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Resting Heart Rate as Predictor for Left Ventricular Dysfunction and Heart Failure

MESA (Multi-Ethnic Study of Atherosclerosis)

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Objectives The objective of this study was to investigate the relationship between baseline resting heart rate and incidence of heart failure (HF) and global and regional left ventricular (LV) dysfunction.

Background The association of resting heart rate to HF and LV function has not been well described in an asymptomatic multi-ethnic population.

Methods Resting heart rate was measured in participants in the MESA (Multi-Ethnic Study of Atherosclerosis) trial at inclusion. Incident HF was registered (n = 176) during follow-up (median 7 years) in those who underwent cardiac magnetic resonance imaging (n = 5,000). Changes in ejection fraction (ΔEF) and peak circumferential strain (Δεcc) were measured as markers of developing global and regional LV dysfunction in 1,056 participants imaged at baseline and 5 years later. Time to HF (Cox model) and Δεcc and ΔEF (multiple linear regression models) were adjusted for demographics, traditional cardiovascular risk factors, calcium score, LV end-diastolic volume, and mass in addition to resting heart rate.

Results Cox analysis demonstrated that for 1 beat/min increase in resting heart rate, there was a 4% greater adjusted relative risk for incident HF (hazard ratio: 1.04; 95% CI: 1.02 to 1.06; $p < 0.001$). Adjusted multiple regression models demonstrated that resting heart rate was positively associated with deteriorating εcc and decrease in EF, even when all coronary heart disease events were excluded from the model.

Conclusions Elevated resting heart rate was associated with increased risk for incident HF in asymptomatic participants in the MESA trial. Higher heart rate was related to development of regional and global LV dysfunction independent of subclinical atherosclerosis and coronary heart disease. (Multi-Ethnic Study of Atherosclerosis [MESA]; NCT00005487) (J Am Coll Cardiol 2014;63:1182–9) © 2014 by the American College of Cardiology Foundation

Resting heart rate is associated with cardiovascular (CV) events and mortality (1). Nevertheless, for many years, resting heart rate has not been included among the main CV risk factors, partially because of interdependence with other risk factors (2). Another reason might have been our incomplete understanding of the mechanisms linking resting heart rate to CV events.

Being related to sympathetic overactivity, atherosclerosis, and plaque vulnerability, resting heart rate–mediated arterial stress has gained much focus among the potential mechanisms underlying CV disease progression and clinical manifestations (3). It is well known that elevated resting heart rates are associated with greater mortality from CV disease (CVD) in particular but also from non-CVD (1,4).

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Several prior studies have also reported the association between resting heart rate and left ventricular (LV) dysfunction (5) and/or heart failure (HF) in epidemiological studies (1,6–8) and in patients with coronary heart disease (CHD) (9,10). On the other hand, few clinical studies have explored the relationships between resting heart rate and LV dysfunction and/or HF among asymptomatic individuals without a history of CVD. Resting heart rate and LV stroke volume are closely regulated for providing adequate cardiac output. During the early phases of LV dysfunction and progression toward HF, subtle reduction of LV function might therefore be accompanied by a compensatory increase in resting heart rate (5), even before the elevated heart rate is identified as a marker of excessive neuroendocrine activation (11). In this regard, there are no studies investigating resting heart rate with incident HF and with myocardial dysfunction in a large asymptomatic population of men and women.

Therefore, we hypothesized that: 1) resting heart rate may be related to HF independently of hypertension, diabetes; and CHD; and 2) an increased resting heart rate might be an early marker of LV dysfunction that precedes traditional indexes of LV dysfunction and clinical disease. We explored the relationship between resting heart rate at baseline and incident HF in a large multi-ethnic population of both sexes free of CVD at enrollment. We also investigated whether resting heart rate was associated with the development of global and regional LV dysfunction independently of traditional risk markers.

Abbreviations and Acronyms

BMI = body mass index
CHD = coronary heart disease
COPD = chronic obstructive pulmonary disease
CV = cardiovascular
CVD = cardiovascular disease
εcc = circumferential strain
EF = ejection fraction
HDL = high-density lipoprotein
HF = heart failure
LV = left ventricular

Methods

Study population. The MESA (Multi-Ethnic Study of Atherosclerosis) study has been described elsewhere (12). Between 2000 and 2002, 6,814 men and women who identified themselves as white (38%), African American (28%), Hispanic (22%), or Chinese American (12%) and were age 45 to 84 years were recruited from 6 U.S. communities in Maryland, Illinois, North Carolina, California, New York, and Minnesota. On entry, all participants underwent an extensive evaluation that consisted of clinical questionnaires, physical examination, electrocardiogram (ECG) for measurement of resting heart rate, and laboratory tests including fasting plasma glucose, triglycerides, and total and high-density lipoprotein (HDL) cholesterol levels (13). Individuals with a history of CVD were excluded. Institutional review boards at each of the participating centers approved the study protocol, and informed consent was obtained from each participant.

CV events during the follow-up period. All events in the MESA study were adjudicated by the morbidity and mortality committee composed of cardiologists, epidemiologists, and general clinicians who review the reports generated by a team of trained individuals who interview participants by phone and gather the appropriate records on each of the reported events. MESA participants who developed events were admitted to different hospitals in the community, including the centers where they are followed as participants of the MESA study. A telephone interviewer contacted each participant (or representative) every 6 to 9 months to inquire about all interim hospital admissions, CV outpatient diagnoses, and deaths. Medical records and information were successfully obtained for an estimated 98% of hospitalized CV events and 95% of outpatient CV diagnostic encounters. Two physicians reviewed all records for independent endpoint classification and assignment of event dates. Reviewers assigned a diagnosis of myocardial infarction based on a combination of symptoms, ECG findings, and cardiac biomarker levels. The definition of angina was adapted from the Women's Health Initiative criteria. Reports of percutaneous coronary intervention and bypass surgery were obtained from medical records. CHD was defined as myocardial infarction, angina, percutaneous coronary intervention, or bypass surgery (13). Chronic obstructive pulmonary disease (COPD) status and severity were defined according to the American Thoracic Society/European Respiratory Society COPD criteria (14).

Details regarding the MESA trial processes and criteria for verifying, classifying, and adjudicating CV events have been previously reported (13,15,16). A precise definition of each individual outcome and adjudication of clinical events for the MESA study are available online (12). The endpoint for this substudy was a composite of probable and definite HF. In addition to clinical HF symptoms or signs, probable HF further required a physician diagnosis of HF and medical treatment for HF. Definite HF also required: 1) pulmonary edema/congestion by chest radiograph; and/or 2) dilated ventricle or poor LV function by echocardiography or ventriculography or evidence of LV diastolic dysfunction. The Online Appendix details the criteria used for adjudication of events in the MESA trial. The risk associated with elevated heart rate was tested by comparing time to HF events with resting heart rate as a continuous variable, as well as analyzing resting heart rate classified into quartiles.

Cardiac magnetic resonance imaging at baseline and follow-up. Cardiac magnetic resonance imaging (MRI) was performed in 5,098 participants and, as an ancillary study protocol, 1,793 participants underwent tagged MRI studies; among these, 1,115 participants underwent repeated tagged MRI scans with an identical protocol 5 years later. The complete cardiac MRI protocol has been previously described elsewhere (13,17). Change in global systolic LV function was quantified as ejection fraction change (ΔEF) from baseline to follow-up and was calculated by subtracting the baseline from the corresponding follow-up values.

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LV strain analysis. As a marker of regional myocardial systolic function, myocardial circumferential midwall shortening was quantified as circumferential strain (εcc) and analyzed by harmonic phase imaging (Diagnosoft, Palo Alto, California) (18). Average minimal value of εcc from 4 LV wall segments (septal, anterior, inferior, and lateral) at midventricular level was calculated, and change in regional LV function from baseline to follow-up was quantified as Δεcc by subtracting the baseline εcc from the corresponding follow-up value. A positive Δεcc indicated a decline in regional LV function.

Statistical analysis. Continuous variables are presented as mean ± SD and compared between groups using 2-sample Student *t* tests. Categorical variables are presented as percent proportions and compared between groups using chi-square tests.

Cox proportional hazard models were constructed for the analysis of the association of risk factors with incident HF by adjustment for the following variables: resting heart rate (continuous or in quartiles), age, ethnicity, sex, current alcohol use, intentional exercise ≥600 metabolic equivalent (MET) min/week, college-level education, systolic and diastolic blood pressure, diabetes, body mass index (BMI), current smoking, HDL cholesterol level, triglyceride level, current medications (lipid-lowering drugs, beta-blockers, and calcium channel blockers [nondihydropyridines]), LV end-diastolic volume and mass indexed to height, computed tomography coronary calcium score (0 or higher than 0), and baseline LVEF (replaced by baseline εcc in regional LV function analysis). Hazard ratios (HRs) were calculated with associated 95% CI and reported for 1-U increases in continuous variables or reclassification of categorical variables to a different level. Participants lost to follow-up were censored at the time of the last follow-up, and missing values were handled based on an a priori analytical plan, that is, only participants who had missing data on a variable needed for a particular model were excluded from that analysis. In backwards stepwise multivariable linear regression models, we investigated Δεcc and ΔEF separately as continuous variables. The same variables were used for the Cox analyses. Statistical analyses were performed using SPSS version 19 (SPSS Inc., Chicago, Illinois).

Results

Participant characteristics and HF events. Of the 6,814 MESA study participants, 5 participants had pre-baseline events and were excluded, and ECG resting heart rate was available in 6,766. Technically adequate data from baseline MRI were available in 5,000 and from the follow-up cardiac MRI in 942 participants. Baseline characteristics according to resting heart rate quartiles and incident HF are shown in Table 1. The mean age of the participants was 62 years (range 44 to 84 years); 53% of the participants were female, 12% were Chinese American, 28% were African American, 22% were Hispanic, and 39% were white. Participants with the highest resting heart rate (70 to 130 beats/min) versus lowest quartile (36 to 56 beats/min) were more likely to be female, less likely to be college graduates and to exercise ≥600 METS per week, and more likely to have higher BMI, to have higher diastolic blood pressure, to be diabetic, and to have higher total cholesterol and triglyceride levels. At inclusion they had less LV mass indexed to height, lower LV end-diastolic volume index, slightly lower EF, and worse regional LV function (less negative εcc).

HF events. There were 176 HF events through 9 years of follow-up (median 7 years), of which 140 were definite and 36 were probable. The differences in baseline characteristics between those who developed HF versus those who did not are presented in Table 1. Participants who developed HF were older and more likely to be male. They were less likely to be Chinese American and more likely to be African American. They had higher BMI, higher resting heart rate, higher systolic blood pressure, and higher triglyceride levels, had lower HDL cholesterol levels, and were more likely to have diabetes and a positive coronary calcium score. Furthermore, they had higher LV mass index and LV end-diastolic volume index and lower LV EF at inclusion. A total of 142 participants were diagnosed with COPD, with 33 of them diagnosed with COPD at entry. Twenty-seven participants also developed HF during follow-up.

Resting heart rate and HF events. Adjusted analyses of resting heart rate as a continuous variable demonstrated that for every increase of 1 beat/min, there was a 4% greater risk for incident HF (Table 2). Adjusted resting heart rates for incident HF relative to a resting heart rate ≤55 beats/min are shown in Figure 1, classified by quartile. When compared with a resting heart rate ≤55 beats/min (lowest quartile), higher resting heart rate quartiles were associated with greater relative risks for incident HF. Importantly, for the highest resting heart rate quartile, we observed a more than 3-fold greater adjusted relative risk for incident HF (Table 2).

The association between resting heart rate as a continuous variable and incident HF was confirmed in adjusted Cox analysis stratified by sex with HRs of 1.07 (95% CI: 1.03 to 1.10; $p \leq 0.001$) and 1.03 (95% CI: 1.01 to 1.05; $p = 0.028$) for women and men, respectively. Furthermore, in adjusted analyses stratified by ethnicity, we also found increased relative risk for incident HF in white and African-American participants; with HRs of 1.05 (95% CI: 1.01 to 1.08; $p = 0.005$) and 1.04 (95% CI: 1.01 to 1.07; $p = 0.030$), respectively. We did not find significant association between adjusted resting heart rate and HF events in Hispanic and Chinese-American participants (HR: 1.03 [95% CI: 0.98 to 1.08; $p = 0.24$] and HR: 1.06 [95% CI: 0.92 to 1.22; $p = 0.43$]). However, the point estimates reflect a trend similar to that shown in white and African-American participants.

The participants with HF events versus no HF events were more likely at baseline to have hypertension (76% vs. 44%), have diabetes (27% vs. 10%), develop CHD during follow-up (42% vs. 4%), and have/develop COPD (19% vs. 2%), all of which are established risk factors for incident HF.

Table 1 Baseline Characteristics Stratified by Resting Heart Rate Quartiles and by Absence or Presence of Incident HF Events During Follow-Up

	Resting Heart Rate Quartiles				HF Events	
	Q1 (36–56 beats/min) (n = 1,268)	Q2 (57–62 beats/min) (n = 1,311)	Q3 (63–69 beats/min) (n = 1,265)	Q4 (70–130 beats/min) (n = 1,126)	No HF (n = 4,888)	HF (n = 112)
Demographic characteristics						
Age, yrs	62 ± 10	61 ± 10*	61 ± 10*	61 ± 10	61 ± 10	68 ± 8†
Female	528 (41.7)	711 (54.2)*	719 (56.8)*	644 (57.4)*	2,583 (52.8)	37 (33.0)†
Ethnicity						
White	509 (40.1)	494 (37.7)	505 (39.9)	423 (37.7)	1,907 (39.1)	48 (42.9)
Chinese American	141 (11.1)	199 (15.2)*	178 (14.1)	135 (12.0)	648 (13.3)	5 (4.5)†
African American	349 (27.5)	319 (24.3)*	314 (24.8)	296 (26.4)	1,249 (25.6)	35 (31.3)†
Hispanic	269 (21.2)	299 (21.2)	268 (21.2)	269 (24.0)	1,084 (22.2)	24 (22.2)
College graduate	666 (52.7)	648 (49.6)	628 (49.6)	518 (46.3)*	2,429 (49.8)	48 (43.2)
Exercise ≥600 MET min/week	855 (67.4)	817 (62.3)	752 (59.5)*	607 (54.1)*	2,984 (61.1)	65 (58.0)
BMI, kg/m^2	26.9 ± 4.3	27.6 ± 4.8*	27.9 ± 5.2*	28.8 ± 5.4*	27.7 ± 4.9	28.8 ± 5.0†
Current smoking	156 (12.3)	165 (12.6)	153 (12.1)	158 (14.1)	614 (12.6)	21 (18.8)
Medical characteristics						
Resting heart rate, beats/min	52 ± 4	60 ± 2*	66 ± 2*	76 ± 6*	63 ± 9	66 ± 11†
Systolic BP, mm Hg	125.5 ± 23.4	124.7 ± 21.3	124.9 ± 20.2	126.9 ± 19.8	125.2 ± 21.2	137.8 ± 20.7†
Diastolic BP, mm Hg	70.3 ± 10.2	71.3 ± 10.4*	72.3 ± 10.0*	73.7 ± 10.2*	71.8 ± 10.3	73.3 ± 11.1
Diabetes	93 (7.3)	114 (8.7)	146 (11.5)*	226 (20.1)*	544 (11.1)	34 (30.4)†
Total cholesterol, mg/dl	191 ± 33	196 ± 35*	193 ± 36	198 ± 37*	194 ± 35	190 ± 35
HDL cholesterol, mg/dl	51 ± 15	52 ± 16	51 ± 15	51 ± 15	51 ± 15	49 ± 14
Triglycerides, mg/dl	120 ± 70	125 ± 71	136 ± 81*	146 ± 113*	131 ± 85	135 ± 77
Medication						
Lipid-lowering medications	202 (15.9)	192 (14.7)	207 (16.4)	183 (16.3)	766 (15.7)	27 (24.1)†
Beta-blockers	197 (15.6)	116 (8.9)*	91 (7.2)*	47 (4.2)*	437 (8.9)	15 (13.4)†
Calcium channel blockers	150 (11.8)	140 (10.7)	143 (11.3)	158 (14.1)	571 (11.7)	25 (22.3)†
ACE inhibitors or ARBs	133 (10.5)	147 (11.2)	143 (11.3)	172 (15.3)*	567 (11.6)	30 (26.8)†
Cardiac parameters						
Coronary calcium present	648 (51.1)	601 (45.8)	606 (47.9)	559 (49.8)	2,345 (50.0)	84 (75.0)†
LV mass index, g/m	91.3 ± 20.1	85.7 ± 20.1*	84.6 ± 20.9*	85.1 ± 21.6*	86.3 ± 20.3	110.2 ± 31.8†
LV end-diastolic volume index, ml/m	80.0 ± 16.3	75.7 ± 15.9*	74.1 ± 16.7*	72.0 ± 16.9*	75.3 ± 16.3	87.7 ± 27.0†
LV ejection fraction, %	69.3 ± 7.0	69.8 ± 7.1	68.9 ± 7.3	67.9 ± 8.3*	69.2 ± 7.2	63.7 ± 12.2†
LV circumferential strain, %‡	−18.0 ± 2.7	−18.1 ± 2.3	−17.8 ± 2.5	−17.1 ± 3.0*	−17.6 ± 2.6	−15.9 ± 3.6†

Values are mean ± SD or n (%). *$p < 0.05$ relative to lowest resting heart rate quartile (Q1). †$p < 0.05$ relative to no HF. ‡Circumferential myocardial strain (shortening) measured in a subset; Q1: n = 227, Q2: n = 218, Q3: n = 209, Q4: n = 168.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; HF = heart failure; LV = left ventricular; MET = metabolic equivalent.

However, in a subanalysis excluding participants with interim CHD events and COPD, resting heart rate remained associated with incident HF in adjusted Cox models (HR: 1.04 [95% CI: 1.01 to 1.07; p = 0.003]). We observed a preserved elevated HR for incident HF for resting heart rate ≥70 beats/min relative to a resting heart rate ≤56 beats/min (HR: 4.55 [95% CI: 1.87 to 11.09; p = 0.001]). This suggests that the resting heart rate is a predictor for incident HF independently of blood pressure, diabetes, COPD, and clinical CHD. In addition, in this study, heart rate was not associated with CHD in Cox regression analysis in both univariate and multivariate models.

Resting heart rate and change in regional and global LV function. Results of the stepwise, backwards multiple linear regression analysis adjusted for demographics, traditional CV risk factors, markers of subclinical atherosclerosis, and LV structure and function at baseline are shown in Table 3 for change in regional LV function and in Table 4 for change in global systolic LV function. A greater resting heart rate was associated with reduced regional LV function (Δεcc; $p < 0.001$), as well as reduced global LV function (ΔEF; $p < 0.001$). In repeated analyses excluding participants with CHD events, the associations between resting heart rate and Δεcc, as well as with ΔEF, did not change and remained statistically significant, suggesting that increased resting heart rate is an independent predictor for the development of regional as well as global LV dysfunction. Figure 2 shows end-diastolic mass to end-diastolic volume ratios at baseline and follow-up across 4 quartiles of heart rate for men and women. Mass-volume ratio was greater in men and was high at high heart rates. The increase in

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Table 2 The Relationship of Resting Heart Rate to HF Events

Model	No./No. at Risk	Cox Models for HF Events: Unadjusted HR (95% CI)	Cox Models for HF Events: Adjusted* HR (95% CI)
Heart rate, beats/min	112/4,963	1.02 (1.01–1.04)	1.04 (1.02–1.06)
Heart rate, beats/min, in quartiles			
Q1 (<57)	18/1,267	1.00 (referent)	1.00 (referent)
Q2 (57–62)	28/1,311	1.11 (0.71–1.74)	2.62 (1.41–4.87)
Q3 (63–69)	28/1,264	1.09 (0.70–1.71)	2.57 (1.36–4.89)
Q4 (>69)	38/1,121	1.72 (1.13–2.61)	3.76 (2.00–7.07)

Model includes heart rate, age, ethnicity, sex, alcohol use, intentional exercise, and education level as covariates (demographics); systolic and diastolic BP, diabetes, BMI, smoking status, total and HDL cholesterol levels, triglyceride levels, and current medications (statins, beta-blockers, and calcium channel blockers) (conventional risk factors); and LV end-diastolic volume, LV mass index, computed tomography coronary calcium score (0 or higher than 0), and baseline ejection fraction.
HF = heart failure; HR = hazard ratio; other abbreviations as in Table 1.

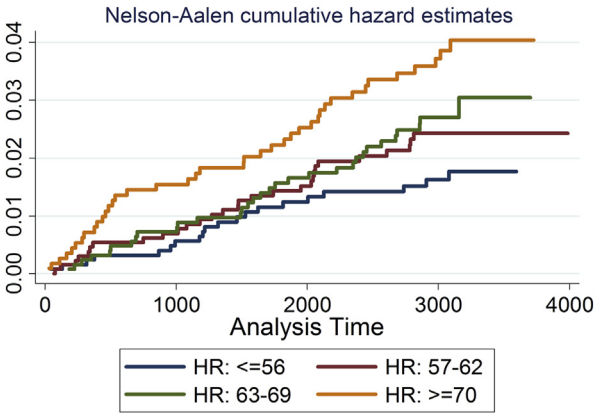

Figure 1 Cumulative Hazard for Incident Heart Failure Split by Baseline Resting Heart Rate Groups

Resting heart rate (HR) ≤56 beats/min is reference. The HR groups are defined as ≤56 **(blue)**, 57–62 **(red)**, 63–69 **(green)**, and ≥70 **(yellow)**.

mass-volume ratio was greater at higher heart rates both in univariate analysis (coefficient 0.003; $p < 0.001$) as well as after adjustment for demographics, traditional CV risk factors, and value at baseline (coefficient 0.003; $p < 0.001$).

Discussion

The present study demonstrated that in a large multiethnic cohort without symptoms of CVD at enrollment, elevated heart rate was strongly associated with the development of regional and global LV dysfunction, as well as incident HF. These findings were independent of demographic confounders, established CV risk factors, and markers of subclinical atherosclerosis, as well as LV structure and function at inclusion. In Cox models and regression models excluding participants with incident CHD events, resting heart rate remained an important predictor for incident HF, as well as for declining regional and global LV function. This indicates that resting heart rate was related to incident HF independently of blood pressure, diabetes, COPD, and clinical CHD and that resting heart rate is an important predictor of progressive subclinical LV dysfunction.

To our knowledge, few previous studies have addressed the associations of resting heart rate with LV dysfunction and incident HF in a population of asymptomatic individuals at baseline (7,8). The adjusted HR for incident HF was of comparable magnitude as in other previous studies that included symptomatic participants at baseline (8). The majority of previous studies addressing resting heart rate as a CV risk factor have focused on either mortality (6,19) or coronary artery disease events (20). Consistent with our findings, previous studies have demonstrated an increased risk for incident HF associated with resting heart rates >70 beats/min (9,21). Resting heart rate has often been demonstrated to predict CHD events and hypertension, with or without diabetes, all of which are important contributing etiologies to the development of HF. Several studies have related resting heart rate to longstanding hypertension, CHD, or presence and/or development of valvular heart disease (3) It has been therefore suggested that increasing heart rate may promote CHD, which in turn may contribute to incident or progressive HF. The relationship between HF and heart rate and CHD and heart rate has been explored previously in the SHIFT (Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial) (22) and BEAUTIFUL (Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction) (9) studies, with the heart rate–reducing drug ivabradine. In the SHIFT study (22), in participants receiving ivabradine, reduced heart rates were observed in addition to fewer hospital admissions for worsening HF and deaths due to HF over 28 months of follow-up. In the BEAUTIFUL trial (9), participants receiving ivabradine did not show a significant reduction in the primary composite endpoints, but a specified subgroup of patients with heart rates >70 beats/min did show a reduction in secondary endpoints. These 2 studies, along with the present study, suggest that higher heart rate may be directly related to HF.

Resting heart rate as an independent predictor of incident HF. In the current study, resting heart rate predicted incident HF independently of hypertension, markers of subclinical atherosclerosis, diabetes, and cigarette smoking. Furthermore, this association remained unchanged even after participants with CHD events were excluded. This suggests that resting heart rate is related to pathophysiological processes leading to HF over and above the effects of clinical hypertension, diabetes, and atherosclerosis. These processes may include the contributions of preclinical stages of hypertension and diabetes, as well as other mechanisms such as inflammation (16), and pathways similar to tachycardia induced cardiomyopathy among other alternative etiologies (23). Because resting heart rate was not related to

Table 3 Stepwise Backwards Multiple Linear Regression Analysis for the Change in Regional LV Function (Δεcc) With Resting Heart Rate

	Change in Regional LV Function (Δεcc)	
	Overall Analysis (R^2 = 0.37) (N = 804) B* (95% CI)	CHD Events Excluded (R^2 = 0.37) (N = 769) B* (95% CI)
Heart rate, beats/min	0.03 (0.01 to 0.06)	0.03 (0.01 to 0.06)
Age, yrs	0.03 (0.01 to 0.05)	0.03 (0.00 to 0.05)
Current smoking	1.12 (0.44 to 1.80)	1.16 (0.46 to 1.85)
Systolic BP, mm Hg	−0.02 (−0.03 to −0.01)	−0·02 (−0.03 to −0.01)
Diastolic BP, mm Hg	0.03 (0.00 to 0.06)	0.03 (0.01 to 0.06)
LV mass, g	0.01 (0.01 to 0.02)	0.01 (0.01 to 0.02)
LV εcc, %	−0.82 (−0.90 to −0.74)	−0.82 (−0.90 to −0.74)

Model includes heart rate, age, ethnicity, sex, alcohol use, intentional exercise, and education level as covariates (demographics); systolic and diastolic BP, diabetes, BMI, smoking status, total and HDL cholesterol levels, triglyceride levels, and current medications (statin, beta-blockers, and calcium channel blockers) (conventional risk factors); and LV end-diastolic volume, LV mass index, computed tomography coronary calcium score (0 or higher than 0), and baseline εcc. *Regression coefficients are the differences in Δεcc (%) per 1-beat/min change in resting heart rate.

CHD = coronary heart disease; εcc = circumferential strain; other abbreviations as in Table 1.

Table 4 Stepwise Backwards Multiple Linear Regression Analysis for the Change in Global LV function (ΔEF) With Resting Heart Rate

	Change in Global LV Function (ΔEF)	
	Overall Analysis (R^2 = 0.17) (N = 954) B* (95% CI)	CHD Events Excluded (R^2 = 0.18) (N = 890) B* (95% CI)
Heart rate, beats/min	−0.08 (−0.13 to −0.03)	−0.07 (−0.13 to −0.02)
Age, yrs	−0.07 (−0.13 to −0.02)	0.04 (−0.09 to 0.02)
Men compared with women	−1.60 (−2.73 to −0.48)	−1.35 (−2.49 to −0.21)
Smoking status	−2.50 (−4.18 to −0.88)	−2.16 (−3.88 to −0.45)
LV end-diastolic volume index, ml/m	−14.8 (−18.9 to −10.7)	−14.1 (−18.3 to −9.8)
LV mass index, g/m	3.29 (−0.26 to 6.83)	
LV ejection fraction (%)	−0.45 (−0.52 to −0.38)	−0.47 (−0.55 to −0.40)

The same model as that used in Table 3, except that baseline ejection fraction (EF) is included rather than εcc. *Regression coefficients are the differences in ΔEF (%) per 1-beat/min change in resting heart rate.

Abbreviations as in Tables 1 and 3.

CHD events, the association between elevated heart rate and incident HF might be explained by such alternative mechanisms. Undiagnosed atherosclerotic or microvascular coronary artery disease associated with or not associated with diabetes may also represent a contributing factor to explain the role of resting heart rate as a predictor of incident HF in the diabetic and glucose intolerant group. A strong relationship has been demonstrated between HF or LV dysfunction in individuals with diabetes (24) or poor glycemic control (25).

Another possible mechanism is that low resting heart rate reflects enhanced vagal tone that may protect against arrhythmias including tachycardias (26). Autonomic imbalance has been associated with increased cardiac mortality (27) and arrhythmias (28). The heart rate profile during exercise and during recovery after exercise has also been demonstrated to be a strong predictor of sudden death in a large cohort of healthy individuals (2). Low heart rate may also result in increased shear stress between blood flow and arterial endothelium, which is beneficial due to increased production of vasodilating agents such as nitrogen oxide (29). In our study, the quartile with low heart rate had a range of heart rates that is quite low compared with optimal heart rate, but it has to be noted that the number of participants on beta-blockers was similarly high in this group (≈14%). Considering the fewer number of events in this category, this further adds to literature describing the benefits of using beta-blockers for heart rate reduction.

In patients with HF, heart rate reduction by beta-blockade reduces oxygen requirement for nonmechanical work and increases mechanical efficiency, but these benefits are abolished if resting heart rate is kept constant by atrial pacing (30). Long-standing increase in resting heart rate may increase cardiac oxygen requirement and contribute to LV remodeling, leading subsequently to LV dysfunction and HF. Therefore, there is increasing evidence supporting the concept that abnormalities in autonomic balance may precede manifestations of HF and may contribute to the early identification of individuals at risk for sudden death (6).

A high heart rate leads to greater myocardial oxygen consumption and decreased myocardial perfusion, the latter by shortening the duration of diastole. An increased heart rate might be directly related to diastolic HF. Women have been observed to be more susceptible to incident HF with preserved EF than men. This might explain the observation that the HR for heart rate was greater in women compared

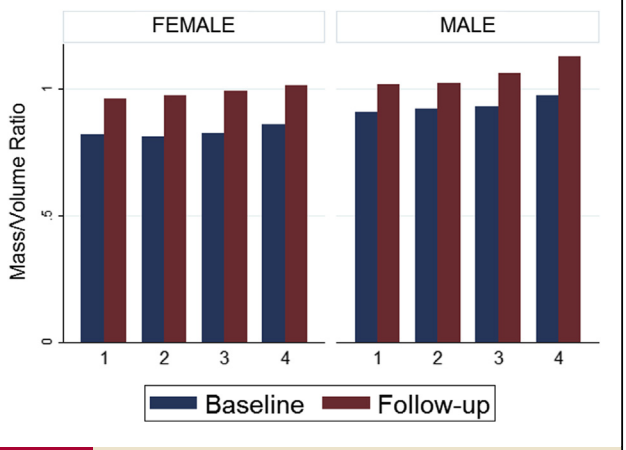

Figure 2 End-Diastolic Mass to End-Diastolic Volume Ratios Seen for Quartiles of Resting Heart Rate and Categorized by Sex at Baseline and Follow-Up

The resting heart rate quartiles are defined as ≤56 beats/min (group 1), 57 to 62 (group 2), 63 to 69 (group 3), and ≥70 (group 4). Average mass/volume ratio at baseline **(blue)** and follow-up **(red)**. Abbreviation as in Figure 1.

with men in this study, as has been observed previously in literature for prediction of CVD (31).

Regional function and HF. Quantification of myocardial strain from MRI has been demonstrated as an accurate marker of incipient LV dysfunction (15,32). Assessment of regional myocardial strain has also been recently shown to be superior to LVEF for prediction of mortality in patients with suspected cardiac disease (33). This is the first study to associate regional myocardial dysfunction with resting heart rate in a large population of asymptomatic individuals at baseline. These findings strengthen and add further evidence to the findings of decreased EF in individuals with higher resting heart rates and support the assumption that higher resting heart rate may promote progressive LV dysfunction and subsequent HF. In addition, higher mass-volume ratio as a measure of concentric LV remodeling (34) was significantly related to higher heart rates, indicating that increased heart rates may promote adverse remodeling.

Study limitations. Reliable evaluation of the associations between resting heart rate and CV events other than HF, as well as of ethnicity in relation to resting heart rate and CV events, requires additional studies. Moreover, the general applicability of our results may be limited by selection and survival biases. In this regard, because MESA study participants had no known CVD at baseline, older individuals undergoing MRI in this cohort may represent a healthier sample of the population at large. In addition, the mechanisms by which HF events result from resting heart rate level were not elucidated by these observational data. As stated in the Methods section, change in EF was calculated by subtracting the baseline examination measure from the follow-up examination, as previously described (35). In addition, the diagnosis of HF may not be as definitive as for other CV events such as stroke or myocardial infarction. Therefore, in the MESA trial, we required that participants be symptomatic with physician-diagnosed HF documented in the medical records that were adjudicated by physician reviewers. Finally, apparently preserved LV function at rest may be revealed as reduced LV function during physical activity.

Conclusions

In an ethnically diverse population free of symptomatic CVD at baseline, the resting heart rate was strongly associated with incident HF during follow up and with declining regional and global LV function. These associations may be mediated through hypertension, diabetes, and coronary atherosclerosis. However, our study suggested that the relationships of heart rate with LV dysfunction and incident HF may also be mediated by independent pathways, raising the possibility that heart rate may be an independent risk factor for HF.

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Key Words: cardiac MRI ■ coronary heart disease ■ heart failure ■ left ventricular dysfunction ■ myocardial strain ■ resting heart rate.

APPENDIX

For information on the criteria used for adjudication of events in the MESA trial, and for supplemental tables, please see the online version of this article.