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Relation of Short-Term Heart Rate Variability to Incident Heart Failure (From the Multi-Ethnic Study of Atherosclerosis)

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Abstract

Whether autonomic dysfunction predates the development of symptomatic heart failure (HF), or is simply a consequence of severe HF, is unknown. We hypothesized that reduced heart rate variability (HRV, a marker of abnormal autonomic function) at baseline is associated with incident HF in individuals free of clinically recognized cardiovascular disease. In the Multi-Ethnic Study of Atherosclerosis (MESA), a community-based study of subclinical cardiovascular disease in adults age 45–84 years, we measured HRV using a standard 30-second 12-lead electrocardiogram to measure the standard deviation of normal-to-normal intervals (SDNN) and the root mean square of successive differences in R-R intervals (RMSSD). During a median follow-up of 7.6 years, 95 participants developed HF (incidence rate, 2.7/1000 person-years). After adjusting for age, sex, and ethnicity, hazard ratios for incident HF by RMSSD tertile were 2.4 (95% confidence interval [CI] 1.4–4.2) for the lowest tertile and 1.7 (95% CI 1.0–3.2) for the middle tertile (highest tertile = referent group; P for trend<0.001). The inverse association between RMSSD and incident HF persisted after adjustment for additional covariates, including diabetes, systolic blood pressure, heart rate, subclinical atherosclerosis, left ventricular endsystolic volume, interim myocardial infarction, and high sensitivity C-reactive protein (P for trend=0.009). A similarly significant inverse association was also observed for SDNN. In conclusion, baseline autonomic dysfunction is risk factor for the development of HF in a multiethnic cohort. These population-based findings implicate autonomic dysfunction in the pathogenesis of HF, and decreased short-term HRV may be a novel form of Stage B (asymptomatic) HF.

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DISCLOSURES

None.

Keywords

autonomic nervous system; heart rate variability; heart failure; epidemiology

Abnormal functioning of the autonomic nervous system, as reflected by reduced heart rate variability (HRV), has been identified in a variety of chronic cardiovascular disease states such as coronary artery disease (CAD), hypertension, and heart failure (HF).^{1–6} While decreased HRV has been previously described in both asymptomatic left ventricular (LV) systolic dysfunction and symptomatic systolic HF,^{7–10} the relationship between HRV and incident HF has not been evaluated, and whether decreased HRV is a cause or consequence of the HF syndrome is also unknown. Subclinical abnormalities in cardiac structure and function may be associated with abnormal autonomic function through maladaptive neurohormonal activation.¹¹ In addition, risk factors for HF, such as diabetes mellitus and CAD, are also associated with autonomic dysfunction.⁷ Finally, reduced HRV may be a sign of sympathetic activation, which can lead to increased sodium retention and thereby precipitate the HF syndrome in at-risk patients.¹¹ We therefore hypothesized that decreased short-term HRV is associated with increased incident HF in persons free of clinical cardiovascular disease. We tested this hypothesis in the Multi-Ethnic Study of Atherosclerosis (MESA), a large, population-based multi-ethnic cohort of participants without known clinical cardiovascular disease.

METHODS

The design of MESA has been described in detail previously.¹² Briefly, MESA is a multicenter, population-based cohort study of 6 communities in the United States (Illinois, North Carolina, Maryland, California, New York, and Minnesota). Participants were recruited between July 2000 and August 2002. Participants defined themselves as white (38%), African American (28%), Hispanic (22%), or Chinese American (12%). All MESA participants were free of clinical cardiovascular disease at baseline. The MESA study was approved by the institutional review boards of all participating centers, and all participants gave written, informed consent. For the present analysis, we included 4652 MESA participants who had undergone measurement of RMSSD and SDNN, cardiac magnetic resonance (CMR) imaging, and had follow-up data.

Baseline short-term HRV was quantified similar to a prior study¹³ by using time-domain analysis of 3 sequential 10-second ECGs (recorded after thirty minutes of supine rest). ECGs were obtained using a Marquette MAC-1200 instrument (GE Medical Systems, Milwaukee, WI) and analyzed electronically by a central ECG reading center, which was blinded to all clinical and non-ECG data of the participants. From the 3 consecutive 10-second ECGs, after discarding ectopic beats, time-domain HRV parameters, including the standard deviation of normal-tonormal intervals (SDNN) and the root-mean square of successive differences in R-R intervals (RMSSD), were documented on each participant with available and interpretable ECG data. All HRV parameters were calculated based on previously published guidelines.¹⁴

A telephone interviewer contacted each participant (or their proxy) every 6–9 months in order to inquire about outpatient cardiovascular diagnoses, interim hospitalizations, and death. For each event, medical records were obtained. Two MESA investigators independently reviewed all records for cardiovascular events. Incident HF, the primary outcome for the present study, was adjudicated by the MESA investigators using validated clinical criteria for symptomatic HF based on the Cardiovascular Health Study and the Women's Health Initiative Study.^{15–17} Criteria for the diagnosis of incident HF required: (1)

physician-diagnosed, symptomatic HF; (2) medical treatment for HF; and (3) one or more of the following: pulmonary edema/pulmonary vascular congestion on chest radiography; dilated LV or reduced LV systolic function by echocardiography or ventriculography; or evidence of LV diastolic dysfunction.

In addition to undergoing HRV analysis and outcomes ascertainment, all participants underwent comprehensive baseline testing which included documentation of comorbidities; measurement of blood pressure and heart rate; laboratory testing (including fasting lipid profile, fasting glucose, and high-sensitivity C-reactive protein); computed tomography (CT) of the chest for the determination of coronary artery calcium (CAC) score; and CMR imaging for the evaluation of LV size and function. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medications. Diabetes was defined as fasting glucose ≥ 126 mg/dl or the use of diabetic medications.¹⁸ Obesity was defined as body-mass index ≥ 30 kg/m². Physical activity was defined as the number of metabolic equivalent (MET)-minutes per week spent doing intentional leisure-time exercise (e.g., moderate walking exercise, dance, and vigorous sports).

CT scanning (for CAC) and CMR imaging (for LV structure and function) in MESA have been described in detail previously.^{19,20} For the present study, we included data on CAC score as a marker of subclinical atherosclerosis at baseline. In addition, we included the following CMR parameters: LV mass, LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, and stroke volume. Interim myocardial infarction (MI) was diagnosed based on a combination of symptoms, ECG, and cardiac biomarker levels.

Correlation between RMSSD and SDNN was assessed using Pearson's correlation coefficient. For descriptive purposes only, participants were classified into RMSSD and SDNN groups based on tertiles of each HRV parameters within the entire cohort (RMSSD tertiles: low < 16 ms; middle 16 and < 27 ms; high: ≥ 27 ms; and SDNN tertiles: low < 14.6 ms; middle 14.6 and < 24.3 ms; high: ≥ 24.3 ms). Baseline characteristics were compared across the tertiles of RMSSD and SDNN with significance tests by chi-square for categorical variables or analysis of variance (or Kruskal-Wallis when appropriate) for continuous variables. We also further examined the associations between baseline characteristics and HRV parameters modeled as continuous variables (instead of tertiles). Statistical significance was tested using linear regressions (continuous variables), Cochran-Armitage trend tests (dichotomous variables), or quantile regressions (nonparametric comparisons).

For all survival analyses, the follow-up interval was defined for each participant as the elapsed time between the baseline visit to the date of most recent follow-up (MESA telephone follow-up 9), the date of death, or date of incident HF. Median follow-up for the cohort was 7.6 years. Annualized incidence rates of HF per 1000 person-years according to tertiles of RMSSD or SDNN were calculated with the number of cases of HF as the numerator and number of person-years as the denominator.

Cox proportional hazards models were used to investigate the association of incident HF and tertiles of RMSSD and SDNN separately, with the highest tertile as the reference group in 3 models: model 1 (adjusted for age, gender, and ethnicity), model 2 (all variables in model 1 plus education, physical activity, smoking status, diabetes, systolic blood pressure, presence of CAC, LV end-systolic volume, and resting heart rate), model 3 (all variables in model 2 plus time-varying incident myocardial infarction [myocardial infarction occurring prior to or on the date of incident HF]), and model 4 (all variables in model 3 plus C-reactive protein). Linear trend across the tertiles was performed on the log-transformed RMSSD or SDNN as

a continuous variable because of highly skewed distribution. The proportionality assumption was confirmed for all Cox regression models.

Covariates were screened for inclusion into multivariable models if they were associated with HRV parameters (either RMSSD or SDNN) in MESA or prior published studies of HRV. From this list, covariates thought to be plausibly associated with both HRV and HF (based on external clinical judgment) were chosen for inclusion into the multivariable models. Additional covariates were added if there was a known prior association between the covariate and HF. Several covariates associated with HRV parameters (such as CMR parameters) were collinear; therefore, only one of a group of collinear variables selected for entry into the final multivariable models. All analyses were conducted using SAS statistical software version 9.2 (SAS Institute Inc, Cary, NC). $P < 0.05$ was considered statistically significant.

RESULTS

Our study included 4652 MESA participants (53.0% women; 38.7% white, 13.4% Chinese, 25.2% African-American, and 22.7% Hispanic) with a mean age of 61.2 years at baseline. The two calculated HRV parameters (SDNN and RMSSD) were highly correlated, with Pearson correlation coefficient of 0.95 ($P < 0.001$). The characteristics of the participants by RMSSD and SDNN tertiles are displayed in Table 1. Participants in the lowest tertile of both SDNN and RMSSD were older, more often male, and less likely African-American. These participants were also more likely to be taking angiotensin converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, or anti-hypertensive or lipid lowering therapies in general.

Hypertension, increased blood pressure (including increased systolic blood pressure and increased pulse pressure), and increased heart rate were all associated with reduced HRV. Factors related to metabolic syndrome and diabetes (lower HDL-cholesterol, higher triglycerides, higher fasting glucose, and higher prevalence of diabetes) were all present in the lowest SDNN and RMSSD tertiles. However, LDL-cholesterol and body-mass index were similar across tertiles. Subclinical markers of atherosclerosis and abnormal LV structure and function (i.e., subclinical HF) were also present in the lowest SDNN and RMSSD tertiles: prevalence of CAC score > 10 , LV mass, and LV volumes were all higher (and stroke volume lower) in participants with the lowest HRV. We observed similar results when the aforementioned relationships between baseline characteristics and HRV parameters were analyzed using continuous HRV data instead of tertiles.

During a median follow-up of 7.6 years, 95 participants developed HF and 98 participants suffered a myocardial infarction, revealing incidence rates of 2.7 per 1,000 person-years for both HF and 2.8 per 1,000 person-years for myocardial infarction. New-onset HF has previously been shown to occur more commonly in MESA participants who were older, male, obese, currently smoking, hypertensive, and diabetic.²¹ Several of these factors were also present in MESA participants in the lowest HRV tertiles (Table 1).

There was a significant difference in the cumulative hazard of incident HF among participants in the lowest and middle RMSSD tertiles compared to the highest tertile ($P < 0.001$ and $P = 0.029$, respectively; Figure 1). In age-, gender-, and race-adjusted analyses, the hazard ratio (HR) of HF was 2.40 (95% CI, 1.37–4.22) for the lowest RMSSD tertile and 1.74 (95% CI, 1.01–3.15) for the middle tertile compared with individuals in the highest tertile (P for trend < 0.001 ; Table 2, model 1). These significant inverse associations persisted after adjustment for physical activity, diabetes, systolic blood pressure, heart rate, CAC, and LV end-systolic volume (P for trend = 0.004, model 2), and further adjustment for time-

varying incident myocardial infarction (P for trend=0.009, model 3). Further adjustment for C-reactive protein (model 4) did not attenuate the association. Similar, but less strong inverse relationships were also observed with SDNN and incident HF. Similar findings were also demonstrated when alternative LV parameters (e.g., LV mass, LV end-diastolic volume, and LV ejection fraction) were substituted for LV end-systolic volume in the multivariable analyses.

In stratified analyses, we found that the association between HRV and incident HF varied by CAC score. The association between HRV and incident HF was strongest in those with CAC score ≥ 10 (Table 3).

DISCUSSION

In a multi-ethnic, population-based study of participants free of cardiovascular disease at baseline, we found that reduced baseline HRV, as determined by SDNN and RMSSD on 3 consecutive 12-lead, 10-second ECGs, is independently associated with increased incident HF. Our finding of reduced HRV preceding HF is important for two reasons. First, the findings of reduced HRV in persons without overt signs and symptoms of cardiovascular disease may be a form of “Stage B” HF (asymptomatic cardiac dysfunction prior to the onset of HF²²), and may identify those who are at high risk for developing the HF syndrome thereby allowing for prevention of HF. Indeed, individuals with reduced HRV were more likely to have increased LV mass and larger LV volumes. Second, the finding that reduced HRV precedes the onset of HF is provocative, because it suggests that autonomic dysfunction may be involved in the pathogenesis of HF. Alternatively, reduced HRV may be associated with subclinical cardiac dysfunction or risk factors associated with the development of HF such as cardiac remodeling and diabetes mellitus. Accordingly, we found that the lowest tertile of HRV is associated with HF risk factors (diabetes, increased CAC [indicative of asymptomatic, subclinical coronary atherosclerosis]), and adverse cardiac remodeling (increased LV end-systolic volume and increased LV mass). However, low HRV remains associated with incident HF even after adjusting for both HF risk factors and indicators of cardiac remodeling.

HF can be considered a state of autonomic imbalance, described as a generalized sympathetic activation and relatively decreased parasympathetic tone.^{11,23} HRV, as measured by SDNN and RMSSD, has emerged as a simple and reliable means to assess underlying autonomic tone;^{24–26} thus, it is not surprising that HRV has been associated with severity of HF and adverse outcomes in studies of patients with prevalent HF. However, once the overt, symptomatic HF syndrome develops, HRV can be severely reduced. Therefore, in patients with established HF, short-term HRV may have reduced predictive value since reduced HRV will be present in most HF patients, and thus may perform less well as a tool for risk stratification. To determine both time- and frequency-domain HRV characteristics, the majority of prior studies of HRV in HF used 24-hour Holter monitoring which would be difficult to apply to lower-risk patients. Short-term HRV may therefore be especially useful in the type of individuals studied in MESA—those with cardiovascular risk factors who have not yet developed overt, clinical HF.

In addition to revealing an independent association between reduced HRV and incident HF, we validated several previously known associations between clinical factors and reduced HRV in a large ethnically diverse population-based cohort.^{7,14,27,28} We found that those individuals in the lowest HRV tertiles were older; more likely diabetic and with higher fasting glucose; less physically active; and more likely to have evidence of subclinical CAD based on increased prevalence of CAC score > 10 . We also replicated prior studies which have not found an association between HRV and obesity.²⁸ Our study is the largest study of

HRV and its association with cardiac structure and function measured by CMR imaging. Using CMR techniques, we were able to find associations between reduced HRV and several CMR parameters suggestive of subclinical HF.

Reasons for the independent association between reduced HRV and incident HF in MESA are likely complex. Increased sympathetic activity, reduced cardiac vagal activity, neuroendocrine dysfunction, and increased cytokines have all been found to contribute to the decreased HRV found in patients with prevalent HF. Since HF is a syndrome, it is likely that these abnormalities are already occurring in those who have risk factors and are on their way to developing the HF syndrome. However, it is also possible that reduced HRV is indicative of a deranged autonomic nervous system that is causing the HF syndrome. For example, sympathetic activation leads to increased renal sodium retention¹¹ and may cause fluid overload (thereby precipitating clinically overt HF) in the vulnerable patient. Inflammation has also been linked with both HRV and HF;^{29,30} however, adjustment for C-reactive protein, a marker of inflammation, did not attenuate the association between reduced HRV and incident HF.

Interestingly, we found that our results differed when stratified by CAC score. The association between HRV and incident HF was strongest in the group of participants with CAC score < 10. This finding may be explained by the fact that once overt HF risk factors such as coronary atherosclerosis develop, those risk factors drive much of the risk for HF. However, in individuals without such risk factors, such as those with CAC score < 10, autonomic dysfunction may be more important in the pathogenesis of HF.

The strengths of our study include a large, ethnically diverse group of participants with no known clinical cardiovascular disease at the time of enrollment, all of whom underwent detailed phenotyping which included evaluation of CAC and CMR-based LV structure and function analysis. In addition, the time-domain HRV parameters used in our study were obtained from 3 consecutive 10-second 12-lead ECGs, and therefore could be applied universally in the clinical setting. The use of only time-domain, and not frequency-domain, HRV parameters, and the lack of more prolonged ECG data could also be viewed as a limitation of our study. In addition, in short-term HRV recordings, SDNN has been found to be less stable over time on repeated recordings (and therefore may be less reproducible) compared to other HRV parameters such as RMSSD.³¹ However, our use of short-term, time-domain HRV parameters increases the clinical applicability of our findings, and the similarity of the findings for RMSSD and SDNN suggest that both parameters could be useful in predicting incident HF. We are also limited by the use of only HRV parameters to gauge the health of the autonomic nervous system. While HRV provides some insight into autonomic function, autonomic control of the sinoatrial node (which is thought to be the basis for HRV) may differ from functioning of the rest of the autonomic nervous system. Furthermore, although we adjusted for several covariates, residual confounding by unmeasured covariates cannot be excluded. Finally, although we found that decreased baseline HRV was associated with an increased incidence of future HF, we cannot prove a causal relationship between autonomic dysfunction and HF.

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References

1. Palatini P, Julius S. Relevance of heart rate as a risk factor in hypertension. *Curr Hypertens Rep.* 1999; 1:219–224. [PubMed: 10981069]
2. Palatini P. Heart rate as a risk factor for atherosclerosis and cardiovascular mortality: the effect of antihypertensive drugs. *Drugs.* 1999; 57:713–724. [PubMed: 10353296]
3. Bilchick KC, Fetters B, Djoukeng R, Fisher SG, Fletcher RD, Singh SN, Nevo E, Berger RD. Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). *Am J Cardiol.* 2002; 90:24–28. [PubMed: 12088774]
4. La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opasich C, Riccardi PG, Traversi E, Cobelli F. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation.* 2003; 107:565–570. [PubMed: 12566367]
5. Makikallio TH, Huikuri HV, Hintze U, Videbaek J, Mitrani RD, Castellanos A, Myerburg RJ, Moller M. Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure. *Am J Cardiol.* 2001; 87:178–182. [PubMed: 11152835]
6. Soejima K, Akaishi M, Meguro T, Oyamada K, Yoshikawa T, Mitamura H, Ogawa S. Age-adjusted heart rate variability as an index of the severity and prognosis of heart failure. *Jpn Circ J.* 2000; 64:32–38. [PubMed: 10651204]
7. De Jong MJ, Randall DC. Heart rate variability analysis in the assessment of autonomic function in heart failure. *J Cardiovasc Nurs.* 2005; 20:186–195. [PubMed: 15870589]
8. Jiang W, Hathaway WR, McNulty S, Larsen RL, Hansley KL, Zhang Y, O'Connor CM. Ability of heart rate variability to predict prognosis in patients with advanced congestive heart failure. *Am J Cardiol.* 1997; 80:808–811. [PubMed: 9315600]
9. Aronson D, Burger AJ. Gender-related differences in modulation of heart rate in patients with congestive heart failure. *J Cardiovasc Electrophysiol.* 2000; 11:1071–1077. [PubMed: 11059968]
10. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol.* 1993; 22:6A–13A. [PubMed: 8509564]
11. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol.* 2009; 54:375–385. [PubMed: 19628111]
12. 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]
13. Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. *Am J Epidemiol.* 1997; 145:899–908. [PubMed: 9149661]
14. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation.* 1996; 93:1043–1065. [PubMed: 8598068]
15. Curb JD, McTiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, Johnson KC, Proulx-Burns L, Pastore L, Criqui M, Daugherty S. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol.* 2003; 13:S122–S128. [PubMed: 14575944]
16. Schellenbaum GD, Heckbert SR, Smith NL, Rea TD, Lumley T, Kitzman DW, Roger VL, Taylor HA, Psaty BM. Congestive heart failure incidence and prognosis: case identification using central adjudication versus hospital discharge diagnoses. *Ann Epidemiol.* 2006; 16:115–122. [PubMed: 15964203]
17. Schellenbaum GD, Rea TD, Heckbert SR, Smith NL, Lumley T, Roger VL, Kitzman DW, Taylor HA, Levy D, Psaty BM. Survival associated with two sets of diagnostic criteria for congestive heart failure. *Am J Epidemiol.* 2004; 160:628–635. [PubMed: 15383406]
18. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, Lernmark A, Metzger BE, Nathan DM. Position statement executive summary: guidelines and recommendations for

- laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care*. 2011; 34:1419–1423. [PubMed: 21617111]
19. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2006; 113:30–37. [PubMed: 16365194]
 20. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, Pearson G, Sinha S, Arai A, Lima JA, Bluemke DA. Cardiovascular function in multi-ethnic study of atherosclerosis: normal values by age, sex, and ethnicity. *AJR Am J Roentgenol*. 2006; 186:S357–S365. [PubMed: 16714609]
 21. Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, Szklo M, Lima JA. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol*. 2008; 51:1775–1783. [PubMed: 18452784]
 22. Goldberg LR, Jessup M. Stage B heart failure: management of asymptomatic left ventricular systolic dysfunction. *Circulation*. 2006; 113:2851–2860. [PubMed: 16785351]
 23. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol*. 2009; 54:1747–1762. [PubMed: 19874988]
 24. Makikallio TH, Tapanainen JM, Tulppo MP, Huikuri HV. Clinical applicability of heart rate variability analysis by methods based on nonlinear dynamics. *Card Electrophysiol Rev*. 2002; 6:250–255. [PubMed: 12114847]
 25. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol*. 2008; 51:1725–1733. [PubMed: 18452777]
 26. Bleasdale RA, Frenneaux MP. Cardiac resynchronisation therapy: when the drugs don't work. *Heart*. 2004; 90(Suppl 6):vi2–vi4. [PubMed: 15564421]
 27. Carnethon MR, Prineas RJ, Temprosa M, Zhang ZM, Uwaifo G, Molitch ME. The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. *Diabetes Care*. 2006; 29:914–919. [PubMed: 16567837]
 28. Tacoy G, Acikgoz K, Kocaman SA, Ozdemir M, Cengel A. Is there a relationship between obesity, heart rate variability and inflammatory parameters in heart failure? *J Cardiovasc Med (Hagerstown)*. 2010; 11:118–124. [PubMed: 19809354]
 29. Araujo F, Antelmi I, Pereira AC, Latorre Mdo R, Grupi CJ, Krieger JE, Mansur AJ. Lower heart rate variability is associated with higher serum high-sensitivity C-reactive protein concentration in healthy individuals aged 46 years or more. *Int J Cardiol*. 2006; 107:333–337. [PubMed: 16503254]
 30. Lanza GA, Sgueglia GA, Cianflone D, Rebuzzi AG, Angeloni G, Sestito A, Infusino F, Crea F, Maseri A. Relation of heart rate variability to serum levels of C-reactive protein in patients with unstable angina pectoris. *Am J Cardiol*. 2006; 97:1702–1706. [PubMed: 16765117]
 31. Tarkkainen TH, Timonen KL, Tiittanen P, Hartikainen JE, Pekkanen J, Hoek G, Ibal-Mulli A, Vanninen EJ. Stability over time of short-term heart rate variability. *Clin Auton Res*. 2005; 15:394–399. [PubMed: 16362542]

Figure 1. Cumulative Hazard of Heart Failure According to Tertiles of RMSSD

RMSSD = root mean square of successive differences in NN intervals on a 30-second, 12-lead electrocardiographic recording.

Table 1

Baseline characteristics of participants by heart rate variability tertiles

Variable	Tertiles of RMSSD			P value [§]	Tertiles of SDNN			P value [§]
	Low (1.0 – 15.9)	Middle (16.0 – 26.9)	High (27.0 – 328.0)		Low (0.90 – 14.5)	Middle (14.6 – 24.2)	High (24.3 – 208.1)	
Number of patients	1492	1602	1558		1555	1565	1532	
Age (years)								
mean (SD)	64.1 (9.6)	60.8 (9.8)	59.0 (10.0)	<0.001	64.4 (9.7)	60.4 (9.7)	58.8 (10.0)	<0.001
< 65 years	49.4%	61.9%	68.2%	<0.001	47.1%	63.3%	69.7%	<0.001
Male sex	50.4%	47.9%	42.9%	<0.001	48.0%	49.3%	43.7%	0.005
Race								
White	41.9%	39.9%	34.5%		38.8%	39.7%	37.6%	
Chinese	16.3%	14.7%	9.2%		16.9%	14.2%	8.9%	
African-American	18.3%	22.8%	34.2%	<0.001	19.4%	23.5%	32.8%	<0.001
Hispanic	23.5%	22.6%	22.1%		24.8%	22.6%	20.7%	
Education > high school	62.9%	67.3%	66.0%	0.028	62.0%	66.2%	68.2%	0.001
Body-mass index (kg/m ²)	27.7 (4.8)	27.5 (4.8)	28.0 (5.1)	0.022	27.6 (4.9)	27.6 (4.9)	28.0 (5.0)	0.071
Body-mass index 30 kg/m ²	27.1%	27.4%	30.5%	0.071	26.9%	27.7%	30.5%	0.059
Cigarette smokers	10.3%	11.9%	15.5%	<0.001	10.5%	12.5%	14.8%	0.001
Physical activity, MET-min/wk (median [IQR])								
Women	630 (0 to 1687)	735 (82 to 1852)	840 (210 to 1890)	0.027	660 (0 to 1657)	765 (105 to 1860)	825 (210 to 1890)	0.026
Men	967 (157 to 2224)	1050 (315 to 2325)	1114 (315 to 2682)	0.123	1080 (315 to 2235)	922 (157 to 2340)	1200 (330 to 2625)	0.043
Medication use								
Beta-blocker	8.4%	7.6%	9.1%	0.311	9.3%	8.1%	7.8%	0.283
Angiotensin converting enzyme-inhibitor/ angiotensin receptor blocker	17.8%	12.1%	11.8%	<0.001	18.8%	10.8%	11.9%	<0.001
Calcium channel blocker	13.8%	10.6%	11.0%	0.010	14.7%	10.0%	10.5%	<0.001
Hypertension	40.0%	32.3%	31.9%	<0.001	42.3%	31.0%	30.5%	<0.001
Lipid-altering	18.2%	16.1%	13.3%	0.001	18.5%	15.7%	13.2%	<0.001
Systolic blood pressure (mmHg)	128.4 (20.8)	124.6 (20.8)	123.1 (21.6)	<0.001	128.7 (21.3)	124.1 (20.4)	123.1 (21.5)	<0.001
Diastolic blood pressure (mmHg)	73.0 (10.3)	71.9 (10.1)	70.8 (10.3)	<0.001	72.6 (10.3)	71.8 (10.0)	71.2 (10.4)	0.001

Variable	Tertiles of RMSSD			P value [§]	Tertiles of SDNN			P value [§]
	Low (1.0 – 15.9)	Middle (16.0 – 26.9)	High (27.0 – 328.0)		Low (0.90 – 14.5)	Middle (14.6 – 24.2)	High (24.3 – 208.1)	
Hypertension	49.1%	38.8%	38.6%	<0.001	50.9%	37.1%	38.0%	<0.001
Pulse pressure (mmHg)	55.4 (16.6)	52.8 (16.7)	52.2 (17.0)	<0.001	56.1 (17.0)	52.3 (16.3)	51.9 (16.9)	<0.001
Heart rate (bpm)	68.0 (9.4)	62.3 (8.0)	58.5 (7.9)	<0.001	66.4 (9.8)	62.3 (8.4)	59.8 (8.4)	<0.001
Total cholesterol (mg/dl)	196.3 (35.6)	194.8 (36.5)	192.6 (33.8)	0.017	195.4 (35.6)	195.4 (35.8)	192.8 (34.5)	0.057
HDL cholesterol (mg/dl)	50.6 (14.9)	50.8 (14.8)	52.2 (15.3)	0.008	50.8 (14.7)	50.9 (15.4)	51.9 (15.0)	0.090
LDL cholesterol (mg/dl)	117.4 (30.8)	117.9 (32.7)	116.7 (30.1)	0.580	116.8 (31.0)	118.2 (32.2)	117.0 (30.5)	0.422
Triglycerides (mg/dl) [Median (IQR)]	122.0 (84.0 to 177.0)	113.0 (79.0 to 163.0)	100.0 (72.0 to 149.0)	<0.001	120.0 (83.0 to 172.0)	113.0 (80.0 to 163.0)	100.0 (72.0 to 150.0)	<0.001
Fasting glucose (mg/dl)	100.9 (33.6)	95.2 (27.7)	92.3 (23.3)	<0.001	101.1 (35.2)	94.9 (26.2)	92.0 (22.3)	<0.001
Diabetes mellitus	15.8%	10.4%	8.3%	<0.001	16.0%	10.3%	7.9%	<0.001
C-reactive protein (mg/L) [Median (IQR)]	2.0 (0.9 to 4.4)	1.7 (0.7 to 3.7)	1.7 (0.7 to 3.9)	0.003	1.9 (0.8 to 4.3)	1.7 (0.7 to 3.8)	1.7 (0.7 to 3.9)	0.019
Coronary artery calcium score > 10	49.6%	39.7%	31.7%	<0.001	48.8%	40.4%	31.2%	<0.001
Magnetic resonance imaging								
LV mass (g)	144.0 (39.9)	142.5 (37.1)	147.2 (40.9)	0.002	143.2 (39.8)	143.8 (38.0)	146.6 (40.2)	0.037
LV end-diastolic volume (ml)	122.1 (29.8)	125.9 (31.3)	130.0 (31.9)	<0.001	122.0 (30.5)	126.7 (30.8)	129.5 (31.7)	<0.001
LV end-systolic volume (ml)	38.5 (16.3)	39.3 (16.8)	41.2 (16.6)	<0.001	37.9 (16.2)	39.8 (16.6)	41.3 (16.8)	<0.001
LV ejection fraction (%)	69.2 (7.7)	69.5 (7.3)	68.8 (6.9)	0.056	69.6 (7.6)	69.2 (7.1)	68.7 (7.1)	0.002
LV stroke volume (ml)	83.7 (18.8)	86.6 (19.8)	88.7 (20.3)	<0.001	84.1 (19.5)	86.9 (19.4)	88.2 (20.2)	<0.001
Follow-up time, y [median (IQR)]	7.6 (7.3 to 7.8)	7.6 (7.4 to 7.8)	7.6 (7.4 to 7.8)	0.703	7.6 (7.3 to 7.8)	7.6 (7.4 to 7.8)	7.6 (7.4 to 7.8)	0.882

*Data shown are means (SD) unless otherwise indicated.

Abbreviations: RMSSD, root mean squared differences of successive differences (msec); SDNN, standard deviation of N-N intervals (msec); LV, left ventricular; IQR, inter-quartile range. Of the 6814 MESA participants at baseline, 6351 had measurements for RMSSD or SDNN and completed the follow-up 9 telephone interview. Of these persons, 31 had no follow-up time, 1629 were missing MRI data, and 39 were excluded because of missing key covariates of interest, leaving a sample of 4652 participants for analysis. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or current use of antihypertensive medications. Diabetes was defined as fasting glucose ≥ 126 mg/dl or use of diabetic medications (2003 American Diabetes Association criteria). Physical activity was defined as the number of MET-minutes per week spent doing intentional leisure-time exercise (included moderate walking exercise, dance and vigorous sports).

[§]P value for test of difference across tertiles of RMSSD or SDNN using chi-square test (categorical variables) or analysis of variance (continuous variables) or Kruskal-Wallis test (nonparametric comparisons). Findings were unchanged when continuous values of RMSSD and SDNN were used (instead of tertiles) in these analyses.

Table 2
Incidence rates and hazard ratios (95% CI) for heart failure by heart rate variability tertiles

	Tertiles of RMSDD			Tertiles of SDNN		
	Low (1.0 – 15.9)	Middle (16.0 – 26.9)	High (27.0 – 328.0)	Low (0.90 – 14.5)	Middle (14.6 – 24.2)	High (24.3 – 208.1)
Heart failure (HF)						
N / total	49/1492	32/1602	17/1558	50/1555	28/1565	20/1532
Person-years	10512	11396	11105	10937	11140	10935
Rate per 1000 person-years	4.7	2.8	1.5	4.6	2.5	1.8
Model [¶]		HR (95% CI)			HR (95% CI)	
1	2.40 (1.37 to 4.22) *	1.74 (1.01 to 3.15) *	1.0 (reference)	1.88 (1.11 to 3.20) *	1.28 (0.72 to 2.28)	1.0 (reference)
2	2.24 (1.20 to 4.18) *	1.94 (1.07 to 3.54) *	1.0 (reference)	1.71 (1.00 to 3.00) *	1.38 (0.77 to 2.47)	1.0 (reference)
3	1.83 (1.00 to 3.50) *	1.96 (1.07 to 3.58) *	1.0 (reference)	1.50 (0.84 to 2.69)	1.29 (0.72 to 2.32)	1.0 (reference)
4	1.85 (1.00 to 3.53) *	1.90 (1.04 to 3.47) *	1.0 (reference)	1.49 (0.83 to 2.67)	1.23 (0.68 to 2.23)	1.0 (reference)
						P trend[§]
						<0.001
						0.002
						0.007
						0.008

Abbreviations: HR, hazard ratios; CI, confidence interval.

[¶]Model 1: adjusted for age, gender, and race (White, African-American, Chinese, Hispanic); Model 2: adjusted for all variables in model 1 plus education more than high school (yes/no), physical activity (gender-specific tertiles: low, middle, high), current cigarette smoking (yes/no), diabetes (yes/no), prevalence of coronary artery calcium score > 10 (yes/no), LV end-systolic volume, heart rate, and systolic blood pressure; Model 3: adjusted for all variables in model 2 plus time-varying incident MI (i.e. MI occurred prior to or on date of incident HF); Model 4: adjusted for all variables in model 3 plus C-reactive protein.

* P<0.05 compared to the reference group (the highest tertile).

[§]P for linear trend tested by entering the log-transformed value of RMSDD or SDNN as a continuous variable in the model.

Table 3

Hazard ratios (95% CI) for incident heart failure by heart rate variability tertiles, stratified by coronary artery calcium score

Model [¶]	CAC score ≤ 10, N=2766				CAC score > 10, N=1862			
	RMSSD				RMSSD			
	P trend [§]				P trend [§]			
	Low (1.0 – 15.9)	Middle (16.0 – 26.9)	High (27.0 – 328.0)		Low (1.0 – 15.9)	Middle (16.0 – 26.9)	High (27.0 – 328.0)	
Model [¶]	HR (95% CI)	HR (95% CI)	HR (95% CI)	P trend [§]	HR (95% CI)	HR (95% CI)	HR (95% CI)	P trend [§]
Unadjusted	5.32 (1.76 to 16.02) [*]	2.20 (0.66 to 7.30)	1.0 (reference)	<0.001	1.75 (0.93 to 3.32)	1.41 (0.72 to 2.76)	1.0 (reference)	0.029
1	4.36 (1.41 to 13.45) [*]	2.11 (0.63 to 7.05)	1.0 (reference)	0.004	1.73 (0.90 to 3.31)	1.48 (0.75 to 2.91)	1.0 (reference)	0.045
2	3.85 (1.08 to 13.69) [*]	2.02 (0.58 to 7.01)	1.0 (reference)	0.023	1.79 (0.87 to 3.69)	1.85 (0.93 to 3.70)	1.0 (reference)	0.089
3	3.93 (1.05 to 14.68) [*]	1.89 (0.53 to 6.77)	1.0 (reference)	0.031	1.49 (0.71 to 3.13)	1.85 (0.92 to 3.70)	1.0 (reference)	0.107
Model [¶]	SDNN				SDNN			
	P trend [§]				P trend [§]			
	Low (0.90 – 14.5)	Middle (14.6 – 24.2)	High (24.3 – 208.1)		Low (0.90 – 14.5)	Middle (14.6 – 24.2)	High (24.3 – 208.1)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	P trend [§]	HR (95% CI)	HR (95% CI)	HR (95% CI)	P trend [§]
Unadjusted	2.88 (1.09 to 7.58) [*]	1.52 (0.53 to 4.37)	1.0 (reference)	<0.001	1.67 (0.90 to 3.09)	1.06 (0.53 to 2.09)	1.0 (reference)	0.004
1	2.24 (0.83 to 6.07)	1.39 (0.48 to 4.02)	1.0 (reference)	0.005	1.54 (0.82 to 2.87)	1.10 (0.55 to 2.18)	1.0 (reference)	0.014
2	1.57 (0.54 to 4.56)	1.27 (0.43 to 3.78)	1.0 (reference)	0.029	1.59 (0.82 to 3.07)	1.36 (0.67 to 2.73)	1.0 (reference)	0.042
3	1.80 (0.58 to 5.60)	1.45 (0.47 to 4.49)	1.0 (reference)	0.027	1.30 (0.66 to 2.56)	1.28 (0.63 to 2.60)	1.0 (reference)	0.118

Abbreviations: CAC, coronary artery calcium; HR, hazard ratios; CI, confidence interval

[¶]Model 1: adjusted for age, gender, and race (White, African-American, Chinese, Hispanic); Model 2: adjusted for all variables in model 1 plus education more than high school (yes/no), physical activity (gender-specific tertiles: low, middle, high), current cigarette smoking (yes/no), diabetes (yes/no), heart rate, LV end-systolic volume, and systolic blood pressure; Model 3: adjusted for all variables in model 2 plus time-varying incident MI (i.e. MI occurred prior to or on date of incident HF).

^{*} P<0.05 compared to the reference group (the highest tertile).

[§]P for linear trend tested by entering the log-transformed value of RMSSD or SDNN as a continuous variable in the model.