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Normal Findings on Noninvasive Cardiac Assessment and the Prediction of Heart Failure: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background—It is unknown if normal findings on noninvasive cardiac assessment are able to identify individuals who are low risk for developing heart failure (HF).

Methods—We examined if normal findings on the routine electrocardiogram (ECG) and cardiac magnetic resonance imaging (MRI) were able to identify individuals who are low risk for developing HF in 4,986 (mean age=62 ± 10 years; 52% women; 39% White; 13% Chinese-American; 26% Black; 22% Hispanic) participants from the Multi-Ethnic Study of Atherosclerosis who were free of clinically apparent HF at baseline. A normal ECG was defined as the absence of

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major abnormalities by Minnesota Code Classification, and a normal MRI was defined as absence of structural abnormalities and systolic dysfunction.

Results—There were 3,988 (80%) participants with normal findings at baseline on both ECG and MRI, 894 (18%) who had either a normal ECG or normal MRI, and 104 (2%) who had abnormal findings on ECG and MRI. Over a median follow-up of 12.2 years, 177 (3.6%) HF events occurred. Normal ECG (HR=0.41, 95%CI=0.29, 0.56) and MRI (HR=0.32, 95%CI=0.23, 0.45) were each associated with lower risk of HF compared with abnormal, and their combination was associated with a lower HF risk (HR=0.13, 95%CI=0.08, 0.21) than either in isolation.

Conclusion—Normal findings on noninvasive cardiac assessment identify individuals in whom the risk of HF is low. Further studies are needed to explore the utility of this low-risk profile in HF prevention strategies.

Keywords

heart failure; noninvasive cardiac assessment; epidemiology

INTRODUCTION

Despite improvements in medical therapies, heart failure (HF) continues to place a significant burden on the United States health care system. An estimated 5.7 million Americans have HF, and the prevalence is expected to increase by 46% between 2012 and 2030 [1, 2]. Therefore, the accurate prediction of future HF events is of paramount importance to appropriately target preventive therapies and deliver necessary medical care.

Numerous risk factors for HF have been identified (e.g., diabetes, hypertension, dyslipidemia) [3–5]. In this framework of risk factor identification, the severity of biological and structural abnormalities are clearly associated with an increased risk of HF. However, several reports have shown that much information is obtained from normal findings, as those with favorable risk factor profiles have a decreased risk for cardiovascular disease-related mortality [6, 7]. Additionally, a favorable risk factor profile reclassifies persons to lower risk categories [8], implicating a role for normal findings to influence the decision to initiate or, more importantly, reduce certain risk factor modification strategies (e.g., lipid-lowering therapies).

The resting 12-lead electrocardiogram (ECG) is the most widely used tool for cardiovascular risk assessment. Several reports have demonstrated that ECG abnormalities in asymptomatic persons are predictive of incident HF [9–12]. Similarly, abnormalities of left ventricular structure and function on cardiac magnetic resonance imaging (MRI) are predictive of HF development [13, 14]. However, whether the presence of normal findings on routine ECG and cardiac MRI can identify individuals at a reduced risk for HF is currently unknown. Therefore, the purpose of this analysis was to examine the association of normal findings on the routine ECG and cardiac MRI with HF development in the Multi-Ethnic Study of Atherosclerosis (MESA).

METHODS

Study Population

Details of MESA have been reported previously [15]. Briefly, between July 2000 and September 2002, a total of 6,814 persons were recruited at 6 field centers in the United States (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). Participants were required to be between 45 and 84 years of age and to have no clinical cardiovascular disease. All participants provided informed consent and the study protocol was approved by the Institutional Review Boards at each participating institution. Participants were excluded if they did not undergo baseline ECG or cardiac MRI measurements. Additionally, we excluded participants without baseline covariates or follow-up data.

Baseline Characteristics

Participant characteristics were collected during the initial MESA visit. Age, sex, and race/ethnicity were self-reported. Smoking was defined as ever (e.g., current or former) versus never smoker. Blood samples were obtained after a 12-hour fast and measurements of total cholesterol, high-density lipoprotein cholesterol, and plasma glucose were used. Diabetes was defined as fasting glucose values ≥ 126 mg/dL or a history of diabetes medication use. Blood pressure was measured 3 times after 5 minutes in the seated position, and the mean of the last 2 values was used. The use of aspirin, lipid-lowering therapies, and antihypertensive medications was self-reported. Body mass index was computed as the weight in kilograms divided by the square of the height in meters.

Electrocardiogram (ECG)

In MESA, 12-lead digital ECGs were obtained by trained technicians using GE MAC 1200 electrocardiographs using standardized procedures. ECGs were transmitted electronically to the MESA ECG Reading Center located at the Epidemiological Cardiology Research Center (Wake Forest School of Medicine, Winston-Salem, NC). All ECGs were automatically processed, after visual inspection for technical errors and quality, using the 2001 version of the GE Marquette 12-SL program (GE, Milwaukee, Wisconsin, USA). Normal ECGs were defined as the absence of significant (e.g., major) abnormalities using the Minnesota Code classification system [16]. This included the absence of major ventricular conduction defects (complete left or right bundle branch block, major ventricular conduction delay with QRS ≥ 120 ms), major Q wave abnormalities, isolated major ST/T wave abnormalities, left ventricular hypertrophy, advanced atrioventricular block, electronic pacemaker, atrial fibrillation/flutter, and others.

Cardiac MRI

Participants in MESA underwent cardiac MRI assessment during the baseline study visit using standard procedures. The MESA cardiac MRI protocol, image analysis, and inter- and intra-reader reproducibility have been previously reported [13]. A normal cardiac MRI was defined by the absence of left ventricular enlargement (left ventricular end-diastolic mass (g)

normalized to body surface area (m^2) within sex-specific limits: men: $<106.2 \text{ g/m}^2$; women: $<84.6 \text{ g/m}^2$) and systolic dysfunction (ejection fraction $<55\%$) [17].

Heart Failure

The ascertainment of incident HF events has been previously described [18]. Participants were followed for incident cardiovascular events from baseline through December 31, 2013. At intervals of 9–12 months, a telephone interviewer contacted each participant to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, procedures, and deaths. Additionally, MESA occasionally identified medical encounters through cohort clinic visits, participant call-ins, medical record abstractions, or obituaries. Next of kin interviews for out of hospital cardiovascular deaths also were used. The outcome of interest for this analysis was the composite of probable and definite HF events. Definite or probable HF required symptoms, such as shortness of breath or edema, as asymptomatic disease is not a MESA endpoint. In addition to symptoms, probable HF required a physician diagnosis and also for the patient to be receiving medical treatment for HF. Definite HF required one or more other criteria, such as pulmonary edema/congestion by chest X-ray; dilated ventricle or poor left ventricular function by echocardiography or ventriculography; or evidence of left ventricular diastolic dysfunction [19]. For this analysis, systolic and diastolic HF events were grouped together.

Statistics

Participants were grouped into the following 3 categories based on their baseline cardiac assessment: 1) abnormal ECG + abnormal MRI (referent); 2) normal ECG or normal MRI; 3) normal ECG + normal MRI. Descriptive statistics were compared between the 3 categories. Categorical data were compared using the chi-square method, and the Kruskal-Wallis procedure was used for continuous data. Kaplan-Meier estimates were computed for the cumulative incidence of HF events during the study period. The 1-, 5-, and 10-year cumulative incidence estimates were tabulated. Follow-up time was defined as the time from the initial study visit until one of the following: HF development, loss to follow-up, death, or end of the study period (December 31, 2013). Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association of the above categories with HF. Multivariable models included the following covariates: Model 1 included age, sex, and race; Model 2 included Model 1 covariates with the addition of systolic blood pressure, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol, smoking, antihypertensive medications, lipid-lowering therapies, and aspirin. Statistical significance was defined as $p < 0.05$. SAS Version 9.4 (Cary, NC) was used for all analyses.

RESULTS

A total of 4,986 (mean age = 62 ± 10 years; 52% women; 39% White; 13% Chinese-American; 26% Black; 22% Hispanic) participants were included in the final analysis. Of these, 3,988 (80%) had normal ECG + normal MRI, 894 (18%) had either a normal ECG or normal MRI, and 104 (2%) had an abnormal ECG + abnormal MRI. Baseline characteristics stratified by these groups are summarized in Table 1. As shown, participants with abnormal ECG + abnormal MRI were more likely to be older, male, to have diabetes and higher values

of systolic blood pressure and LV mass, but lower high-density lipoprotein cholesterol, compared with those with normal ECG or normal MRI.

Over a median follow-up of 12.2 years (25th–75th percentiles=11.6, 12.8), a total of 177 (3.6%) HF events were detected. The 1-, 5-, and 10-year cumulative incidence estimates of HF events in each category are tabulated in Table 2. As shown, for all time periods, the cumulative incidence of HF was lower for those with normal ECG + normal MRI findings compared with other categories. The cumulative incidence of HF for each category is depicted graphically in Figure 1.

The risk estimates for HF across categories of normal ECGs and/or normal MRI findings are shown in Table 3. In isolation, the normal ECG (HR=0.41, 95%CI=0.29, 0.56) and normal MRI (HR=0.32, 95%CI=0.23, 0.45) were associated with a reduced risk of HF. The risk for HF was lowest for those with normal ECG + normal MRI (HR=0.13, 95%CI=0.08, 0.21) (Table 3).

DISCUSSION

In this analysis from MESA, the absence of significant abnormalities on the 12-lead ECG, and the absence of structural abnormalities and systolic dysfunction by cardiac MRI, were associated with a lower risk for HF development compared with those who had abnormal findings on these measurements. Overall, the findings of this analysis suggest that persons with normal noninvasive cardiac profiles represent a group in whom the risk of future HF is unlikely, and this profile possibly is able influence the decision to implement certain risk factor modification strategies with aims to prevent HF.

Prior reports have focused on the association of abnormalities on the ECG and cardiac MRI with incident HF events. Data from the Women's Health Initiative [9], Atherosclerosis Risk In Communities study [10], MESA [11], and Health, Aging, and Body Composition study [12], have shown that ECG abnormalities predict incident HF. Similar findings have been reported for cardiac MRI measures, such as enlarged left ventricular mass and diameter [13, 14]. The results from the studies mentioned above clearly indicate that abnormalities detected on routine ECG and cardiac MRI assessment are associated with an increased risk of incident HF events among individuals without baseline cardiovascular disease.

In the present study, we have demonstrated that important prognostic information regarding HF development is obtained with normal findings on the routine ECG and cardiac MRI. The protective benefit for HF development was independent of well-known risk factors. Presumably, participants with these normal findings were less susceptible to the deleterious effects of common risk factors through favorable genetics, healthful behaviors, and other unmeasured factors. However, further research is needed to better characterize this population and to determine which factors (e.g., genetics) most positively influence the maintenance of normal findings on the routine ECG and cardiac MRI. Nonetheless, we have demonstrated that important prognostic information is obtained on normal findings of noninvasive cardiac assessment. Furthermore, providers are likely to encounter normal findings on noninvasive cardiac tools [20], and these data allow providers to inform patients

of their low risk if this profile is present, and to encourage healthful behaviors that are known to reduce future HF events [21].

By 2030, the prevalence of HF is projected to increase by 23% with more than 26% of cases expected to occur in persons >80 years of age [1]. This coincides with an increase in the projected total medical costs related to HF to nearly \$53.1 billion [1]. Due to the rather large burden that will be placed on the health care system to treat HF and finance the care provided, an in-depth understanding of risk factors is of paramount importance for the development of interventions aimed at prevention. The findings of this analysis suggest that persons who have normal findings on the routine ECG, and the absence of structural abnormalities and systolic dysfunction on cardiac MRI, are less likely to develop HF, despite the presence of well-known risk factors. This possibly has important implications regarding the clinical decision to initiate certain risk factor modification strategies, as these therapies potentially are unnecessary in the right clinical setting (e.g., normal ECG and normal structural profile). For example, the identification of this normal cardiac profile on noninvasive cardiac assessment possibly is beneficial when contemplating invasive strategies to reduce the risk of future HF events in persons who are intermediate risk. However, further research is needed to determine the underlying mechanisms that reduce HF risk in this population before changes in clinical practice are recommended.

The current study should be interpreted in the context of several limitations. Incident HF cases were identified by subsequent study visits, follow-up phone calls, and the examination of hospitalization data including International Classification of Diseases codes. Despite these efforts to account for all HF events, some cases possibly were missed. Although we classified ECG abnormalities using the Minnesota Code, the most widely used classification system in population studies [16], it is possible that our results vary with different definitions. Similarly, normal cardiac MRI findings were defined by the absence of left ventricular enlargement and systolic dysfunction. Despite the detailed information that is obtained during cardiac MRI, the definition used in this study is easily interpreted by clinicians across multiple specialties. Also, the definition used was highly protective of future HF events, indicating that the criteria used were adequate to describe a normal cardiac MRI profile for HF risk assessment. Finally, several potential confounders were included in our multivariable models but similar to other epidemiological studies we acknowledge that residual confounding remains a possibility.

In conclusion, we have shown that normal findings on the routine ECG and cardiac MRI identify individuals in whom the risk of HF is low. This provides clinicians with valuable information regarding HF risk assessment in the face of normal findings on noninvasive cardiac assessment.

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Figure 1. Cumulative Incidence of Heart Failure*

* Cumulative incidence curves are statistically different (log-rank $p < 0.001$).

Table 1

Baseline Characteristics (N=4,986)

Characteristic	Abnormal ECG + Abnormal MRI (n=104)	Normal ECG or Normal MRI (n=894)	Normal ECG + Normal MRI (n=3,988)	P-value*
Age, mean $\pm$ SD, years	66 $\pm$ 10	63 $\pm$ 10	61 $\pm$ 10	<0.001
Male (%)	69 (66)	536 (60)	1,769 (44)	<0.001
Race				<0.001
White (%)	42 (40)	366 (41)	1,539 (39)	
Chinese-American (%)	3 (3.0)	78 (9.0)	570 (14)	
Black (%)	40 (39)	267 (30)	973 (24)	
Hispanic (%)	19 (18)	183 (20)	906 (23)	
Ever smoker (%)	65 (63)	464 (52)	1,886 (47)	<0.001
Diabetes (%)	25 (24)	143 (16)	468 (12)	<0.001
Systolic blood pressure, mean $\pm$ SD, mm Hg	140 $\pm$ 27	128 $\pm$ 22	124 $\pm$ 21	<0.001
Body mass index, mean $\pm$ SD, kg/m ²	28 $\pm$ 4.6	28 $\pm$ 4.7	27 $\pm$ 5.0	0.11
HDL cholesterol, mean $\pm$ SD, mg/dL	48 $\pm$ 15	50 $\pm$ 15	52 $\pm$ 15	<0.001
Total cholesterol, mean $\pm$ SD, mg/dL	191 $\pm$ 41	193 $\pm$ 36	195 $\pm$ 35	0.21
LV mass/BSA, mean $\pm$ SD, g/m ²	84 $\pm$ 23	69 $\pm$ 13	63 $\pm$ 10	<0.001
Antihypertensive medications (%)	53 (51)	358 (40)	1,349 (34)	<0.001
Lipid-lowering medications (%)	19 (18)	159 (18)	615 (15)	0.17
Aspirin use (%)	34 (33)	227 (25)	895 (22)	0.011

* Statistical significance for continuous data was tested using the Kruskal-Wallis test and categorical data was tested using the chi-square method.

BSA=body surface area; ECG=electrocardiogram; HDL=high-density lipoprotein; LV=left ventricle; MRI=magnetic resonance imaging; SD=standard deviation.

Table 2

1-, 5-, and 10-year Cumulative Incidence of Heart Failure

Category	1-year (%)	5-year (%)	10-year (%)
Abnormal ECG + Abnormal MRI	6.8	15	25
Normal ECG or Normal MRI	0.7	3.1	5.6
Normal ECG + Normal MRI	0.2	0.9	2.2

ECG=electrocardiogram; MRI=magnetic resonance imaging.

Table 3**Risk of Heart Failure**

Category	Events/No at risk	Model 1* HR (95%CI)	P-value	Model 2† HR (95%CI)	P-value
Abnormal ECG	56/524	Ref	-	Ref	-
Normal ECG	121/4,462	0.34 (0.25, 0.47)	<0.001	0.41 (0.29, 0.56)	<0.001
Abnormal MRI	53/578	Ref	-	Ref	-
Normal MRI	124/4,408	0.31 (0.23, 0.43)	<0.001	0.32 (0.23, 0.45)	<0.001
Abnormal ECG + Abnormal MRI	26/104	Ref	-	Ref	-
Normal ECG or Normal MRI	57/894	0.22 (0.14, 0.35)	<0.001	0.27 (0.17, 0.44)	<0.001
Normal ECG + Normal MRI	94/3,988	0.10 (0.07, 0.16)	<0.001	0.13 (0.08, 0.21)	<0.001

* Adjusted for age, sex, and race/ethnicity.

† Adjusted for Model 1 with the addition of systolic blood pressure, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol, smoking, antihypertensive medications, lipid-lowering therapies, and aspirin.

CI=confidence interval; ECG=electrocardiogram; HR=hazard ratio; MRI=magnetic resonance imaging.