Received: 31 July 2017 | Revised: 2 October 2017 | Accepted: 20 October 2017

DOI: 10.1111/jch.13171

ORIGINAL PAPER

WILEY

Association of ambulatory blood pressure variability with coronary artery calcium

Bailey DeBarmore MHS, RDN[1] | Feng-Chang Lin PhD[2,3] | Laura A. Tuttle CCRP[4] | Emily Olsson CCRP[4] | Alan Hinderliter MD[5] | Jeffrey L. Klein MD[5] | Anthony J. Viera MD, MPH[4]

[1]Department of Epidemiology, Gillings School of Global, Public Health University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[2]Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[3]Translational and Clinical Sciences Institute, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[4]Department of Family Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[5]Department of Medicine, Division of Cardiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Correspondence
Bailey DeBarmore, MHS, RDN, University of North Carolina at Chapel Hill School of Public Health, Chapel Hill, NC, USA.
Email: bdebarmo@live.unc.edu

Funding information
National Heart, Lung, and Blood Institute, grant numbers: R01 HL098604T32 and HL00705541ULI RR025747.

Blood pressure (BP) variability is associated with progression to clinical atherosclerosis. The evidence is inconclusive if BP variability predicts cardiovascular outcomes in low-risk populations. The aim of this study was to analyze the association of 24-hour BP variability with coronary artery calcium (CAC) among a group of individuals without coronary artery disease. The Masked Hypertension Study targeted patients with borderline high BP (120–149 mm Hg systolic and/or 80-95 mm Hg diastolic). Ambulatory blood pressure monitoring (ABPM) was performed at two time-points, 8 days apart. CAC was measured at exit visit via cardiac CT and reported as Agatston Score. Weighted standard deviations and average real variability were calculated from ABPM. Of the 322 participants who underwent cardiac CT, 26% (84) had CAC present, 52% (168) were female, and 21% (64) were black. BP variability did not differ by CAC group. In this low cardiovascular risk group, CAC was not associated with 24-hour ambulatory BP variability.

1 | INTRODUCTION

Hypertension is the most prevalent and treatable cardiovascular risk factor and is associated with an increased risk of myocardial infarction, stroke, renal failure, and death.[1] Traditional cardiovascular risk factors include family history of coronary heart disease, history of smoking, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, hypertension, and diabetes.[2] In patients at increased cardiovascular disease risk, increased blood pressure (BP) variability may be a stronger predictor of cardiovascular morbidity and mortality than mean BP values.[3-5] BP variability has been associated with progression from subclinical to clinical atherosclerosis in addition to development and severity of vascular and renal organ damage.[4] Visit-to-visit BP variability has been associated with increased risk of stroke and masked hypertension among those with existing cardiovascular disease.[3,6] The current evidence for BP variability as a predictor of cardiovascular outcomes in low risk cardiovascular populations remains inconclusive.[7,8]

Blood pressure can be measured in clinic visits, at home, or via ambulatory monitoring. Clinic measurements and home measurements provide one to a few BP values at a time, and variability can be assessed by indices between clinic visits or days of home BP measurements.[8] In contrast, ambulatory BP monitoring (ABPM) provides intermittent BP measurements throughout 24 hours, allowing for minimum and maximum difference calculations, assessment of nighttime dipping, and daytime and nighttime BP variability.

Coronary artery calcification (CAC) reflects the presence and extent of subclinical coronary atherosclerosis. Traditional

cardiovascular risk factors, such as older age, diabetes, dyslipidemia, hypertension, male sex, and smoking are also risk factors for coronary calcification,[9] as are chronic inflammation and calcium imbalance. An interesting subgroup of the general adult population is patients who have CAC, but are otherwise free of cardiovascular risk factors. Research demonstrates that this subgroup experiences a higher incidence of coronary events compared to those who are free of risk factors and do not have CAC.[2] CAC can be reported as Agatston score,[10] in ordinal score categories,[11] continuously, or as present/absent.[12]

Research has shown an association between visit-to-visit BP variability and CAC progression over 3-5 years.[6] To our knowledge, the relationship between 24-hour BP variability and CAC has not been examined. If short-term BP variability is a risk factor for coronary artery disease, drug therapy that reduces variability could be of benefit. The aim of the analyses we present in this paper was to analyze the association of short-term (24-hour) blood pressure variability with CAC among a group of individuals without a clinical history of coronary artery disease.

2 | METHODS

2.1 | Study setting and design

For the Masked Hypertension Study, participants were recruited mostly from 12 primary care clinics in central North Carolina using both passive and active recruitment methods. Flyers placed throughout participating clinics described a study of persons who were recently told their blood pressure was "a little high or borderline" along with additional eligibility criteria. Clinicians were also invited to refer eligible patients. Potential eligibility was confirmed via phone by a research assistant using most recent office blood pressure (BP) measurements, and again in person with a nurse BP measurement at the initial research appointment (visit 1).

This study sought to target patients with recent BP measurements between 120-149 mm Hg systolic and/or 80-95 mm Hg diastolic in office for the primary objective of classifying individuals with borderline office BP who may have had one of four BP phenotypes: sustained normotension, white-coat hypertension, masked hypertension, or sustained hypertension. Thus, those with higher blood pressures, who were more likely to have sustained hypertension, and those with lower blood pressures, who were more likely to be normotensive, were not eligible.

These analyses represent ancillary objectives to examine the association between ambulatory BP variability and CAC. The longitudinal flow of subject participation spanned 2.5 weeks, with the initial appointment (visit 1) occurring on day 1, visit 2 on day 2, visit 3 on day 9, and visit 4 on day 10. Ambulatory blood pressure monitors were worn between visit 1 and visit 2 (ABPM1) and between visit 3 and visit 4 (ABPM2). CAC was measured at the exit visit via cardiac CT, which occurred between days 10 and days 17 (Figure 1).

2.2 | Eligibility criteria

Patients were eligible for the initial research visit if they were at least 30 years of age, had a clinic systolic BP of 120-149 mm Hg or diastolic BP of 80-95 mm Hg, were able and willing to wear a BP monitor for 24-hours, able to make necessary clinic visits, and able to read and speak English. Potential participants were excluded for pregnancy, history of persistent atrial fibrillation or other arrhythmia, diabetes, known heart disease, history of dementia or other mental conditions precluding wearing of a 24-hour monitor, or currently taking antihypertensive medication. Patients were excluded at the initial research appointment if they had a systolic BP ≥ 160 mm Hg or ≤ 110 mm Hg, or a diastolic BP ≥ 100 mm Hg or ≤ 70 mm Hg measured in the research clinic.

2.3 | Measurements

All participants underwent a clinical and laboratory evaluation at their initial research visit. Age, race/ethnicity, smoking status, multiple research clinic blood pressures, and medications were collected and recorded. Weight and height were measured and body mass index was calculated. Blood and urine samples were collected for laboratory tests, including total cholesterol and HDL.

2.4 | Ambulatory blood pressure

Ambulatory BP monitors were fitted by trained research assistants and participants were provided with standard instructions, which have been described elsewhere.[13] The Oscar 2 has undergone independent validation for use in adults.[14,15] To be included in analyses, a participant had to have a minimum of 14 daytime readings.[13] Self-report was used to adjust for sleep and wake times.[16]

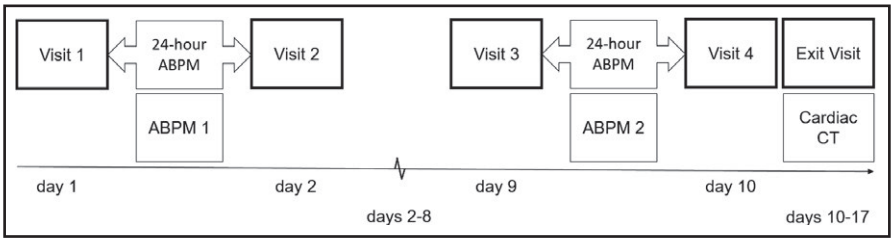

FIGURE 1 Subject participation spanned 2.5 weeks, with 24-hour ambulatory blood pressure monitors worn between visits 1 and 2, and visits 3 and 4. Coronary artery calcium (CAC) was measured at the exit visit via cardiac CT, occurring within a week following visit 4

Choice of standard deviation (SD), weighted SD (WSD), or average real variability (ARV) for assessing ambulatory BP variability is an important consideration in studying cardiovascular risk for several reasons. Standard deviations report the dispersion of values around the mean and WSD incorporates duration of BP highs and lows, however, neither considers the proximity of individual BP measurements together.[17]

Ambulatory 24-hour WSD was calculated by summing the weighted daytime and nighttime BP standard deviations, weighted by the number of BP readings in the daytime and nighttime period.

$$WSD = \frac{(SD_{daytime} * N_{daytime}) + (SD_{nighttime} * N_{nighttime})}{N_{daytime} + N_{nighttime}}$$

SD refers to the BP standard deviation for daytime or nighttime and N is the total number of BP readings for daytime or nighttime.

ARV is calculated by averaging the difference in absolute values of consecutive BP readings[17] and may better predict cardiovascular risk.[18] Ambulatory 24-hour ARV was calculated for systolic and diastolic BP using the following formula:[18]

$$ARV = \frac{1}{N-1} \sum_{K=1}^{N-1} |BP_{k+1} - BP_k|$$

where k ranges from 1 to N-1, and N is the total number of BP readings.

Spikes and sudden drops in blood pressure can only be captured in a variability measure such as ARV, which accounts for the order of BP measurements. Figure 2 compares ambulatory systolic blood pressure (SBP) variability measured with SD and ARV between 2 subjects. Considering only the SD values in analyses, these 2 subjects would appear the same with SD 14. However, the ARV values differ substantially, with subject A displaying frequent spikes and drops throughout the 24-hour period (ARV 16.7) and subject B displaying much less variability (ARV 5.9).

2.5 | Coronary artery calcium

CT scanning for coronary artery calcium was an optional assessment that most participants chose to undergo. Scans were conducted using a 64-slice MDCT dual source CT. An electrocardiogram signal from the participant was monitored to enable synchronization with the scanner. Scan parameters included tube voltage 120 kV, tube current 100 mAs/rotation collimation of 64 × 0.6 mm, and rotation time 330 ms, resulting in a temporal resolution of 0.87 ms. Sequential scanning mode was used when heart rate and scan time allowed to minimize radiation exposure, otherwise spiral acquisitions were performed. Approximate radiation exposure was 1-2 mSv for sequential scans and 2-3 mSv for spiral acquisitions. A standard calcium-scoring kernel (B35f) was used for reconstruction of the CT data. Images were reconstructed with a slice thickness of 3.0 mm. Calcifications were quantified with scoring software. All lesions with a detection threshold of >130 HU were marked by an experienced observer and the CAC load in each patient was computed using Agatston scoring. All studies were read by a single cardiologist (J.L.K.) with training and expertise in cardiac CT, blinded to patient characteristics.

Agatston scores were introduced in the 1990s and serve as a common clinical measure.[10] Agatston scores >100 and >400 have both previously been used as cutoffs to define patients at high-risk of cardiovascular events, with Agatston score = 0 defined as low risk.[12,19]

Participants were categorized as CAC present (Agatston score >0) or CAC absent (Agatston score = 0) for analyses. Some reports have suggested that the presence of any CAC (Agatston score >0) is considered clinically significant.[20]

2.6 | Data analysis

To measure ambulatory BP variability, weighted standard deviations (WSD) and average real variability (ARV) were calculated from 24-hour ambulatory systolic and diastolic BP between visit 1 and 2 (ABPM1) and between visit 3 and 4 (ABPM2). The number of participants with WSD may differ from those with ARV, as some participants did not have sufficient quality daytime or nighttime measurements to calculate the weighted average of the daytime and nighttime BP variation.

Mean WSD and ARV values for systolic and diastolic ABP were compared between those with CAC present vs those without CAC via Student t tests. We assessed the relationship between ARV, WSD, and Agatston score using Spearman correlations. We also assessed reproducibility of ABP variability measures between two sessions by calculating the Pearson's correlation coefficients and intraclass correlation

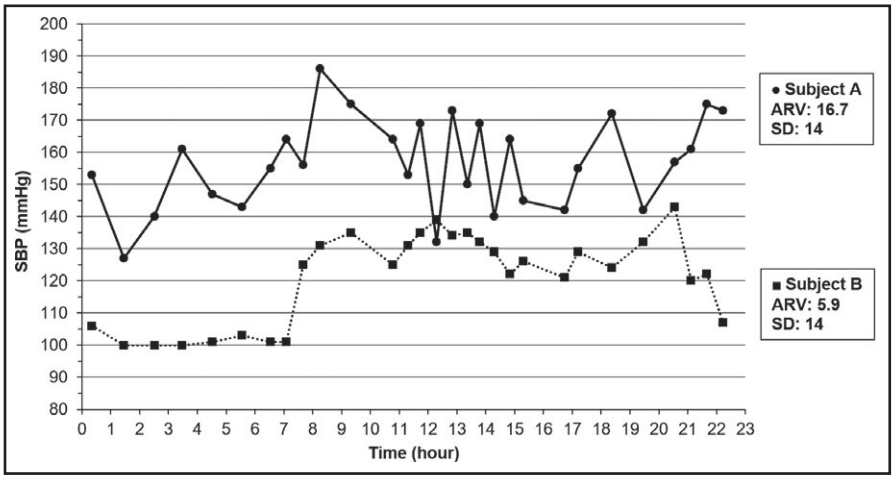

FIGURE 2 Comparison of 2 participants' ambulatory systolic blood pressure variability over 24-hour period through visualization, and calculation of average real variability (ARV) and standard deviation (SD). Data points for subject A display more variability from time-point to time-point compared to subject B. The ARV measure captures this contrast, but the SD does not

TABLE 1 Participant characteristics

	Total	Calcium not present	Calcium present
N	322	238	84
Age group (%)			
30-44 y	133 (41)	123 (52)	10 (12)
45-64 y	160 (50)	103 (43)	57 (68
≥65 y	29 (9)	12 (5)	17 (20)
Female	168 (52)	146 (61)	22 (26)
Race (%)			
White	246 (76)	173 (73)	73 (87)
Black	64 (20)	56 (24)	8 (10)
Other	12 (4)	9 (4)	3 (4)
Education level (%)			
Some high school	3 (1)	3 (1)	0
High school graduate	18 (6)	12 (5)	6 (7)
Some college	66 (20)	48 (20)	18 (21)
College graduate	235 (73)	175 (74)	60 (71)
Insurance status (%)			
Private	236 (73)	180 (76)	56 (67)
Public	38 (12)	28 (12)	10 (12)
Both	23 (7)	11 (5)	12 (15)
Uninsured	23 (7)	18 (8)	5 (6)
Self-reported health (%)			
Excellent/very good	217 (67)	155 (65)	62 (74)
Good	88 (27)	68 (29)	20 (24)
Fair or poor	17 (5)	15 (6)	2 (2)
Current smoker (%)	19 (6)	13 (5)	6 (7)
Alcohol drinker (%)	50 (16)	37 (16)	13 (16)
Married or living with partner (%)	209 (65)	148 (63)	61 (73)
BMI (%)			
Normal (<25 kg/m^2)	81 (25)	61 (26)	20 (24)
Overweight (25-29 kg/m^2)	116 (36)	82 (35)	34 (41)
Obese (≥30 kg/m^2)	125 (39)	95 (40)	30 (36)
Agatston score[a]	0 (1.9)	0 (0)	31 (137)
SBP ARV[b]		12.3 (2.7)	12.8 (2.9)
SBP WSD[b]		12.7 (3.0)	13.4 (3.1)
DBP ARV[b]		9.1 (2.2)	8.7 (2.2)
DBP WSD[b]		9.6 (2.4)	9.5 (2.4)
Total cholesterol	200 (38)	200 (37)	202 (39)
HDL cholesterol	57 (18)	58 (19)	52 (13)
Non-fasting glucose	88 (13)	87 (12)	91 (13)
Clinic blood pressure[b]			
SBP	129 (12)	128 (11)	131 (14)
DBP	78 (9)	80 (9)	80 (10)
Ambulatory blood pressure[b]			
SBP	138 (13)	138 (13)	137 (13)
DBP	81 (8)	82 (8)	80 (9)

DBP, diastolic blood pressure; SBP, systolic blood pressure; BMI, body mass index. HDL, high density lipoprotein; WSD, weighted standard deviations.

Total cholesterol, HDL cholesterol, and non-fasting glucose in mg/dL. Clinic and ambulatory blood pressure in mm Hg.

N (Column %) or Mean (SD).

[a]Agatston Score; Median (IQR). "Other" race: Asian or other. Alcohol drinker defined as 5 or more drinks per month.

[b]Clinic blood pressure measured at visit 4. Ambulatory blood pressure reported from ambulatory data between visits 3 and 4 (ABPM 2). BP variability (ARV average real variability and WSD weighted standard deviation) reported for ABPM 2.

coefficients (ICC) for both systolic and diastolic blood pressure variability. Finally, we explored the independent effect of CAC on ABP variability using linear regression for systolic blood pressure variability at the second time-point, adjusting for confounders (age, sex, race, education level, smoking status, alcohol drinking, BMI, total cholesterol, average SBP, and average DBP). As a sensitivity analysis, we repeated the regression analysis using Agatston score as a continuous variable in the association with ARV and WSD. Analyses were done using SAS 9.4 and figures were created using StataIC version 14.

3 | RESULTS

3.1 | Study population

Of the 322 participants who underwent cardiac CT, 26% (84) had CAC present on their scan, 52% (168) were female, and 21% (64) were black (Table 1). Most participants in the study population were between the ages of 30 and 64 (91%), had at least some college (20%) or a college degree (73%), had private insurance (73%), and described their health as "excellent" or "very good" (67%). Over half of participants reported being married or living with their partner, 16% reported consuming at least 5 alcoholic drinks per month, and 6% were current smokers. These demographic and lifestyle measures were not statistically different across groups with and without CAC present.

Participants were near evenly distributed between body mass index (BMI) categories, with 25% in the normal range, 36% in the overweight range, and 39% in the obese range. Median Agatston score among those with CAC present was 31 (IQR: 137), with a range among all participants of 0 to 5985. Mean total cholesterol was 200 mg/dL (SD: 38 mg/dL) and HDL cholesterol was 57 mg/dL (SD: 18 mg/dL). Half of the participants had total cholesterol below 200 mg/dL (48%) and the majority had HDL cholesterol at least 50 mg/dL or higher (60%). Average ambulatory SBP was slightly higher than research

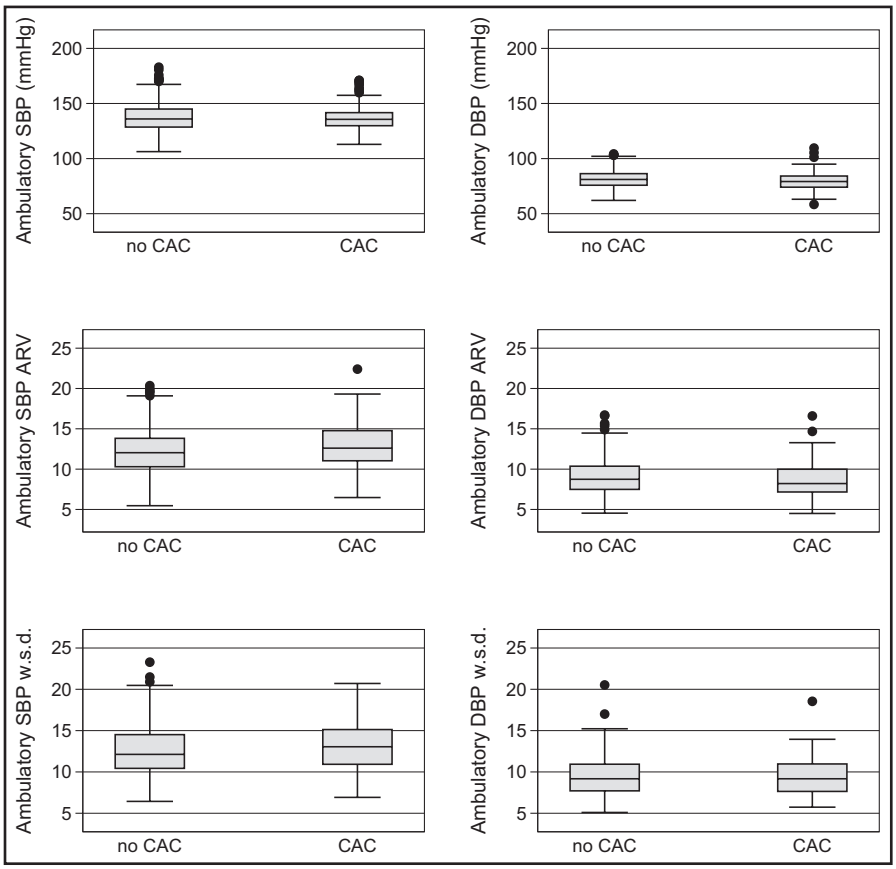

FIGURE 3 Distribution of ambulatory BP, average real variability (ARV), and weighted standard deviation (WSD) by coronary artery calcium (CAC) status. Top panel shows distribution of mean ambulatory systolic BP (SBP) and diastolic BP (DBP) by CAC status (yes/no). Middle and bottom panel shows distribution of ambulatory BP variability, measured by ARV and WSD, by CAC status. WSD: weighted standard deviation. ARV: average real variability

clinic SBP in those with and without CAC present (138 ± 13 mm Hg vs 129 ± 12 mm Hg, respectively), but diastolic BP (DBP) values were similar. Based on traditional cardiovascular risk factors, this patient population represents a relatively low cardiovascular risk group.

3.2 | Ambulatory blood pressure variability and CAC

Neither ambulatory systolic nor diastolic BP on average differed notably between CAC groups (Table 1, Figure 3). Mean ambulatory BP variability did not differ by CAC groups (Table 1) in either measure of variability (WSD and ARV) or between sessions (ABPM1 vs ABPM2) (Table 1). In the correlation analyses, neither measure of variability correlated well with Agatston score (Table 2). However, the ARV correlated well with WSD for both SBP and DBP in at the 2nd time-point (Table 2) and when comparing paired sessions for each participant (Figure 4), where Pearson's correlation coefficients ranged from 0.38 to 0.51. The reproducibility assessed by ICC was significant. The ARV in DBP has the largest intraclass correlation coefficient (ICC 0.52, 95% CI: 0.44-0.60), while the ARV in SBP has the smallest intraclass correlation coefficient (ICC 0.39, 95% CI: 0.30-0.49; Figure 4).

Using linear regression for variability in the 2nd, we found that there was no statistically significant association between CAC presence and BP variability, even after adjustment for age, sex, race, and education (Model 1), as well as further adjustment for smoking, alcohol

TABLE 2 Correlation between ARV, WSD, and Agatston score

	SBP WSD	DBP ARV	DBP WSD	Agatston Score
SBP ARV	0.76	0.56	0.51	0.04
	<0.001	<0.001	<0.001	0.347
SBP WSD		0.50	0.68	−0.03
		<0.001	<0.001	0.538
DBP ARV			0.79	0.00
			<0.001	0.973
DBP WSD				−0.05
				0.271

ARV, average real variability; DBP, diastolic blood pressure; SBP, systolic blood pressure; WSD, weighted standard deviation.
Pearson correlation coefficients (first row in cell), *P*-value (second row).

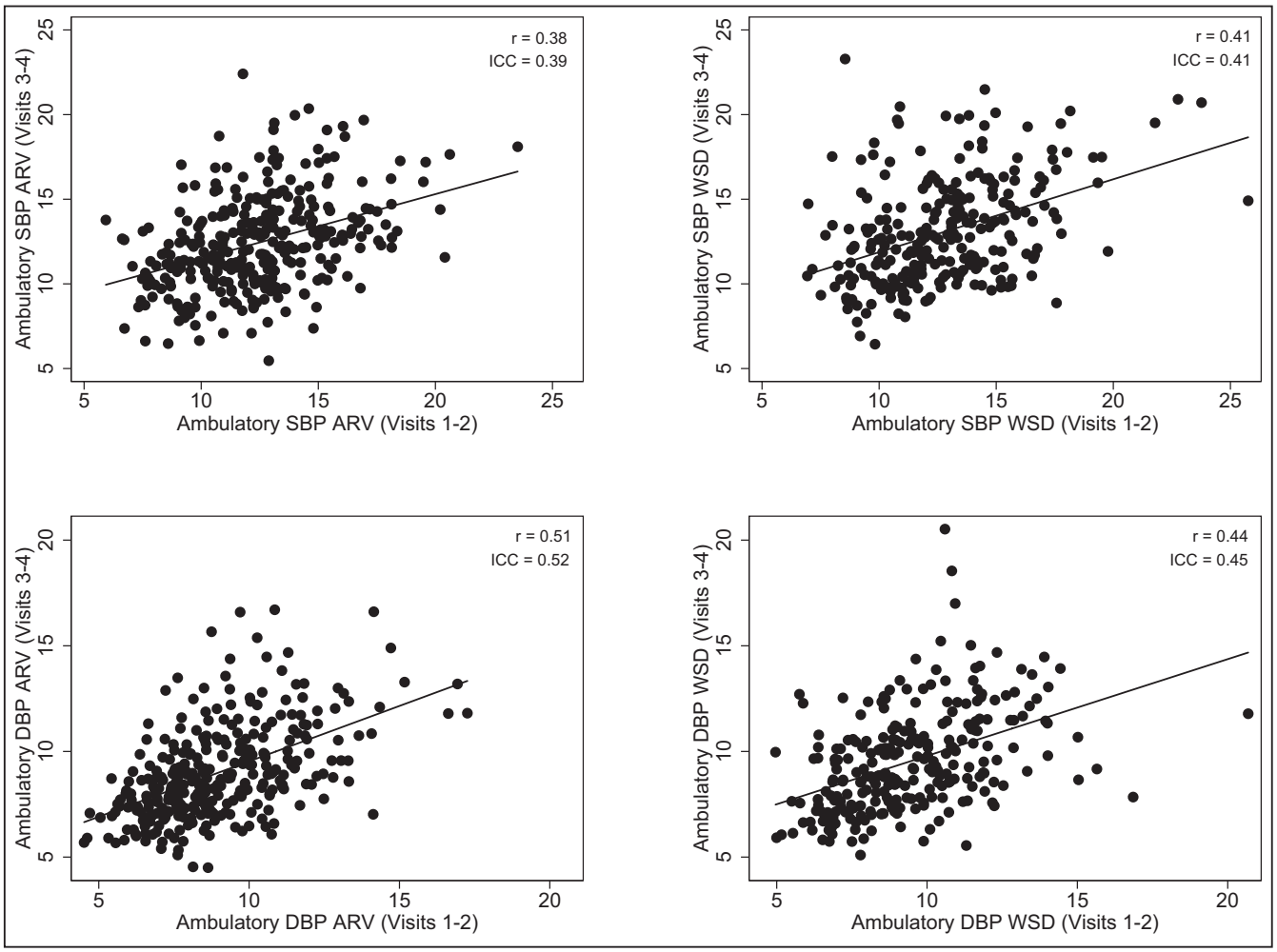

FIGURE 4 Correlation between Visit 1-2 and Visit 3-4 ambulatory blood pressure variability. Top panel shows correlation of ambulatory systolic BP (SBP) WSD and ARV between ABPM1 and ABPM2. Bottom panel shows correlation of ambulatory diastolic BP (DBP) WSD. and ARV between ABPM1 and ABPM2. Pearson *rho* coefficients and intraclass correlation (ICC) noted in top right corners. ARV: average real variability; WSD: weighted standard deviation

use, BMI, total cholesterol, average SBP, or average DBP (Model 2). When modeling the relationship with the continuous Agatston score, we did not see appreciable change in the point estimates with adjustment (Crude: Beta 0.0003, Model 1: 0.0001, Model 2: 0.0001; Table 3), but we did see a difference in the point estimates using dichotomized CAC (Crude: Beta 0.53, Model 1: 0.23, Model 2: 0.34; Table 3). The model fit improved significantly using Model 2 covariates, as assessed via likelihood ratio tests (*P*-values shown, Table 3).

4 | DISCUSSION

In these Masked Hypertension Study analyses, we utilized ABPM data to describe the association of short-term ambulatory BP variability with CAC, a marker of subclinical vascular disease, in a cohort at low risk of cardiovascular events. There was no difference in ambulatory BP variability by CAC presence when comparing mean WSD and ARV values. Given the lack of evidence for an association in comparing the means across CAC groups for both ARV and WSD, for both systolic and diastolic, and for both time-points, we posit that 24-hour ambulatory BP variability may not be associated with coronary calcification in a low cardiovascular risk group. We did find that ARV and WSD are well correlated, and that the implications of our analyses did not differ depending on the variability measure we chose. However, previous research has shown different conclusions using ARV vs SD or WSD.[17,18]

Limitations of these analyses include the small sample size of 322 participants with CAC measured and the even smaller number with CAC present, as these were secondary analyses and study design was not based on a power calculation specific to this question. The absence of other major risk factors for coronary artery disease may mitigate the detrimental effects of BP variability. It is plausible that BP variability would be associated with CAC, as it may be related to the pathophysiology of blood pressure and calcification; however, variation over a 24-hour period compared to visit-to-visit variability represent temporally different questions. As the parent study of these analyses was designed to examine short-term reproducibility of ABPM, these data are cross-sectional in nature, which limits their applicability to other research questions. Also, these

TABLE 3 Crude and adjusted association of Agatston score with 2nd time-point ambulatory systolic blood pressure variability

Systolic BP ARV				
	Beta	**95% CI**	**Wald *P*-value***	**Model *P*-value†**
Agatston score				
Crude	0.0003	−0.005, 0.001	.425	–
Model 1	0.0001	−0.001, 0.001	.763	.04
Model 2	0.0001	−0.001, 0.001	.840	<.0001
CAC > 0				
Crude	0.53	0.04, 1.02	.034	–
Model 1	0.23	−0.58, 1.04	.576	.08
Model 2	0.34	−0.39, 1.06	.359	<.0001
Systolic BP WSD				
	Beta	**95% CI**	**Wald *P*-value***	**Model *P*-value†**
Agatston score				
Crude	−0.0002	−0.001, 0.001	.680	–
Model 1	−0.0006	−0.001, 0.0003	.227	.04
Model 2	−0.0006	−0.001, 0.0002	.145	<.0001
CAC > 0				
Crude	0.69	0.13, 1.25	.017	–
Model 1	0.13	−0.80, 1.08	.779	.19
Model 2	0.25	−0.62, 1.12	.576	<.0001

Beta coefficient represents the estimated change in second time-point SBP average real variability (or weighted standard deviation) for a 1-unit change in Agatston score (or for coronary artery calcium (CAC) > 0 vs CAC = 0), fit with linear regression. Model 1 adjusted for age (years), sex (male/female), race (white (ref), black, other), and education (did not finish high school (ref), finished high school, college). Model 2 adjusted for covariates of Model 1 + smoker (yes/no), alcohol drinker (yes/no), body mass index (kg/m^2), total cholesterol ($\log_{10}$), ambulatory SBP (mm Hg) and ambulatory DBP (mm Hg).

*Wald *P*-value tests whether Beta = 0.

†Model *P*-value represents the *P*-value for the likelihood ratio test, comparing the full model to the crude model. A significant model *P*-value indicates an improved fit compared to the crude model.

results may be limited in their generalizability, as our sample was made up primarily of well-educated, English-speaking participants.

Other researchers have found that BP variability does not provide additional risk stratification or prognostic value beyond BP level for cardiovascular risk.[7,8,21] However, in hypertensive patients, a number of studies found independent prognostic utility of BP variability in cardiovascular risk prediction[4,5,22] and cardiovascular and cerebrovascular events.[3-5] Conflicting findings may be due to study population differences, specifically comparing high cardiovascular risk patients to low-to-moderate risk patients, and not due to a lack of relationship between BP variability, cardiovascular risk, and coronary artery calcification.

Future studies could aim to include individuals with a family history of early-onset coronary artery disease to assess if ambulatory BP variability is associated with CAC in this subgroup as an additional way to stratify risk.

5 | CONCLUSIONS

In this sample of 322 low cardiovascular risk individuals coronary artery calcification was not associated with increased 24-hour ambulatory blood pressure variability.

ACKNOWLEDGMENTS

This study was funded by grant R01 HL098604 from the National Heart Lung and Blood Institute with additional support provided by ULI RR025747 from the National Institutes of Health. B.M.D. receives support from the NIH T32 Grant HL00705541. There are no other funding disclosures.

CONFLICTS OF INTEREST

Dr. Viera has served on the Medical Advisory Board for Suntech Medical, a manufacturer of a brand of ambulatory blood pressure monitor. There are no other conflicts of interest.

AUTHOR CONTRIBUTIONS

B.D., F.C.L, and A.J.V were responsible for drafting and revising the manuscript. B.D. and F.C.L. were responsible for the data analysis. L.A.T., E.O., A.H., and J.L.K. contributed to revising the manuscript. L.A.T and E.O. were responsible for management of study procedures and data collection.

ORCID

Bailey DeBarmore http://orcid.org/0000-0002-9911-0917

Anthony J. Viera http://orcid.org/0000-0001-5770-2052

REFERENCES

1. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults. *JAMA*. 2014;311:507.
2. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358:1336-1345.
3. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895-905.
4. Parati G, Ochoa JE, Lombardi C, Bilo G. Blood pressure variability: assessment, predictive value, and potential as a therapeutic target. *Curr Hypertens Rep*. 2015;17:1-18.
5. Zawadzki MJ, Small AK, Gerin W. Ambulatory blood pressure variability. *Blood Press Monit*. 2017;22:53-58.
6. Okada H, Fukui M, Tanaka M, et al. Visit-to-visit variability in systolic blood pressure is a novel risk factor for the progression of coronary artery calcification. *Hypertens Res*. 2013;36:996-999.
7. Dolan E, O'Brien E. Is it daily, monthly, or yearly blood pressure variability that enhances cardiovascular risk? *Curr Cardiol Rep*. 2015;17:15-19.
8. Asayama K, Schutte R, Li Y, Hansen TW, Staessen JA. Blood pressure variability in risk stratification: what does it add? *Clin Exp Pharmacol Physiol*. 2014;41:1-8.
9. Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Généreux P. Coronary artery calcification: pathogenesis and prognostic implications. *J Am Coll Cardiol*. 2014;63:1703-1714.
10. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15:827-832.
11. Blair KJ, Allison MA, Morgan C, et al. Comparison of ordinal versus Agatston coronary calcification scoring for cardiovascular disease mortality in community-living individuals. *Int J Cardiovasc Imaging*. 2014;30:813-818.
12. Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. *JACC Cardiovasc Imaging*. 2009;2:675-688.
13. Viera AJ, Lin F-C, Tuttle LA, et al. Reproducibility of masked hypertension among adults 30 years and older. *Blood Press Monit*. 2014;19:208-215.
14. Goodwin J, Bilous M, Winship S, Finn P, Jones SC. Validation of the Oscar 2 oscillometric 24-h ambulatory blood pressure monitor according to the British Hypertension Society protocol. *Blood Press Monit*. 2007;12:113-117.
15. Jones SC, Bilous M, Winship S, Finn P, Goodwin J. Validation of the OSCAR 2 oscillometric 24-hour ambulatory blood pressure monitor according to the International Protocol for the validation of blood pressure measuring devices. *Blood Press Monit*. 2004;9:219-223.
16. Booth JN III, Muntner P, Diaz KM, et al. Evaluation of criteria to detect masked hypertension. *J. Clin. Hypertens*. 2016;18:1086-1094.
17. Mulè G, Calcaterra I, Costanzo M, et al. Average real variability of 24-h systolic blood pressure is associated with microalbuminuria in patients with primary hypertension. *J Hum Hypertens*. 2016;30:164-170.
18. Mena L, Pintos S, Queipo NV, Aizpurua JA, Maestre G, Sulbaran T. A reliable index for the prognostic significance of blood pressure variability. *J Hypertens*. 2005;23:505-511.
19. Blaha M, Budoff MJ, Shaw LJ, et al. Absence of coronary artery calcification and all-cause mortality. *JACC Cardiovasc Imaging*. 2009;2:692-700.
20. Naghavi M, Falk E, Hecht HS, et al. From vulnerable plaque to vulnerable patient-part III: executive summary of the screening for heart attack prevention and education (SHAPE) task force report. *Am J Cardiol*. 2006;98(Suppl 1):2-15.
21. Boggia J, Asayama K, Li Y, Hansen TW, Mena L, Schutte R. Cardiovascular risk stratification and blood pressure variability on ambulatory and home blood pressure measurement. *Curr Hypertens Rep*. 2014;16:1-10.
22. Pierdomenico SD, Di Nicola MA, Esposito AL, et al. Prognostic value of different indices of blood pressure variability in hypertensive patients. *Am J Hypertens*. 2009;22:842-847.

How to cite this article: DeBarmore B, Lin F-C, Tuttle LA, et al. Association of ambulatory blood pressure variability with coronary artery calcium. *J Clin Hypertens*. 2018;20:289–296. https://doi.org/10.1111/jch.13171