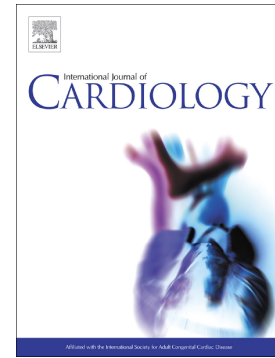


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Blood Pressure Variability in Normotensive Perimenopausal Women: Non-Dipping Status, Maximum Blood Pressure and Arterial Stiffness

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Abstract

Background Postmenopausal women are more likely to have uncontrolled hypertension and are at higher risk of cardiovascular disease compared with age-matched men. Blood pressure variability is emerging as a predictor of adverse cardiovascular outcomes and may be implicated in the relationship between menopause and worsened vascular health in women. We conducted

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an observational study, BRAVE (Blood pResure And Vascular hEalth around menopause) to study this relationship.

Methods Normotensive perimenopausal women were recruited. Blood pressure variability was measured through 24-hour blood pressure monitoring. Vascular health was assessed through arterial stiffness (carotid-femoral pulse wave velocity), carotid intima-media thickness and endothelial function (reactive hyperemic index). Multivariate models were performed to identify factors associated with blood pressure variability and arterial stiffness in perimenopausal women.

Results Forty-nine healthy women (mean age 52.9 ± 4.0 , 63% postmenopausal) were recruited. There was a high prevalence (40%) of night non-dipping, a measure of an abnormal pattern of blood pressure variability. Aside from night dipping, other measures of blood pressure variability were similar between premenopausal and postmenopausal women. In the multivariate analysis, body mass index was the only factor associated independently with different measures of blood pressure variability, including the maximum overnight blood pressure ($\beta=1.95$, $p<0.01$). The latter was also significantly associated with arterial stiffness ($\beta=0.035$, $p=0.048$). Finally, poor sleep was independently associated with an increase in arterial stiffness.

Conclusions Abnormal blood pressure variability, particularly night non-dipping, is common in normotensive perimenopausal women. Maximum overnight blood pressure is independently associated with arterial stiffness and may identify women at higher cardiovascular risk.

Keywords: hypertension, women, menopause, blood pressure variability, arterial stiffness, sleep quality.

Introduction

In women, hypertension is a leading risk factor for death[1] and cardiovascular diseases, such as stroke[2] and myocardial infarction (MI)[3]. Hypertension and cardiovascular disease are more prevalent in men until about the age of sixty years, whereby the prevalence of hypertension in women exceeds that in men[1]. Furthermore, women are twice as likely to have uncontrolled hypertension[4], leading to a significant and disproportionate burden of the disease in women.

Menopause has long been thought to explain this phenomenon, with sex hormones having a “protective” effect on the cardiovascular system. However, studies investigating the relationship between menopause and hypertension have given conflicting results[5], [6]. The largest study to date demonstrated in a cohort of 18,000 Italian women that menopause was responsible for an increase in blood pressure (BP) of approximately 3 mmHg, after accounting for important confounders[7]. However, it has been increasingly recognized that beyond mean BP, the oscillations in BP over time, namely the BP variability (BPV), is a strong predictor of cardiovascular morbidity and mortality[8]. Furthermore, BPV has prognostic value in hypertensive adults irrespective of their baseline cardiovascular risk[9], representing therefore an additional tool for cardiovascular risk stratification[10].

The mechanisms underlying BPV are not fully understood but it can result from structural changes, such as stiffened arteries[11] and thicker arterial walls[12], or functional changes, such as inability of vessels to dilate[13]. Arterial stiffness, a composite indicator of vascular health, is a strong predictor of cardiovascular events[14]. Carotid-femoral pulse wave velocity (cf-PWV) is considered the gold-standard measure of aortic stiffness[15].

To date, limited data exist on the association between BPV measurements and arterial stiffness in healthy, normotensive individuals[16], while no data are available in healthy perimenopausal women.

Therefore, our objectives were to evaluate in healthy perimenopausal women (i) the patterns of BPV; (ii) factors associated with abnormal patterns of BPV; and (iii) the association between BPV and arterial stiffness.

Methods

The BRAVE (Blood pRessure And Vascular hEalth around menopause) is an observational cross-sectional study of healthy perimenopausal women. The study design called for collecting health and lifestyle information through questionnaires, BP readings, as well measurements of macrovascular and microvascular vascular health, to assess the relationship between BPV and vascular health around the time of menopause. The study was approved by the Institutional Review Board of McGill University (approval 12-338-BMB), and all participants provided informed consent.

Women were recruited from the community in Montreal, Canada following wide-spread advertisement. Women were enrolled if they were: 1) between stages -2 (i.e. beginning to have irregular cycles) to +2 (8 years post menopause) according to the Stages of Reproductive Aging Workshop (STRAW) menopausal staging system[17], 2) fluent in English or French, and 3) able to provide informed consent. Women were excluded if they a) had a known clinical history of vascular disease (i.e. myocardial infarction, cerebrovascular event, peripheral arterial disease, revascularization procedure), had been diagnosed with hypertension or were taking antihypertensive medications, had diabetes mellitus, cancer or other end-stage disease that could affect the measurements, b) were using hormone therapy, or c) had surgical menopause (hysterectomy with or without oophorectomy).

Baseline Clinical and Behavioral Characteristics

Information on baseline socio-demographic and clinical characteristics were obtained through questionnaires. Behavioral and lifestyle data were also collected and variables created using pre-specified cutoffs; poor sleep was defined as Pittsburgh Sleep Quality Index (PSQI) ≥ 5 [18], depression as a Patient Health Questionnaire-9 (PHQ-9) score $> 19/36$ [19], being anxious as a State Trait Anxiety Inventory (STAI) score $> 54/80$ [20], being physically active as a Godin Activity Rate ≥ 35 [21], and feeling socially supported as a Multidimensional Scale of Perceived Social Support (MSPSS) score in the upper tertile of the sample[22].

Menopausal stage was assessed according to the STRAW system, using the self-reported date of the last menstrual period. Women were considered postmenopausal if their last menstrual cycle was at least 1 year ago. Otherwise, they were classified as premenopausal. Menopausal symptoms were also collected using the Menopausal Rating Scale (MRS)[23].

Procedures - Measurements

On Day 1, resting BP was measured using the automated oscillometric device BpTRU (VSM MedTech Ltd, Vancouver, Canada) according to the Hypertension guidelines[24]. The Oscar2 ABPM (SunTech Medical Inc., USA) was installed to the participants by the research technician, to record BP over the subsequent 24 hours (i.e. over Day 2) at 20-minute intervals. In the same visit, participants were given a home BP monitor (A&D Medical, Mississauga Canada) to be used daily for 1 week, i.e. over Days 3 to 9. Home BP was recorded twice in the morning

and twice in the evening at 2-minute intervals after being seated in a quiet environment for at least 5 minutes[24]. The research technician explained the proper use of the home BP and ABPM and provided reminder cards and supporting material with instructions. Participants returned for a second visit on Day 10, where office BP, height, weight and waist and hip circumferences were measured, as well as non-invasive assessments of vascular measures were performed by trained vascular technicians.

Specifically, arterial stiffness was assessed via applanation tonometry using the Sphygmocor System (AtCor Medical, Sydney, Australia) with the participant in the supine position after 10-min resting in a quiet, controlled environment as previously described[25]. Cf-PWV was measured in duplicate, and additional measurements were obtained until cf-PWV values were within 0.5 m/s; the average of these 2 cf-PWV values was used for the analyses[26]. The heart rate (HR) and the mean arterial pressure (MAP) were both calculated by the Sphygmocor System. The HR was derived from the 3-lead electrocardiogram (ECG) recording that is used to calculate the pulse transit time for the cf-PWV computation. The MAP was calculated using the area under the curve of a calibrated peripheral waveform, rather than using form-factor equations, as the latter methods are less accurate[27]. The distance for the PWV measurements was calculated based on the subtraction method (suprasternal notch-umbilicus-femoral artery) minus (suprasternal notch-carotid artery)[15]. Normal values for cf-PWV in women in this age group are 7.5-8.4 m/s[28].

Carotid intima media thickness (cIMT) was measured using a Philips iu22 (Andover, Mass) 3D/4D ultrasound machine and a linear 9-3 MHz probe on both the left and right carotid arteries and the average of the two values was used in subsequent analyses. Normal values for cIMT in this population are approximately 0.55-0.70 mm[29].

Endothelial function was assessed with peripheral arterial tonometry (PAT) using the Endo-PAT2000 device (Itamar Medical Ltd., Caesarea, Israel)[30]; it assesses microvascular blood flow in the finger, and is reported as the natural log of the reactive hyperemic index (ln(RHI)). There are no clearly defined normal values, but lnRHI in healthy subjects has been shown to range from 0.26-1.03[30].

Blood Pressure Variability Assessment

We assessed day-to-day variability, 24-hour BPV, and night dipping as they are the most commonly reported medium- and short-term measures of BPV[8]. We also included maximum daytime and overnight values since maximum BP has been shown to have some predictive value[31]. The coefficient of variation (CV) of the BP measurements was used to assess day-to-day and 24-hour BP variability, which allows for an assessment of the effect of variability independent of the mean BP. The CV was calculated as the ratio of the standard deviation of the BP values to the mean value of the BP measurements; this was done for the systolic as well as the diastolic BP. Maximum daytime and overnight values as well as the night dipping pattern- defined as a 10% drop in systolic and diastolic BP at night[32]- were measured using the 24-hour ABPM. Other patterns of reverse dipping and extreme dipping were not investigated due to their low incidence in our sample.

Non-dipping (i.e. a less than 10% nocturnal drop in BP), an abnormal pattern of BPV, has been strongly associated with cardiovascular mortality[32]. Conversely, due to the large heterogeneity in the prior studies reporting BPV as maximum daytime and overnight values, we cannot use established reference values for these other measures, and we reported the data as continuous. Higher values of maximum BP have also been linked to worse outcomes[33].

Statistical Analysis

We compared baseline socio-demographic and clinical characteristics, and different BPV measures between pre- and postmenopausal women using Chi-square tests (for proportions) and t-tests (for continuous variables).

Univariate and multivariable linear regression analysis was used to identify the factors associated with BPV. Univariate analysis was performed for each BPV measure and associations with $p < 0.10$ were included in the final model. In measures of variability where the CV of the values was not used, namely maximum BP, mean BP was adjusted for separately.

Exploratory correlation analysis was performed to assess the relationship between the different measures of BPV and each of the vascular measures. If a significant correlation was found, univariable and multivariable regressions were used to further characterize the relationship. For the covariates, we used factors that were found to be significant in the univariate analysis, as well as those that were found to be important in the literature in terms of

their associations with both BP and vascular health. These included age, body mass index (BMI), physical activity, poor sleep, smoking, level of stress, alcohol intake and anxiety[34, 35]. The different multivariate models were compared using the Akaike Information Criterion (AIC) scores to select the best model.

Statistical analyses were performed using SAS (SAS Institute, Cary, North Carolina). Statistical tests were 2-sided and differences with $p \leq 0.05$ were considered statistically significant.

Results

Fifty women who met the eligibility criteria were recruited. However, one woman was unable to complete the BP recordings, leaving 49 women in the sample.

Clinical and Lifestyle Characteristics

Among the 49 women, 63% were postmenopausal (Table 1). They were mostly Caucasian, married, or common law with a low cardiac risk factor burden but frequently having poor sleep quality, and symptoms related to the menopausal transition. The postmenopausal group was slightly older and had a lower BMI. Otherwise, the two groups were similar with respect to cardiovascular risk factors and had similar mean BP. Lifestyle and psychosocial factors were also similar in both groups (Table 1).

Blood Pressure Variability and Vascular Measures

BPV values, as measured by 24-hour CV, were normal for this population[36]. Conversely, around 40% of the participants were non-dippers, having less than 10% drop in their systolic and diastolic BP over-night (Table 2). There were no statistically significant differences in any BPV measures between pre- and postmenopausal women, though max systolic daytime and overnight BP were much higher in postmenopausal women. Overall, the vascular health measures – cf-PWV, cIMT and ln(RHI) - fell within a narrow range of normal or healthy values. Similarly, there were no differences in the vascular health measures between premenopausal and postmenopausal women (Table 2).

Factors Associated with Blood Pressure Variability in Healthy Perimenopausal Women

In the univariate analyses (not shown), BMI, smoking status and alcohol use were associated with some measures of variability, though no single variable was correlated with all the BPV measures. Menopausal status was also not correlated with any BPV measures. Poor sleep was not correlated with either night dipping or overnight maximum BP.

In the adjusted multivariate analysis, only BMI ($\beta=2.46$, $p<0.01$) and mean BP ($\beta=0.71$, $p<0.01$) were independently associated with maximum overnight diastolic BP (Table 3). The BMI was also independently associated with the maximum daytime diastolic BP ($\beta=1.95$, $p<0.01$). (Table 3)

Blood Pressure Variability and Vascular Measures

Correlation analyses were performed between the BPV and vascular measures, i.e. cf-PWV, cIMT and ln(RHI) (Supplementary Table S1). Of those, only cf-PWV was significantly correlated with multiple measures of BPV, specifically with diastolic night dipping, maximum daytime diastolic BP and maximum overnight diastolic BP. Scatterplots demonstrating these correlations are shown in Supplementary figures 1-3. The cIMT and ln(RHI) were not correlated with any of the BPV measures (Supplementary Table S1).

Multivariate analyses looking at the association between cf-PWV and BPV were performed with adjustments for age, BMI, physical activity, smoking status, poor sleep, confidence managing stress, premenopausal status and hours of housework. Traditional risk factors such as hypercholesterolemia were of very low prevalence and not significantly associated with cf-PWV in the univariate analysis. In multivariate models, only maximum overnight diastolic BP was independently associated with cf-PWV (Table 4). A separate model that also included adjustments for mean arterial pressure (MAP) and heart rate (HR) did not alter the results significantly. Night dipping was not associated with cf-PWV (Table 4) in the multivariate models (fully adjusted, $\beta=0.02$, $p=0.32$). In these multivariate models (Supplementary Table S2a-c), physical activity and sleep quality had large effects on the cf-PWV. Poor sleep led to an increase in cf-PWV of 0.7-1.0 m/s. Those who were physically active had a decrease in cf-PWV of 0.6-0.8 m/s. We explored whether poor sleep modified the

relationship between maximum overnight diastolic BP and cf-PWV by creating models with and without poor sleep, however, it did not significantly alter their relationship.

Discussion

This study assessed BPV and vascular markers in normotensive perimenopausal women to better understand the changes in cardiovascular risk associated with menopausal transition. A high prevalence of night non-dipping pattern, i.e. 40% was noted in this cohort of healthy perimenopause women despite normal mean BP. BMI was the only variable independently associated with multiple measures of BPV in this healthy cohort. BPV did not change significantly between premenopausal and postmenopausal women. However, arterial stiffness, measured by cf-PWV, was independently associated with BPV, specifically the maximum overnight BP even in this normotensive population. Finally, poor sleep quality was associated with increased arterial stiffness.

Non-dipping has been associated with 2.5-fold increased risk of cardiovascular mortality compared to dipping[32] in a study of 1500 healthy Japanese adults of whom approximately 30% were non-dippers. A study of perimenopausal women in Italy found a weak association between blunted night dipping and worsening of left ventricular wall motion[37]. The mechanism linking night dipping to cardiovascular mortality is unclear; it may be attributed to a prolonged exposure to higher BPs over a 24-hour period. If our finding of high prevalence of non-dipping in normotensive perimenopausal women is validated in larger cohorts, it may suggest that this population is at greater risk for cardiovascular disease.

We did not demonstrate any relationship between BPV and menopause. The loss of estrogen in menopause leads to increased sympathetic nervous activity and changes in endothelial function[1] which could theoretically lead to greater variation in BP. A previous study did find increased BPV in postmenopausal women[36], but it recruited patients from a hypertension clinic. Our study in contrast excluded women with any history of cardiovascular disease or hypertension. Furthermore, the premenopausal women in our study were in the early stage of menopause; they may not have been considered premenopausal in other studies. BPV does not seem to change between the early and late stages of the menopausal transition, though we cannot rule out that it may change prior to the onset of menopause.

We also investigated the relationship between BPV and micro- and macrovascular measures in normotensive, perimenopausal women. Only arterial stiffness's gold-standard measure, cf-PWV, correlated with multiple measures of BPV. A recent large cohort study demonstrated that greater very short- to mid-term BPV is associated with higher central arterial stiffness and maladaptive carotid arterial remodeling[38], although this association has not been evaluated before specifically in normotensive perimenopausal women. Though previous studies have found a relationship between BPV and cIMT[39] as well as endothelial function[13, 40], the results vary greatly depending on the specific measure of BPV used. For example, short-term or 24-hour BPV may be influenced primarily by the sympathetic nervous system, whereas mid-term or day-to-day BPV may be more influenced by arterial stiffness[41]. Results may also vary based on the population being studied- healthier individuals are less likely to have large changes in BP[9]. In the case of endothelial function, the evaluation method used might play a role. We assessed reactive hyperemia (ln(RHI)) of the fingertip using EndoPAT, which is less operator dependent, while other studies used flow mediated dilatation (FMD)[13]. Finally, it is noteworthy that our population had vascular health within the "optimal"[28] range for arterial stiffness, and normal range for cIMT[42] accounting for age and sex. The relatively narrow range of values may lead to an underestimate of the impact of different factors on vascular health.

We conducted multivariate models assessing the relationship between arterial stiffness and BPV, adjusting for confounders, including mean BP. Among BPV measures, only the maximum overnight diastolic BP was significantly associated with arterial stiffness after adjusting for confounders, including mean BP. Overnight diastolic BP seem to be an important measure of BPV as previous studies have found that both overnight[10] and diastolic[43] BP values to be more predictive than daytime and systolic ones. Maximum BP has previously been shown to be correlated with target organ damage[31] and arterial stiffness[33]. However, due to the cross-sectional study design, we cannot assess whether maximum overnight BP precedes arterial stiffness or vice versa.

With the high prevalence of non-dipping, we were interested in seeing if sleep played a role. We found that 60% of women reported poor sleep as measured by the PSQI, but counterintuitively, poor sleep was not associated with non-dipping. Other studies have found

conflicting results, with one finding no relationship in menopausal women[35] and another finding a strong relationship[44], albeit in hypertensive patients. Our results may indicate that non-dipping, i.e. elevated BP at night, is a result of intrinsic changes of the vascular system rather than being caused by disrupted sleep or increased activity at night.

We also found that poor sleep was related to almost 1 m/s increase in cf-PWV. This is important as previous studies have demonstrated that a 1 m/s increase in cf-PWV is associated with a 15% increased risk in cardiovascular events and mortality[45]. It has been suggested that this relationship could be mediated by abnormal BPV[46]. We explored whether the effect of poor sleep was mediated by maximum overnight BP; however, our models did not confirm this hypothesis, though our sample size was limited. This is in line with other studies of menopausal women, which have found poor sleep quality to be an independent predictor for arterial stiffness[47]. In animal models, poor sleep quality was shown to affect haematopoiesis and cause atherosclerosis[48]. If sleep is found to have a causal relationship with arterial stiffness, improving sleep quality may play an important role in the prevention of cardiovascular disease. However, further research is required to disentangle the relationship between sleep, BPV and arterial stiffness.

There are very few studies that have studied predictors of BPV. Mean BP[8] is an important predictor and menopausal status[35], physical activity[34], stress[34, 35], smoking and BMI[49] have been identified as possible predictors. Our study could not directly examine predictors of BPV as its cross-sectional nature does not allow us to determine the temporal relationship between variables. We found only BMI to be independently associated with BPV after accounting for mean BP. This could be due to the good health state of the study population, as BPV seems to be a more useful measure in populations at higher cardiovascular risk[11]. Our findings are consistent with the importance of BMI as a risk factor for cardiovascular disease.

There were some limitations to our study. Firstly, the cross-sectional design meant that we were unable to determine the direction of causality in our associations. We were also unable to study women as they transitioned through the different stages of menopause. The small sample size similarly limited us to comparing the broader categories of pre vs. post menopausal women, rather than all the stages of the menopausal transition, as defined by the STRAW guidelines[17]. Finally, we used only surrogates for vascular health such as arterial

stiffness and atherosclerosis rather than clinical endpoints. This study serves as a proof-of-concept; future large prospective trials would allow to better unravel the relationship between menopause, BPV and vascular health.

There are multiple implications of our findings. Firstly, the increased prevalence of abnormal BPV despite normal office BP readings points to increased cardiovascular risk and potential need for closer monitoring of these women. Secondly, we provide some evidence that maximum overnight BP, as a BPV measurement independently associated with cf-PWV, may be a predictor of arterial stiffness, and hence cardiovascular risk. Currently, clinical guidelines recommend home or 24-hour BPM only if the initial office BP is abnormal[50]. Our findings indicate that perimenopausal women with normal office BP may benefit from 24-hour BPM. Elevated maximum overnight BP would help better stratify their risk and signal the need for an intervention to slow arterial stiffening and vascular aging. Twenty-four-hour ABPM are routinely done in clinical practice and maximum daytime and night-time BP would therefore be a relatively easy and convenient marker for both clinicians and perimenopausal women. However, more research would be required to confirm and expand our findings before BPV is incorporated into routine clinical practice in perimenopausal women.

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Supplementary data

Supplementary material

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Table 1: Baseline Clinical and Sociodemographic Characteristics of Healthy Perimenopausal Women

	Overall (N=49)	Pre- menopausal (N=18)	Post- menopausal (N=31)	p value
Demographics				
Age, mean (SD)	52.9 (4.0)	49.2 (2.5)	55.0 (3.2)	<0.0001
Caucasian	41 (82)	14 (77.8)	27 (87.0)	0.44
Married or Common Law	37 (74)	13 (72.2)	23 (74.2)	1.00
Primary Earner	21 (42)	7 (38.9)	14 (45.3)	0.67
CVD Risk Factors				
BMI, mean (SD)	25.4(4.1)	27.0 (4.8)	24.3 (3.4)	0.03
Smoking				
Current	2 (4)	2 (11)	0 (0)	0.75
Past	13 (26)	5 (27.8)	9 (29.0)	0.93
Alcohol Consumption*	12 (25.5)	4 (25.5)	8 (27.6)	1.00
Physically Active [†]	20 (40.8)	7 (38.9)	13 (41.9)	0.31
Hypercholesterolemia	9 (18)	1 (5.5)	8 (25.8)	0.13
Family History of CVD	17 (36)	4 (23.5)	12 (41.4)	0.22
Office Systolic BP (mmHg), mean (SD)	112.7 (11.4)	111.7 (15.0)	113.5 (9.1)	0.60
Office Diastolic BP (mmHg), mean (SD)	76.2 (8.1)	76.0 (9.4)	76.4 (7.5)	0.88
Psychosocial Scores				
Depressed [‡]	4 (8.1)	2 (11.1)	2 (6.5)	0.24
Anxious [§]	3(6.1)	1 (5.6)	2 (6.5)	1.00
Supported	16(32.7)	5 (27.8)	11 (35.5)	0.81
Severe Menopausal Symptoms [¶]	30(61.2)	14 (77.8)	16 (51.6)	0.13

Poor sleep[#] 30(61.2) 11 (61.1) 19 (61.3) 1.00

Data are reported as numbers and percentage of individuals, n (%), unless otherwise specified.

Abbreviations: CVD, cardiovascular disease; BMI, body mass index; BP, blood pressure; SD, standard deviation

*Drinking more than 2 drinks a day

†Godin Activity rate estimating METs/week \geq 35

‡Patient Health Questionnaire 9 >19/36

§ State Trait Anxiety Inventory >54/80

|| Multidimensional Scale of Perceived Social Support, upper tertile

¶ Menopausal Rating Scale >20

Pittsburgh Sleep Quality Index \geq 5

Table 2. Blood Pressure Variability and Vascular Markers in Healthy Perimenopausal Women

	All (n=49)	Premenopausal (n=18)	Postmenopausal (n=31)	p value
Blood Pressure Variability				
CV of Day-to-day Systolic BP Variability	7.5 (1.8)	7.7 (1.5)	7.4 (1.9)	0.64
CV of Day-to-day Diastolic BP Variability	7.1 (1.9)	6.8 (1.9)	7.3 (1.8)	0.42
CV of 24 hr Systolic BP Variability	11.5 (2.4)	11.7 (1.8)	11.5 (2.8)	0.81
CV of 24 hr Diastolic BP Variability	15.9 (4.2)	15.3 (3.3)	16.2 (4.6)	0.45
Non-dipping n, %	20 (40.8)	6 (33.3)	14 (45.2)	0.20
Max Daytime BP, Systolic (mmHg)	158.3 (25.3)	146.8 (31.5)	165.0 (18.8)	0.51

Max Daytime BP, Diastolic (mmHg)	87.9 (24.1)	89.4 (31.6)	87.0 (19.8)	0.75
Max Overnight BP, Systolic(mmHg)	144.8 (23.1)	125.6 (27.2)	155.9 (19.1)	0.46
Max Overnight BP, Diastolic (mmHg)	70.7 (14.8)	72.5 (17.6)	69.7 (13.5)	0.55
Vascular Health				
Carotid-Femoral PWV (m/s)	7.15 (1.51)	7.16 (2.14)	7.15 (1.03)	0.98
Carotid Intimal Medial Thickness (mm)	0.57 (0.06)	0.57 (0.05)	0.57 (0.07)	0.76
Ln (Reactive Hyperemic Index)	0.80 (0.28)	0.82 (0.5)	0.79 (0.27)	0.68

Data are reported as the mean and standard deviation unless otherwise specified

Abbreviations: CV, coefficient of variation; SBP, blood pressure; PWV, pulse wave velocity

Table 3. Multivariate Models of Factors Associated with Different Measures of BPV

Variables	24hr CV		Night Dipping		Max Daytime BP,		Max Overnight BP,	
	β	p	β	p	β	p	β	p
Age	0.14 [-0.22- 0.49]	0.4	0.43 [-0.37-1.24]	0.28	0.29 [-1.32-1.9]	0.72	0.02 [-0.76-0.8]	0.95
Body Mass Index	-0.04 [-0.38- 0.3]	0.8	0.59 [-0.3-1.47]	0.19	2.46 [0.69-4.23]	0.01	1.95 [1.09-2.81]	<0.01
Smoking	-1.45 [-5.29- 2.4]	0.4	-2.64 [-11.84-6.55]	0.56	4.23 [-14.16- 22.61]	0.64	3.05 [-5.85-11.95]	0.49
Heavy	-0.06 [-3.95-	0.9	-0.64 [-9.65-8.36]	0.87	3.04 [-14.97-	0.73	-2.25 [-10.97-6.47]	0.60

Drinking	3.83]	8			21.04]			
Activity	0.23	0.8	-0.58	0.86	-6.66	0.32	-2.22	0.49
	[-2.54-	7	[-7.27-6.12]		[-20.04-6.73]		[-8.71-4.26]	
	3.01]							
Poor sleep	-0.97	0.4	3.95	0.24	5.12	0.44	5.04	0.12
	[-3.78-	9	[-2.76-10.65]		[-8.29-18.52]		[-1.46-11.53]	
	1.84]							
Mean BP*	-	-	0.05	0.83	0.87	0.08	0.71	<0.01
			[-0.44-0.55]		[-0.12-1.86]		[0.23-1.19]	

* Mean BP was not included in the model for 24-hour CV since it is already accounted for (CV=SD/mean)

Abbreviations: BP, blood pressure; BPV, blood pressure variability; CV, coefficient of variation

BPV Measures	Model 1		Model 2		Model 3	
	β	p value	β	p value	β	p value
Max Overnight BP, Diastolic (mmHg)	0.003	<0.01	0.055	<0.01	0.047	0.01
	[0.039-		[0.022-		[0.013-	
	0.086]		0.089]		0.08]	
Max Daytime BP, Diastolic (mmHg)	0.029	<0.01	0.014	0.16	0.008	0.38
	[0.013-		[-0.006-		[-0.011-	
	0.045]		0.034]		0.027]	
Night Dipping, Diastolic BP (%)	0.048	0.03	0.037	0.07	0.021	0.27
	[0.004-		[-0.003-		[-0.017-	
	0.092]		0.076]		0.06]	

Legend: Model 1 was unadjusted; Model 2 adjusted for body mass index and physical activity; Model 3 adjusted for body mass index, physical activity, poor sleep, menopausal status, hours of housework, confidence dealing with stress, smoking status and age.

Abbreviations: BP, blood pressure; BPV, blood pressure variability

Table 4. Unadjusted and Adjusted Multivariate Models for cf-PWV in Healthy Perimenopause Women

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