared with normotension.

Arterial stiffness, an important surrogate marker for atherosclerosis and predictor of CV and renal disease, is mainly determined with aging and high BP. Nocturnal rather than daytime BP was demonstrated a more specific determinant of arterial stiffness in non-elderly subjects with dipper hypertension. But little is known about nocturnal BP or night-to-day BP ratio, an index of BP circadian pattern, which is a more specific determinant of arterial stiffness in those with non-dipper hypertension.

We performed a post hoc analysis of a chronotherapeutic study of the NARRAS trial (National Clinical Trial (NCT) Identifier Number: NCT02940548), aiming to explore the relationship of nocturnal BP, arterial stiffness in young and middle-aged adults with non-dipper hypertension.

2 | METHODS

The design and the rationale of the NARRAS trial have been described previously. In brief, young and middle-aged adults (aged 18–65 years) with non-dipper hypertension were randomly assigned to receive nifedipine gastrointestinal therapeutic system (GITS) and amlodipine besylate, either in the morning or at night. The patients were followed for 8 weeks. Twenty-four hour Ambulatory BP monitoring (ABPM), brachial-ankle pulse wave velocity (ba PWV) and biochemical assay were performed at baseline and end of the 8 week. The nighttime systolic BP reduction, dipping pattern restoration, as well as changes of ba PWV were observed in this trial. We pre-specified the time frame of nighttime as 06:00–22:00 and nighttime as 22:00–06:00 during daytime (06:00–22:00) and every 30 min during nighttime (22:00–06:00). Daytime and nocturnal BP were documented as the mean values from each of the two periods. Nocturnal BP dipping was assessed by measuring the percent (%) difference between mean daytime systolic BP and nocturnal systolic BP.

2.1 | 24 hour ABPM

Twenty-four hour ambulatory BP was measured on the non-dominant arm using a Spacelabs 90217 device (Spacelabs Healthcare Inc, Issaquah, Richmond, Washington, USA) at baseline. BP was assessed every 20 min during daytime (06:00–22:00) and every 30 min during nighttime (22:00–06:00). Daytime and nocturnal BP were documented as the mean values from each of the two periods.

2.2 | Ba PWV

Arterial stiffness was evaluated using ba PWV, which was measured bilaterally using an automated waveform analyzer (Omron Colin VP-1000 plus, Omron Healthcare Co., Ltd. Kyoto, Japan) in the supine position. Waveform data are obtained from volume plethysmographic sensors within the cuffs that were placed on the right brachium and both ankles. The time intervals between the wave detected at the right brachium and those at both ankles were measured. The distances between the brachium and the ankles were automatically calculated.

2.3 | Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) if they were normally distributed or median (interquartile range, IQR) if they were not normally distributed. Categorical variables were summarized as numbers and percentages. The Student’s t-test or Mann-Whitney U test were used where appropriate for the univariate analysis of the continuous variables and the Chi-square test for the categorical variables. The bivariate associations of ba PWV with demographic, biochemical measurements, office and 24-h ambulatory BP were assessed with Pearson’s coefficient of correlation. Multiple step-wise regression was performed for analysis of independent variable. The variables entered into the regression model as covariates were
TABLE 1 Demographic, clinical and biochemical data of the study population

|                      | ba PWV ≥ 1400 cm/s (n = 51) | ba PWV < 1400 cm/s (n = 26) | P value |
|----------------------|------------------------------|-----------------------------|---------|
| Age (years)          | 50.8 (10.1)                  | 39.6 (11.3)                 | 0       |
| Gender (male)        | 28 (54.9%)                   | 14 (53.8%)                  | 0.93    |
| Height (cm)          | 166.4 (7.4)                  | 167.9 (8)                   | 0.409   |
| Weight (kg)          | 71.4 (13.8)                  | 74.1 (13.6)                 | 0.441   |
| Body mass index (kg/m²) | 25 (7.4)                    | 26.2 (3.9)                  | 0.598   |
| Office systolic BP (mmHg) | 147.9 (8.9)            | 146.4 (10.9)                | 0.522   |
| Office diastolic BP (mmHg) | 95.5 (6.9)                  | 97.7 (4.8)                  | 0.067   |
| Heart rate (bpm)     | 77.2 (9.2)                   | 74 (6.6)                    | 0.107   |
| 24 h systolic BP (mmHg) | 138.5 (8.5)                   | 133 (6.7)                   | 0.006   |
| 24 h diastolic BP (mmHg) | 87.5 (8.5)                   | 87.2 (5.3)                  | 0.822   |
| Daytime systolic BP (mmHg) | 140.7 (8.9)                   | 134.9 (7.4)                 | 0.005   |
| Daytime diastolic BP (mmHg) | 88.9 (8.7)                   | 88.8 (5.1)                  | 0.952   |
| Nocturnal systolic BP (mmHg) | 133.8 (9)                    | 128.9 (5.4)                 | 0.024   |
| Nocturnal diastolic BP (mmHg) | 83.2 (8.7)                   | 83.4 (6.3)                  | 0.93    |
| Night-to-day systolic BP ratio | 0.957 (0.035)              | 0.951 (0.047)               | 0.284   |
| Creatinine (umol/L)  | 68.7 (17.1)                  | 66 (18.2)                   | 0.655   |
| Uric acid (mmol/L)   | 359.9 (103.7)                | 360.7 (112.1)               | 0.983   |
| Total cholesterol (mmol/L) | 4.9 (0.9)                    | 4.9 (1)                     | 0.783   |
| High density lipoprotein cholesterol (mmol/L) | 1.3 (0.3)                   | 1.2 (0.3)                   | 0.464   |
| Low density lipoprotein cholesterol (mmol/L) | 2.9 (0.8)                    | 3.1 (0.9)                   | 0.546   |
| Triglyceride (mmol/L) | 1.8 (1.3)                    | 1.8 (1.4)                   | 0.97    |
| Glucose (mmol/L)     | 5.5 (0.9)                    | 5.4 (0.9)                   | 0.34    |

Abbreviations: BP, blood pressure; bpm, beat per minute. Variables are presented as mean (standard deviation).

selected on the basis of bivariate associations, or established clinical or pathophysiological relationships with ba PWV. Data were analyzed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY). All tests of significance were two-tailed. A P value ≤ 0.05 was considered statistically significant.

3 | RESULTS

A total of 77 untreated non-dipper hypertensive patients (mean age 47.0 ± 11.7 years) were included in this analysis. Patients were divided into two groups according to the ba PWV ≥ 1400 cm/s or < 1400 cm/s. Baseline demographic parameters including gender, height, weight, body mass index (BMI) were not different between the two groups, except that those with abnormal arterial stiffness were older (50.8 ± 10.1 vs. 39.6 ± 11.3 years). Daytime, nocturnal and 24-h average systolic BP in ABPM were higher in those with abnormal arterial stiffness, while daytime, nocturnal and 24-h average diastolic BP, night-to-day systolic BP ratio, office systolic/diastolic BP, heart rate, as well as glucose and lipids profile were not different between the two groups (Table 1).

Pearson’s correlation analysis demonstrated that age (r = 0.535, p < 0.001), body height (r = −0.248, p = 0.03) and weight (r = −0.282, p = 0.013) were related to ba PWV. When considering for non-dipping pattern and 24-h ambulatory BP profile, the correlation analysis revealed neither daytime systolic BP nor night-to-day systolic BP ratio, but nocturnal systolic BP, was related to ba PWV (r = 0.297, P = 0.009) (Figure 1). In addition, nocturnal systolic BP was found the only independent variable related to ba PWV, even after age-adjusted correlation analysis was performed (r = 0.28, P = 0.014) (Table 2).

To avoid the underestimation of the role of night-to-day systolic BP ratio on ba PWV, a further 2 × 2 factorial analysis was performed. The patients were divided into 4 subgroups, according to the median nocturnal systolic BP greater than or equal to 132.1 mmHg, or less and night-to-day systolic BP ratio great than or equal to 0.95, or less. No difference was found in ba PWV within the 4 subgroups (P = 0.161) and the interaction between nocturnal BP and night-to-day BP ratio was not significant (F = 2.306, P = 0.133) (Supplementary Materials (I), Tables 1 and 2).

In a multiple stepwise regression analysis, we included all the candidate explanatory variables (P value < 0.2 in Pearson’s correlation) to evaluate the independent determinants of ba PWV. Nocturnal systolic
FIGURE 1  Scatterplots on baPWV vs nocturnal systolic BP, daytime systolic BP, or night/day systolic BP ratio

TABLE 2  Correlation analysis of the ba PWV

|                       | Unadjusted | P value | Age-adjusted | P value |
|-----------------------|------------|---------|--------------|---------|
| Age (years)           | 0.535      | 0       | −0.117       | 0.315   |
| Gender (male)         | −0.195     | 0.09    | −0.156       | 0.178   |
| Height (cm)           | −0.248     | 0.03    | −0.179       | 0.122   |
| Weight (kg)           | −0.282     | 0.013   | −0.138       | 0.234   |
| Body mass index (kg/m²) | −0.215   | 0.061   | −0.138       | 0.234   |
| Office systolic BP (mmHg) | 0.107  | 0.352   | 0.173        | 0.136   |
| Office diastolic BP (mmHg) | −0.111 | 0.335   | 0.082        | 0.481   |
| Heart rate (bpm)      | 0.014      | 0.907   | 0.098        | 0.398   |
| 24 h systolic BP (mmHg) | 0.2      | 0.081   | 0.198        | 0.086   |
| 24 h diastolic BP (mmHg) | 0.017    | 0.886   | 0.137        | 0.237   |
| Daytime systolic BP (mmHg) | 0.147  | 0.201   | 0.144        | 0.214   |
| Daytime diastolic BP (mmHg) | 0.007  | 0.952   | 0.109        | 0.35    |
| Nocturnal systolic BP (mmHg) | 0.297  | 0.009   | 0.28         | 0.014   |
| Nocturnal diastolic BP (mmHg) | 0.05   | 0.668   | 0.153        | 0.188   |
| Night-to-day systolic BP ratio | 0.198 | 0.085   | 0.173        | 0.136   |
| Creatinine (umol/L)   | −0.141     | 0.222   | −0.104       | 0.372   |
| Uric acid (mmol/L)    | −0.072     | 0.536   | 0.026        | 0.822   |
| TC (mmol/L)           | 0.082      | 0.48    | 0.022        | 0.851   |
| HDL-C (mmol/L)        | 0.085      | 0.463   | −0.047       | 0.687   |
| LDL-C (mmol/L)        | 0.015      | 0.894   | 0.055        | 0.639   |
| Triglyceride (mmol/L) | 0.082      | 0.478   | 0.059        | 0.611   |
| Glucose (mmol/L)      | 0.034      | 0.768   | −0.017       | 0.885   |

Abbreviations: BP, blood pressure; bpm, beat per minute; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol.

BP, other than night-to-day BP ratio was significantly and independently associated with arterial stiffening ($\beta = 8.662$, 95% confidence interval (CI): 2.511–14.814, $P = 0.006$). The standardized $\beta$ in the regression model demonstrated that for every SD of increase in nocturnal BP, ba PWV would increase by 0.264 SD. The other independent determinant was age ($\beta = 10.57$, 95% CI: 6.099–15.042, $P < 0.001$) and weight was marginally related to ba PWV ($\beta = −3.835$, 95% CI: −7.658–−0.013, $P = 0.049$) (Table 3). In addition, to prevent the collinearity of body height, weight and body mass index (BMI), we preferred BMI to enter the regression model. The multiple stepwise regression analysis demonstrated that the predictions of age and nocturnal systolic BP on ba PWV were not changed (Supplementary materials (I), Table 3).

4  | DISCUSSIONS

Advanced age and elevated BP are two major independent risk factors of vascular aging, which accelerate aortic stiffening via elastin...
TABLE 3  Independent determinants of ba PWV in stepwise regression model

| Explanatory variables entering the multivariable modela | Standardized β | Unstandardized β | 95%CI for β | P value |
|--------------------------------------------------------|----------------|------------------|-------------|---------|
| (adjusted R²= 0.351, P < 0.001)                         |                |                  |             |         |
| Age                                                    | 0.455          | 10.57            | 6.099–15.042| <0.001  |
| Weight                                                 | −0.193         | −3.835           | −7.658–0.013| 0.049   |
| Nocturnal systolic BP                                  | 0.264          | 8.662            | 2.511–14.814| 0.006   |

Abbreviation: BP, blood pressure.
a: adjusted for gender (male = 1, female = 0), height, body mass index, 24-h systolic BP, night-to-day systolic BP ratio.

degradation and increase in wall stress. In young and middle-aged population with relatively preserved arterial elasticity, it is not clear which is the most potent factor related to the vascular stiffening. In the cross-sectional analysis of the baseline parameters of NARRAS trial, nocturnal systolic BP and age were found to be the most specific determinants of ba PWV in this study population, even after adjusted with other variables in stepwise regression analysis.

PWV is generally accepted as a simple, non-invasive and reproducible method for arterial stiffness measurement. As hypertension-mediated organ damage (HMOD) on artery, PWV has been recommended evaluation for CV risk stratification in hypertension guidelines. Ba PWV, an index combining elastic and muscular peripheral arterial stiffness, has been developed as an automatic cuff-based method with increased easiness and acceptability. It has been shown that ba PWV correlates well with aortic PWV and that most of the changes in ba PWV following treatment is due to changes in aortic PWV. A cutoff value of 1400 cm/s in ba PWV was found to be adequate to detect atherosclerotic vascular damage and CV risk in middle-aged Asian population. Our study found that the non-dipper hypertensive patients with abnormal ba PWV (≥1400 cm/s) demonstrated a higher daytime, nighttime or 24-h average systolic BP in ABPM relative to those with normal arterial elasticity, while the office BPs were not different in comparison. This result indicates that 24-h ambulatory systolic BP burden other than occasional BP measurement might have an impact on arterial stiffening.

Night-to-day systolic BP ratio ≥ 0.9 is usually defined as non-dipping pattern, which is more common in patients with diabetes, chronic kidney diseases (CKD) and autonomic dysfunction and reflects an inadequacy of the mechanisms regulating BP. It can be the consequence of baroreflex or autonomic dysfunction, relative nocturnal volume overload, and abnormal sodium handling of the underlying diseases. Investigation demonstrated that increased PWV was associated with non-dipping pattern in untreated hypertensive patients. Raised nocturnal BP was also revealed as the independent predictor of non-dipping pattern, but the relationship of nocturnal BP and PWV was not analyzed in the study.

Although high nocturnal BP is sometimes accompanied by a non-dipping pattern, both are not always present together and the significance of nocturnal BP and the non-dipping pattern differs. Nocturnal BP represents the minimal BP that the subject needs for adequate organ perfusion. High nocturnal BP overloads the cardiovascular system with a negative impact on the heart and the kidney, as well as the vasculatures. Nocturnal hypertension has been reported prevalent at less than 5% in the general population, more frequent (more than 10% for isolated nocturnal hypertension) in young Asians and common in clinical settings, reaching up to 50% individuals with hypertension, diabetes or CKD. Previous studies demonstrated that nocturnal hypertension was associated with CV risks. It predicted CV events (stroke, myocardial infarction and CV death) and organ damage better than diurnal BP. Nocturnal hypertension was found evident in more than half of the study population referred to a tertiary hospital-based hypertension clinic, and associated with more pronounced organ damage as assessed by measures of PWV and pulse wave analysis (PWA). Nevertheless, investigations showed that nocturnal hypertension was associated albuminuria independently of circadian BP pattern. These findings are in line with our study, as the results demonstrated nocturnal systolic BP was independently associated with arterial stiffness, even after adjusted with demographic variables, 24-h ambulatory BP profile as well as night-to-day BP ratio in multiple stepwise regression analysis. In addition, elevated nocturnal BP in young was found associated with cognitive dysfunction in midlife in CARDIA study. These results underscore the compelling needs of 24-h ABPM or home BP monitoring with arterial PWV measurement property to identify the elevated nocturnal BP for CV risk stratification in clinical settings.

5 | LIMITATIONS

First, the cross-sectional nature of the analysis could not provide the causal effects of nocturnal BP on arterial stiffness. Despite that numerous studies have revealed that elevated BP had an impact on arterial stiffness in hypertensive, diabetic or CKD patients, several studies have shown that higher levels of aortic stiffness in normotensive individuals are associated with accelerated BP elevation and increased risk for new onset hypertension during follow-up. Further studies are warranted to elucidate the exact relationship between nocturnal BP and arterial stiffening. Second, despite that different candidate explanatory variables were included in multiple regression analysis, some confounders not included, such as smoking, drinking, exercise habit and sleeping status, might have potentials on the determination of arterial stiffness. Third, all the subjects included in the cross-sectional analysis were non-dippers, which limited the comparison of effects of
non-dipping or dipping pattern, as well as nocturnal BP in this two situations on ba PWV.

6 | CONCLUSIONS AND CLINICAL IMPLICATIONS

Nocturnal systolic BP rather than night-to-day systolic BP ratio appears to be a more specific determinant for arterial stiffness, as assessed by ba PWV in young and middle-aged adults with non-dipper hypertension.

The findings from the NARRAS trial highlighted the necessity of 24-h ambulatory BP measurement in routine clinical settings, as an elevated nocturnal BP is related to arterial stiffening and indicates higher CV risk. This is particularly important for young population in which the arterial function is relatively normal at the early stage, as the inadequate nocturnal BP control will potentially injure the vasculature and increase CV risk in later years.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

J Liu conceived and conceptualized the study, and wrote the first draft of the article. J Liu and X Su had full access to all of the data of the study and take responsibility for the integrity and the accuracy of the data analysis. J Liu, Y Nie, Z Zeng, and H Chen contributed to the data collection and take responsibility for the integrity and the accuracy of the data of the article. J Liu and X Su had full access to all of the data of the study. J Liu conceived and conceptualized the study, and wrote the first draft of the article.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all participants before inclusion.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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