Nighttime Blood Pressure Dipping in Young Adults and Coronary Artery Calcium 10–15 Years Later

The Coronary Artery Risk Development in Young Adults Study

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Abstract—Nighttime blood pressure (BP) dipping can be quantified as the ratio of mean nighttime (sleep) BP to mean daytime (awake) BP. People whose dipping ratio is ≥0.90 have been referred to as nondippers, and nondipping is associated with cardiovascular disease events. We examined the relationship between systolic nighttime BP dipping in young adults and the presence of coronary artery calcium (CAC) 10 to 15 years later using data from the ambulatory BP monitoring substudy of the Coronary Artery Risk Development in Young Adults Study. Among 239 participants with adequate measures of both nighttime and daytime readings and coronary artery calcium, the systolic BP dipping ratio ranged from 0.72 to 1.24 (mean, 0.88; SD, 0.06), and CAC was present 10 to 15 years later in 54 participants (22.6%). Compared with those whose systolic BP dipping ratio ranged from 0.88 to 0.92 (quartile 3), the 57 participants (23.9%) with less pronounced or absent dipping (ratio, 0.92–1.24; quartile 4) had an unadjusted odds ratio of 4.08 (95% CI, 1.48–11.2) for the presence of CAC. The 60 participants (25.1%) with a more pronounced dipping (ratio, 0.72–0.85; quartile 1) also had greater odds for presence of CAC (odds ratio, 4.76 [95% CI, 1.76–12.9]). When modeled as a continuous predictor, a U-shaped relationship between systolic BP dipping ratio and future CAC was apparent and persisted after adjustment for multiple potential confounders ($P<0.001$ for quadratic term). Both failure of systolic BP to dip sufficiently and "overdipping" during nighttime may be associated with future subclinical coronary atherosclerosis. (***Hypertension*. 2012;59:1157-1163.)** ● **Online Data Supplement**

Key Words: ambulatory blood pressure ■ diurnal blood pressure ■ blood pressure dipping ■ coronary artery calcium ■ subclinical atherosclerosis

Ambulatory blood pressure (BP) monitoring (ABPM) provides the best noninvasive assessment of a person's average BP.[1] The use of 24-hour ABPM also uniquely permits assessment of a person's BP during sleep. BP normally decreases ("dips") during sleep, and people whose BP dips ≤10% from their daytime baseline BP have been referred to as "nondippers." In patients with hypertension, nondipping is associated with target organ damage and cardiovascular events independent of the overall BP.[2–7] Nondipping may be a risk factor for cardiovascular disease even when the 24-hour BP average is not elevated.[7] In one study of normotensive individuals, the nondipping pattern was shown to be associated with cardiac hypertrophy and remodeling.[8] In a small study of men with angiographically proven coronary artery disease, 72% exhibited a nondipping BP pattern compared with 46% of matched controls without known coronary artery disease.[9] Another study showed that levels of von Willebrand factor, d-dimer, fibrinogen, and P-selectin were significantly higher among patients with documented coronary artery disease who were nondippers.[10] Whether the nighttime BP dipping pattern during young adulthood is associated with development of atherosclerosis later in life is not known.

The Coronary Artery Risk Development in Young Adults (CARDIA) Study presents a unique opportunity to examine this association. A substudy conducted at the year 5 CARDIA examination collected ambulatory BP readings on a subset of CARDIA participants. We used these data to analyze the association between nighttime dipping and the presence of coronary artery calcium, an indicator of atherosclerosis, measured 10 to 15 years later at the year 15 and year 20 CARDIA examinations. We hypothesized that BP dipping in young adults

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would be inversely related to later presence of coronary artery calcium and that the relationship would be maintained after adjustment for traditional atherosclerosis risk factors.

Methods

Overall Design

CARDIA is an ongoing prospective cohort study conducted at 4 sites throughout the United States.[11] The CARDIA Study and this substudy were approved by the appropriate institutional review boards, and informed consent was obtained from each study participant.

Study Participants

As described previously,[12] ABPM was performed at only 1 CARDIA Study site (Birmingham, AL). A list of people randomly chosen from the 4 race/sex subgroups was generated at the CARDIA Coordinating Center. After excluding individuals whose jobs would make ABPM difficult (eg, truck drivers, delivery people), a total of 316 people (147 men and 169 women; 112 whites and 204 blacks) participated in the substudy.

Ambulatory BP Monitoring

Ambulatory BP was monitored over a 24-hour period using a Suntech Accutracker II (Suntech Medical, Morrisville, NC), using an appropriately sized cuff inflated approximately every 20 minutes.[13] To reduce anticipation effects, the inflation schedule was variable. If any value outside preset limits (systolic ≥220 or ≤80 mm Hg; diastolic ≥130 or ≤40 mm Hg) was detected during a recording, that measurement was rejected, and another measurement was immediately made. In addition, a change of 50 mm Hg in systolic pressure, 40 mm Hg in diastolic pressure, or 50 mm Hg in pulse pressure also triggered a rejection and a new reading.

Participants were asked to record in a diary their activities and sleep times during the monitoring session. We defined a "daytime sleeper" as someone who, based on the reports in the diary, accumulated ≥6 hours of sleep between the hours of 10:00 AM and 10:00 PM and had ≤1 hour of accumulated sleep between 12:00 AM and 6:00 AM. For everyone else, we defined nighttime as 12:00 AM to 6:00 AM and daytime as 10:00 AM to 10:00 PM. For a session to be deemed adequate, we required a minimum of 10 daytime measurements and 5 nighttime measurements during these specific intervals. In total, 1 person was excluded because of being a daytime sleeper, and 34 participants were excluded because of inadequate daytime or nighttime measurements, leaving 281 participants in the cohort at baseline. Our primary exposure for this analysis was "BP dipping ratio," defined as the ratio of mean nighttime systolic BP to mean daytime systolic BP.

Sleep quality during the ABPM session was also recorded in the diary completed by participants. We defined "poor sleep quality" during the ABPM session as any report of being unable to fall asleep, being awakened >5 times, or not being able to sleep at all.

Coronary Artery Calcium

In CARDIA, coronary artery calcium was assessed at year 15 (10 years after the ABPM session) and at year 20 (15 years after the ABPM session) using cardiac computed tomography scanning. Consenting participants underwent 2 sequential scans using a multidetector, electrocardiographically gated computed tomography scanner (General Electric Lightspeed) with a standard phantom for calibration. Total coronary artery calcium score was calculated using a modified Agatston method.[14] Readers were masked to participant characteristics, as well as the paired scan results. Scans were selectively overread by an expert in cardiovascular imaging. The validity and reproducibility of these methods have been described previously.[15,16] We used CARDIA year 15 results only if year 20 results were not available and adjusted for examination year in our final models.

Clinic BP Measurements

We used the BP measured at the CARDIA year 5 visit (same year as the ABPM) as baseline clinic BP. Before the study visit, participants were asked to refrain from smoking and heavy physical activity. After 5 minutes of rest, 3 seated right arm BP measurements were recorded at 1-minute intervals. Using an appropriately sized cuff, the first-phase and fifth-phase Korotkoff sounds were taken as the systolic and diastolic BPs, respectively, using a random 0 sphygmomanometer. Clinic BP was determined by the average of the second and third readings.

Additional Covariates

Additional covariates included education level, body mass index, presence of diabetes mellitus, family history of hypertension, family history of diabetes mellitus, smoking, serum cotinine level, cholesterol levels, and physical activity (please see the Methods section in the online-only Data Supplement).

Analysis

We divided BP dipping ratio into quartiles. Characteristics of the participants were analyzed overall and then by quartile of dipping ratio. Coronary artery calcium score was available for 213 participants 15 years after their ABPM session (ie, at CARDIA year 20). Of the remaining 68 participants, coronary artery calcium was available for 26 of them 10 years after their ABPM session (ie, at CARDIA year 15). In total, we had coronary artery calcium data on 239 (85%) of the 281 participants. Participants without a coronary artery calcium measurement tended to be slightly younger (mean, 28.6 versus 30.4 years; $P=0.003$) and have slightly higher nighttime systolic BP (109.5 versus 105.0 mm Hg; $P=0.015$). To be sure that we included important confounders in the models, we examined the associations between baseline participant characteristics and later presence of CAC (please see Table S1, available in the online-only Data Supplement).

We calculated unadjusted and adjusted odds ratios for the presence of coronary artery calcium using the BP dipping quartile centered on 10% lower nocturnal rather than daytime systolic BP as the reference group. This quartile had the lowest odds of coronary calcium. Logistic regression was used to analyze the association between BP dipping ratio and the probability of coronary artery calcium at year 20 (or year 15 if year 20 was not available), with adjustment for other covariates and with testing for nonlinearity in the dipping ratio association with coronary calcium by adding a quadratic term of the dipping ratio. We assessed the goodness of fit of the model by fitting a spline function. In addition, we stratified our analyses by sex and by race and tested for interactions in the full model. We also assessed for effect modification by baseline smoking status. As a supplementary analysis, we reexamined the relationship of BP dipping with future CAC when defining BP dipping as the difference between the daytime and nighttime average levels rather than the ratio of the two.

To further evaluate for possible confounding, we compared modifiable risk factors of participants across the 4 quartiles at the time of the coronary artery calcium measurement to assess whether there were significant differences compared with when measured at baseline. Those risk factors with differences at a P value <0.10 were added to a final multivariable model. Data analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC) and R version 2.12.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of Sample

The mean age of participants at baseline was 30 years; 131 (47%) of 281 were men, and 177 (63%) of 281 were black (Table 1). Twenty (7%) of 281 had known hypertension. Few had known diabetes mellitus, but more than half were overweight or obese. Among this study sample, 79 (28%) of 281 were current smokers at baseline. Mean body mass index among the participants was 26.6 kg/m^2. Mean clinic BP at

Table 1. Characteristics of Sample at Baseline (CARDIA y 5) by Dipping Ratio Quartiles (N=281)

		Quartile: Dipping Ratio*				
Characteristic	Total	Q1: 0.72–0.85	Q2: 85–0.88	Q3: 0.88–0.92	Q4: 0.92–1.24	*P* Value
Age, mean (SD), y	30.2 (3.7)	30.8 (3.7)	29.5 (3.5)	29.9 (4.2)	30.5 (3.2)	0.14
Age categories, %						
23–29 y	43.4	32.9	56.3	44.3	40.0	0.04
30–36 y	56.6	67.1	43.7	55.7	60.0	
Male, %	46.6	47.1	40.9	44.3	54.3	0.43
Race categories, %						
Black	63.4	44.3	60.6	70.0	78.6	0.001
White	36.7	55.7	39.4	30.0	21.4	
Education, mean (SD), y	13.5 (2.0)	13.5 (2.4)	13.6 (1.9)	13.5 (1.9)	13.3 (1.8)	0.90
BMI, mean (SD), kg/m^2	26.6 (5.2)	25.6 (4.7)	26.5 (5.6)	26.4 (5.5)	27.9 (5.0)	0.08
BMI categories, %						
Normal (<25 kg/m^2)	43.0	51.4	47.9	44.3	28.6	0.08
Overweight (25–29 kg/m^2)	31.0	31.4	26.8	31.4	34.3	
Obese (≥30 kg/m^2)	26.0	17.2	25.3	24.3	37.1	
Current smoker, %	28.1	32.9	21.1	17.1	41.4	0.005
Pack-years of tobacco, mean (SD)	2.6 (5.5)	3.6 (7.0)	2.5 (6.6)	1.7 (3.3)	2.5 (4.3)	0.21
Serum cotinine level (ng/mL) at year 0, mean (SD)	64.8 (129)	81.5 (157)	50.0 (121)	54.5 (113)	73.4 (119)	0.41
High-density lipoprotein cholesterol (mg/dL), mean (SD)	50.8 (14)	51.2 (15)	52.1 (13)	52.9 (15)	46.9 (12)	0.054
Low-density lipoprotein cholesterol (mg/dL), mean (SD)	111.1 (30)	117.3 (32)	111.6 (31)	106.4 (26)	108.8 (31)	0.17
Known diabetes mellitus, %	2.5	0	4.2	2.9	2.9	0.43
Known hypertension, %	7.1	5.7	9.9	4.3	8.6	0.55
Glucose level (mg/dL) at y 7, mean (SD)	92.7 (34)	87.7 (6.9)	91.1 (32.3)	92.2 (24.2)	100.9 (56.7)	0.19
Baseline clinic SBP (mm Hg), mean (SD)	109.1 (11)	108.3 (8.6)	110.1 (11.8)	108.5 (10.7)	109.6 (11.2)	0.73
Baseline clinic DBP (mm Hg), mean (SD)	73.1 (9.8)	71.3 (9.8)	74.0 (10.9)	73.5 (8.3)	73.5 (10.0)	0.34
Clinic pulse pressure (mm Hg), mean (SD)	36.0 (8.2)	37.1 (9.1)	36.1 (7.8)	35.0 (7.4)	36.0 (8.5)	0.54
Alcohol intake (mL/d), mean (SD)	11.6 (20.4)	13.4 (22.9)	9.6 (15.8)	10.6 (20.3)	12.6 (22.2)	0.68
Physical activity (kcal/d), mean (SD)	317.1 (267.2)	326.4 (275.0)	282.7 (267.7)	354.3 (285.5)	305.3 (239.0)	0.43
Family history of hypertension, %	59.1	58.6	60.6	60.0	57.1	0.98
Family history of diabetes mellitus, %	16.0	18.6	14.1	12.9	18.6	0.71
Poor sleep quality during ABPM, %	16.4	18.6	16.9	12.9	17.1	0.82

CARDIA indicates Coronary Artery Risk Development in Young Adults Study; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitoring; BMI, body mass index; Q, quartile.

*Quartiles of mean nocturnal SBP/mean daytime SBP ratio: Q1, 0.7197–0.8454 (n=70); Q2, 0.8455–0.8809 (n=71); Q3, 0.8810–0.9203 (n=70); Q4: 0.9204–1.2358 (n=70).

baseline was 109/73 mm Hg. Mean low-density lipoprotein cholesterol was 111 mg/dL, and mean high-density lipoprotein cholesterol was 51 mg/dL.

At the time when coronary artery calcium was assessed, the only examined characteristic that differed (at a significance level $P<0.10$) across the quartiles of year 5 BP dipping ratio was smoking status (please see Table S2). The actual rate of smoking cessation was greatest among those in quartile 1, although the differences across quartiles were not significant ($P=0.52$).

BP Dipping

Nighttime BP dipping ranged from 28% (ie, average nighttime BP was 28% less than average daytime BP; BP dipping ratio, 0.72) to −24% (ie, BP rose during nighttime; dipping ratio, 1.24). As shown in Table 1, there was a significantly greater percentage of blacks in the higher ratio quartiles (ie, those with less dipping, including risers). Body mass index also was greater in the higher ratio quartiles, but the difference across quartiles was not statistically significant. There was a greater proportion of smokers in the lowest and highest quartiles. During the ABPM session, poor sleep quality was greatest among those in the first quartile, although the difference was not statistically significant across the quartiles.

The ambulatory BP averages within each BP dipping ratio quartile are shown in Table 2. The mean (±SD) 24-hour ambulatory BP average was 116/68 mm Hg (±10/7 mm Hg) and did not differ significantly between the groups.

Later Prevalence of Coronary Artery Calcium

A total of 54 participants (22.6%) had a nonzero Agatston coronary artery calcium score. Compared with those in the

Table 2. Mean BPs (mm Hg) of Sample at Baseline (CARDIA y 5) by Dipping Ratio Quartiles (N=281)

		Quartile: Dipping Ratio				
BP	Total	Q1: 0.72–0.85	Q2: 0.85–0.88	Q3: 0.88–0.92	Q4: 0.92–1.24	*P* Value
24-h systolic ABPM average, mean (SD)	115.5 (10.0)	114.7 (9.4)	117.1 (11.0)	113.7 (9.7)	116.6 (9.7)	0.16
24-h diastolic ABPM average, mean (SD)	68.0 (6.6)	67.9 (6.2)	69.1 (7.5)	66.7 (5.8)	68.3 (6.8)	0.18
Daytime systolic ABPM average, mean (SD)	119.2 (10.6)	121.0 (10.4)	121.7 (11.5)	117.1 (10.1)	117.2 (9.7)	0.01
Nighttime systolic ABPM average, mean (SD)	105.7 (11.1)	98.6 (8.8)	105.0 (9.8)	105.3 (9.0)	113.9 (11.2)	<0.001
Daytime diastolic ABPM average, mean (SD)	71.1 (7.2)	72.7 (7.0)	72.8 (8.0)	69.6 (6.1)	69.5 (7.1)	0.003
Nighttime diastolic ABPM average, mean (SD)	58.9 (7.6)	55.0 (5.8)	58.3 (7.4)	58.3 (6.5)	64.1 (7.9)	<0.001

CARDIA indicates Coronary Artery Risk Development in Young Adults Study; BP, blood pressure; ABPM, ambulatory blood pressure monitoring; Q, quartile.

Quartiles of mean nocturnal systolic BP/mean daytime systolic BP ratio: Q1, 0.7197–0.8454 (n=70); Q2, 0.8455–0.8809 (n=71); Q3, 0.8810–0.9203 (n=70); Q4, 0.9204–1.2358 (n=70).

quartile of nighttime to daytime systolic BP dipping ratio of 0.88 to 0.92, those whose nighttime to daytime systolic BP ratio was 0.92 to 1.24 (less dipping) had 4 times the odds (odds ratio, 4.08 [95% CI, 1.48–11.2]) of having coronary artery calcium. In addition, those in the quartile of BP dipping ratio of 0.72 to 0.85 (more dipping) also had significantly higher odds (odds ratio, 4.76 [95% CI, 1.76–12.9]) of having coronary artery calcium (Table 3). Although only 6 (10%) of 59 participants in the third quartile and 9 (14%) of 63 in the second quartile had coronary artery calcium, 21 (35%) of 60 in the first quartile and 18 (32%) of 57 in the fourth quartile did so. This U-shaped relationship persisted after adjustment for covariates (Table 3 and Figure 1). In the final adjusted analysis, compared with those in the third quartile (dipping ≈8% to 12%), those in the fourth quartile (dipping <8% to −24%) had 5.70 (95% CI, 1.27–25.80) times the odds of having coronary artery calcium 10 to 15 year later, and those in the first quartile had 5.30 times the odds (95% CI, 1.41–20.20; Table 3).

A spline function did not improve the fit of the predictive model. In fact, the spline and the quadratic functions overlap almost perfectly where there are data (Figure 1). The performance of the spline indicates that there is more ambiguity at the extremes, where there are few data.

In the full model, there was an interaction between sex and race ($P=0.03$). Although the U-shaped relationship (adjusted) between baseline dipping quartile and future presence of coronary artery calcium was evident in each sex-race subgroup, it was weakest in white women (Figure 2). There was no interaction with smoking status ($P=0.22$), and the U-shaped relationship persisted (though not statistically significant in most quartile comparisons) among both smokers and nonsmokers (please see Table S3).

Discussion

We found that among a sample of adults with a mean age of 45 years, the presence of coronary artery calcium was lowest in those whose nighttime BP exhibited a dip of ≈10% on ABPM performed 10 to 15 years earlier. The presence of coronary artery calcium was greater not only among those participants whose BP dipped less than ≈8% but also among those whose BP dipped more than ≈15%. These results persisted after adjustment for multiple potential confounders, including the average ambulatory and clinic BP levels. Our findings suggest that nondipping and overdipping are potential risk factors for subclinical atherosclerosis beginning in young adulthood, even in the absence of hypertension.

Our finding that coronary artery calcium was more common among those who would be categorized as nondippers (including risers) is consistent with most other literature on the adverse associations with this abnormal diurnal BP pattern,[2–8] although the only other study of which we are aware of that examined coronary artery calcium and BP dipping found no association.[17] That study included 298 white subjects with a mean age of 40 years and defined dipping as the difference between daytime and nighttime BP levels rather than as a ratio. As a supplementary analysis, we, therefore, reanalyzed our data using the difference instead of the ratio and found that the U-shaped curve persisted (Table S4).

Although average nighttime:daytime BP ratio <0.80 has been defined as "extreme dipping" and in at least a couple of studies it has been associated with an increased risk of cerebrovascular disease in older adults, a large meta-analysis examining the prognostic significance of nighttime BP patterns found no difference between dippers and extreme dippers in the rate of cardiovascular events.[6,18–20] The median age of the 3468 patients included in the meta-analysis was 63 years, and 61% were under antihypertensive treatment, making the populations in that analysis quite different than the cohort examined in our study.

Studies of biomarkers and other intermediate outcomes also suggest that extreme dipping is not benign. Among 98 hypertensive patients whose mean age was 57 years, plasma B-type natriuretic peptide levels were higher among the extreme dippers than the dippers and higher yet among the risers (also called reverse dippers).[21] Another study of 314 untreated hypertensives (mean age, 48 years) showed a J-shaped relationship between nighttime:daytime BP ratio and pulse wave velocity, with a nadir around a ratio of 0.90 to 0.94.[22] Finally, among treated hypertensive patients with coronary artery disease, nocturnal ischemia was shown to be significantly more frequent in overdippers than in dippers and nondippers.[23]

It has been suggested that an alternative way of looking at extreme dipping is that it represents an excessive daytime rise above a basal nighttime level. This has been described as "extreme blipping."[24] However, our inclusion of daytime ambulatory BP averages would control for this possibility.

Table 3. Presence of Coronary Artery Calcification (CARDIA y 20 or y 15) by Quartile of Baseline Mean Nighttime to Daytime Systolic BP Ratio (N=239)

Quartile	% With CAC	OR	95% CI	*P* Value	Nonlinearity (Quadratic) *P* Value
Crude (n/N)*					<0.001
Q1 (21/60)	35.0	4.76	1.76–12.9	0.002	
Q2 (9/63)	14.3	1.47	0.49–4.42	0.49	
Q3 (6/59)	10.2	1.00 (ref)			
Q4 (18/57)	31.6	4.08	1.48–11.2	0.007	
Adjusted for age, sex, race, baseline smoker, BMI, and HDL-C					0.038
Q1		4.49	1.48–13.6	0.008	
Q2		1.50	0.45–5.08	0.51	
Q3		1.00 (ref)			
Q4		2.81	0.90–8.72	0.07	
Adjusted for y 5 ASBP, ADBP, SDBP					0.001
Q1		4.21	1.44–12.3	0.009	
Q2		1.23	0.39–3.83	0.72	
Q3		1.00 (ref)			
Q4		3.92	1.31–11.8	0.015	
Adjusted for additional y 5 covariates and CAC exam year†					0.012
Q1		5.76	1.53–21.8	0.01	
Q2		1.37	0.33–5.74	0.67	
Q3		1.00 (ref)			
Q4		6.19	1.38–27.8	0.017	
Additionally adjusted for smoking status in CAC year					0.015
Q1		5.34	1.41–20.2	0.014	
Q2		1.21	0.29–5.11	0.80	
Q3		1.00 (ref)			
Q4		5.73	1.27–25.8	0.023	

OR indicates odds ratio; ref, referent; ASBP, awake systolic blood pressure average; ADBP, awake diastolic blood pressure average; SDBP, sleep diastolic blood pressure average; CAC, coronary artery calcium; Q, quartile; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure.

*n/N indicates No. of cases/total No. of subjects with known non-0 Agatston score.

†Data were adjusted for age, sex, race, education, BMI, baseline smoker, ASBP, ADBP, SDBP, serum cotinine level, low-density lipoprotein cholesterol, HDL-C, known diabetes mellitus, known hypertension, baseline clinic systolic BP, baseline clinic diastolic BP, pack-years of tobacco, alcohol intake, physical activity, family history of hypertension, family history of diabetes mellitus, and poor sleep quality during ABPM.

Some investigators postulate that it is the extreme amplitude in the circadian BP variation ("overswinging") rather than the extreme dipping, per se, that is a risk factor for cardiovascular disease. In a study of 297 adults, those whose circadian BP amplitude exceeded the 90th percentile based on sex- and age-matched peers had a higher rate of ischemic strokes, nephropathy, angina, and retinopathy.[25] The differences in strokes and nephropathy between those with and without abnormal circadian amplitude were statistically significant among both hypertensives and normotensives. Dipping status alone, however, was not discriminatory.

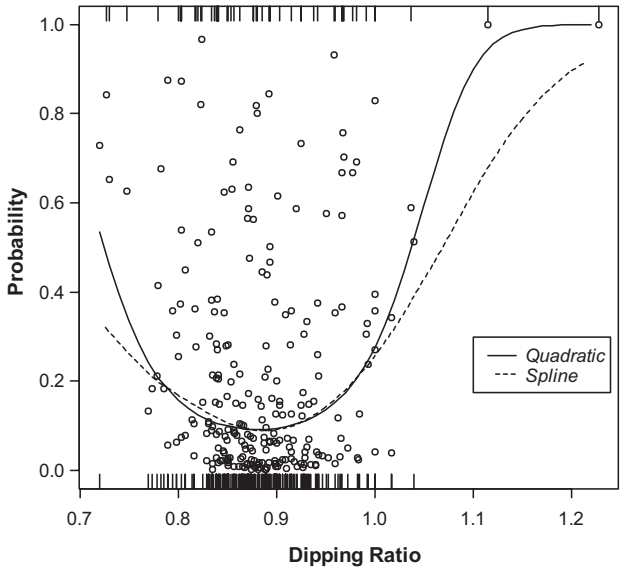

Figure 1. Dipping ratio and probability of coronary artery calcium 10 to 15 years later. The figure shows the individual predicted probability of having coronary artery calcium, indicated by circles, in adjusted logistic regression analysis with quadratic dipping ratio as the predictor of interest and covariates in the final model in Table 3. The rug at the bottom of the graph indicates individuals in whom coronary artery calcium was absent, whereas the rug at the top of the graph indicates those in whom coronary artery calcium was present. Goodness of fit is shown by a spline function that does not specify the relation between the ratio and the likelihood of the occurrence. Even after adjustment for possible confounding factors, the lowest risk of having the Agatston score >0 is still around the 0.9 ratio, and both nondipper (high ratio) and overdipper (low ratio) are at a higher risk of having coronary artery calcification. —, quadratic; - - -, spline.

Our study is unique in that we examined a cohort of adults who were young and largely healthy at baseline. Nevertheless, abnormal night-to-day BP patterns despite otherwise optimal BP seem to be related to the presence of subclinical coronary atherosclerosis over a decade later. Mechanistically, it seems most plausible that alterations in sympathetic nervous system activity (eg, baroreceptor sensitivity) would explain an association with altered diurnal BP pattern and cardiovascular sequelae. However, the pathophysiologies between nondippers and extreme dippers (or overswingers) may be different.

Limitations

Our findings need to be interpreted in the context of some limitations. We do not know the reproducibility of dipping ratio among these participants, which may be worse at the extremes (ie, extreme dipping and rising).[26] We did not have measurements of coronary artery calcium at baseline, so we do not know with certainty that it developed over the years subsequent to the measurement of ambulatory BP. However, coronary artery calcium is very rare in young adults[27] and was present in only 4.5% (17 of 379) at year 10 in the

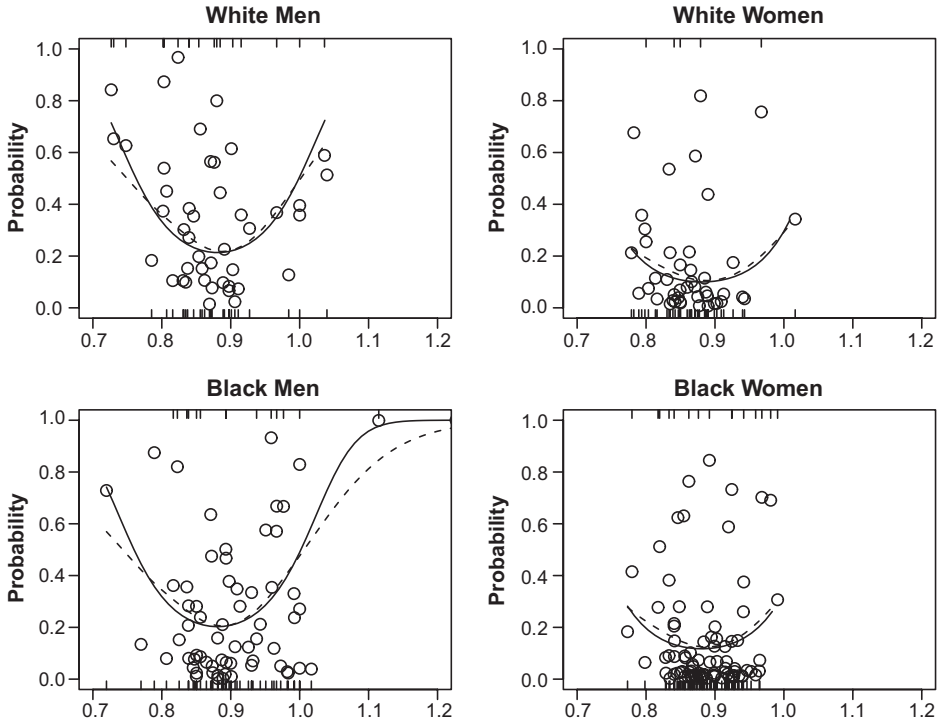

Figure 2. Dipping ratio and probability of coronary artery calcium 10 to 15 years later, stratified by sex and race subgroups. The figure shows the adjusted analysis results across each of the 4 sex-race subgroups. The U-shaped relationship between nighttime systolic blood pressure (BP) dipping (and its quadratic term as a covariate) and the presence of future coronary artery calcium is present in all 4 groups. Circles indicated the predicted probability. The top rug represents the coronary artery calcium cases and the bottom represents the noncases.

CARDIA cohort,[28] suggesting that the altered nocturnal BP dipping observed in our cohort preceded the development of subclinical coronary atherosclerosis. We were unable to find differences in known predictors, such as cholesterol, clinic BP, glucose, or smoking, either at baseline or follow-up examinations to the extent that they would provide an alternative explanation for our findings, though the possibility of residual confounding cannot be ruled out. For example, although tobacco use and cotinine level were included in the final models, it remains possible that tobacco use continues to operate as a confounder because of its influence on BP variability.[29] Our analyses stratified by baseline smoking status experienced relatively small sample sizes, which may explain the instability in the significance of the comparisons. Given these limitations, our findings ought to be replicated in larger samples before drawing a more robust conclusion.

Nocturnal BP may be affected by disruption of sleep by the ambulatory BP monitor itself.[30] By our definition, however, only 16% of participants with adequate ambulatory BP data had poor sleep quality, and our results were unchanged when this factor was included in multivariable analysis. Although a strength of our study is the biracial cohort, the CARDIA ABPM substudy took place in 1 region of the country within the "stroke belt." Although BP patterns may vary across regions of the country, it seems unlikely that the association itself between those BP patterns and coronary calcium would vary.

Perspectives

Our analysis suggests that coronary artery calcium may be a potential mediator of the relationship between abnormal nighttime BP pattern and cardiovascular disease. As suggested by previous literature, the residual cardiovascular disease risk associated with abnormal nighttime BP among patients with hypertension warrants rigorous testing of interventions (eg, chronotherapy) in clinical trials.[31] However, what do we make of the possible risk associated with abnormal ambulatory BP patterns in people who do not have hypertension, as suggested in this study and others?[7,8,31] First, the findings may be of prognostic importance, implying that, when abnormal BP patterns are detected, they can be a harbinger of greater cardiovascular disease risk in years to come. Those at increased risk may warrant more aggressive control of risk factors and closer monitoring for development of hypertension.[32] Second, if future research demonstrates that abnormal diurnal BP patterns in youth are associated with adverse clinical outcomes, evaluation of interventions (either pharmacological or nonpharmacologic) to restore a healthier BP pattern may also be warranted in this group. The challenges of conducting such research are formidable.

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Disclosures

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Nighttime Blood Pressure Dipping in Young Adults and Coronary Artery Calcium 10–15 Years Later: The Coronary Artery Risk Development in Young Adults Study

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NIGHTTIME BLOOD PRESSURE DIPPING IN YOUNG ADULTS AND CORONARY ARTERY CALCIUM 10-15 YEARS LATER: THE CARDIA STUDY

Short title: Nighttime BP and coronary artery calcium

ON-LINE SUPPLEMENT

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Methods Supplement

Measurement of Covariates

Education was determined by self-report of highest grade level achieved. Body mass index (BMI) was calculated based on measured height and weight at the baseline visit. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dl or use of hypoglycemic agents at baseline (CARDIA year 5). Family history of hypertension and family history of diabetes were determined by self-report. Current smoking, defined as regular cigarette smoking (at least five cigarettes a week almost every week for at least three months) was assessed by self-report. Additionally, serum cotinine, a biochemical marker of nicotine uptake, was measured at year 0.

High density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels were measured in a fasting serum sample at year 5. Physical activity was assessed by the CARDIA physical activity questionnaire, which measured the self-reported frequency of participation in 13 different categories of recreational sports and exercise in the past 12 months.[1] Physical activity scores were computed by multiplying the frequency of participation by the intensity of activity and reported as "exercise units."

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Table S1. Participant Characteristics and their Association with Coronary Artery Calcification at Year 20 or Year 15

	Year 20 (n=213)			Year 15 (n=26)		
Characteristic	**CAC**	**No CAC**	**p-value**	**CAC**	**No CAC**	**p-value**
Age, mean (SD), y	31.9 (3.0)	30.0 (3.6)	<0.001	32.8 (2.6)	29.7 (3.6)	0.08
Male, %	59.2	39.0	0.01	100.0	52.4	0.05
Black, %	55.1	64.0	0.26	60.0	71.4	0.62
Education, mean (SD) years	13.3 (2.0)	13.7 (1.8)	0.15	14.2 (3.2)	13.3 (2.2)	0.45
BMI, mean (SD) kg/ m^2	27.9 (4.9)	26.3 (5.3)	0.07	25.2 (3.6)	26.1 (4.8)	0.71
Baseline smoker, %	53.1	18.3	<0.001	40.0	19.1	0.32
Serum cotinine level (ng/ml), mean (SD)	125.7 (153.7)	41.2 (107.5)	<0.001	198.4 (281.0)	55.7 (113.1)	0.32
High density lipoprotein (mg/dl), mean (SD)	49.0 (15.6)	51.2 (13.0)	0.32	39.6 (6.7)	53.0 (14.1)	0.05
Low density lipoprotein (mg/dl), mean (SD)	122.4 (31.3)	107.4 (28.1)	0.002	128.8 (31.3)	110.1 (24.3)	0.15
Known diabetes mellitus, %	6.1	0.6	0.01	20.0	0.0	0.04
Known hypertension, %	4.1	6.7	0.50	0.0	9.5	0.47
Glucose level (mg/dl) at year 7, mean (SD)	101.1 (41.7)	87.4 (9.0)	0.03	168.8 (180.3)	89.3 (6.8)	0.38
Baseline clinic SBP (mm Hg), mean (SD)	109.7 (10.0)	108.7 (10.0)	0.54	108.0 (6.7)	105.5 (11.3)	0.64
Baseline clinic DBP (mm Hg), mean (SD)	73.3 (9.2)	73.1 (9.6)	0.90	71.2 (5.9)	72.9 (9.3)	0.71
Clinic pulse pressure (mm Hg), mean (SD)	36.4 (8.1)	35.6 (7.7)	0.52	36.8 (7.5)	32.6 (7.6)	0.28

Pack-years of tobacco at year 5, mean (SD)	5.2 (7.0)	1.6 (4.1)	0.001	5.7 (7.8)	2.7 (5.2)	0.30
Alcohol intake (ML/day), mean (SD)	23.7 (30.0)	8.0 (15.1)	0.001	7.4 (14.0)	5.7 (11.0)	0.78
Physical activity (Kcal/d), mean (SD)	308.9 (274.9)	350.3 (283.8)	0.36	258.2 (156.8)	323.9 (222.8)	0.49
Family history of hypertension, %	69.4	60.4	0.26	20.0	42.9	0.35
Family history of diabetes, %	20.4	12.2	0.15	20.0	14.3	0.75
Poor sleep quality, %	10.2	20.1	0.11	20.0	9.5	0.51
Dipping quartile* at baseline, %						
Q1	36.7	22.6	0.004	60.0	9.5	0.07
Q2	16.3	29.3		20.0	28.6	
Q3	12.2	28.7		0.0	28.6	
Q4	34.7	19.5		20.0	33.3	

*Quartiles of mean nocturnal systolic BP/mean daytime systolic BP ratio: **Q1:** 0.7197-0.8454 (n=70); **Q2:** 0.8455-0.8809 (n=71); **Q3:** 0.8810-0.9203 (n=70); **Q4:** 0.9204-1.2358 (n=70)

SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitoring

Table S2. Characteristics of Participants at Time of CAC* Measurement by Dipping Ratio Quartiles (N=281)

Characteristic	Total	Q1: 0.72-0.85	Q2: 0.85 - 0.88	Q3: 0.88-0.92	Q4: 0.92-1.24	p-value
Age, mean (SD) years	45.0 (3.9)	45.8 (3.9)	44.2 (4.0)	44.8 (4.2)	45.2 (3.5)	0.17
BMI, mean (SD) kg/ m^2	30.3 (7.0)	29.2 (7.2)	30.5 (6.9)	30.4 (6.9)	31.2 (6.9)	0.47
Current smoker, %	17.8	15.7	15.5	10.0	30.0	0.01
Smoking cessation rate, %	12.5	17.1	9.9	10.0	12.9	0.52
Pack-years of tobacco, mean (SD)	4.5 (9.5)	5.9 (11.8)	4.1 (10.9)	2.9 (5.8)	5.0 (8.3)	0.28
High density lipoprotein cholesterol (mg/dl), mean (SD)	52.3 (16.6)	52.7 (20.3)	54.0 (16.7)	52.7 (13.5)	49.6 (15.0)	0.52
Low density lipoprotein cholesterol (mg/dl), mean (SD)	109.7 (28.9)	112.8 (28.7)	109.7 (29.0)	108.1 (28.3)	108.2 (30.2)	0.80
Known diabetes mellitus, %	7.8	2.9	8.5	8.6	11.4	0.29
Known hypertension, %	27.8	22.9	31.0	27.1	30.0	0.71
Glucose level (mg/dl), mean (SD)	99.8 (41.9)	92.8 (11.6)	96.7 (36.9)	105.8 (56.9)	104.0 (48.1)	0.27
Clinic SBP (mm Hg), mean (SD)	116.1 (16.6)	114.0 (13.7)	114.8 (13.3)	118.0 (21.3)	117.6 (16.9)	0.45
Clinic DBP (mm Hg), mean (SD)	73.8 (11.4)	71.4 (10.8)	74.7 (10.2)	75.0 (14.0)	74.2 (9.9)	0.29
Clinic pulse pressure (mm Hg), mean (SD)	42.3 (10.5)	42.6 (8.9)	40.1 (9.3)	43.2 (10.4)	43.4 (13.1)	0.28

*If CAC measurement not available, Year 20 data were used

Quartiles of mean nocturnal systolic BP/mean daytime systolic BP ratio: **Q1:** 0.7197-0.8454 (n=70); **Q2:** 0.8455-0.8809 (n=71); **Q3:** 0.8810-0.9203 (n=70); **Q4:** 0.9204-1.2358 (n=70)

Table S3. Association of Blood Pressure Dipping Quartile with Future Coronary Artery Calcification (CAC), Stratified by Baseline Smoking Status

Non-Smokers

	% with CAC	OR	95% confidence interval	p-value	Test for nonlinearity p-value
Crude (n/N)*					0.006
Q1 (10/43)	23.3	3.49	1.01-12.1	0.049	
Q2 (6/49)	12.2	1.61	0.42-6.08	0.49	
Q3 (4/50)	8.0	1.00 (ref)			
Q4 (6/35)	17.1	2.38	0.62-9.16	0.21	
Adjusted for age, sex, race, BMI, and HDL-C					0.13
Q1		3.68	0.92-14.6	0.065	
Q2		1.66	0.38-7.27	0.50	
Q3		1.00 (ref)			
Q4		1.71	0.39-7.54	0.48	
Adjusted for Year 5 ASBP, ADBP, SDBP					0.007
Q1		2.19	0.56-8.56	0.26	
Q2		1.02	0.25-4.20	0.97	
Q3		1.00 (ref)			
Q4		3.10	0.73-13.3	0.13	
Adjusted for additional year 5 covariates† and CAC exam year					0.12
Q1		1.14	0.17-7.84	0.90	
Q2		0.88	0.12-6.64	0.90	
Q3		1.00 (ref)			
Q4		2.14	0.22-21.2	0.51	

Smokers

	% with CAC	OR	95% confidence interval	p-value	Test for nonlinearity p-value
Crude (n/N)*					0.18
Q1 (11/17)	64.7	6.42	1.00-41.2	0.05	
Q2 (3/14)	21.4	0.96	0.13-7.23	0.96	
Q3 (2/9)	22.2	1.00 (ref)			
Q4 (12/22)	54.6	4.20	0.71-24.9	0.11	
Adjusted for age, sex, race, BMI, and HDL-C					0.22
Q1		7.75	1.04-57.5	0.045	
Q2		1.47	0.16-13.8	0.74	
Q3		1.00 (ref)			
Q4		5.03	0.72-35.3	0.10	
Adjusted for Year 5 ASBP, ADBP, SDBP					0.19
Q1		7.81	1.13-53.9	0.037	
Q2		1.03	0.13-7.94	0.98	
Q3		1.00 (ref)			
Q4		2.78	0.36-21.7	0.33	
Adjusted for additional year 5 covariates† and CAC exam year					0.077
Q1		24.0	1.26-459.6	0.034	
Q2		1.32	0.06-27.8	0.86	
Q3		1.00 (ref)			
Q4		11.7	0.47-295.2	0.13	

OR, odds ratio; ref, referent; ASBP, awake systolic blood pressure average; ADBP, awake diastolic blood pressure average; SDBP, sleep diastolic blood pressure average; CAC, coronary artery calcium.

*** n/N:** No. of cases/Total number of subjects with known non-zero Agatston score

† Adjusted for age, sex, race, education, BMI, ASBP, ADBP, SDBP, LDL-C, HDL-C, known diabetes, known hypertension, baseline clinic systolic BP, baseline clinic diastolic BP, alcohol intake, physical activity, family history of hypertension, family history of diabetes, poor sleep quality during ABPM.

Table S4. Presence of Coronary Artery Calcification (CARDIA Year 20 or Year 15) by Quartile of Baseline Mean Nighttime to Daytime Systolic BP Difference (N=239)

Quartile	% with CAC	OR	95% confidence interval	p-value
Crude (n/N)*				
Q1 (18/64)	28.1	4.30	(1.48-12.5)	0.007
Q2 (15/66)	22.7	3.24	(1.10-9.54)	0.03
Q3 (5/60)	8.3	1.00 (ref)		
Q4 (16/49)	32.7	5.33	(1.79-15.9)	0.003
Adjusted for additional Year 5-covariates† and CAC exam year				
Q1		4.46	(0.98-20.3)	0.053
Q2		5.12	(1.24-21.2)	0.024
Q3		1.00 (ref)		
Q4		8.00	(1.74-36.8)	0.008
Additionally-adjusted for smoking in CAC exam year				
Q1		4.05	(0.90-18.4)	0.07
Q2		4.40	(1.06-18.2)	0.04
Q3		1.00 (ref)		
Q4		6.90	(1.51-31.4)	0.013

CAC, coronary artery calcium; OR, odds ratio; ref, referent
*** n/N:** No. of cases/Total number of subjects with known non-zero Agatston score
† Adjusted for age, sex, race, education, BMI, baseline smoker, ASBP, ADBP, SDBP, serum cotinine level, LDL, HDL, known diabetes, known hypertension, baseline clinic systolic BP, baseline clinic diastolic BP, pack-years of tobacco, alcohol intake, physical

activity, family history of hypertension, family history of diabetes, poor sleep quality during ABPM, and CAC exam year.

Quartiles of mean nocturnal systolic BP minus mean daytime systolic BP ratio: **Q1:** -37 to -19 (n=75); **Q2:** -18 to -14 (n=74); **Q3:** -13 to -9 (n=71); **Q4:** -8 to 27 (n=61)