Nighttime Blood Pressure Dipping in Postmenopausal Women With Coronary Heart Disease

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BACKGROUND
Blunted nighttime blood pressure (BP) dipping is prognostic of cardiovascular morbidity and mortality. This relationship may be stronger among women than men. The present study hypothesized that coronary artery disease (CAD) and advancing age would be associated with reduced BP dipping in postmenopausal women. The effects of daytime physical activity and nighttime sleep quality on BP dipping were also examined.

METHODS
54 postmenopausal women with CAD (≥50% occlusion of at least one major coronary vessel) and 48 age-matched (range 50–80 years) postmenopausal women without CAD (non-CAD) underwent 24-h ambulatory BP monitoring and actigraphic evaluations of daytime physical activity and nighttime sleep efficiency.

RESULTS
Women with CAD evidenced higher nighttime systolic BP (SBP) ($P = 0.05$) and blunted SBP dipping ($P = 0.017$), blunted diastolic BP (DBP) dipping ($P = 0.047$), and blunted pulse pressure dipping ($P = 0.01$), compared to non-CAD women. Multivariable regression models showed that the presence of CAD, age, daytime physical activity, and nighttime sleep efficiency were independently related to the magnitude of SBP dipping, together accounting for 25% of its variability. DBP dipping showed similar associations.

CONCLUSIONS
For postmenopausal women, the presence of CAD and advancing age are accompanied by blunted nighttime BP dipping, which may increase the risk of adverse cardiovascular events. Lifestyle changes that increase daytime physical activity and improve nighttime sleep quality may help improve cardiovascular risk by enhancing nighttime BP dipping.

Keywords: *ambulatory blood pressure monitoring; blood pressure; blood pressure dipping; coronary artery disease; hypertension; physical activity; sleep efficiency; women's health*

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Nighttime blood pressure (BP) is a stronger predictor of cardiovascular risk than clinic or daytime ambulatory BP.[1] Blunted nighttime BP "dipping," the magnitude of fall in BP from day to night, is a strong prognostic indicator of cardiovascular morbidity and mortality for both hypertensive and nonhypertensive individuals.[1–3] Clinical characteristics associated with blunted nighttime BP dipping include advancing age, increasing body mass index (BMI), diabetes, renal and cardiovascular disease, smoking and administration of a greater number of antihypertensive medications.[4] Female sex also has been identified as an independent predictor of blunted nighttime BP dipping.[4] In addition, greater target organ damage has been observed among women who experience an attenuated BP dip at night,[5,6] and the association between nighttime BP and cardiovascular outcome has been recently reported to be stronger in women compared with men.[7]

The association between BP dipping and coronary artery disease (CAD) has not been evaluated systematically, but there is converging evidence suggesting that the presence of CAD may be associated with blunted dipping. In a study of men, an association between non-dipping and CAD was found to be independent of angina, risk factors, and lipid abnormalities.[8] For women, the postmenopausal years are accompanied by increased cardiovascular risk that appears related to their altered reproductive hormone profile, as well as advancing age.[9] However, few studies have examined diurnal BP profiles in postmenopausal women. The present study sought to evaluate the hypothesis that the presence of CAD would be associated with blunted nighttime BP dipping in postmenopausal women. We also assessed whether two modifiable behavioral characteristics, daytime physical activity and nighttime sleep quality, which have been shown to influence BP dipping in other populations,[10,11] might also represent potentially modifiable influences on BP dipping for postmenopausal women.

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METHODS

Study subjects. The study sample consisted of 102 postmenopausal women, aged 50–80 years who were recruited to participate in a study of the acute effects of female reproductive hormones administered via transdermal patches.[12] The present sample was drawn from women randomized to a placebo transdermal patch, and was comprised of both women with established CAD (defined by cardiac catheterization documenting ≥50% occlusion of at least one major coronary vessel), and women with no documented evidence of CAD (non-CAD). Postmenopausal status was defined by amenorrhea ≥12 months, and was confirmed by a reproductive hormone panel. Exclusion criteria included: use of hormone replacement therapy, oral contraceptives, or selective estrogen receptor modulators within 30 days of enrollment; congestive heart failure NYHA Class >II; pacemaker dependency; uncontrolled hypertension (defined by a resting BP ≥180/105 mm Hg); persistent atrial fibrillation or tachyarrhythmia, myocardial infarction and/or percutaneous coronary intervention within 30 days of enrollment; coronary artery bypass grafting within 3 months of enrollment; uncorrected valvular disease; hypertrophic or restrictive cardiomyopathy; uncorrected thyroid disease; persistent tachyarrhythmia; a diagnosed sleep disorder; and BMI ≥40 kg/m^2. The protocol was approved by the institutional review board at Duke University Medical Center and written informed consent was obtained from all study participants.

Female reproductive hormones. A blood sample was drawn from an antecubital vein and collected in a serum separator tube, left to clot for 30 min, centrifuged at room temperature for 15 min at 3,000 rpm, transferred to a serum transfer tube, and refrigerated before being assayed the same day for serum follicle-stimulating hormone by immunochemiluminometric assay (LabCorp, Burlington, NC).

24-h ambulatory BP monitoring. The Oscar 2 Ambulatory BP Monitor (ABPM) (SunTech Oscar 2, Raleigh, NC) was worn for 24 h, starting between 11:00 AM and 1:00 PM on a weekday, until the same time the following day. The Oscar 2 is a noninvasive ABPM that uses oscillometric technology and has been validated according to the International Protocol for the validation of BP measuring devices.[13,14] Systolic BP (SBP) and diastolic BP (DBP) were measured every 20 min during the day and every 30 min during nighttime sleep. Pulse pressure was computed as SBP-DBP for each ABP reading. Artifactual readings were deleted according to criteria previously described.[15]

Physical activity and sleep quality. A wrist-watch style actigraph (Mini-Mitter, Sunriver, OR) was worn during the same 24-h ABPM period and used to assess physical activity during the day and at night. The Actiware-Sleep software (Mini Mitter) analyzed nighttime activity data to calculate an index of sleep quality (sleep efficiency; the percent of time asleep during the sleep period).[16]

Data analysis. Waking and sleep periods, defined by self-report, and confirmed by actigraphy, were used to compute mean daytime BP and mean nighttime BP values, respectively. In order to be considered an acceptable ABPM study, acceptance criteria of a minimum of 6 readings during the sleep-period and 10 readings during the awake-period were applied. In our study sample, the average number of acceptable sleep ABP readings was 16 ± 4, and the average number of awake-period readings was 35 ± 10. Nighttime SBP dipping was defined as the percentage of the decline in nighttime SBP ((mean daytime SBP-mean nighttime SBP/mean daytime SBP) × 100%); SBP dipping defined in this way is a continuous variable that was the primary dependent variable assessed in this report. In addition, and solely for descriptive purposes, a SBP dip ≥10% was classified as normal "dipper," while <10% was classified as "non-dipper." Descriptive statistics were means with s.d. for continuous variables and counts with percentages for categorical variables. Student's *t*-tests and χ^2-tests were used for the comparison of characteristics of study participants with CAD versus non-CAD participants. Multivariable regression analyses were employed in a planned model to evaluate the independent and combined effects of CAD, age, daytime activity and sleep quality on SBP and DBP dipping. Secondary supportive analyses for the evaluation of robustness of findings from the planned model allowed other potential explanatory factors (including history of hypertension, alcohol use, tobacco use, antihypertensive medications, high-density lipoprotein and low-density lipoprotein cholesterol) to be available for entry into the planned model by stepwise selection (SLE = 0.05). All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Sample characteristics

Sample characteristics are presented in **Table 1** and are categorized by study group. The sample consisted of 54 postmenopausal women with CAD and 48 non-CAD controls. The groups were similar in age, weight, BMI, ethnicity, clinic SBP and DBP, follicle-stimulating hormone, triglycerides, daytime SBP, and nighttime DBP. No significant differences in prevalence of diabetes, smoking or angiotensin receptor blocker use were observed, but CAD patients were more likely to have had a previous diagnosis of hypertension ($P < 0.001$). As expected, some CAD patients had a history of MI, percutaneous coronary intervention and coronary artery bypass grafting, and had more frequent use of β-blockers, statins, nitrates, and angiotensin-converting enzyme inhibitors ($P < 0.01$). High-density lipoprotein levels were lower ($P = 0.002$) in CAD patients when compared with the non-CAD controls, whereas low-density lipoprotein levels were higher ($P = 0.002$).

Diurnal BP variation

As shown in **Table 2**, nighttime SBP was higher in CAD patients ($P = 0.05$), whereas daytime SBP was similar. In contrast, daytime DBP was higher in non-CAD subjects ($P = 0.012$), whereas nighttime DBP was similar. CAD patients were characterized by a higher pulse pressure than non-CAD

Table 1 | Study sample ($n = 102$) characteristics in CAD patients and non-CAD controls

	CAD ($n = 54$)	Non-CAD ($n = 48$)	*P* diff
Demographics			
Age (years)	66 ± 8	66 ± 7	0.77
Height (m)	1.59 ± 0.05	1.62 ± 0.06	0.02
Weight (kg)	74 ± 12	72 ± 13	0.47
Body mass index (kg/m^2)	29.2 ± 4.9	27.4 ± 4.4	0.06
Ethnicity (% minority)	15 (28)	10 (21)	0.41
Smoker (yes)	8 (16%)	4 (8%)	0.26
Alcohol (yes)	20 (37%)	29 (60%)	0.02
Clinical characteristics			
Clinic SBP (mm Hg)	140 ± 20	137 ± 17	0.43
Clinic DBP (mm Hg)	65 ± 11	69 ± 11	0.14
Hypertension Hx	35 (65%)	13 (27%)	<0.001
Myocardial infarction Hx	18 (33%)	0 (0%)	<0.001
Coronary artery bypass graft Hx	12 (22%)	0 (0%)	<0.001
Percutaneous coronary intervention Hx	25 (46%)	0 (0%)	<0.001
FSH (IU/l)	56 ± 27	55 ± 25	0.91
Total cholesterol (mg/dl)	203 ± 43	230 ± 40	<0.01
HDL (mg/dl)	53 ± 15	63 ± 19	<0.01
LDL (mg/dl)	116 ± 35	137 ± 31	<0.01
Triglycerides (mg/dl)	178 ± 94	147 ± 71	0.08
Diabetes	8 (16%)	2 (4%)	0.09
β-Blockers	43 (80%)	5 (10%)	<0.001
Statins	43 (80%)	2 (4%)	<0.001
Nitrates	8 (15%)	0 (0%)	<0.01
ACE inhibitors	31 (57%)	4 (8%)	<0.001
ARB	6 (11%)	3 (6%)	0.50

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; DBP, diastolic blood pressure; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure.

Table 2 | Twenty-four hour ambulatory blood pressure and actigraphy measures in CAD and non-CAD postmenopausal women

	CAD patients ($n = 54$)	Non-CAD controls ($n = 48$)	*P* diff
Ambulatory blood pressure			
Daytime SBP (mm Hg)	123 ± 12	122 ± 10	.80
Nighttime SBP (mm Hg)	116 ± 12	111 ± 13	0.050
Daytime DBP (mm Hg)	62 ± 9	68 ± 8	0.01
Nighttime DBP (mm Hg)	56 ± 7	58 ± 7	0.36
24-h SBP (mm Hg)	120 ± 11	118 ± 10	0.35
24-h DBP (mm Hg)	60 ± 7	64 ± 7	0.03
Daytime PP (mm Hg)	60 ± 11	55 ± 8	0.01
Nighttime PP (mm Hg)	59 ± 10	53 ± 9	0.001
24-h PP (mm Hg)	60 ± 10	55 ± 8	<0.01
SBP Dip (%)	5.2 ± 7.7	8.9 ± 7.7	0.02
DBP Dip (%)	8.8 ± 10.1	12.6 ± 9.3	0.047
PP Dip (%)	0.7 ± 9.4	3.7 ± 10.0	0.01
Dipping classification			
SBP "Non-Dipper" (%)	42 (78%)	24 (50%)	<0.01
DBP "Non-Dipper" (%)	27 (50%)	16 (33%)	0.09
24-h Actigraphy			
Daytime physical activity (units)	17.2 ± 7.1	16.5 ± 6.7	.61
Sleep efficiency (%)	80.9 ± 9.7	81.8 ± 9.9	.67

CAD, coronary artery disease; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

controls that was evident during waking hours ($P = 0.01$) and during nighttime sleep ($P = 0.001$). The magnitude of SBP, DBP, and pulse pressure dipping was blunted in CAD patients compared with non-CAD controls ($P < 0.05$); and 78% of women with CAD were characterized as SBP "non-dippers," compared to 50% of their non-CAD counterparts ($P = 0.003$).

Multivariable regression models

Regression analyses were used to assess the multivariable relationship of BP dipping with planned models that included CAD, age, physical activity, and sleep quality. Results of these analyses, which also controlled for mean 24-h BP, are summarized in Table 3. CAD, age, physical activity, and sleep quality were independently associated with SBP dipping and together accounted for ~25% of its variance (Table 3). The interaction between age CAD status and age was nonsignificant ($P = 0.99$) and therefore not included in the planned model. The robustness of the planned model was supported by a secondary analysis that found no other potential explanatory variables (alcohol use, tobacco use, medications, high-density lipoprotein, and low-density lipoprotein cholesterol) met criteria for entry into the model, indicating that the planned model for SBP dipping was robust. The association between CAD and blunted SBP dipping was accounted for primarily by women with CAD showing higher nighttime SBP compared to their non-CAD counterparts (Table 2). Independently of CAD, the association of advancing age with reduced SBP dipping also was linked to increasing nighttime SBP. As shown in Figure 1, advancing age was associated with a progressive increase in nighttime SBP ($P = 0.001$); whereas age was unrelated to daytime SBP ($P = 0.79$). Physical activity and sleep efficiency were both directly related to the magnitude of SBP dipping, as denoted by their positive β-coefficients (Table 3). It is of note that increased daytime physical activity was related to greater SBP dipping due to an association with lower nighttime SBP ($R = -0.22$, $P = 0.03$), rather than higher daytime SBP ($R = -0.06$, $P = 0.58$).

Similar findings emerged for DBP dipping, with CAD, age, physical activity, and sleep quality again being independent explanatory variables in a model that explained 23% of the total variance (Table 3). In secondary supportive analyses, no

Table 3 | Multivariable regression models of blood pressure (BP) dipping, defined as daytime-minus-nighttime BP expressed as a continuous variable in terms of percentage change from daytime BP

Systolic BP Dip							
Characteristic	**B**	***b***	**95% CI**	***P***	**Adjusted R^2**	**Model F**	**Mod el *P***
					0.247	7.63	<0.001
24-h Mean SBP	0.01	0.02	−0.12, 0.15	0.84			
Age (year)	−0.32	−0.30	−0.52, −0.13	0.001			
CAD/non-CAD (1/0)	−3.54	−0.23	−6.3, -0.84	0.01			
Sleep efficiency (%)	0.27	0.33	0.13, 0.41	<0.001			
Physical activity (units)	0.28	0.24	0.07, 0.49	<0.01			
Diastolic BP Dip							
Characteristic	**B**	***b***	95% CI	***P***	**Adjusted R^2**	**Model F**	**Model *P***
					0.228	6.95	<0.001
24-h Mean SBP	0.16	0.12	−0.08, 0.4	0.19			
Age (year)	−0.37	−0.27	−0.61, −0.12	<0.01			
CAD/non-CAD (1/0)	−3.09	−0.16	−6.6, 0.42	0.08			
Sleep efficiency (%)	0.34	0.34	0.16, 0.52	<0.001			
Physical activity (units)	0.29	0.21	0.03, 0.56	<0.05			

B, nonstandardized regression coefficient; *b*, standardized regression coefficient; CAD, coronary artery disease; CI, confidence intervals; SBP, systolic blood pressure.

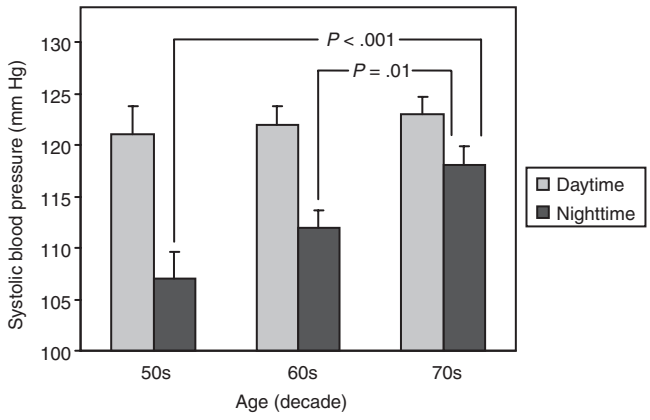

Figure 1 | Daytime and nighttime systolic blood pressure (mean ± s.e.) associated with advancing age in postmenopausal women. Age is shown according to decade, depicting women in their 50s ($n = 20$), 60s ($n = 45$), and 70s ($n = 37$).

background variables met entry criteria for inclusion in the model, indicating that the planned model also was robust for DBP dipping.

DISCUSSION

Few studies have documented the relationship between CAD and nighttime BP dipping. This report provides evidence that postmenopausal women with CAD may be exposed to a higher nighttime BP load than non-CAD women, which could put them at higher risk for further target organ damage and adverse clinical outcomes. Advanced age also was independently associated with blunted BP dipping. This finding is consistent with previous reports demonstrating that BP dipping decreases with age and older individuals are more likely to exhibit non-dipping BP patterns.[4,17] Indeed, although the prevalence of non-dipper staus was highest in postmenopausal women with CAD (78%), non-dipping status was also evident in 50% of the "non-CAD" postmenopausal women in our study sample. We also noted that ambulatory pulse pressure was elevated during both the daytime and nighttime in women with CAD. Elevated pulse pressure may be a reflection of increased arterial stiffness, and has been identified as an independent marker of heightened cardiovascular risk.[18,19] Moreover, pulse pressure has been shown to be associated specifically with an increased risk of coronary, rather than cerebrovascular events.[20,21]

Our analyses also sought to determine whether daytime physical activity and nighttime sleep quality might account for some of the variation in BP dipping associated with CAD and advancing age. Multivariable regression models showed that both of these behavioral characteristics were associated with BP dipping and were independently associated with SBP dipping; however, they did not account for the relationships with CAD or age, which also remained independently related to SBP dipping when all of these factors were included in multivariable regression models.

Our findings provide further evidence for the role of physical activity in cardiovascular health, and support previous reports that increased levels of physical activity may benefit BP dipping.[22–24] Evidence regarding the role of physical activity and BP dipping, however, has been inconsistent, and may be related to study sample characteristics.[25] To our knowledge, there are no studies that have examined this relationship in postmenopausal women. The present study suggests that in this sample, increasing daytime physical activity may be beneficial to the diurnal BP profile. Moreover, this finding was not secondary to an association of increased physical activity with higher daytime SBP, but due to its association with lower nighttime SBP.

In our study sample, sleep efficiency also was independently associated with BP dipping. Poorer sleep efficiency has been related to BP dipping in other studies as well.[26,27] Sleep efficiency is particularly useful measurement in older adults, as sleep efficiency generally declines with age.[28,29] Older adults typically spend more time in bed, but their actual sleep time tends to decrease. Improvements in sleep efficiency have been observed in several studies through the use of sleep-restriction therapy and/or sleep hygiene education.[30–32] Increasing physical activity during the day also has been found to improve sleep efficiency.[30,33–35] Enhancing BP dipping by reducing nocturnal BP is associated with improved prognosis in hypertension.[35] Interventions aimed at improving nighttime BP may be especially important in high-risk postmenopausal women given recent reports of a stronger association between nighttime BP and poorer cardiovascular outcomes among women compared to men.[6,7] Recent evidence that nighttime dosing of antihypertensive medications lowers nocturnal BP and is associated with a reduction in subsequent cardiovascular events suggests that chronotherapy may be one effective therapeutic strategy.[36] Our findings suggest that the diurnal BP profile of postmenopausal women may benefit from lifestyle changes aimed at increasing physical activity and improving overall sleep quality.

Limitations of the present study include the cross sectional design, which precludes inferences regarding causal/directional relationships by which BP dipping and CAD are related. In view of evidence that nighttime BP dipping may have limited reproducibility,[37] we also note that our findings are based upon a single 24-h ABPM session for each participant. The absence of any measure of renal function in our study is also a limitation. Although a diagnosed sleep disorder was an exclusion criterion, we cannot rule out the possibility that obstructive sleep apnea and sleep disordered breathing, which are associated with blunted nighttime BP dipping[38,39] may have contributed to our findings. It is also possible that cuff inflations during the sleep period may have disrupted sleep and contributed to atypically higher nighttime BP in some participants.[40] The effects of cardiovascular medications, as well as the timing of their administration, which were more commonly prescribed to women with CAD than their non-CAD counterparts, may also have affected the magnitude of diurnal BP variation.[36,41] Our observations should therefore be considered to depict the association of CAD with blunted nighttime BP dipping in postmenopausal women who are characterized by contemporary medical management of CAD.

In summary, this observational study shows that CAD and advancing age are associated with blunted nighttime BP dipping in postmenopausal women. Our findings draw attention to the high prevalence of elevated nighttime BP and blunted diurnal BP dipping in postmenopausal women and suggest a need to take this cardiovascular risk factor into consideration in the treatment of hypertension and/or heart disease. Our findings also raise the possibility that efforts to increase physical activity and improve sleep efficiency may help reduce cardiovascular risk in postmenopausal women by improving nighttime BP dipping.

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