Heart, Lung and Circulation (2019) **28,** 1197–1205
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.07.003

ORIGINAL ARTICLE

Morning Blood Pressure Surge Relates to Autonomic Neural Activity in Young Non-Dipping Adults: The African-PREDICT Study

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Received 23 April 2018; received in revised form 24 May 2018; accepted 4 July 2018; online published-ahead-of-print 30 July 2018

Background It is well established that an exaggerated morning blood pressure surge (MBPS) is associated with an increased risk for cardiovascular disease development in hypertensive individuals. However, in non-dipping individuals, a lower surge was reportedly associated with increased cardiovascular risk. Sympathetic nervous system activity is involved in 24-hour blood pressure fluctuations, including night-time dipping and the MBPS. To better understand this interaction, we investigated associations of MBPS with heart-rate variability and baroreceptor sensitivity in young healthy dippers and non-dippers.

Methods We included black and white men and women (n = 827), aged 20-30 years and determined the MBPS using two formulas: the sleep-trough and dynamic morning surge. For autonomic function we determined baroreceptor sensitivity and heart-rate variability.

Results The majority of non-dippers in this population were black (70.4%), presenting lower sleep-trough and dynamic morning surge (all $p < 0.001$). Heart-rate variability was comparable between dippers and non-dippers, whereas baroreceptor sensitivity was higher in non-dippers ($p = 0.021$). Despite a suppressed MBPS profile in non-dippers, we found both sleep-trough ($\beta = -0.25$; $p = 0.039$) and dynamic morning surge ($\beta = -0.14$; $p = 0.047$) to be inversely and independently associated with 24-hour heart-rate variability (total power). These results were absent in dippers.

Conclusions In conclusion, we found a higher night-time blood pressure coupled with lower MBPS in young healthy non-dippers. Furthermore, this lower MBPS was independently and negatively associated with autonomic neural activity, suggesting increased autonomic function involvement in MBPS suppression of non-dippers. The predictive value of suppressed nocturnal dipping pattern should be investigated while taking autonomic neural activity into account.

Keywords Autonomic neural activity • Dippers • Morning blood pressure surge • Non-dippers

Introduction

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The value of not only obtaining a single blood pressure measurement, but a 24-hour blood pressure recording became clear over the past decade [1–4]. This is due to blood pressure fluctuations throughout the day-night period, with higher blood pressure during the day and lower at night [5,6], reflecting the physiological dipping pattern of nocturnal blood pressure. Morning blood pressure surge (MBPS) is also a normal physiological response to increased sympathetic nervous system activity characterised by increased blood pressure in the morning hours at awakening [7–10]. In hypertensive patients, MBPS is exaggerated and has predictive value for cardiovascular events and mortality [2,5,7–9,11–13].

The sympathetic nervous system plays an important role in blood pressure regulation, including the MBPS. Its regulatory role includes increasing both blood propulsion by the heart and blood vessel resistance to blood flow, leading to acute increases in arterial pressure [14]. The magnitude of the MBPS is further influenced by various factors including alcohol use, smoking and physical activity [13,14]. Importantly, MBPS is mainly influenced by blunted nocturnal blood pressure dipping which is common in black populations, increasing the risk for cardiovascular disease [15–21]. In non-dippers, over-activity of the sympathetic nervous system is associated with insufficient nocturnal blood pressure dipping [15]. In fact, increased sympathetic nervous system activity may lead to blunted nocturnal dipping as reported in other studies [16,17,22], with impaired nocturnal blood pressure dipping identified as a risk factor for cardiovascular events [18,23].

To better understand the involvement of autonomic function and the MBPS with autonomic function, we investigated associations of the MBPS with heart-rate variability and baroreceptor sensitivity in a large group of young healthy adults, including dippers and non-dippers.

Materials and Methods

Study Design, Population Demographics and Basic Procedures

This study is embedded in the African Prospective study on the Early Detection and Identification of Cardiovascular Disease and Hypertension (African-PREDICT). The aim of the African-PREDICT study is to understand the early pathophysiology accompanying cardiovascular disease (CVD) development and to identify novel early markers or predictors for the development of CVD by following young, healthy adults over a period of 10 years. The African-PREDICT study is conducted at the Hypertension Research and Training Clinic on the Potchefstroom campus of the North-West University and is registered on ClinicalTrials.gov (NCT03292094). This study complies with all applicable requirements of the Declaration of Helsinki and also obtained approval from the Health Research Ethics Committee of the North-West University, South Africa. Black and white men and women were included in the study after an initial screening procedure. Participants with a mean clinic blood pressure of ≥140 mmHg and/or ≥90 mmHg, who were infected with human immunodeficiency virus, previously diagnosed with a chronic disease, pregnant, or breastfeeding were excluded. All procedures were explained to the participants before measurements commenced. This study included cross-sectional baseline data from the first 827 participants of the African-PREDICT study, with complete ambulatory blood pressure recordings.

Cardiovascular Measurements

Participants were fitted with a 24-hour ambulatory blood pressure and ECG apparatus (CardioXplore®, CE0120, Meditech, Budapest, Hungary) to measure ambulatory blood pressure, and determine MBPS, dipping status and heart-rate variability (HRV). The apparatus was programmed to take blood pressure recordings every 30 minutes during the day (6am to 10pm) and every hour during the night (10pm to 6am). Only participants with >70% of valid blood pressure measurements, >20 day measurements and >7 night measurements were included in the final dataset.

Morning blood pressure surge was quantified from ambulatory blood pressure measurements as previously described [24,25]. Sleep-trough and dynamic morning surge were determined from valid 24-hour systolic blood pressure measurements. Sleep-trough surge was determined as the morning systolic blood pressure (2-hour average of four 30-minute blood pressure readings just after waking) minus the lowest nocturnal systolic blood pressure (1-hour average of the three blood pressure readings based on the lowest night-time reading) [8]. Dynamic surge was determined as the moving peak morning systolic blood pressure (highest 1 hour moving average of consecutive systolic blood pressures between 6am and 10am) minus moving lowest night-time systolic blood pressure (lowest 1 hour moving average of consecutive systolic blood pressures between 1am and 6am) [26,27]. The difference in the sample size for sleep-trough (n = 323) and dynamic morning surge (n = 827) is a consequence of missing data regarding waking and sleep times recorded by participants, which are essential for quantifying sleep-trough surge.

Individuals whose night-time blood pressure declined less than 10% were classified as non-dippers, [16,18,28] and those whose night-time blood pressure declined by ≥10% were considered as dippers [16,18,28].

The 24-hour HRV was measured automatically with the Cardio Visions 1.15.2 Personal Edition (Meditech, Budapest, Hungary) software, and analysis was taken from frequency and geometric domains. The frequency domain analysis, determined by the fast Fourier transformation involves low frequency (a major index of sympathetic cardiac tone with a parasympathetic component) and high frequency (a major indicator of parasympathetic activity) [29]. Low frequency-to-high frequency ratio (reflector of sympatho-vagal autonomic balance) and HRV total power (global determinant of overall autonomic modulation) were also determined [29].

Continuous arterial blood pressure was recorded with the Finometer device (Finapres Medical Systems, Amsterdam, the Netherlands) with participants lying in the Fowler's position with their arm at heart level. The cardiovascular data collected with the Finometer was processed using the Beatscope v1.1 software (Finapres Medical Systems) to provide baroreceptor sensitivity. Baroreceptor sensitivity was calculated using the validated cross-correlation baroreflex sensitivity (xBRS) method [30]. This method was proven to yield lower within-patient variance than other methods and was recommended to be used in clinical and experimental settings [30]. This method quantifies the correlation between beat-to-beat systolic blood pressure and R-R interval, resampled at 1 Hz, over 10-second sliding windows. This is a timespan sufficient to accommodate a 10-second variability in rhythm, or several cycles at ventilatory frequencies [30].

Biochemical Sampling and Clinical Procedures

Participants were required to fast overnight for a period of 8 to 10 hours. Blood samples were obtained with a sterile winged infusion set and syringes from the antebrachial vein. Samples were prepared according to standard procedures and stored at −80 °C for future biochemical analyses. The γ-glutamyl transpeptidase (GGT), high sensitivity C-reactive protein (CRP), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were determined in serum and fasting glucose in fluoride plasma (Cobas Integra 400 plus Roche, Basel, Switzerland). Cortisol was quantified using the Roche e411 apparatus (Basel, Switzerland). Aldosterone levels were determined with the Radio Immuno Assay Aldosterone Kit (Beckman Coulter, Immunotech, Radiova, Czech Republic) and cotinine was quantified using the chemiluminescence method on the Immulite (Siemens, Erlangen, Germany).

Body Composition

Anthropometric measurements included body height (SECA stadiometer, SECA), weight (SECA electronic scales, SECA, Birmingham, UK) and waist circumference (validated non-flexible tape measure (Holtain, Crymych, UK)), were measured in triplicate. Body mass index (BMI) was calculated. Body fat percentage and lean mass were obtained through bio-electrical impedance assessment (Biostat 1500, Biostat Ltd, Isle of Man, UK).

Questionnaires

Participants completed a standard general health and demographic questionnaire to obtain basic details regarding their medical history, lifestyle, socio-economic status score (SES) and traditional risk factors such as sex, age, smoking and alcohol consumption. The SES of participants was derived from three categories included in the questionnaire, including skills level, education, and household income. Points were awarded to each of these categories, and the total number of points determined whether a participant was classified into the low, middle, or high SES groups [31]. The Berlin questionnaire was also used to assess sleep apnoea risk [32].

Statistical Analyses

We used IBM SPSS, Version 25 (IBM Corporation, Armonk, NY, USA) for statistical analyses. All variables were tested for normality by visual inspection (QQ-plots) and skewness and kurtosis coefficients. In the case of non-Gaussian distribution, a logarithmic transformation was performed for each skewed variable (24-hour HRV low frequency-to-high frequency ratio, glucose, total cholesterol, LDL cholesterol, triglycerides, GGT, cotinine, CRP, aldosterone and cortisol). Interaction terms were determined with multiple regression analysis to test the main effects of dipping status on the association between MBPS and markers of autonomic function (HRV and baroreceptor sensitivity). We performed independent t-tests and Chi-square tests to compare characteristics of dippers and non-dippers. Partial correlations (with adjustments applied for age, sex and ethnicity) were used to assess the direction of association on markers of interest with MBPS. Multiple regression analyses were performed to confirm associations independent of potential confounders. Several variables were considered for entry into the regression models by using bivariate regression analyses. Finally, the following covariates were included in regression models: age, sex, ethnicity, SES, sleep apnoea risk, 24-hour systolic blood pressure, CRP, LDL cholesterol and cortisol.

Results

Interaction terms (Table 1) indicated an interaction of dipping status with the relationship between dynamic morning surge and markers of autonomic function, namely low frequency and high frequency HRV as well as low frequency-to-high frequency ratio. The general characteristics of the study population are provided in Table 2, stratified by dippers and non-dippers. Body composition was comparable between dippers and non-dippers. The SES as well as the sleep-trough and dynamic morning surge (Figure 1) of non-dippers were lower compared to dippers (all $p < 0.001$). Furthermore, 70.4% of non-dippers were black, with no sex differences between dippers and non-dippers. Markers of autonomic nervous system activity including 24-hour HRV (total power, low frequency, high frequency and low frequency-to-high frequency), aldosterone and cortisol were comparable between the groups, except for baroreceptor sensitivity ($p = 0.021$) which was higher in non-dippers. As expected, night-time ambulatory blood pressure (Figure 1) (all $p < 0.001$) as well as night-time heart-rate ($p = 0.028$) were higher in non-dippers, whereas daytime systolic and diastolic blood pressure (both $p < 0.001$) were lower in non-dippers. Non-dippers had lower total cholesterol ($p = 0.017$) and cotinine ($p = 0.003$) levels, whereas other biochemical

Table 1 Interaction terms of dipping status on the relationship between morning blood pressure surge and markers of autonomic function.

Independent variables	Dipping status, *P*
Sleep-trough surge	
24-h HRV total power, ms^2	0.92
24-h HRV LF, n.u.	0.35
24-h HRV HF, n.u.	0.46
24-h HRV LF/HF ratio	0.72
BRS, ms/mmHg	0.61
Dynamic morning surge	
24-h HRV total power, ms^2	0.19
24-h HRV LF, n.u.	<0.001
24-h HRV HF, n.u.	<0.001
24-h HRV LF/HF ratio	<0.01
BRS, ms/mmHg	0.09

Abbreviations: 24-h, 24-hour; BRS, baroreceptor sensitivity; HF, high frequency; HRV, heart-rate variability; LF, low frequency; LF/HF, low frequency-to-high frequency; n.u., normalised unit.

variables (glucose, LDL cholesterol, HDL cholesterol, triglycerides and GGT) were comparable between dippers and non-dippers.

Partial correlations (Table 3) between MBPS measures and markers of autonomic nervous system activity were performed with adjustments applied for age, sex and ethnicity. In non-dippers only, 24-hour HRV total power correlated inversely with both sleep-trough ($r = -0.24$; $p = 0.044$) and dynamic morning surge ($r = -0.28$; $p = 0.018$).

Multiple regression analyses (Table 4) were performed to determine independent associations of sleep-trough and dynamic surge with HRV total power while taking appropriate covariates into account, namely age, sex, ethnicity, SES, sleep apnoea risk, 24-hour systolic blood pressure, CRP, LDL cholesterol and cortisol. These analyses confirmed the inverse relationship of sleep-trough ($\beta = -0.25$; $p = 0.039$) and dynamic morning surge ($\beta = -0.14$; $p = 0.047$) with HRV total power in non-dippers only. Additionally, dynamic morning surge associated positively with SES ($\beta = 0.19$; $p = 0.016$) in non-dippers; 24-hour systolic blood pressure in non-dippers ($\beta = 0.21$; $p = 0.010$) and dippers ($\beta = 0.17$; $p = 0.010$) and LDL cholesterol in dippers ($\beta = 0.14$; $p = 0.017$).

Discussion

With previous studies indicating that sympathetic nervous system activity is associated with exaggerated MBPS [7,11,33,34], our study is the first to demonstrate an association of lower MBPS with autonomic function in young healthy adults with blunted night-time blood pressure dipping. We found inverse independent associations between HRV total power with two distinct estimates of MBPS in a large young adult population consisting of 41% non-dippers.

In our study population, 16 participants had an exaggerated sleep-trough surge whereas 129 had an exaggerated dynamic morning surge, defined by a surge greater than 37 mmHg [8]. Additionally, notwithstanding which measure of MBPS we used, non-dippers in our study had a lower surge compared to dippers, and is in accordance with previous findings [35]. When considering that both sleep-trough and dynamic morning surge are determined by the difference in morning blood pressure and night-time blood pressure, the lower MBPS observed in non-dippers is not surprising. A surge quantified by a difference in high nocturnal blood pressure (evident in non-dippers) from an increased morning blood pressure (associated with the process of waking), may result in low MBPS. Despite non-dippers having a lower MBPS, their higher night-time systolic blood pressure (Figure 1) profiles pose an increased risk for cardiovascular disease [36]. Previous studies proposed that a higher heart-rate is associated with increased sympathetic nervous activity [37,38]. Non-dippers in our study had a higher night-time systolic blood pressure and heart-rate. These observations in our study population may reflect that non-dippers have increased nocturnal sympathetic activity which is also known to reflect increased risk for cardiovascular disease [39].

It is well established that an exaggerated MBPS has a predictive value for cardiovascular events and mortality in hypertensive and general populations [2,5,7–9,11–13,35]. However, some longitudinal studies suggested that a lower MBPS (observed in non-dippers) also has a predictive value for a higher risk of morbidity and mortality [35,40]. Furthermore, it is known that non-dippers have increased cardiovascular risk due to their high night-time blood pressure profile [36]. Individuals with clinic blood pressure in the hypertensive range were excluded from our study, and importantly, our study population reflects no cardiovascular disease. Importantly, our findings in young healthy non-dippers reflect a higher night-time blood pressure and a significantly lower MBPS than dippers, highlighting the significance of dipping status when interpreting results on MBPS. In young healthy non-dippers, the combination of blunted dipping of nocturnal blood pressure and supressed MBPS may act as a potential risk factor for future cardiovascular disease and events.

In young non-dippers, we found that increased autonomic activity (HRV total power) was associated with a lower morning surge. This is contrary to what one would expect but is likely due to the high night-time blood pressures in non-dippers. Since HRV total power reflects a global determinant of overall autonomic modulation [29], it is unknown whether the driving forces of these associations are increased sympathetic or decreased parasympathetic nervous system activity. In addition, we did not find any significant associations of MBPS with other HRV variables which give an indication of either sympathetic or parasympathetic activity such as low frequency HRV, high frequency and low frequency-to-high frequency ratio [29]. Based on previous

Table 2 Characteristics of the total study population (N = 827).

	Dippers n = 492	Non-dippers n = 335	P
Age, years	24.9 ± 3.13	24.5 ± 3.04	0.039
Ethnicity (black), n (%)	256 (52.0)	236 (70.4)	0.001
Sex (men), n (%)	223 (45.3)	171 (51.0)	0.77
Socio-economic status score	21.3 ± 6.33	19.6 ± 6.28	<0.001
Body composition			
Body mass index, kg/m^2	25.3 ± 5.54	25.2 ± 6.15	0.86
Waist circumference, cm	80.4 ± 12.6	79.6 ± 13.0	0.34
Waist-to-hip ratio	0.78 ± 0.08	0.77 ± 0.08	0.08
Body fat percentage, %	26.1 ± 10.1	27.3 ± 26.3	0.35
Lean mass, kg	52.2 ± 12.0	51.8 ± 11.8	0.62
Morning blood pressure surge			
Sleep-trough surge, mmHg	20.3 ± 9.13	12.3 ± 8.31	<0.001
Dynamic morning surge, mmHg	28.4 ± 10.1	18.1 ± 9.74	<0.001
Cardiovascular profile			
24-h HRV total power, ms^2	5798 ± 3431	5756 ± 3585	0.86
24-h HRV low frequency, n.u.	62.1 ± 12.4	60.8 ± 13.4	0.14
24-h HRV high frequency, n.u.	35.5 ± 11.4	36.3 ± 12.8	0.30
24-h HRV LF/HF ratio	2.09 (1.99; 2.19)	2.10 (1.92; 2.28)	0.26
Baroreceptor sensitivity, ms/mmHg	17.9 ± 9.60	19.9 ± 11.5	0.021
24-hour SBP, mmHg	116 ± 9.32	117 ± 9.41	0.13
24-hour DBP, mmHg	68.7 ± 5.62	68.6 ± 5.89	0.78
24-hour PP, mmHg	47.2 ± 6.95	48.3 ± 7.24	0.028
24-hour heart rate, bpm	74.7 ± 9.89	74.8 ± 10.9	0.94
Daytime SBP, mmHg	122 ± 9.73	119 ± 9.52	<0.001
Daytime DBP, mmHg	74.3 ± 6.07	71.7 ± 6.44	<0.001
Daytime PP, mmHg	47.6 ± 7.25	47.5 ± 7.45	0.89
Daytime heart rate, bpm	79.5 ± 10.5	78.8 ± 11.4	0.30
Night-time SBP, mmHg	105 ± 9.07	113 ± 10.2	<0.001
Night-time DBP, mmHg	60.0 ± 5.90	62.3 ± 7.18	<0.001
Night-time PP, mmHg	46.4 ± 7.12	50.3 ± 8.51	<0.001
Night-time heart-rate, bpm	65.9 ± 10.6	67.5 ± 11.7	0.028
Percentage dipping	14.3 ± 3.24	5.56 ± 4.30	<0.001
Sleep apnoea risk, n (%)	45 (9.15)	30 (8.96)	0.94
Biochemical analyses			
Glucose, mmol/L	4.70 (4.62; 4.78)	4.58 (4.48; 4.68)	0.16
Total cholesterol, mmol/L	4.31 (4.21; 4.41)	4.13 (4.03; 4.23)	0.017
Low density lipoprotein cholesterol, mmol/L	2.84 (2.74; 2.94)	2.71 (2.61; 1.39)	0.07
High density lipoprotein cholesterol, mmol/L	1.32 ± 0.39	1.29 ± 0.37	0.27
Triglycerides, mmol/L	0.97 (0.91; 1.03)	0.90 (0.84; 0.96)	0.44
γ-glutamyl transpeptidase, U/L	25.7 (23.8; 27.6)	27.0 (24.8; 29.2)	0.11
Cotinine, ng/ml	58.6 (48.5; 68.7)	43.2 (32.5; 53.9)	0.003
C-reactive protein, mg/L	2.72 (2.29; 3.15)	3.25 (2.23; 4.27)	0.80
Aldosterone, pg/ml	105 (93.1; 117)	105 (87.4; 123)	0.83
Cortisol, nmol/L	455 (433; 477)	458 (430; 486)	0.92
Health behaviour			
Self-reported smoking, n/total (%)	131/528 (24.8)	79/391 (20.2)	0.12
Self-reported alcohol consumption, n/total (%)	300/525 (57.1)	226/388 (58.3)	0.61

Abbreviations: DBP, diastolic blood pressure; HRV, heart rate variability; LF/HF, low frequency-to-high frequency; n.u., normalised unit; PP, pulse pressure; ROS, reactive oxygen species; SBP, systolic blood pressure.

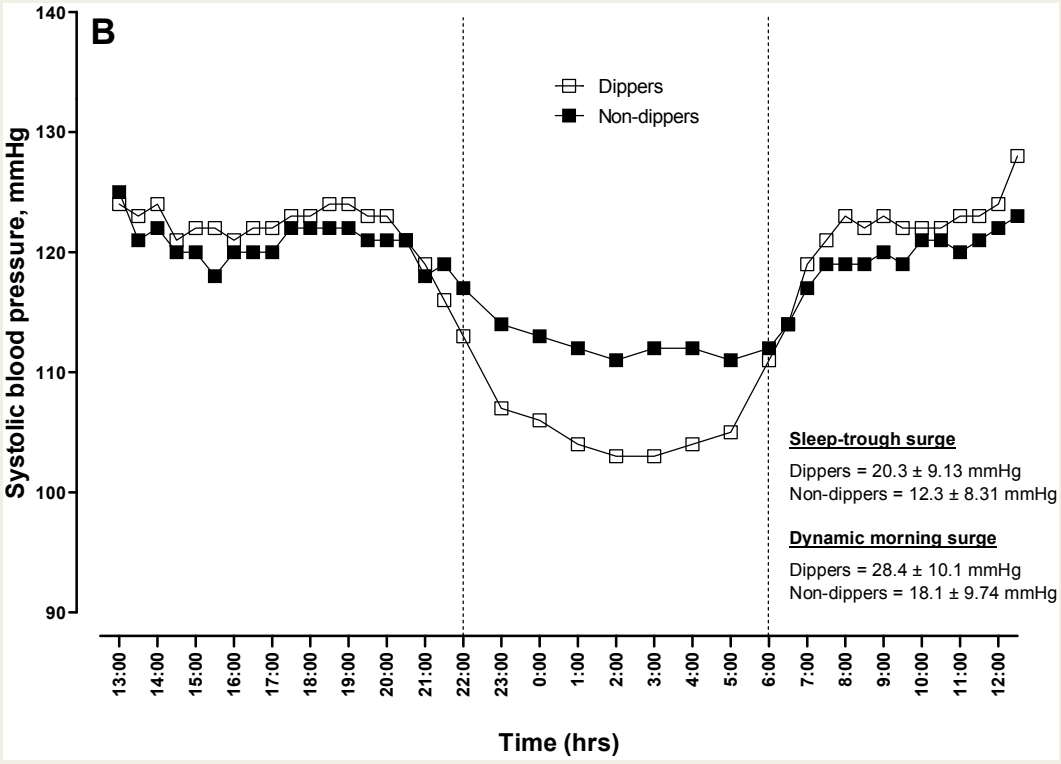

Figure 1 24-hour systolic blood pressure profile of dippers and non-dippers.

Table 3 **Partial correlations of morning blood pressure surge with measures of sympathetic nervous system activity.**

	Sleep-trough surge	
	Dippers n = 112	**Non-dippers n = 211**
24-h HRV total power, ms^2	r = 0.11; p = 0.22	r = −0.24; p = 0.044
24-h HRV low frequency, n.u.	r = −0.09; p = 0.93	r = 0.04; p = 0.77
24-h HRV high frequency, n.u.	r = 0.04; p = 0.62	r = −0.06; p = 0.61
24-h HRV LF/HF ratio	r = −1.00; p = 0.26	r = −0.03; p = 0.79
Baroreceptor sensitivity, ms/mmHg	r = −0.01; p = 0.95	r = −0.05; p = 0.70
	Dynamic morning surge	
	Dippers n = 335	**Non-dippers n = 492**
24-h HRV total power, ms^2	r = −0.01; p = 0.87	r = −0.28; p = 0.018
24-h HRV low frequency, n.u.	r = 0.01; p = 0.88	r = 1.00; p = 0.43
24-h HRV high frequency, n.u.	r = 0.03; p = 0.71	r = −0.11; p = 0.38
24-h HRV LF/HF ratio	r = −0.002; p = 0.99	r = 0.09; p = 0.47
Baroreceptor sensitivity, ms/mmHg	r = −0.03; p = 0.74	r = −0.12; p = 0.34

Adjustments applied for age, sex and ethnicity.

Abbreviations;: HRV, heart rate variability; LF/HF, low frequency-to-high frequency; n.u., normalised unit.

findings and the increased night-time heart-rate of the young non-dippers, we expect sympathetic nervous system over-activity to be the driving force behind this association as it is known to be linked to non-dipping [41,42].

Differences in MBPS, night-time blood pressure and heart-rate between the dippers and non-dippers in our study are supported by previous reports suggesting heightened nocturnal alpha-adrenergic receptor

Table 4 Multiple regression analysis of heart rate variability in dippers and non-dippers.

	Sleep-trough surge	
	Dippers n = 211	**Non-dippers n = 112**
R^2	**0.08**	**0.13**
	Std β (±95% CI)	**Std β (±95% CI)**
24-h HRV total power, ms^2	0.07 (−4.80; 7.27)	−0.25 (−14.7; −0.05)*
Age, years	0.16 (−0.41; 0.73)	0.14 (−0.62; 0.90)
Sex	0.10 (−3.94; 4.41)	− 0.05 (−4.52; 4.42)
Ethnicity	0.03 (−3.67; 3.73)	0.04 (−4.19; 4.27)
Socio-economic score	−0.001 (−0.32; 0.31)	−0.11 (−0.48; 0.26)
Sleep apnoea risk	0.05 (−5.34; 4.91)	−0.15 (−7.68; 7.38)
24-h SBP, mmHg	0.11 (−0.11; 0.33)	0.02 (−0.20; 0.24)
C-reactive protein, mg/L	−0.05 (−2.62; 2.52)	−0.14 (−3.39; 3.11)
LDL cholesterol, mmol/L	0.08 (−11.3; 11.5)	0.04 (−13.8; 15.0)
Cortisol, nmol/L	−0.03 (−4.91; 4.85)	0.19 (−8.06; 8.44)
	Dynamic morning surge	
	Dippers n = 335	**Non-dippers n = 492**
R^2	**0.10**	**0.09**
	Std β (±95% CI)	**Std β (±95% CI)**
24-h HRV total power, ms^2	−0.07 (−6.08; 3.67)	−0.14 (−11.1; −0.05)*
Age, years	−0.02 (−0.41; 0.37)	−0.05 (−0.56; 0.46)
Sex	0.01 (−2.83; 2.85)	−0.08 (−3.55; 3.39)
Ethnicity	0.03 (−2.10; 2.16)	−0.01 (−3.19; 3.17)
Socio-economic score	0.09 (−0.13; 0.31)	0.19 (0.07; 0.45)*
Sleep apnoea risk	0.07 (−4.01; 4.15)	−0.09 (−5.11; 4.93)
24-hour SBP, mmHg	0.17 (0.03; 0.31)*	0.21 (0.03; 0.39)*
C-reactive protein, mg/L	−0.05 (−1.99; 1.89)	−0.07 (−2.48; 2.34)
LDL cholesterol, mmol/L	0.14 (1.79; 18.3)*	0.06 (−10.1; 10.3)
Cortisol, nmol/L	0.05 (−4.40; 4.50)	0.02 (−6.41; 6.45)

Abbreviations: HRV, heart-rate variability; LDL, low density lipoproteins; SBP, systolic blood pressure.
*indicates $p < 0.05$.

sensitivity of the sympathetic nervous system in normotensive and hypertensive non-dippers [41]. Mechanisms indicating the cause of low MBPS due to elevated sensitivity of the alpha-adrenergic receptors have not been fully described. However, a higher density of alpha-adrenergic receptors is responsible for higher peripheral vasoconstriction and blood pressure reactivity, and may lead to impaired decline in night-time blood pressure and possibly, lower MBPS in non-dippers [21].

This study has to be interpreted within the context of its limitations and strengths. Due to the cross-sectional study design, causality cannot be inferred. In addition, we did not assess sympathetic nervous system activity by means of microneurography. Since we did not find any significant associations of low frequency HRV, high frequency HRV or low frequency-to-high frequency ratio with MBPS, we cannot confirm the contribution of sympathetic nervous activity on MBPS. Overall, this study was conducted in highly controlled conditions in a well-equipped research facility. This was the first study to investigate the effect of autonomic neural activity on morning surge, with two methods of estimating surge, namely sleep-trough and dynamic morning surge among a young population.

Conclusions

In conclusion, we found a higher night-time blood pressure coupled with lower MBPS in young healthy non-dippers. Furthermore, this lower MBPS was independently and negatively associated with autonomic neural activity. With studies indicating non-dipping status as a predictor of future cardiovascular complications [36], we need to determine if the suppressed nocturnal dipping profile of young healthy individuals increases their risk for future cardiovascular disease.

Statement of Financial Support

The African-PREDICT study is an ongoing study financially supported by the South African Medical Research Council (SAMRC) with funds from National Treasury under its

Economic Competitiveness and Support Package; the South African Research Chairs Initiative (SARChI) of the Department of Science and Technology and National Research Foundation (NRF) of South Africa; the Strategic Health Innovation Partnerships (SHIP) Unit of the SAMRC with funds received from the South African National Department of Health, GlaxoSmithKline R&D, the UK Medical Research Council and with funds from the UK Government's Newton Fund; as well as corporate social investment grants from Pfizer (South Africa), Boehringer-Ingelheim (South Africa), Novartis (South Africa), the Medi Clinic Hospital Group (South Africa) and in kind contributions of Roche Diagnostics (South Africa).

Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors, and therefore, the NRF does not accept any liability in this regard.

Acknowledgements

The authors are grateful towards all individuals participating voluntarily in the study. The dedication of the support and research staff as well as students at the Hypertension Research and Training Clinic at the North-West University are also duly acknowledged.

Conflicts of Interest

There are no conflicts of interest.

References

[1] Kario K, White WB. Early morning hypertension: what does it contribute to overall cardiovascular risk assessment? J Am Soc Hypertens 2008;2(6):397–402.
[2] Shimizu M, Ishikawa J, Yano Y, Hoshide S, Shimada K, Kario K. The relationship between the morning blood pressure surge and low-grade inflammation on silent cerebral infarct and clinical stroke events. Atherosclerosis 2011;219(1):316–21.
[3] Patel PV, Wong JL, Arora R. The morning blood pressure surge: therapeutic implications. J Clin Hypertens 2008;10(2):140–5.
[4] Lee Y-S, Kim K-S, Nam C-W, Han S-W, Hur S-H, Kim Y-N, et al. Clinical implication of carotid-radial pulse wave velocity for patients with coronary artery disease. Korean Circ J 2006;36(8):565–72.
[5] Neutel J, Schumacher H, Gosse P, Lacourciere Y, Williams B. Magnitude of the early morning blood pressure surge in untreated hypertensive patients: a pooled analysis. Int J Clin Pract 2008;62(11):1654–63.
[6] Marfella R, Gualdiero P, Siniscalchi M, Carusone C, Verza M, Marzano S, et al. Morning blood pressure peak, QT intervals, and sympathetic activity in hypertensive patients. Hypertension 2003;41(2):237–43.
[7] Kario K. Vascular damage in exaggerated morning surge in blood pressure. Hypertension 2007;49(4):771–2.
[8] Kario K. Morning surge in blood pressure and cardiovascular risk evidence and perspectives. Hypertension 2010;56(5):765–73.
[9] Amici A, Cicconetti P, Sagrafoli C, Baratta A, Passador P, Pecci T, et al. Exaggerated morning blood pressure surge and cardiovascular events: A 5-year longitudinal study in normotensive and well-controlled hypertensive elderly. Arch Gerontol Geriatr 2009;49(2):e105–9.
[10] Dodt C, Breckling U, Derad I, Fehm HL, Born J. Plasma epinephrine and norepinephrine concentrations of healthy humans associated with nighttime sleep and morning arousal. Hypertension 1997;30(1):71–6.
[11] Yano Y, Kario K. Nocturnal blood pressure, morning blood pressure surge, and cerebrovascular events. Curr Hypertens Rep 2012;14(3):219–27.
[12] Caliskan M, Caliskan Z, Gullu H, Keles N, Bulur S, Turan Y, et al. Increased morning blood pressure surge and coronary microvascular dysfunction in patient with early stage hypertension. J Am Soc Hypertens 2014;8(9):652–9.
[13] Aatola H, Magnussen CG, Koivistoinen T, Hutri-Kähönen N, Juonala M, Viikari JS, et al. Simplified definitions of elevated pediatric blood pressure and high adult arterial stiffness. Pediatrics 2013;132(1):e70–6.
[14] Hall JE. Guyton and Hall textbook of medical physiology. Elsevier Health Sciences; 2015.
[15] Dauphinot V, Gosse P, Kossovsky MP, Schott A-M, Rouch I, Pichot V, et al. Autonomic nervous system activity is independently associated with the risk of shift in the non-dipper blood pressure pattern. Hypertens Res 2010;33(10):1032.
[16] Sherwood A, Steffen PR, Blumenthal JA, Kuhn C, Hinderliter AL. Nighttime blood pressure dipping: the role of the sympathetic nervous system. Am J Hypertens 2002;15(2):111–8.
[17] Birkenhäger A, Van den Meiracker A. Causes and consequences of a non-dipping blood pressure profile. Neth J Med 2007;65(4):127–31.
[18] Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline the Ohasama Study. Hypertension 2006;47(2):149–54.
[19] Sherwood A, Routledge FS, Wohlgemuth WK, Hinderliter AL, Kuhn CM, Blumenthal JA. Blood pressure dipping: ethnicity, sleep quality and sympathetic nervous system activity. Am J Hypertens 2011;24(9):982–8.
[20] Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med 2006;354(22):2368–74.
[21] Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. J Hypertens 2002;20(11):2183–9.
[22] Abate G, D'Andrea L, Battestini M, Zito M, Di Iorio A. Autonomic nervous activity in elderly dipper and non-dipper patients with essential hypertension. Aging Clin Exp Res 1997;9(6):408–14.
[23] Verdecchia P, Angeli F, Mazzotta G, Garofoli M, Ramundo E, Gentile G, et al. Day-night dip and early-morning surge in blood pressure in hypertension prognostic implications. Hypertension 2012;60(1):34–42.
[24] Kario K, Bhatt DL, Brar S, Cohen SA, Fahy M, Bakris GL. Effect of Catheter-Based Renal Denervation on Morning and Nocturnal Blood PressureNovelty and Significance. Hypertension 2015;66(6):1130–7.
[25] Li Y, Thijs L, Hansen TW, Kikuya M, Boggia J, Richart T, et al. Prognostic value of the morning blood pressure surge in 5645 subjects from 8 populations. Hypertension 2010;55(4):1040–8.
[26] Kario K. Evidence and perspectives on the 24-hour management of hypertension: hemodynamic biomarker-initiated 'anticipation medicine'for zero cardiovascular event. Prog Cardiovasc Dis 2016;59(3):262–81.
[27] Kario K. Perfect 24-h management of hypertension: clinical relevance and perspectives. J Hum Hypertens 2016;31:231–43.
[28] Pierdomenico SD, Pierdomenico AM, Di Tommaso R, Coccina F, Di Carlo S, Porreca E, et al. Morning blood pressure surge, dipping, and risk of coronary events in elderly treated hypertensive patients. Am J Hypertens 2016;29(1):39–45.
[29] Chouchou F, Desseilles M. Heart rate variability: a tool to explore the sleeping brain? Front Neurosci 2014;8:402.
[30] Westerhof BE, Gisolf J, Stok WJ, Wesseling KH, Karemaker JM. Time-domain cross-correlation baroreflex sensitivity: performance on the EUROBAVAR data set. J Hypertens 2004;22(7):1371–80.
[31] Patro BK, Jeyashree K, Gupta PK. Kuppuswamy's socioeconomic status scale 2010—the need for periodic revision. Indian J Pediatr 2012;79(3):395–6.
[32] Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 1999;131(7):485–91.
[33] Grassi G, Bombelli M, Seravalle G, Dell'Oro R, Quarti-Trevano F. Diurnal blood pressure variation and sympathetic activity. Hypertens Res 2010;33(5):381–5.
[34] Yano Y, Kario K. Possible difference in the sympathetic activation on extreme dippers with or without exaggerated morning surge. Hypertension 2009;53(1):e1.
[35] Pierdomenico SD, Pierdomenico AM, Coccina F, Lapenna D, Porreca E. Circadian blood pressure changes and cardiovascular risk in elderly-treated hypertensive patients. Hypertens Res 2016;39(11):805–11.

[36] Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. Hypertension 2011;57(1):3–10.
[37] Tan C, Saito N, Miyawaki I. Changes in Heart Rate and Autonomic Nervous Activity after Orthopedic Surgery in Elderly Japanese Patients. Kobe J Med Sci 2016;62(5):E129–35.
[38] Smeltzer SC, Brenda G. Brunner and Suddarth's Textbook of Medical-Surgical Nursing. Philadelphia: Lippincott Williams and Wilkins; 2004.
[39] Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. Physiol Rev 2010;90(2):513–57.
[40] Israel S, Israel A, Ben-Dov IZ, Bursztyn M. The morning blood pressure surge and all-cause mortality in patients referred for ambulatory blood pressure monitoring. Am J Hypertens 2011;24(7):796–801.
[41] Friedman O, Logan AG. Can nocturnal hypertension predict cardiovascular risk. Integr Blood Press Control 2009;2:25–37.
[42] Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. Br Heart J 1994;71(1):1–2.