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Resting Heart Rate and Coronary Artery Calcium in Postmenopausal Women

Matthew A. Allison, M.D.,[1] JoAnn E. Manson, M.D.,[2] Aaron Aragaki, M.S.,[3] Charles B. Eaton, M.D.,[4] Judith Hsai, M.D.,[5] Lawrence Phillips, M.D.,[6] Lewis Kuller, M.D.,[7] and Maurizio Trevisan, M.D.[8]

Abstract

Objective: To test the hypothesis of a significant association between resting heart rate (RHR) and coronary artery calcium (CAC).
Methods: This is a cross-sectional study of a subset of women enrolled in the estrogen-alone clinical trial of the Women's Health Initiative (WHI). We used a longitudinal study that enrolled 998 postmenopausal women with a history of hysterectomy between the ages of 50 and 59 at enrollment at 40 different clinical centers. RHR was measured at enrollment and throughout the study, and CAC was determined approximately 7 years after the baseline clinic visit.
Results: The mean (standard deviation [SD]) age was 55 (2.8) years. With adjustment for age and ethnicity, a 10-unit increment in RHR was significantly associated with CAC (SD 1.18, 95% confidence interval [CI] 1.01-1.38), but this was no longer significant after adjustment for body mass index (BMI), income, education, dyslipidemia, diabetes, smoking, and hypertension (SD 1.06, 95% CI 0.90-1.25). In a fully adjusted multivariable model, however, there was a significant interaction ($p = 0.03$) between baseline RHR and systolic blood pressure (SBP) for the presence of any CAC. Compared to women with an RHR < 80 beats per minute (BPM) and an SBP < 140 mm Hg, those who had an RHR ≥ 80 BPM and an SBP ≥ 140 mm Hg had 2.66-fold higher odds (1.08-6.57) for the presence of any CAC.
Conclusions: Compared to those with normal BP and RHR, postmenopausal, hysterectomized women with an elevated SBP and RHR have a significantly higher odds for the presence of calcified coronary artery disease.

Introduction

Heart rate is regulated by the autonomic nervous system (i.e., sympathetic and parasympathetic systems). With aging, the influence of the parasympathetic system diminishes, resulting in a relative increase in sympathetic tone, an increase in resting heart rate (RHR), and reduced heart rate variability.[1] Previous studies have found consistent associations between RHR and cardiovascular and noncardiovascular mortality,[2–4] and other studies have linked increased RHR with higher levels of hypertension[5] and cardiovascular morbidity.[4,6,7] Moreover, the increased sympathetic tone (which an increased RHR reflects) has been associated with atherogenesis.[8]

In a regulated process similar to skeletal bone formation,[9] calcium is deposited in atherosclerotic plaques.[10] With the advent of computed tomography (CT), these calcified atheromatous plaques can be detected throughout the vasculature,[11] including the coronary arteries.[12] The extent of coronary artery calcium (CAC) is highly correlated with both the total atheromatous plaque burden[13] and the percent stenosis in that vascular bed.[14] Moreover, several studies have shown CAC to be a strong and independent predictor of incident coronary heart disease (CHD) events in both men and women.[15,16]

Use of CAC as a marker of coronary atherosclerosis is increasingly advocated as a component of individual

[1]University of California San Diego, La Jolla, California.
[2]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.
[3]Fred Hutchinson Cancer Research Center, Seattle, Washington.
[4]Warren Alpert Medical School of Brown University, Providence, Rhode Island.
[5]Astra Zeneca, Wilmington, Delaware.
[6]Emory University, Atlanta, Georgia.
[7]Pittsburgh University, Pittsburgh, Pennsylvania.
[8]Health Sciences System of the Nevada System of Higher Education, Las Vegas, Nevada.

cardiovascular disease (CVD) risk stratification procedures.[17,18] Accordingly, the aim of this study was to determine the magnitude of the associations between CAC and RHR in women with a history of hysterectomy who were between the ages of 50 and 59 years at the time of their enrollment in the Women's Health Initiative (WHI). We hypothesize that women with higher RHR would be at increased risk for higher prevalence and levels of CAC. Additionally, as previous work has demonstrated an increased risk for CHD and mortality among those with prehypertension and elevated RHR,[19] we hypothesized that women with elevations of both blood pressure (BP) and RHR would have the highest odds for CAC.

Materials and Methods

Subjects

The WHI hormone therapy (HT) clinical trials enrolled 27,347 women at 40 clinical sites located across the United States. Of these, 10,739 were enrolled in the WHI Estrogen Trial (ET) using conjugated equine estrogen (CEE). These women were postmenopausal, aged 50–79 years at randomization, had a history of hysterectomy before enrollment, and were randomized to receive CEE, 0.625 mg/day (Premarin, Wyeth Pharmaceuticals, St Davids, PA) or a matching placebo. Methods for data collection, management, and quality assurance have been published previously.[20] The ET was ended after an average of 6.8 years follow-up.

The WHI Coronary Artery Calcium Study (WHI CACS) was a substudy of the WHI ET. All 40 WHI clinical sites were asked to participate in this substudy; 28 agreed. Reasons for site nonparticipation included lack of suitable equipment and logistical concerns. Invitations were mailed to the women at these sites requesting them to undergo a one-time cardiac CT scan to determine CAC by electron beam or multidetector-row CT. Of the women enrolled in the ET, 1,742 were eligible for WHI CACS because they were between 50 and 59 years old at the time of their randomization into the ET and were participants at 1 of the 28 participating sites. Exclusion criteria for study participation included a last measured or reported weight of $\geq$300 lbs (because of technical and equipment-related restrictions), participant request for no further contact or clinic visits, or participant lost to follow-up or deceased since randomization (30.4% of participants were excluded for one or more of these reasons). As a result of these exclusions, informed consent for WHI CACS was provided by 1,079 women (61.6% of those eligible at the 28 clinical centers) who underwent CAC scanning an average of 1.3 years after the ET trial ended. After specific exclusions for the current study, there were 998 women available for analysis. The Human Subjects Review Committee at each participating institution approved the WHI study protocols.

Data collection

Trial participants provided data on a wide range of factors at the ET baseline clinic visit. Ethnicity was determined by self-report, with the following categories: non-Hispanic white, African American/black (non-Hispanic), Hispanic, Asian/Pacific Islander, American Indian/Alaska Native, or unknown (women who indicated other ethnicity or did not answer the question). Education and income were ascertained by self-report from a range of categories. The presence of hypertension, high cholesterol, or diabetes was identified by self-reported use of a medication for these conditions. Smoking was categorized as current, former, or none. Current smoking was defined as smoking at least 100 cigarettes in their lifetime and reporting smoking at baseline, and former smoking was smoking at least 100 cigarettes but reported not smoking at baseline. Use of postmenopausal HT before WHI CEE trial enrollment was ascertained via an in-person interview at the baseline clinic visit. Total physical activity was assessed by questions on a frequency and duration scale for walking and other types of activity and converted to MET-hours per week.[21] Anxiety and depression were assessed using the RAND36 mental health score.[22]

At baseline, women sat quietly for 5 minutes before heart rate was measured by palpating the radial pulse for 30 seconds and BP was measured twice using a conventional mercury sphygmomanometer and appropriately sized cuffs by a trained observer. Anthropometric measurements were obtained at baseline. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Waist and hip circumferences (in cm) were obtained using a standardized measuring tape.

Coronary artery calcified plaque measurements

A standardized protocol was developed based on prior multicenter experience with cardiac CT.[23] Phantom scan and test images were obtained from each CT system to verify technical parameters and CT system performance. Analyses of the measurements were performed by certified staff at the central reading center at Wake Forest University who were masked to participants' treatment assignment. The Agatston score was calculated on a computer workstation (TeraRecon Inc, San Mateo, CA) by experienced image analysts using established parameters (lesion size of >1 mm^2, adjustment for slice thickness, and threshold of 130 Hounsfield units [HU]).[24] After the scan was scored, the participants were provided with a letter documenting their calcium score, which could be reviewed with their healthcare provider if desired.

Women with a history of coronary revascularization before randomization were excluded from the analysis. Also, the reading protocol specified exclusion of coronary stents, pacemakers, metallic clips, and other surgical remnants from the analysis process. Three women with incomplete scans were excluded. Women reporting use of beta-blockers at baseline were excluded, as these drugs may affect heart rate.

Statistical analyses

CAC score was coded as a binary variable (>0 or $=0$). As some results suggest reduced reproducibility of CAC scores from 0 to 10, we also conducted analyses using a CAC score >10 vs. ≤ 10 as an outcome. Baseline RHR, the primary exposure variable, was defined as a continuous variable and a categorical variable based on the groupings <60, 60–69, 70–79, and ≥ 80. These groups were used to provide clinical relevance as well as comparisons to other studies that have been conducted on RHR. Secondary analysis investigated the effect of RHR gathered at baseline and during follow-up.

Baseline characteristics were compared between CAC score (>0 or $=0$). Differences between the groups were assessed using age-adjusted logistic regression models. For the main analysis, multivariable adjusted logistic regression models were used to evaluate the association between the presence of

any CAC and baseline RHR. To control for potential confounding, baseline values of age, race/ethnicity, diabetes, dyslipidemia, smoking, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), high BP medication, consumption of alcohol and regular coffee, RAND36 mental health scale, education, income, and CEE randomization assignment were used as covariates. These variables were selected based on previous studies that have shown them to be associated with CAC or theoretically influential of RHR.

Based on previous studies,[19] we, *a priori*, planned interactions between RHR with both BP and high BP medication use. To further quantify the association between CAC and baseline RHR by BP level, we determined the odds for any CAC by different combinations of RHR/SBP group. Specifically, we examined the odds for CAC when the RHR was ≥80 BPM and the SBP was ≥140 mm Hg, as well as when the RHR was ≥70 BPM and the SBP was ≥130 mm Hg. For these analyses, generalized additive models (GAMs) were also used to graphically display the association between CAC and RHR and further quantify their relationship by statistically evaluating their fits. A p value <0.05 was considered statistically significant. No adjustments were made for multiple comparisons, and exact p values are given. All reported p values are two-sided. The main statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC). Graphs of GAMs and goodness of fit were assessed with R version 2.9.2.

Results

The distribution of CAC in the WHI CACS cohort was positively skewed.[25,26] Therefore, the characteristics of the 998 women included in this analysis were stratified by the presence and absence of CAC (Table 1). There were 464 (46.5%) women with a CAC score >0. Those who had any CAC were significantly older. After adjustment for age, the CAC-positive group had significantly higher levels of BMI, hip and waist circumference, SBP, hypertension, cholesterol medication use, diabetes medication use, and pack-years cigarette smoking while having significantly lower levels of physical activity, annual income, education, and RAND36 mental health scale score.

Baseline RHR was approximately normally distributed, with a mean (SD) of 69 (9) beats per minute (BPM) and was not significantly different by history of HT use (past, 69.3; current, 68.6; never, 69.7). Table 2 presents the characteristics of the cohort by increasing increments of RHR measured at the baseline WHI visit. After adjustment for age, there were significant positive trends across RHR levels for BMI, waist circumference, and both SBP and DBP, as well as for the prevalence of hypertension, prehypertension, diabetes, current smoking, and an annual income <$35,000. Conversely, physical activity levels decreased significantly across increasing RHR levels. The proportion of African Americans increased, whereas the proportion of non-Hispanic whites decreased. The prevalence of having a CAC score >0 also increased across increasing levels of RHR, which was of borderline statistical significance ($p=0.08$).

For a 10-unit increment in baseline RHR, the odds of having a CAC score >0 was 1.17 (95% confidence ratio [CI] 1.00-1.36). The odds ratio (OR) was not appreciably changed with adjustment for age and ethnicity (OR 1.18, 95% CI 1.01-1.38). However, additional adjustment for BMI, income, education, dyslipidemia, diabetes, smoking, and hypertension attenuated the OR to 1.06 (95% CI 0.90-1.25). Of these, addition of BMI or smoking or both, but not the other covariates just listed, to a model containing RHR, age, and ethnicity resulted in the odds for CAC becoming nonsignificant (data not shown). Additional adjustment for alcohol and coffee consumption, RAND36 mental health score, and randomization status did not materially change the OR (1.06, 95% CI 0.90-1.25), nor did further adjustment for SBP and DBP (OR 1.08, 95% CI 0.91-1.28) or physical activity (OR 1.03, 95% CI 08.6-1.24). The results were essentially the same when a CAC score ≥10 (vs. CAC < 10) was used as the outcome.

We also examined the association between baseline RHR groups and the presence of CAC. In unadjusted models and compared to the group with the lowest RHR (<60 BPM), those in the highest group (RHR ≥ 80 BPM) had an OR of 1.77 (95% CI 0.97-3.20) for the presence of CAC, whereas those with an RHR from 70 to 79 BPM and from 60 to 69 BPM had progressively less risk of CAC (OR 1.56, 95% CI 0.91-2.68 and OR 1.38, 95% CI 0.81-2.34, respectively). As before, adjustment for traditional CVD risk factors attenuated the magnitudes of these associations (RHR ≥ 80 BPM: OR 1.49, 95% CI 0.77-2.89; RHR 70–79: OR 1.39, 95% CI 0.76-2.52; RHR 60–69: OR 1.37, 95% CI 0.76-2.44). However, when a CAC score ≥10 vs. <10 was used as the outcome, the associations were more robust. Specifically, compared to those with an RHR < 60 BPM and after adjustment for the traditional CVD risk factors, the odds for a CAC score >10 were 2.19 (95% CI 1.07-4.48), 2.03 (95% CI 1.06-3.88), and 1.93 (95% CI 1.03-3.64) for those with an RHR ≥ 80 BPM, 70–79 BPM, and 60–69 BPM, respectively, with p for trend = 0.10. In a *post-hoc* analysis, combining the categories of RHR > 60 yields an OR (95%CI) of 1.99 (1.07-3.70) and $p=0.03$.

In a fully adjusted multivariable model, there was a significant interaction ($p=0.03$) between baseline RHR and SBP for the presence of any CAC. Figure 1A shows a multivariable adjusted nonparametric estimate of the log odds of CAC among the entire cohort for increasing RHR by SBP subgroups (i.e. <120, 120–139, and ≥140 mm Hg). The association between RHR and CAC was essentially null in those with SBP of <140 mm Hg. Above this level, the odds for CAC appear to increase significantly as the RHR increases, particularly above 80 BPM. More specifically, among those with an SBP ≥ 140 mm Hg and compared to those with an RHR < 80 BPM, those who had an RHR ≥ 80 BPM had a 2.66-fold higher odds (95% CI 1.08-6.57) for the presence of any CAC (Table 3). Figure 1B shows similar associations where subgroups are defined by both SBP and BP medication use. The association between RHR and CAC was not attenuated when we included women on BP medication who did not have SBP ≥ 140 mm Hg.

Compared to those with an RHR < 80 BPM and an SBP < 120 mm Hg, those with an RHR ≥ 80 BPM and an SBP ≥ 140 mm Hg had nearly a 4-fold (OR 3.91, 95% CI 1.55-9.88) higher odds for the presence of any CAC, and the odds were 0.89 (95% CI 0.44-1.81) among those with an RHR ≥ 80 BPM but an SBP < 120 mm Hg. Similarly, those with an RHR ≥ 70 BPM and an SBP ≥ 130 mm Hg had >2-fold (OR 1.92, 95% CI 1.11-3.32) higher odds for any CAC, while the odds were 0.83 (95% CI 0.52-1.31) among those with an RHR ≥ 70 BPM but an SBP < 120 mm Hg. Similar results were seen for women with persistently high SBP and persistently high RHR

Table 1. Baseline Characteristics by Presence and Absence of Coronary Artery Calcium

Characteristic	*CAC = 0* (n = *464*)	*CAC > 0* (n = *534*)	p *value*[a]
Age at baseline (years)[b]	54.7 (2.9)	55.5 (2.8)	< 0.01
Race/ethnicity[c]			0.17
White	396 (74.2)	355 (76.5)	
Black	99 (18.5)	67 (14.4)	
Hispanic	32 (6)	28 (6)	
American Indian	1 (0.2)	7 (1.5)	
Asian/Pacific Islander	1 (0.2)	2 (0.4)	
Unknown	5 (0.9)	5 (1.1)	
Body mass index (kg/m2)[b]	29.7 (6)	31.3 (6)	< 0.01
Waist circumference (cm)[b]	88.5 (13.7)	94.5 (14.2)	< 0.01
Hip circumference (cm)[b]	110.3 (12.7)	113 (12.6)	< 0.01
SBP (mm Hg)[b]	122.4 (14.7)	126.4 (16.2)	< 0.01
DBP (mm Hg)[b]	77.5 (8.9)	77.7 (8.8)	0.50
Baseline hypertension[c,d]			< 0.01
Normotensive	184 (34.5)	124 (26.7)	
Prehypertensive	205 (38.4)	159 (34.3)	
Hypertensive	145 (27.2)	181 (39)	
Pack-years of smoking[b]	7.3 (14.7)	13.6 (19.9)	< 0.01
Smoking status[c]			< 0.01
Never	288 (54.3)	195 (42.2)	
Past	202 (38.1)	186 (40.3)	
Current	40 (7.5)	81 (17.5)	
Cholesterol medication use[c]	32 (6)	54 (11.6)	< 0.01
Diabetes medication use[c]	16 (3)	29 (6.3)	0.02
Randomization status (E-alone arm)[c]	280 (52.4)	222 (47.8)	0.13
Hormone therapy use[c]			0.84
Never	252 (47.2)	220 (47.4)	
Past	165 (30.9)	149 (32.1)	
Current	117 (21.9)	95 (20.5)	
Total energy expenditure/week (MET-hours)[b]	11.1 (13.9)	9.2 (12.5)	0.09
Annual income < $35K[c]	176 (34.7)	194 (43.1)	0.01
Education[c]			< 0.01
≤ High school/GED or less	113 (21.4)	136 (29.6)	
School after high school	237 (44.8)	205 (44.6)	
College degree or higher	179 (33.8)	119 (25.9)	
RAND mental health (quartiles)[c]			0.02
< 68	93 (17.8)	106 (23.2)	
68–79	102 (19.5)	105 (23)	
80–87	151 (28.9)	116 (25.4)	
≥ 88	177 (33.8)	129 (28.3)	

[a]Adjusted for age. **Freq (%)
[b]Mean (standard deviation [SD]).
[c]Frequency (%).
[d]Hypertension definitions: normotensive, SBP < 120, DBP < 80, and no medications; prehypertension, SBP 120–139, DBP 80–89 and no medications; hypertension: SBP ≥ 140 or SBP ≥ 90 or on medication.
BP, blood pressure; CAC, coronary artery calcium; DBP, diastolic blood pressure; E, estrogen; SBP, systolic blood pressure.

over the course of the ET. That is, women with a persistent RHR ≥ 70 BPM and SBP ≥ 130 mm Hg had > 2-fold (OR 2.26, 95% CI 1.25-4.09) higher odds for any CAC, while the odds were 1.19 (95% CI 0.74-1.93) among those with an RHR ≥ 70 BPM but an SBP < 120 mm Hg.

Discussion

In this study of women with a history of hysterectomy and between the ages of 50 and 59 at enrollment in the WHI, RHR, in both continuous and categorical distributions and after adjustment for age and ethnicity, was modestly yet significantly associated with the presence of CAC. With further adjustment for the traditional CVD risk factors and other significant covariates, however, this association was no longer statistically significant. Notably, there was a significant interaction between RHR and SBP for the presence of CAC. Specifically, women with higher levels of both RHR (i.e., ≥ 80 BPM) and SBP (i.e., ≥ 140 mm Hg) were significantly more likely to have any CAC compared to those with lower levels of these variables. Women with higher levels of RHR but normal/lower levels of SBP did not have higher odds for CAC, suggesting that an elevated BP is necessary for the increased risk to be associated with higher levels of RHR.

The association between RHR and CAC was not independent of the traditional CVD risk factors. This suggests that the association between RHR and CAC may be confounded by these risk factors. We explored this hypothesis by examining the effect of each of the individual risk factors on the association between RHR and CAC. In these analyses, the addition

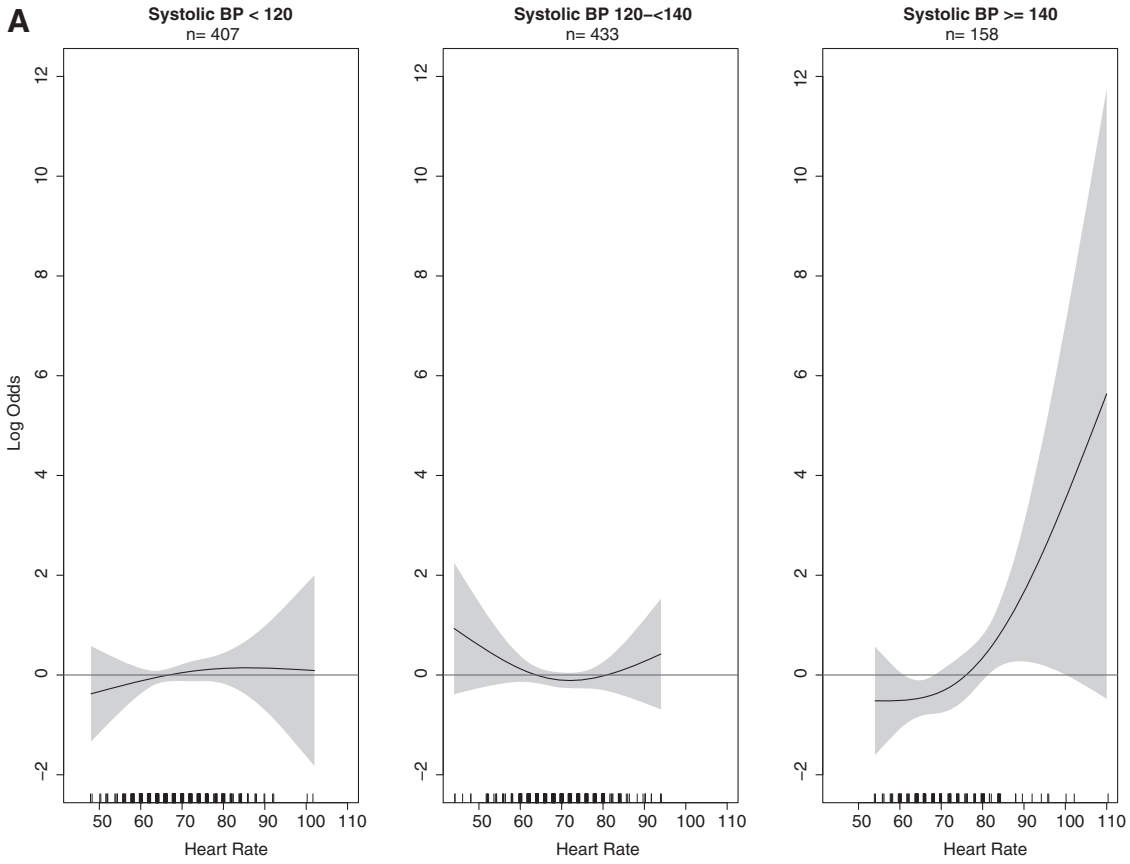
Table 2. Baseline Characteristics by Resting Heart Rate

Characteristic	*Resting heart rate (BPM)*				p *value*[a]
	<60 (n=*78*)	*60–69* (n=*452*)	*70–79* (n=*320*)	*>80* (n=*145*)	
Coronary calcium score >0	33 (43.4)	202 (45)	151 (47.5)	75 (51.7)	0.08
Age at baseline (years)[b]	55.4 (3.1)	55.2 (2.9)	55.2 (2.8)	54.6 (2.8)	0.06
Race/ethnicity[c]					0.46
White	57 (75)	339 (75.5)	252 (79.2)	97 (66.9)	
Black	10 (13.2)	73 (16.3)	43 (13.5)	36 (24.8)	
Hispanic	9 (11.8)	23 (5.1)	18 (5.7)	10 (6.9)	
American Indian	0 (0)	6 (1.3)	2 (0.6)	0 (0)	
Asian/Pacific Islander	0 (0)	0 (0)	2 (0.6)	1 (0.7)	
Unknown	0 (0)	8 (1.8)	1 (0.3)	1 (0.7)	
Body mass index (kg/m^2)[b]	30 (6.8)	30 (5.7)	30.5 (6.2)	31.6 (6.2)	0.01
Waist circumference (cm)[b]	90 (13)	90.1 (13.5)	92 (15.2)	94.1 (14.8)	<0.01
Hip circumference (cm)[b]	109.3 (12.1)	111.3 (12.3)	111.5 (13)	113.4 (13.8)	0.05
SBP (mm Hg)[b]	122.3 (16.7)	123 (15.3)	124.6 (14.8)	128.3 (16.8)	<0.01
DBP (mm Hg)[b]	73.4 (8.7)	77 (8.8)	77.8 (8.3)	81 (8.9)	<0.01
Baseline hypertension[c]					<0.01
Normotensive	31 (40.8)	147 (32.7)	98 (30.8)	30 (20.7)	
Prehypertensive	23 (30.3)	164 (36.5)	125 (39.3)	48 (33.1)	
Hypertensive	22 (28.9)	138 (30.7)	95 (29.9)	67 (46.2)	
Pack-years of smoking[b]	6.5 (13.1)	9.9 (17.1)	11.1 (18.7)	11.2 (18.4)	0.06
Smoking status[c]					0.02
Never	44 (57.9)	216 (48.3)	145 (46.2)	73 (50.3)	
Past	29 (38.2)	182 (40.7)	126 (40.1)	48 (33.1)	
Current	3 (3.9)	49 (11)	43 (13.7)	24 (16.6)	
Cholesterol medication use[c]	7 (9.2)	32 (7.1)	33 (10.4)	12 (8.3)	0.31
Diabetes medication use[c]	2 (2.6)	15 (3.3)	15 (4.7)	12 (8.3)	0.01
Randomization status (E-alone arm)[c]	38 (50)	235 (52.3)	151 (47.5)	75 (51.7)	
Hormone therapy use[c]					0.09
Never	27 (34.6)	213 (47.1)	155 (48.4)	73 (50.3)	
Past	29 (37.2)	144 (31.9)	91 (28.4)	51 (35.1)	
Current	22 (28.2)	95 (21.0)	74 (23.1)	21 (14.5)	
Total energy expenditure/week (MET-hours)[b]	13.8 (17.6)	10.5 (12.5)	9.3 (11.8)	9.3 (15.1)	0.01
Annual income <$35K[c]	19 (26)	166 (38.3)	118 (38.9)	63 (45.3)	
Education[c]					0.23
≤High school/GED or less	11 (14.5)	115 (25.9)	78 (24.8)	40 (27.6)	
School after high school	41 (53.9)	184 (41.4)	149 (47.5)	65 (44.8)	
College degree or higher	24 (31.6)	145 (32.7)	87 (27.7)	40 (27.6)	
RAND mental health (quartiles)[c]					0.42
<68	12 (15.8)	87 (19.9)	60 (19.2)	35 (24.3)	
68 to 79	19 (25)	92 (21.1)	65 (20.8)	31 (21.5)	
80 to 87	21 (27.6)	110 (25.2)	97 (31.1)	37 (25.7)	
≥88	24 (31.6)	148 (33.9)	90 (28.8)	41 (28.5)	

[a]Adjusted for age. **Freq (%)
[b]Mean (SD).
[c]Frequency (%).
BPM, beats per minute.

of BMI or smoking to a model containing RHR, age, and ethnicity caused the odds for CAC (per increment in RHR) to become nonsignificant. The other risk factors did not materially affect the association between RHR and CAC. These results are similar to findings of a study that examined the ability of RHR to enhance the ability of the Systematic COronary Risk Evaluation (SCORE) system to discriminate 10-year risk of CVD mortality.[27] In this study, the addition of RHR to the full SCORE formula did not improve the area under the curve (AUC) or net reclassification index. However, addition of RHR to a reduced formula that contained age, smoking, gender, and BMI did cause significant improvement in discrimination. Combined with our results, these findings suggest that RHR may be used with easily obtained measures to cost-effectively classify future risk of CVD mortality.

Previous studies have demonstrated an association between cigarette smoking and higher RHR,[28,29] and smokers have been shown to have a higher prevalence and levels of CAC.[30] Similarly, individuals with higher BMI have been shown to have higher RHR,[31] potentially due to increased sympathetic nervous system activation.[32,33] Higher BMI has also been associated with a significantly increased odds for having CAC.[34] Because it seems more physiologically plausible that smoking and increased body mass result in a higher RHR (instead of *vice-versa*), and both of these variables were significantly associated with CAC in our study population,


A
Systolic BP < 120
n= 407
Systolic BP 120–<140
n= 433
Systolic BP >= 140
n= 158
Log Odds
Heart Rate

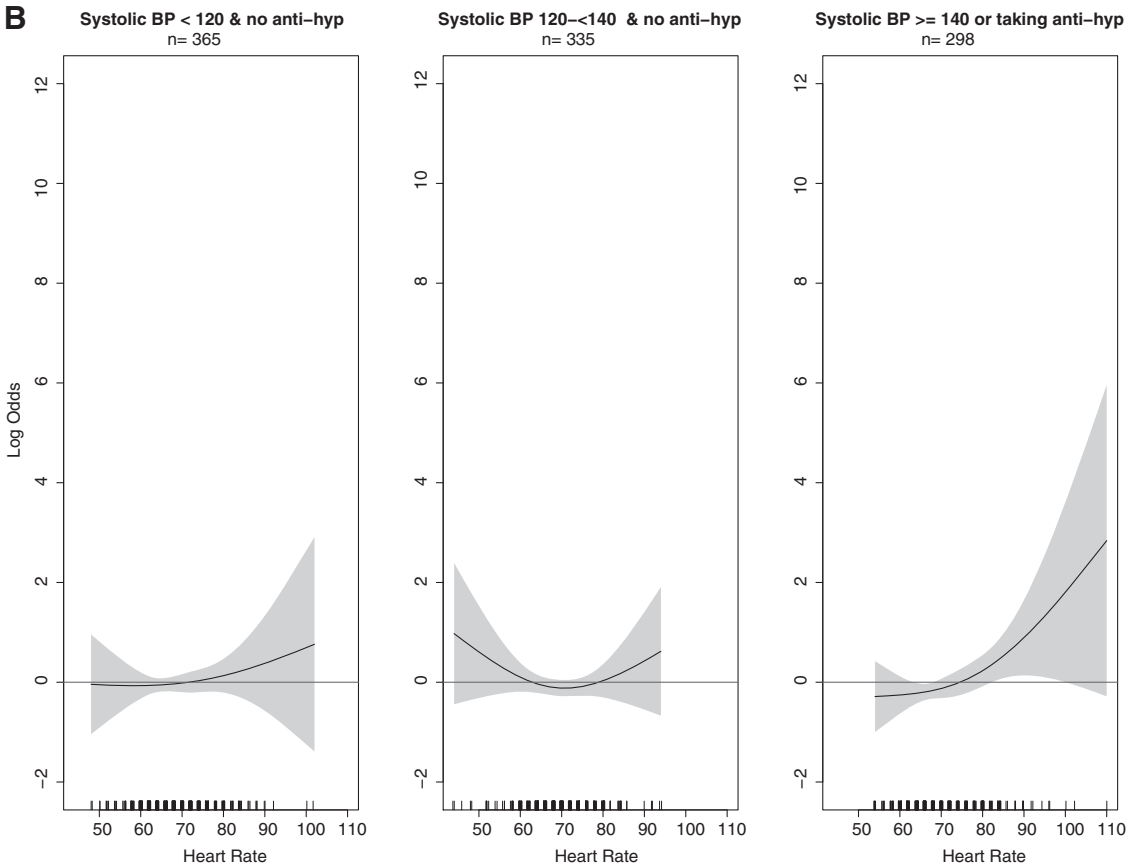

B
Systolic BP < 120 & no anti–hyp
n= 365
Systolic BP 120–<140 & no anti–hyp
n= 335
Systolic BP >= 140 or taking anti–hyp
n= 298
Log Odds
Heart Rate

Table 3. Multivariable Adjusted Odds of Any Coronary Artery Calcium for Resting Heart Rate (≥80 vs. <80 BPM) by Systolic Blood Pressure Subgroups

Systolic blood pressure subgroup[a]	*Odds ratio*	*95% CI*	p *value*[b]
			0.03
Normotensive (SBP < 120)	0.89	(0.44, 1.81)	
Prehypertensive (SBP 120–<140)	0.84	(0.45, 1.58)	
Hypertensive (SBP ≥ 140)	2.66	(1.08, 6.57)	

[a]Adjusted for age, race/ethnicity, education, income, diabetes, dyslipidemia, smoking, BMI, systolic blood pressure, diastolic blood pressure, high blood pressure medication, consumption of alcohol and regular coffee. RAND36 mental health scale, and conjugated equine estrogen randomization assignment were used as covariates.

[b]*p* value for interaction between resting heart rate and systolic blood pressure.

Reference group: RHR < 80 BPM.

CI, confidence interval; BMI, body mass index; RHR, resting heart rate.

we believe smoking and BMI are confounders rather than downstream mediators of the association between RHR and CAC. Thus, RHR could serve as a potential intermediate (and easily measurable) marker of increased risk for coronary artery disease among smokers and those with increased BMI. Notably, as the current study was cross-sectional and not prospective in nature, conclusions about potential mediation effects of these variables can only be made on the basis of existing knowledge of physiology.

An intriguing finding from our study was the significant interaction between RHR and SBP for CAC. As mentioned, women with higher levels for both RHR and SBP had significantly higher odds for the presence of CAC, and this association was dependent on having an SBP > 140 mm Hg. These findings support previous studies that have demonstrated a significantly increased risk for mortality and CHD among those with hypertension[35] or prehypertension[19] and who also have elevated levels of RHR. Interestingly (and similar to our findings), in the latter study, an RHR ≥ 80 BPM was associated with a significantly higher risk for incident CHD. As increased sympathetic activation can cause higher levels of both RHR and SBP,[36] it is possible that this activation may be an important and common contributor to the significantly increased odds for CAC among those who have simultaneously higher levels of RHR and SBP. Indeed, previous studies have demonstrated a significant association between elevated HR and accelerated arterial stiffening among people with hypertension.[37]

Previous studies on the association between heart rate and CAC are limited. In fact, we were not able to find any reports that primarily studied the association between RHR and CAC. Of those studies that examined heart rate and CAC, most looked at the association between exercise-induced changes in heart rate and prevalent CAC. Findings from these studies indicate a strong inverse association between both the chronotropic response and heart rate recovery with the presence and burden of CAC,[38] although this association may be attenuated among young adults.[39] Notably, the Heinz Nixdorf Recall study[38] tested the association between RHR and CAC within its study of exercise and CAC and found, among women, a significantly higher odds of CAC for each 10-BPM increment in RHR, independent of age, sex, and CVD risk factors (OR 1.11, $p = 0.02$). The results of our study extend these findings and suggest that RHR may be a clinically relevant measure that is easy to perform and can be reliably obtained in a short period of time.

The strengths of this study include prospective and systematic collection of subject characteristics and the breadth of variables available for analysis. Conversely, this study is limited by the sample size of the studied cohort and the relatively low and limited distribution of the coronary calcium scores. Although the WHI CACS study was conducted using women enrolled in a randomized clinical trial, the current analysis was observational and cross-sectional in nature and was conducted using a subset of women in the WHI ET clinical trial. Therefore, there could be residual confounding or bias affecting the results. We have attempted to address this issue by considering as many potential confounding variables as possible in the analysis. Finally, the results of this study are limited to those women who are recently postmenopausal and have a history of hysterectomy.

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FIG. 1. **(A)** Association between resting heart rate and coronary artery calcium (CAC) by different systolic blood pressure (SBP) groups. Horizontal line indicates no association between heart rate and CAC. Black curved lines indicate log odds of having any CAC at a given SBP value. Gray shading around black curved lines indicates 95% confidence intervals across the spectrum of SBP values. **(B)** Association between resting heart rate and CAC by different SBP groups and accounting for blood pressure medication use. Horizontal line indicates no association between heart rate and CAC. Black curved lines indicate log odds of having any CAC at a given SBP value. Gray shading around black curved lines indicates 95% confidence intervals across the spectrum of SBP values. Adjusted for age, ethnicity, body mass index, smoking, SBP, antihypertensive medication, and diastolic blood pressure (for both linear and quadratic terms).

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Address correspondence to:
Matthew A. Allison, M.D., M.P.H.
9500 Gilman Drive, Mailcode 0965
La Jolla, CA 92093-0965

E-mail: mallison@ucsd.edu