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Association Between Resting Heart Rate and Inflammatory Biomarkers (High-Sensitivity C-Reactive Protein, Interleukin-6, and Fibrinogen) (from the Multi-Ethnic Study of Atherosclerosis)

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Abstract

Heart rate (HR) at rest is associated with adverse cardiovascular events; however, the biologic mechanism for the relation is unclear. We hypothesized a strong association between HR at rest and subclinical inflammation, given their common interrelation with the autonomic nervous system. HR at rest was recorded at baseline in the Multi-Ethnic Study of Atherosclerosis, a cohort of 4 racial or ethnic groups without cardiovascular disease at baseline and then divided into quintiles. Subclinical inflammation was measured using high-sensitivity C-reactive protein, interleukin-6, and fibrinogen. We used progressively adjusted regression models with terms for physical activity and atrioventricular nodal blocking agents in the fully adjusted models. We examined inflammatory markers as both continuous and categorical variables using the clinical cut point of ≥ 3 mg/L for high-sensitivity C-reactive protein and the upper quartiles of fibrinogen (≥ 389 mg/dl) and interleukin-6 (≥ 1.89 pg/ml). Participants had a mean age of 62 years (SD 9.7), mean resting heart rate of 63 beats/min (SD 9.6) and were 47% men. Increased HR at rest was significantly associated with higher levels of all 3 inflammatory markers in both continuous (p for trend <0.001) and categorical (p for trend <0.001) models. Results were similar among all 3 inflammatory markers, and there was no significant difference in the association among the 4 racial or ethnic groups. In conclusion, an increased HR at rest was associated with a higher level

of inflammation among an ethnically diverse group of subjects without known cardiovascular disease.

It has been suggested that an elevated heart rate (HR) may reflect an imbalance of the autonomic nervous system, favoring a sympathetic dominance.¹ This autonomic imbalance may also contribute to increased inflammation, which is a central process in the development, progression, and destabilization of atherosclerotic plaques.² Previous studies investigating the association between HR at rest and inflammation have been limited because of either missing important covariates such as physical activity and restriction to a single ethnic group or by the inclusion of participants with cardiovascular disease.^{3–6} Therefore, whether there is a consistent and independent association among an ethnically diverse group of subjects without known cardiovascular disease has not been demonstrated. We hypothesized that HR at rest would be independently associated with inflammation as measured by 3 different markers (high-sensitivity C-reactive protein [hs-CRP], interleukin-6 [IL-6], and fibrinogen) and that this association would be consistent across racial or ethnic groups.

Methods

We used participant data from the baseline visit (2000 to 2002) of the Multi-Ethnic Study of Atherosclerosis (MESA).⁷ Participants were excluded if they did not have a HR at rest value ($n = 49$) or were missing all inflammatory markers investigated in this analysis ($n = 31$), which resulted in a total of 6,735 participants included in this analysis.

Participant HR at rest was recorded from a 12-lead electrocardiography performed at rest at the baseline examination. Participants were fasting for at least 12 hours and were instructed to avoid heavy exercise before the examination. Hs-CRP was measured using the Behring Nephelometer-2 (N High Sensitivity CRP; Dade Behring Inc., Deerfield, Illinois; interassay coefficient of variation 2.1% to 5.7%), IL-6 was measured using an ultrasensitive ELISA assay (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, Minnesota; interassay coefficient of variation 6.3%), and fibrinogen was measured using immunoprecipitation of fibrinogen antigen using the BNII nephelometer (N-Antiserum to Human Fibrinogen; Dade Behring Inc, Deerfield, Illinois; interassay coefficient of variation 2.6%). Blood samples were stored at -70°C and analyzed at a central laboratory (University of Vermont, Burlington, Vermont).

All other covariates were obtained from the baseline MESA clinical examination. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the use of a blood pressure–lowering medication; diabetes was defined as a fasting blood glucose level ≥ 126 mg/dl or a self-report of diabetes or taking glucose-lowering medications. Physical activity was measured in MESA using the Typical Week Physical Activity Survey, which assessed the frequency and time spent engaging in various physical activities. There were 28 questions about the typical weekly time spent and frequency engaged in activities including household chores, yard work, leisure time, sports, and occupational activity. This included questions about light, moderate, and vigorous physical activities. Time spent in each activity was multiplied by the MET level to obtain

MET-h/week. We divided participants into approximate quartiles based on reported moderate and vigorous physical activities.⁸ Socioeconomic status was based on total household income and the highest attained level of education. Family history of coronary heart disease (CHD) was defined as a positive history of CHD in a parent, sibling, or child.

Participants were divided into HR at rest quintiles as per most previous HR studies. Inflammation was examined as a continuous variable using linear regression models with robust error variance. Hs-CRP, fibrinogen, and IL-6 were not normally distributed and were therefore log transformed for continuous analyses.

In categorical analyses of the inflammatory variables, we used the clinical cut point for a normal hs-CRP <1 mg/L as the reference group and an elevated hs-CRP of ≥ 3 mg/L. We used cut points of the upper quartile for fibrinogen (389 mg/dl) and IL-6 (1.89 pg/ml) in our population, with the lowest quartile as the reference group. This approximately corresponds to the definition of hyperfibrinogenemia (400 mg/dl); there is no commonly used clinical cut point for IL-6. For our secondary analyses, we used these categorical cut points to calculate prevalence ratio (PR) regression models. Results of these models are interpreted as the PR of having an elevated inflammatory level (as defined previously) compared with a nonelevated level for each HR quintile, with the lowest HR quintile as the reference.

We used progressively adjusted models, with model 1 including age, gender, and race or ethnicity. Model 2 added body mass index, waist circumference, total household income, highest attained level of education, systolic blood pressure, diastolic blood pressure, pulse pressure, antihypertensive medication use, smoking status, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, lipid-lowering medication use, and a family history of CHD. Model 3 added physical activity level and atrioventricular nodal medication use.

We performed subgroup sensitivity analyses modeling the PR of being in the highest inflammatory group (hs-CRP ≥ 3 mg/L or quartile with the highest inflammation) per 10-beats/min change in HR at rest, which corresponded to approximately 1 SD (9.7). In addition, because an hs-CRP ≥ 10 mg/L is likely due to an acute inflammatory reaction, we investigated our 2 primary analyses excluding these participants (n = 591).

Results

At the baseline examination, participants with higher HR at rest were more likely to have a family history of premature CHD, have higher blood pressure, triglycerides, body mass index, diabetes, metabolic syndrome, and use a lipid-lowering medication (Table 1). Median values of hs-CRP and mean values of IL-6 and fibrinogen were higher among those with higher HR at rest. Participants with lower HR at rest were more likely to be men, take an atrioventricular nodal blocker medication, have a higher total household income, have more than a high school education, and have a higher reported physical activity level (p <0.001).

For all 3 inflammatory markers, an increase in HR at rest was associated with an increased percentage of subjects who had an elevated inflammatory level. The absolute percentage of subjects classified with an elevated inflammatory level was highest for hs-CRP (48% in

quintile 5) and similar for fibrinogen (36% in quintile 5) and IL-6 (36% in quintile 5; Figure 1).

In linear regression models, hs-CRP, fibrinogen, and IL-6 increased with increasing HR even after multivariate adjustment including physical activity and atrioventricular nodal blocker medication use (p for trend <0.001 for all 3 markers; Table 2). The relative increase of the regression term from the lowest to highest HR at rest quintile was similar for all 3 inflammatory variables.

Participants with higher HR at rest also had a progressively increased risk of having an elevated inflammatory marker compared with those with lower HR at rest (p for trend <0.001 for all 3 markers; Table 3). In the fully adjusted model, the prevalence of having an elevated inflammatory marker was significantly increased for all HR at rest quintiles, except for the second quintile of fibrinogen, although the PR of 1.11 (95% confidence interval [CI] 0.95 to 1.29) was consistent with the overall graded relation. For the highest quintile of HR at rest, the PR for having an elevated inflammatory marker was similar across the 3 inflammatory markers (PR 1.34, 95% CI 1.21 to 1.49 for hs-CRP; PR 1.51, 95% CI 1.31 to 1.75 for fibrinogen; and PR 1.45, 95% CI 1.27 to 1.67 for IL-6). The association between HR at rest and all 3 inflammatory markers showed some attenuation, but overall, the association was similar when participants with an hs-CRP ≥ 10 mg/L were excluded from the analyses (data not shown).

In subgroup analyses, HR at rest had a significantly stronger association with elevated levels of all the inflammatory markers for men, those without diabetes, and those without metabolic syndrome, with the exception of fibrinogen and metabolic syndrome (Table 4). There was no significant difference in the association between HR at rest and inflammation among the 4 racial or ethnic groups for all 3 inflammatory markers (Table 4 and Figure 2).

Discussion

HR at rest has been established as an independent risk factor for cardiovascular disease and mortality in a number of different cohorts. Kannel et al⁹ reported that HR at rest was associated with a significantly increased 2-year risk of CHD and total mortality in the Framingham Study. In the Finland Cardiovascular Risk Study of 21,853 participants free of cardiovascular disease at baseline, there was a significant increase in CHD mortality and total mortality associated with an increased HR at rest.¹⁰ Moreover, Thomas et al¹¹ found a significant association between an increased HR at rest and cardiovascular mortality among a group of $>60,000$ hypertensive men followed for a mean of 14 years.

Inflammation is associated with the development and progression of atherosclerosis.¹² It has been demonstrated that almost all patients with unstable angina who develop an acute coronary syndrome have increased levels of inflammation before detectable myocardial damage.¹³ Short- and long-term prognoses after an acute coronary syndrome are also associated with the degree of inflammatory response.¹⁴ However, whether there is an interaction between HR at rest and inflammation is still unclear.^{15,16}

Our results demonstrate that HR at rest is significantly associated with increased levels of inflammation as measured by 3 different inflammatory markers. Consistent with previous studies, we found that an increased HR at rest was associated with adverse cardiovascular risk factors including an increase in blood pressure, triglycerides, body mass index, diabetes, and metabolic syndrome. However, our results show that the association of HR with inflammation was independent of these adverse risk factors.

There are a number of biologic mechanisms by which HR at rest and inflammation may be related. In addition to regulating HR at rest and blood pressure, the autonomic nervous system also plays a role in immune system regulation and the inflammatory response. Tumor necrosis factor (TNF) is an inflammatory cytokine that precipitates vascular damage through capillary leakage and microvascular thrombosis.¹⁷ The release of TNF by cardiac myocytes has also been demonstrated to decrease left ventricular function in a murine model.¹⁸ Vagal nerve stimulation has been shown to inhibit inflammation by down regulating the release of TNF and other cytokines from macrophages. It has also been shown to inhibit the endotoxin-induced release of TNF and prevent hypotension and shock.¹

Increased physical fitness is associated with a decreased HR at rest, improved autonomic function, and lower risk of cardiovascular events. Subjects with increased physical fitness have also been shown to have lower levels of inflammation, which has been suggested as a potential mechanism for the observed lower risk of cardiovascular disease.^{19,20} The inverse relation between increased physical fitness and inflammation has been demonstrated to be mediated through an increase in autonomic function, a finding that further supports the importance of autonomic function as part of the inflammatory regulatory system.²¹ We found that the association of HR at rest with inflammation was still present after adjusting for physical activity levels, although physical activity was self-reported and may not fully capture true fitness ability.

In addition, a higher HR may itself directly induce an inflammatory response through an increased frequency of mechanical stress on the vascular endothelium. Cheng et al investigated the effect of different strain levels over time on soluble intercellular adhesion molecule-1, an inflammatory marker that is induced by TNF and associated with a number of inflammatory disorders.^{22,23} They demonstrated that in vitro endothelial cells increased their secretion of soluble intercellular adhesion molecule-1 as a function of both strain and time.

Limitations of this analysis include that the data are from a single time point, and subsequently, the cross-sectional design does not provide information with regard to temporality. There is also the possibility that the single measurement of inflammatory markers may not accurately reflect the long-term inflammatory state of an individual participant. However, the inflammatory markers were measured at a centralized laboratory, and our results were consistent across all 3 markers. Moreover, all 3 inflammatory markers had a low coefficient of variation. Strengths of this study include the use of 3 different inflammatory markers and the adjustment for physical activity and atrioventricular nodal blocker medication use. We were also able to explore the relation between HR at rest and

inflammation among 4 different racial or ethnic groups, which to our knowledge has not been reported by previous analyses.

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References

1. Bernik TR, Friedman SG, Ochani M, DiRaimo R, Ulloa L, Yang H, Sudan S, Czura CJ, Ivanova SM, Tracey KJ. Pharmacological stimulation of the cholinergic antiinflammatory pathway. *J Exp Med*. 2002; 195:781–788. [PubMed: 11901203]
2. Libby P. Inflammation in atherosclerosis. *Nature*. 2002; 420:868–874. [PubMed: 12490960]
3. Piwonska A, Piotrowski W, Broda G, Drygas W, Gluszek J, Zdrojewski T, Kozakiewicz K, Stepaniak U, Badosz P. The relationship between resting heart rate and atherosclerosis risk factors. *Kardiol Pol*. 2008; 66:1069–1075. discussion 1076–1068. [PubMed: 19006028]
4. Rogowski O, Shapira I, Shirom A, Melamed S, Tokar S, Berliner S. Heart rate and microinflammation in men: a relevant atherothrombotic link. *Heart*. 2007; 93:940–944. [PubMed: 17237129]
5. Inoue T, Iseki K, Iseki C, Kinjo K. Elevated resting heart rate is associated with white blood cell count in middle-aged and elderly individuals without apparent cardiovascular disease. *Angiology*. 2012; 63:541–546. [PubMed: 22144667]
6. OHB, Bosch JA, Carroll D, Hemming K, Pilz S, Loerbroks A, Kleber ME, Grammer TB, Fischer JE, Boehm BO, Marz W, Thomas GN. Evidence of a synergistic association between heart rate, inflammation, and cardiovascular mortality in patients undergoing coronary angiography. *Eur Heart J*. 2012; 12:932–941.
7. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol*. 2002; 156:871–881. [PubMed: 12397006]
8. Bertoni AG, Whitt-Glover MC, Chung H, Le KY, Barr RG, Mahesh M, Jenny NS, Burke GL, Jacobs DR. The association between physical activity and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2009; 169:444–454. [PubMed: 19075250]
9. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J*. 1987; 113:1489–1494. [PubMed: 3591616]
10. Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *Am Heart J*. 2010; 159:612–619. e613. [PubMed: 20362720]
11. Thomas F, Rudnicki A, Bacri AM, Bean K, Guize L, Benetos A. Cardiovascular mortality in hypertensive men according to presence of associated risk factors. *Hypertension*. 2001; 37:1256–1261. [PubMed: 11358937]
12. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002; 105:1135–1143. [PubMed: 11877368]
13. Liuzzo G, Biasucci LM, Gallimore JR, Caligiuri G, Buffon A, Rebuszi AG, Pepys MB, Maseri A. Enhanced inflammatory response in patients with preinfarction unstable angina. *J Am Coll Cardiol*. 1999; 34:1696–1703. [PubMed: 10577559]

14. Pietila KO, Harmoinen AP, Jokiniitty J, Pasternack AI. Serum C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment. *Eur Heart J*. 1996; 17:1345–1349. [PubMed: 8880019]
15. Jensen MT, Marott JL, Allin KH, Nordestgaard BG, Jensen GB. Resting heart rate is associated with cardiovascular and all-cause mortality after adjusting for inflammatory markers: the Copenhagen City Heart Study. *Eur J Prev Cardiol*. 2012; 19:102–108. [PubMed: 21525123]
16. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Hansen JF. C-reactive protein, heart rate variability and prognosis in community subjects with no apparent heart disease. *J Intern Med*. 2006; 260:377–387. [PubMed: 16961675]
17. Tracey KJ. The inflammatory reflex. *Nature*. 2002; 420:853–859. [PubMed: 12490958]
18. Bozkurt B, Kribbs SB, Clubb FJ Jr, Michael LH, Didenko VV, Hornsby PJ, Seta Y, Oral H, Spinale FG, Mann DL. Pathophysiologically relevant concentrations of tumor necrosis factor- α promote progressive left ventricular dysfunction and remodeling in rats. *Circulation*. 1998; 97:1382–1391. [PubMed: 9577950]
19. Church TS, Barlow CE, Earnest CP, Kampert JB, Priest EL, Blair SN. Associations between cardiorespiratory fitness and C-reactive protein in men. *Arterioscler Thromb Vasc Biol*. 2002; 22:1869–1876. [PubMed: 12426218]
20. Jae SY, Heffernan KS, Lee MK, Fernhall B, Park WH. Relation of cardiorespiratory fitness to inflammatory markers, fibrinolytic factors, and lipoprotein(a) in patients with type 2 diabetes mellitus. *Am J Cardiol*. 2008; 102:700–703. [PubMed: 18773991]
21. Jae SY, Heffernan KS, Yoon ES, Lee MK, Fernhall B, Park WH. The inverse association between cardiorespiratory fitness and C-reactive protein is mediated by autonomic function: a possible role of the cholinergic antiinflammatory pathway. *Mol Med*. 2009; 15:291–296. [PubMed: 19603105]
22. Cheng JJ, Wung BS, Chao YJ, Wang DL. Cyclic strain enhances adhesion of monocytes to endothelial cells by increasing intercellular adhesion molecule-1 expression. *Hypertension*. 1996; 28:386–391. [PubMed: 8794821]
23. van de Stolpe A, van der Saag PT. Intercellular adhesion molecule-1. *J Mol Med (Berl)*. 1996; 74:13–33. [PubMed: 8834767]

Figure 1.
Percentage of participants with an hs-CRP ≥ 3 mg/L or in the upper quartile of fibrinogen (≥ 389 mg/dl) or IL-6 (1.89 pg/ml) by resting heart rate quintile.

Figure 2.

Fully adjusted prevalence ratio for having an hs-CRP ≥ 3 mg/L or being in the upper quartile of fibrinogen (≥ 389 mg/dl) or IL-6 (≥ 1.89 pg/ml) per 10-beat/min change in baseline resting heart rate among different ethnicities.

Table 1

Participant characteristics by baseline resting heart rate quintile

Characteristic	Baseline HR Quintile					p Value for Trend
	1	2	3	4	5	
Resting heart rate (beats/min)*	50.9 (36–55)	58.1 (56–60)	62.9 (61–65)	68.3 (66–71)	78 (72–130)	<0.001
Age (yrs)	62.9 ± 10.1	61.9 ± 10.3	61.8 ± 10.2	61.6 ± 10.1	62.5 ± 10.2	0.09
Men	60.2	47.1	43.3	43.1	41.2	<0.001
Race						
White	38.9	38.5	39.2	37.5	37.3	0.81
Black	30.9	26.2	25.1	27.1	29.0	0.01
Hispanic	19.9	22.7	22.5	22.5	23.1	0.26
Chinese	10.2	12.6	13.2	19.9	10.6	0.04
Current smoker	12.1	13.6	12.2	14.0	13.2	0.49
Family history coronary heart disease	41.6	42.6	40.3	41.8	48.0	0.01
Systolic blood pressure (mm Hg)	126.9 ± 24	124.7 ± 21	126.2 ± 21	125.9 ± 20	129.7 ± 20	<0.001
Diastolic blood pressure (mm Hg)	70.3 ± 10	70.7 ± 10	71.9 ± 10	72.9 ± 10	74.2 ± 10	<0.001
Low-density lipoprotein (mg/dl)	115.8 ± 30	118.8 ± 30	116.8 ± 33	116.8 ± 32	117.9 ± 33	0.46
High-density lipoprotein (mg/dl)	50.8 ± 14	51.5 ± 15	51.3 ± 15	50.7 ± 15	50.3 ± 15	0.16
Triglycerides [†] (mg/dl)	101 (72, 146)	105 (76, 151)	114 (78, 162)	118 (80, 170)	124 (85, 181)	<0.001
Body mass index (kg/m ²)	27.5 ± 4.9	27.9 ± 5.2	28.2 ± 5.3	28.7 ± 5.8	29.6 ± 5.9	<0.001
Waist circumference (cm)	96.1 ± 13.3	97.1 ± 14.2	97.6 ± 13.9	98.8 ± 14.8	101.7 ± 15.2	<0.001
Hypertension medication	40.3	33.7	33.9	36.5	41.6	<0.001
AV blocker medication	20.7	12.9	11.7	9.6	8.0	<0.001
Lipid-lowering medication	15.0	14.2	16.1	16.7	19.1	0.01
Diabetes mellitus	7.5	8.8	10.4	15.0	23.3	<0.001
Metabolic syndrome	28.7	30.4	33.6	40.3	49.7	<0.001
Moderate and vigorous physical activities [‡]	105 ± 101	100 ± 104	95 ± 102	92 ± 92	84 ± 89	<0.001
\$40,000 income	55.4	51.4	52.9	48.8	48.4	<0.001
High school education	68.6	65.6	64.2	60.4	59.5	<0.001
Hs-CRP [†] (mg/L)	1.4 (0.7–3.1)	1.7 (0.7–3.9)	2.0 (0.9–4.3)	2.2 (0.9–4.7)	2.8 (1.2–5.7)	<0.001
IL-6 (mg/L)	1.4 ± 1.1	1.5 ± 1.1	1.5 ± 1.1	1.7 ± 1.3	1.9 ± 1.5	<0.001

Characteristic	Baseline HR Quintile					p Value for Trend
	1	2	3	4	5	
Fibrinogen (mg/dl)	334 ± 69	339 ± 68	344 ± 72	350 ± 71.7	370 ± 85	<0.001
D-dimer (pg/ml)	0.4 ± 0.7	0.3 ± 0.7	0.4 ± 0.8	0.4 ± 1.2	0.4 ± 0.9	0.02

Data presented as mean ± SD or percentages, unless otherwise indicated.

* Mean and inimum to maximum values.

[†] Median and interquartile range.

[‡] MET-h/week.

Table 2

Estimated increase in high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and interleukin-6 (IL-6) stratified by baseline resting heart rate quintile*

Marker	Resting Heart Rate Quintile, β Coefficient					p for Trend
	1	2	3	4	5	
Hs-CRP (mg/L)						
Unadjusted	Reference	0.15 [†]	0.31 [†]	0.42 [†]	0.61 [†]	<0.001
Model 1	Reference	0.13 [†]	0.28 [†]	0.37 [†]	0.53 [†]	<0.001
Model 2	Reference	0.11 [†]	0.24 [†]	0.30 [†]	0.37 [†]	<0.001
Model 3	Reference	0.11 [†]	0.24 [†]	0.30 [†]	0.37 [†]	<0.001
Fibrinogen (mg/dl)						
Unadjusted	Reference	0.02	0.03 [†]	0.05 [†]	0.10 [†]	<0.001
Model 1	Reference	0.01	0.02 [†]	0.04 [†]	0.08 [†]	<0.001
Model 2	Reference	0.01	0.02 [†]	0.03 [†]	0.06 [†]	<0.001
Model 3	Reference	0.01	0.02 [†]	0.03 [†]	0.06 [†]	<0.001
IL-6 (pg/ml)						
Unadjusted	Reference	0.07 [†]	0.07 [†]	0.19 [†]	0.29 [†]	<0.001
Model 1	Reference	0.09 [†]	0.09 [†]	0.21 [†]	0.29 [†]	<0.001
Model 2	Reference	0.09 [†]	0.08 [†]	0.18 [†]	0.22 [†]	<0.001
Model 3	Reference	0.09 [†]	0.08 [†]	0.18 [†]	0.22 [†]	<0.001

Model 1: age, gender, and race.

Model 2: model 1 + body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, pulse pressure, antihypertensive medication use, smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, lipid-lowering use, family history of CHD, household income, and educational attainment.

Model 3: model 2 + physical activity level and atrioventricular nodal blocker use.

* Hs-CRP, fibrinogen, and IL-6 are presented using log-transformed values.

[†] Indicates p <0.05 compared with zero.

Table 3

Prevalence ratios for having an elevated inflammatory marker, high-sensitivity C-reactive protein (hs-CRP) ≥ 3 mg/L or being in the upper quartile of fibrinogen (≥ 389 mg/dl) or interleukin-6 (IL-6; ≥ 1.89 pg/ml)

Marker	Resting Heart Rate Quintile					p for Trend
	1	2	3	4	5	
Hs-CRP (mg/L)						
Unadjusted	Reference	1.21 (1.08–1.36)*	1.40 (1.26–1.57)*	1.57 (1.41–1.75)*	1.80 (1.62–2.00)*	<0.001
Model 1	Reference	1.16 (1.01–1.30)*	1.29 (1.16–1.44)*	1.42 (1.28–1.58)*	1.57 (1.42–1.74)*	<0.001
Model 2	Reference	1.13 (1.02–1.25)*	1.24 (1.12–1.37)*	1.31 (1.18–1.45)*	1.33 (1.20–1.47)*	<0.001
Model 3	Reference	1.14 (1.02–1.27)*	1.25 (1.13–1.38)*	1.33 (1.20–1.47)*	1.34 (1.21–1.49)*	<0.001
Fibrinogen (mg/dl)						
Unadjusted	Reference	1.17 (1.07–1.36)*	1.37 (1.19–1.58)*	1.46 (1.27–1.69)*	2.01 (1.76–2.30)*	<0.001
Model 1	Reference	1.10 (0.95–1.28)	1.25 (1.08–1.44)*	1.33 (1.15–1.53)*	1.68 (1.47–1.93)*	<0.001
Model 2	Reference	1.08 (0.93–1.26)	1.22 (1.05–1.41)*	1.27 (1.10–1.46)*	1.47 (1.28–1.70)*	<0.001
Model 3	Reference	1.11 (0.95–1.29)	1.23 (1.07–1.43)*	1.31 (1.13–1.51)*	1.51 (1.31–1.75)*	<0.001
IL-6 (pg/ml)						
Unadjusted	Reference	1.16 (1.02–1.34)*	1.15 (0.99–1.32)	1.49 (1.31–1.70)*	1.71 (1.50–1.94)*	<0.001
Model 1	Reference	1.19 (1.04–1.36)*	1.14 (0.99–1.31)	1.47 (1.29–1.68)*	1.64 (1.44–1.86)*	<0.001
Model 2	Reference	1.16 (1.02–1.33)*	1.16 (1.01–1.33)*	1.39 (1.22–1.59)*	1.42 (1.24–1.62)*	<0.001
Model 3	Reference	1.18 (1.03–1.35)*	1.17 (1.02–1.34)*	1.42 (1.25–1.63)*	1.45 (1.27–1.67)*	<0.001

Model 1: age, gender, and race.

Model 2: model 1 + body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, pulse pressure, antihypertensive medication use, smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, lipid-lowering use, family history of CHD, household income, and educational attainment.

Model 3: model 2 + physical activity level and atrioventricular nodal blocker use.

* Indicates $p < 0.05$.

Table 4

Prevalence ratios for having a high-sensitivity C-reactive protein (hs-CRP) ≥ 3 mg/L or being in the upper quartile of fibrinogen (≥ 389 mg/dl) or interleukin-6 (IL-6; ≥ 1.89 pg/ml) per 10-beat/min change in baseline resting heart rate

Variable	Hs-CRP	Fibrinogen	IL-6
Age (yrs)			
<65 (n = 3,780)	1.05 (1.01–1.09)	1.10 (1.04–1.17)	1.06 (0.99–1.27)
65 (n = 2,955)	1.09 (1.04–1.14)	1.15 (1.08–1.22)	1.15 (1.09–1.21)*
Gender			
Male (n = 3,550)	1.20 (1.14–1.27)	1.27 (1.18–1.36)	1.18 (1.11–1.25)
Female (n = 3,185)	1.03 (0.99–1.07)*	1.08 (1.03–1.14)*	1.06 (1.00–1.11)*
Race/ethnicity			
White (n = 2,581)	1.07 (1.01–1.13)	1.16 (1.06–1.27)	1.08 (0.99–1.17)
Black (n = 1,862)	1.05 (1.00–1.10)	1.09 (1.02–1.15)	1.10 (1.02–1.18)
Chinese (n = 803)	1.15 (0.84–1.56)	1.12 (0.72–1.76)	1.33 (0.96–1.84)
Hispanic (n = 1,489)	1.10 (1.04–1.17)	1.19 (1.09–1.29)	1.13 (1.06–1.21)
Hypertension			
Yes (n = 3,717)	1.05 (1.01–1.09)	1.10 (1.05–1.16)	1.12 (1.06–1.19)
No (n = 3,018)	1.11 (1.06–1.16)	1.18 (1.10–1.27)	1.07 (1.00–1.13)
Diabetes			
Yes (n = 5,882)	0.98 (0.92–1.05)	1.06 (0.96–1.16)	1.08 (0.99–1.17)
No (n = 853)	1.09 (1.05–1.13)*	1.16 (1.10–1.22)*	1.11 (1.06–1.17)*
Metabolic syndrome			
Yes (n = 4,302)	1.04 (1.00–1.08)	1.10 (1.04–1.16)	1.05 (0.99–1.10)
No (n = 2,427)	1.13 (1.09–1.18)*	1.17 (1.10–1.24)	1.22 (1.15–1.30)*
Smoking			
Current (n = 876)	1.05 (0.98–1.12)	1.10 (0.98–1.23)	1.12 (1.02–1.24)
Former (n = 2,463)	1.07 (1.02–1.12)	1.19 (1.11–1.29)	1.10 (1.03–1.18)
Never (n = 3,375)	1.06 (1.01–1.11)	1.11 (1.04–1.17)	1.07 (1.00–1.15)
Atrioventricular nodal blocker use			
Yes (n = 861)	1.06 (0.99–1.14)	1.23 (1.12–1.34)	1.17 (1.07–1.28)
No (n = 5,874)	1.07 (1.03–1.10)	1.12 (1.07–1.17)	1.09 (1.05–1.15)

Results presented using fully adjusted model.

* p for interaction <0.05.