Original Article

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Association of ambulatory blood pressure with aortic valve and coronary artery calcification

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Objective: We aimed to investigate the effect of ambulatory blood pressure (BP) on aortic valve calcification (AVC) and coronary artery calcification (CAC), which are subclinical atherosclerotic diseases.

Methods: In this population-based, cross-sectional study, we assessed office BP, mean ambulatory BP (24-h, awake, and asleep), and variability of ambulatory BP, as determined by the coefficient of variation (awake and asleep). AVC and CAC were quantified using an Agatston score (>0) based on computed tomography scanning. We calculated relative risks (RRs) and 95% confidence intervals (CIs) with a 1-standard deviation increment in each BP index for the presence of AVC and CAC using a multivariate-adjusted Poisson regression with robust error variance.

Results: Of 483 participants (mean age: 66.8 years), 154 (31.9%) and 310 (64.2%) had AVC and CAC, respectively. The presence of AVC was associated with office systolic BP (SBP; RR, 1.15; 95% CI, 1.03–1.28), awake diastolic BP (DBP) variability (RR, 1.12; 95% CI, 1.01–1.25), and asleep SBP variability (RR, 1.14; 95% CI, 1.03–1.27). The presence of CAC was associated with office SBP (RR, 1.08; 95% CI, 1.01–1.15), mean 24-h SBP (RR, 1.10; 95% CI, 1.04–1.16), mean awake SBP (RR, 1.11; 95% CI, 1.04–1.17), mean asleep SBP (RR, 1.07; 95% CI, 1.01–1.13), and asleep SBP variability (RR, 1.07; 95% CI, 1.01–1.13).

Conclusion: These findings highlight the association of ambulatory BP indices with both AVC and CAC, but with different effects on their presences.

Keywords: ambulatory blood pressure, aortic valve calcification, blood pressure variability, coronary artery calcification

Abbreviations: AVC, aortic valve calcification; CAC, coronary artery calcification; CV, coefficient of variation; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis

INTRODUCTION

Aortic valve calcification (AVC) and coronary artery calcification (CAC) are crucial subclinical atherosclerotic diseases that are associated with an increased risk of cardiovascular diseases (CVDs) [1,2]. Lipid infiltration and chronic inflammation play an important role in the development of AVC and CAC [3,4], and conventional atherosclerotic risk factors, such as age, body mass index (BMI), smoking, dyslipidemia, diabetes mellitus, and hypertension, contribute to the pathogenesis of AVC and CAC [5–7]. Although AVC and CAC are closely correlated with each other, they have independent prognostic values [8].

Elevated blood pressure (BP) is a potentially modifiable risk factor for CVDs [9], and its prevalence is high, particularly in the East Asian and Pacific regions [10]. Recent international hypertension management guidelines place increasing weight on BP measurement methods outside the medical office (e.g., 24-h ambulatory BP measurement) to assess CVD risk [11–13]. Indeed, 24-h ambulatory BP measurements are superior to conventional office BP measurements in predicting CVDs [14]. However, to date, few studies have investigated the association between ambulatory BP and AVC [15]. Studies on the association between ambulatory BP and CAC have yielded conflicting results; some suggest an association with systolic BP (SBP) alone [16], with diastolic BP (DBP) alone [17], or with both SBP and DBP [18]. Moreover, independent of absolute ambulatory BP levels, awake or asleep BP variability, based on ambulatory BP measurements, has a prognostic implication for CVDs [19–21], although its association with AVC or CAC remains unknown.

Therefore, we aimed to investigate the effect of ambulatory BP indices (mean 24-h/awake/asleep values and awake/asleep variability) on AVC and CAC burden in

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apparently healthy Japanese men from a population-based cohort. Identification of the factors associated with AVC and CAC can potentially lead to a decreased CVD risk.

METHODS

Data source and study population

The Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) is an ongoing prospective, population-based cohort of a sample of apparently healthy Japanese men. The study design and recruitment details have been previously reported [22]. In brief, from May 2006 through March 2008, residents of Kusatsu City, Shiga, were randomly selected based on the Basic Resident Registry of the city. We invited 2379 Japanese men aged 40–79 years to participate in the study; a total of 1094 men agreed to a baseline examination. In follow-up examinations conducted from October 2010 through August 2014, 853 of the participants were reassessed. Furthermore, we invited all 853 participants who had taken the follow-up examination; among these participants, 326 declined to be examined, and the remaining 527 received a more extensive cardiovascular evaluation, including ambulatory BP measurement, from October 2014 to September 2015. In this study, we excluded a total of 44 participants with a history of stroke ($n = 23$), myocardial infarction ($n = 9$), triglyceride level $\geq$400 mg/dl ($n = 7$; because Friedewald's formula was applied to estimate low-density lipoprotein cholesterol [LDL-C] levels), and without computed tomography (CT) information ($n = 5$), and finally data from 483 participants were analyzed (mean age: 66.8 years; standard deviation [SD]: 7.2 years). All participants provided written informed consent. The study was approved by the Institutional Review Board of Shiga University of Medical Science.

Computed tomography protocol and image analysis

The detailed methodology for cardiac CT in SESSA has been previously published [22,23]. We determined the presence of AVC and CAC based on CT images during the follow-up examination in SESSA via a 16-channel multidetector-row CT using an Aquilion scanner (Canon Medical Systems, Tokyo, Japan). We acquired images at 70% of the cardiac cycle using an electrocardiogram triggering during a single breath-hold. The images were obtained from the level of the aortic root through the heart at a slice thickness of 3 mm and a scan time of 320 ms. The presence of AVC and CAC was defined as a minimum of three contiguous pixels with a density of at least 130 Hounsfield units and was determined using AccuImage software (AccuImage Diagnostics, South San Francisco, California, USA); this software implements the widely accepted Agatston method [24]. The total CAC score was calculated by multiplying the pixel area (mm^2) by the density score (1: 130–199 Hounsfield units; 2: 200–299 Hounsfield units; 3: 300–399 Hounsfield units; and 4: $\geq$400 Hounsfield units) derived from the maximal Hounsfield units within this area. The total AVC score was measured and quantified for any calcified lesion present within the aortic valve leaflets, using the same definition as that for CAC [25].

Office blood pressure measurement

A trained physician placed an appropriately-sized cuff on the right arm of each participant. After resting for 5 min while sitting in a silent room without crossing the legs or speaking, office BP was measured using an automated sphygmomanometer (BP-8800SF; Omron Healthcare Co. Ltd., Kyoto, Japan) [26]. The physician was completely out of the room before office BP measurement, and then returned and measured BP to minimize the white-coat effect and observer bias. Referring to the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) guideline [27] and the Japanese Society of Hypertension guideline [28] at the time of the baseline survey of our study, office BP was measured twice consecutively at an interval of 30 s; the mean of the two BP readings was used for analysis.

Ambulatory blood pressure measurement

At the time of this study, we referred to the ESH/ESC guideline in 2007 [27] and the Japanese Circulation Society guideline in 2010 [29]. The detailed method for the measurement of ambulatory BP in SESSA has been reported previously [30]. Ambulatory BP was measured with an appropriately-sized cuff on the patient's nondominant arm using a fully automatic cuff-oscillometric method device (FM 800; Fukuda Denshi, Tokyo, Japan) [31]. The device was set to measure BP every 30 min during the day and every 60 min during the night [32–34] in consideration of compliance and feasibility of the measurements. If arm pain or numbness developed because of frequent measurement, BP was measured every 60 min throughout the day. Artifactual ambulatory BP readings were defined according to the criteria described in the Ohasama Study [35] and omitted from the analysis: SBP $<$60 mmHg and mean BP $<$40 mmHg; SBP $>$250 mmHg and/or mean BP $>$200 mmHg with no similar preceding or subsequent respective value; pulse pressure $\leq$10 mmHg; and abrupt increase or decrease in systolic and/or mean BP, pulse pressure, and/or heart rate by $\geq$50% from the value measured immediately before or after the respective readings. We only analyzed ambulatory BP recordings in which valid readings were at least 70% of the expected readings [36]; no participants were excluded because of this criterion. The mean BP obtained via ambulatory BP assessment was calculated over a 24-h period and separately for awake and asleep times based on the actual awake and asleep times reported in the participant's diary. We also used the coefficient of variation (CV), which was derived by dividing the SD by the corresponding mean, as an index of ambulatory BP variability during the awake and asleep periods. CV can serve as a competent indicator of BP variability as it is less affected by BP levels and is relatively easy to calculate in clinical practice [37].

Covariate assessment

Blood samples were obtained after a 12-h fasting period and tested at a single laboratory (Shiga Laboratory; MEDIC, Shiga, Japan). Lipid measurements were standardized annually according to the protocol of the Centers for Disease Control and Prevention/Cholesterol Reference Method

Laboratory Network. Total cholesterol and triglycerides levels were measured using enzymatic assays, and high-density lipoprotein cholesterol (HDL-C) levels were measured using a direct method. Friedewald's formula was used to calculate LDL-C levels when the triglycerides level was <400 mg/dl. Plasma glucose levels were determined by sodium fluoride-treated plasma using a hexokinase glucose-6-phosphate-dehydrogenase enzymatic assay. Glycated hemoglobin (HbA1c) was measured using a latex agglutination assay according to the standardized method of the National Glycohemoglobin Standardization Program. Serum creatinine levels were measured using an enzymatic assay (Espa CRE-liquid II; NIPRO, Osaka, Japan). The estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2) was calculated using the serum creatinine levels: $194 \times \text{serum creatinine (mg/dl)}^{-1.094} \times \text{age}^{-0.287}$ [38].

Each participant provided data on their medical history and lifestyle factors using a self-administered questionnaire; trained technicians confirmed the accuracy of the completed questionnaires with the participants. Demographic characteristics, smoking status (i.e., current, former, or never), alcohol drinking status (yes and no), medication use (e.g., antihyperglycemic, antihypertensive, and antihyperlipidemic medication use), and medical history (e.g., stroke and myocardial infarction) were also recorded. BMI was calculated as weight (kg) divided by height squared (m^2). Hypertension was defined as office SBP ≥140 mmHg and/or office DBP ≥90 mmHg and/or taking antihypertensive medications. Diabetes mellitus was defined as HbA1c ≥6.5% and/or fasting plasma glucose level ≥126 mg/dL and/or taking antihyperglycemic medications.

Statistical analysis

Data were presented as the mean ± SD for continuous variables or numbers with percentages for categorical variables. Differences in patient characteristics were evaluated using an unpaired Student's *t*-test or chi-square test. For the main analysis, the presence of AVC [7,25] and CAC [39] was defined as a dichotomous variable with an Agatston score of >0. We performed multivariate-adjusted Poisson regression with robust error variance [40] to estimate the relative risks (RRs) and 95% confidence intervals (CIs) per 1-SD increment of each BP index for the presence of AVC and CAC; because the prevalence of both AVC and CAC was >10% in this cohort, odds ratios (ORs) could not be interpreted as RRs. In the model, we adjusted for the following potential confounding factors: age, smoking status (current, former, or never), alcohol drinking (yes or no), BMI, eGFR, LDL-C level, HDL-C level, diabetes mellitus (yes or no), antihypertensive medication use (yes or no), and antihyperlipidemic medication use (yes or no). In addition to general adjustments, ambulatory BP variability during the awake and asleep periods was adjusted by the mean BP levels during the awake and asleep periods, respectively.

For the sensitivity analysis, we stratified AVC and CAC into four categories according to the Agatston score (0, >0 and <100, ≥100 and <300, and ≥300), in line with previous studies [2,41,42], and evaluated their association with ambulatory BP indices using a multivariate ordinal logistic regression model adjusted for the same confounding factors as those in the main analysis. Furthermore, we conducted a stratified analysis by antihypertensive medication use and then examined the multiplicative interactions between antihypertensive medication use and BP indices for AVC and CAC. All statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). A two-sided *P*-value of <0.05 was considered statistically significant. Due to the explorative study design, we did not adjust for multiple testing, thereby considering significant results as hypothesis generation.

RESULTS

Of the 483 participants included in the analysis, 154 (31.9%) and 310 (64.2%) had AVC and CAC, respectively. The characteristics of the participants with or without AVC or CAC are shown in Table 1. Compared with participants without AVC, those with AVC were older and more likely to have a higher prevalence of diabetes mellitus, hypertension, antihypertensive medication use, and antihyperlipidemic medication use, as well as lower eGFR. Similarly, compared with participants without CAC, those with CAC were older and more likely to have a higher prevalence of diabetes mellitus, hypertension, antihypertensive medication use, and antihyperlipidemic medication use. In terms of BP indices, compared with participants without AVC, those with AVC had higher levels of office SBP, pulse pressure, ambulatory mean SBP over 24-h and while asleep, and all ambulatory BP variability, including SBP and DBP variability while awake and asleep. Meanwhile, compared with participants without CAC, those with CAC had higher levels of office SBP, pulse pressure; ambulatory mean SBP over 24-h, while awake, and while asleep; and ambulatory SBP variability while asleep.

Based on the Poisson regression with robust error variance, after adjusting for potential confounding covariates, the presence of AVC was significantly associated with office SBP (RR, 1.15; 95% CI, 1.03–1.28), awake DBP variability (RR, 1.12; 95% CI, 1.01–1.25), and asleep SBP variability (RR, 1.14; 95% CI, 1.03–1.27; Fig. 1A). However, the presence of CAC was associated with office SBP (RR, 1.08; 95% CI, 1.01–1.15), mean 24-h SBP (RR, 1.10; 95% CI, 1.04–1.16), mean awake SBP (RR, 1.11; 95% CI, 1.04–1.17), mean asleep SBP (RR, 1.07; 95% CI, 1.01–1.13), and asleep SBP variability (RR, 1.07; 95% CI, 1.01–1.13) after adjusting for the same covariates as those used for AVC (Fig. 1B). The sensitivity analysis showed that the point estimates of the BP indices for the presence of AVC were substantially equivalent to those in the main analysis, but not all were statistically significant (Figure S1A, Supplemental Digital Content, http://links.lww.com/HJH/B930). There was a significant association between CAC and office SBP (OR, 1.23; 95% CI, 1.03–1.46; $P = 0.020$), mean 24-h SBP (OR, 1.22; 95% CI, 1.03–1.45; $P = 0.022$), and mean awake SBP (OR, 1.24; 95% CI, 1.05–1.48; $P = 0.013$; Figure S1B, Supplemental Digital Content, http://links.lww.com/HJH/B930).

The association of AVC with office and ambulatory mean BP parameters was similar between participants with and without antihypertensive medication use (all *P* values for heterogeneity > 0.1). Additionally, its associations with ambulatory BP variability were similar between the two

TABLE 1. Characteristics of the participants with or without AVC or CAC

		AVC[a]			CAC[a]		
	Overall $n = 483$	Absence $n = 329$	Presence $n = 154$	*P* value	Absence $n = 173$	Presence $n = 310$	*P* value
Age (years)	66.8 ± 7.2	65.3 ± 7.7	70.1 ± 4.7	<0.001	64.4 ± 8.3	68.2 ± 6.2	<0.001
Smoking status, *n* (%)				0.107			0.104
Current	92 (19.1)	71 (21.6)	21 (13.6)		40 (23.1)	52 (16.8)	
Former	289 (59.8)	189 (57.5)	100 (64.9)		93 (53.8)	196 (63.2)	
Alcohol drinker, *n* (%)	393 (81.4)	273 (83.0)	120 (77.9)	0.184	143 (82.7)	250 (80.7)	0.586
Body mass index (kg/m^2)	23.3 ± 2.9	23.2 ± 2.9	23.6 ± 2.8	0.140	23.1 ± 3.0	23.4 ± 2.9	0.354
LDL-C (mg/dl)	117.9 ± 30.1	117.0 ± 29.8	119.6 ± 30.8	0.382	116.8 ± 29.8	118.5 ± 30.4	0.558
HDL-C (mg/dl)	61.1 ± 17.4	61.7 ± 17.8	60.0 ± 16.3	0.337	61.9 ± 16.3	60.7 ± 17.9	0.494
Diabetes mellitus, *n* (%)	101 (20.9)	58 (17.6)	43 (27.9)	0.010	16 (9.3)	85 (27.4)	<0.001
eGFR (ml/min per 1.73 m^2)	70.2 ± 13.1	71.5 ± 13.0	67.4 ± 12.8	0.001	71.5 ± 13.8	69.4 ± 12.6	0.104
Antihypertensive medication use, *n* (%)	177 (36.7)	107 (32.5)	70 (45.5)	0.006	42 (24.3)	135 (43.6)	<0.001
Antihyperlipidemic medication use, *n* (%)	95 (19.7)	50 (15.2)	45 (29.2)	<0.001	22 (12.7)	73 (23.6)	0.004
Hypertension, *n* (%)	262 (54.2)	157 (47.7)	105 (68.2)	<0.001	70 (40.5)	192 (61.9)	<0.001
Office (mmHg)							
SBP	131.0 ± 16.8	128.9 ± 16.3	135.3 ± 17.2	<0.001	127.3 ± 16.4	133.0 ± 16.7	<0.001
DBP	77.0 ± 10.1	77.0 ± 10.3	76.8 ± 9.8	0.829	76.9 ± 10.1	77.0 ± 10.1	0.908
Pulse pressure	54.0 ± 12.5	51.9 ± 11.6	58.5 ± 13.3	<0.001	50.4 ± 11.5	56.0 ± 12.7	<0.001
Ambulatory BP mean (mmHg)							
24-h SBP	122.8 ± 13.4	122.0 ± 13.2	124.8 ± 13.6	0.031	119.4 ± 11.8	124.7 ± 13.8	<0.001
24-h DBP	76.3 ± 8.1	76.7 ± 8.0	75.4 ± 8.3	0.120	76.4 ± 8.3	76.2 ± 8.1	0.757
Awake SBP	127.0 ± 13.9	126.2 ± 14.1	128.7 ± 13.5	0.066	123.4 ± 12.7	129.0 ± 14.2	<0.001
Awake DBP	79.0 ± 8.6	79.4 ± 8.6	78.1 ± 8.4	0.122	79.0 ± 8.7	79.0 ± 8.5	0.970
Asleep SBP	114.7 ± 15.1	113.5 ± 13.9	117.1 ± 17.2	0.015	111.3 ± 12.5	116.6 ± 16.0	<0.001
Asleep DBP	71.0 ± 9.3	71.3 ± 8.8	70.3 ± 10.3	0.289	71.1 ± 9.1	70.9 ± 9.4	0.756
Ambulatory BP variability (%)[b]							
Awake SBP	10.3 ± 3.2	10.0 ± 3.2	10.8 ± 3.2	0.024	10.0 ± 2.7	10.4 ± 3.4	0.138
Awake DBP	12.2 ± 3.7	11.9 ± 3.6	12.9 ± 3.8	0.004	11.8 ± 3.6	12.5 ± 3.7	0.054
Asleep SBP	9.0 ± 3.0	8.8 ± 2.8	9.5 ± 3.4	0.009	8.6 ± 2.7	9.2 ± 3.2	0.025
Asleep DBP	11.4 ± 4.5	11.1 ± 4.2	12.1 ± 5.1	0.018	11.0 ± 4.3	11.7 ± 4.6	0.094

Data are presented as mean ± standard deviation for continuous variables or count (%) for categorical variables. Differences in characteristics were evaluated using an unpaired Student's *t*-test or chi-square test. Hypertension was defined as office SBP ≥140 mmHg and/or office DBP ≥90 mmHg and/or taking antihypertensive medications. Diabetes mellitus was defined as HbA1c ≥6.5% and/or fasting plasma glucose ≥126 mg/dl and/or taking antihyperglycemic medications.
AVC, aortic valve calcification; BP, blood pressure; CAC, coronary artery calcification; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
[a]Presence of AVC and CAC was defined by an Agatston score >0.
[b]We used the coefficient of variation as an index of ambulatory BP variability.

groups, whereas the impact of asleep SBP variability on the presence of AVC was more pronounced among participants not taking antihypertensive medication (*P* values for heterogeneity = 0.008; Figure S2A, Supplemental Digital Content, http://links.lww.com/HJH/B930). However, for the association with CAC, no BP parameters were significantly different between participants with and without antihypertensive medication use (all *P* values for heterogeneity > 0.3; Figure S2B, Supplemental Digital Content, http://links.lww.com/HJH/B930).

DISCUSSION

In this population-based, cross-sectional study of apparently healthy, middle-aged to older Japanese men, the prevalence of AVC was almost 50% that of CAC, when defined by an Agatston score of >0. In addition, ambulatory BP measurements played a role in identifying both AVC and CAC, even after adjusting for other conventional cardiovascular risk factors. However, the effects on their presence were different: AVC was associated with awake DBP variability and asleep SBP variability, whereas CAC was associated with mean SBP levels (24-h, awake, and asleep) and asleep SBP variability.

Our findings support a previous observation demonstrating an association between elevated SBP at a medical office and AVC [7]. Meanwhile, few studies have investigated the relationship between BP outside a medical office, such as ambulatory BP, and AVC. In 737 older American patients (majority Hispanic, mean age of 71 years), higher mean ambulatory DBP levels (24-h, awake, and asleep), but not SBP levels, were associated with the presence of AVC [15]. However, our study revealed a lower association between ambulatory DBP levels and AVC; instead, ambulatory SBP levels had a positive, albeit insignificant, correlation with AVC. The reasons for our results differing from those of a previous study are unclear, but there may be several explanations for these differences. The previous study [15] measured AVC using transthoracic echocardiography. Measurement of AVC using multidetector CT, as performed in this study, is reliable, objective, reproducible, and provides an incremental prognostic value for survival beyond echocardiography [43]. Moreover, differences in the participants' characteristics between studies may have affected the results: the previous study [15] included Hispanic patients with a mean age of 71 years who had relatively poor profiles of CVD risk factors (i.e. the prevalence of a history of hypertension, diabetes

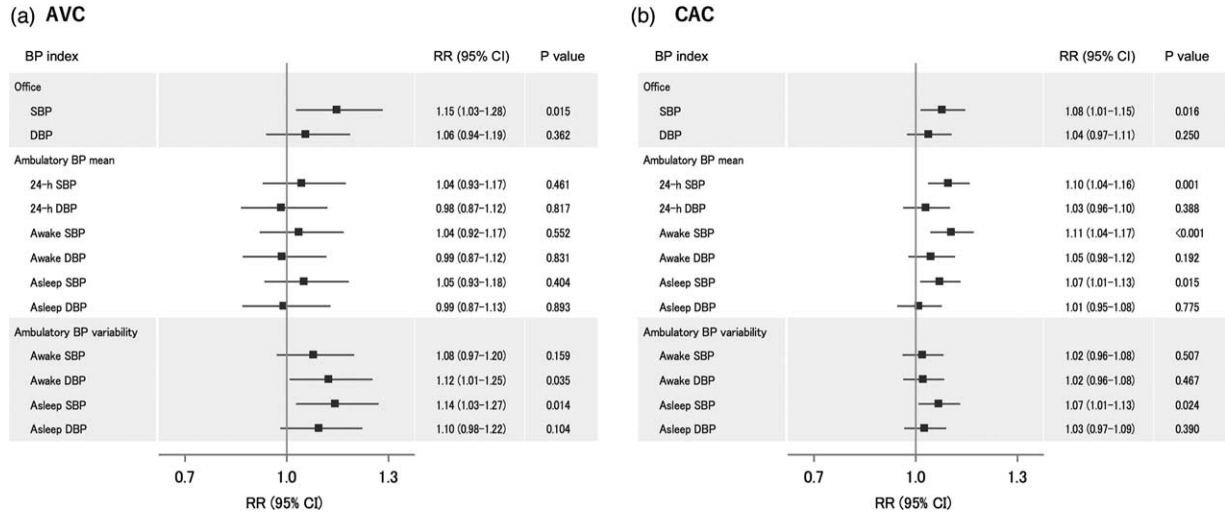

FIGURE 1 Association between office and ambulatory BP parameters with the presence of (a) AVC and (b) CAC. Solid squares and horizontal lines indicate point estimates and 95% confidence intervals (CI) for the presence of (a) AVC and (b) CAC, defined by an Agatston score >0. We used the coefficient of variation as an index of ambulatory BP variability. In multivariate-adjusted Poisson regression with robust error variance, relative risks (RRs) were calculated with 1-standard deviation increment in office SBP (16.8 mmHg) and DBP (10.1 mmHg); ambulatory mean 24-h SBP (13.4 mmHg) and DBP (8.1 mmHg); ambulatory mean awake SBP (13.9 mmHg) and DBP (8.6 mmHg); ambulatory mean asleep SBP (15.1 mmHg) and DBP (9.3 mmHg); ambulatory awake SBP (3.2%) and DBP variability (3.7%); and ambulatory asleep SBP (3.0%) and DBP variability (4.5%). Data were adjusted for age, smoking status (current, former, or never), alcohol drinking (yes/no), body mass index, estimated glomerular filtration rate, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes mellitus (yes/no), antihypertensive medication use (yes/no), and antihyperlipidemic medication use (yes/no). In addition to general adjustments, ambulatory BP variability while awake and asleep was adjusted by the mean BP levels while awake and asleep, respectively. AVC, aortic valve calcification; BP, blood pressure; CAC, coronary artery calcification; DBP, diastolic blood pressure; SBP, systolic blood pressure.

mellitus, and hyperlipidemia was 78, 30, and 68%, respectively). Furthermore, given that SBP is more strongly associated with CVDs than DBP in the elderly [32], it may be reasonable to accept our findings that SBP levels, rather than DBP levels, tend to correlate with AVC.

There was a positive correlation between SBP levels in the office setting and CAC in the present study, which was in line with the results of previous studies [6,16–18]. The findings that SBP but not DBP was associated with CAC and AVC can pathophysiologically be related to the stiffening of the arterial tree. Indeed, the pulse pressure is robust and important correlates for calcified atherosclerosis in different vascular beds, including carotid artery, coronary artery, thoracic aorta, and abdominal aorta [44]. However, there is still no consensus on the association between ambulatory BP and CAC. Our study revealed an association between CAC and mean ambulatory SBP levels (24-h, awake, and asleep). Similarly, Choi *et al.* [16] studied 722 Korean patients with chronic kidney disease (mean age: 65.0 years) and found that CAC was associated with higher mean ambulatory SBP levels (24-h, awake, and asleep). However, a study of 298 White American participants (mean age: 40.0 years) found that ambulatory DBP during the awake and asleep periods were each associated with the presence of CAC [17]. Zhang *et al.* [18] studied 557 African-American participants (mean age: 58.0 years) and found that higher asleep SBP and higher awake and asleep DBP were correlated with the presence of CAC. There are a number of possible explanations for these different results; a significant explanation may be differences in the age distribution of participants across the studies. The Framingham investigators found that DBP was a predominant determinant of coronary heart disease in participants aged <50 years, with the importance of SBP increasing with increasing age [45]. Hence, studies of a younger population generally support the association between DBP and CAC. Morever, given the sex [46] or racial disparities [47] in the involvement of BP in CVDs, differences between our study and others may have led to a discrepancy in the association between ambulatory BP levels and CAC.

Previous studies have evaluated short-term BP variability in animals [48] or day-bay-day basis in humans [49]; our study is the first evaluation of the relationship between short-term BP variability and AVC or CAC. The mechanisms by which short-term BP variability is associated with AVC or CAC have yet to be understood; however, several explanations have been proposed. Previous experimental studies suggested that enhanced BP variability, even in the absence of hypertension, can induce arterial remodeling, including vascular smooth muscle cell proliferation and extracellular matrix deposition [50], and lead to increased oscillatory shear stress on the vascular wall, promoting endothelial dysfunction [51,52]; these reactions can consequently contribute to the development of atherosclerosis. In the present study, awake DBP variability was associated with AVC. In addition to the fact that the aortic valve is generally more susceptible to shear stress changes during diastole [3], in this study, the degree of DBP variability during the awake period was 7% greater than that during the asleep period and was also highest among all measurements of ambulatory BP variability, which may have contributed to our results. In contrast to the aortic valve, in the coronary artery, a low and oscillating wall shear stress is typically observed during systole [53]. There was no significant correlation between DBP variability and CAC. Moreover, we found a significant association between asleep SBP variability and AVC, as well as CAC. Compared with awake BP variability,

asleep BP variability is less likely to be influenced by activities such as physical activity, stressful situations, and other environmental factors [54]; thus, it is more likely to reproduce actual BP variability and better reflect the mechanisms involved in BP regulation. Several observational studies reported the impact of asleep SBP variability on future CVDs [19–21], which may be explained in part by its association with subclinical atherosclerosis, including AVC or CAC. Nonetheless, the exact mechanism that could explain our findings is unclear; further research is warranted to confirm these observed relationships.

Our study had several limitations. First, our results may not be widely generalizable given that we only analyzed data from middle-aged to older men who were subjected to ambulatory BP monitoring within a sample obtained from a single area in Japan. Additionally, participants who were excluded in the analysis of 24-h ambulatory BP measurement were older and had worse profiles of cardiovascular risk factors (e.g. eGFR, antihypertensive medication use, or hypertension) at the baseline examination than those who were included in this analysis (Table S1, Supplemental Digital Content, http://links.lww.com/HJH/B930). Participants who did not undergo ambulatory BP measurement may have been at higher risk for developing AVC or CAC. Therefore, we may have underestimated effects and associations between ambulatory BP indices with AVC and CAC in the present study. Second, the number of variables assessed was limited, and measured or unmeasured confounders were present; although we used a multivariate-adjusted Poisson regression with robust error variance to reduce potential confounding, we cannot eliminate this limitation. Third, the numbers of ambulatory BP measurements (median [25, 75 percentiles]: 25 [24, 26]) were smaller than those used in previous studies, which may affect the validity of the results. A large number of measurements may be responsible for the more pronounced association with AVC or CAC. Although there are no standard guidelines for the minimum number of BP readings, as well as the optimal intervals between readings, required to reliably estimate BP values and variability [55], more frequent measurements may be related to a better assessment, which could lead to a more precise association with AVC or CAC. The number of office BP measurements in our study also did not comply with the 2021 ESH guidelines [12], which recommend taking three measurements at 1-min intervals and using the average of the last two; thus, our results may have been less accurate and underestimated. Fourth, the small sample size and low prevalence of AVC may have contributed to a lack of power to detect a significant association between ambulatory BP indices and AVC. Fifth, we did not adjust for multiple comparisons and the results should be considered exploratory rather than confirmatory. Therefore, significance should be interpreted with caution, and further research is needed to confirm our findings. We however performed exploratory Bonferroni correction (threshold for significance = 0.002; $\alpha = 0.05/24$), after which only the association with CAC and mean 24-h SBP and mean awake SBP. These associations may be considered valid results, but the lack of significant associations for other variables may be partially influenced by limited power due to the relatively small samples. Finally, ambulatory BP monitoring was performed approximately 3 years (median [25, 75 percentiles]: 2.8 [2.4, 3.1] years) after the CT scan, which may have affected the results; however, given that AVC or CAC was more frequently observed with increasing age, we may have confirmed a more solid association between ambulatory BP indices and AVC or CAC if the CT scan had been performed in the same period as the ambulatory BP monitoring.

The findings of this study have important implications. First, the prevalence of AVC was almost 50% that of CAC in apparently healthy middle-aged to older adults. Second, ambulatory BP indices were associated with AVC and CAC but had different effects on their presence. Although AVC and CAC are closely correlated in terms of shared pathogenic factors, our findings suggest that they may operate via different mechanisms. Third, asleep SBP variability was correlated with both AVC and CAC. Further studies should investigate whether and how a higher magnitude of short-term BP variability should be treated to reduce the risk of CVDs.

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Conflicts of interest

There are no conflicts of interest.

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