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Baseline ST elevation and myocardial scar: Results from the multi-ethnic study of atherosclerosis

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ABSTRACT

Background: The mechanism of ST elevation on baseline electrocardiograms (ECG) unknown but it may be associated with abnormal myocardial substrate. This paper evaluates whether clinically unrecognized myocardial scar on cardiac magnetic resonance imaging (CMR) is associated with ST elevation at baseline.
Methods: The Multi-Ethnic Study of Atherosclerosis (MESA) study is a population-based cohort in the United States. Participants were aged 45 through 84 years and free of clinical cardiovascular disease at enrollment in 2000–2002. Our cohort included 1365 participants who underwent both ECG and contrast enhanced CMR in the 5th examination (2010−2012). Multivariable logistic regression examined the association of ST elevation and CMR defined regional myocardial scar after adjusting for cardiovascular risk factors.
Results: Of 1365 participants (58 ±9 years, 52% men), 105 (8%) had scar on CMR. Of these, the scar in 40 participants followed an ischemic pattern and in the other 65 participants followed a non-ischemic pattern. ST elevation at the 5th examination was present in 435 participants: 40 (0.9%) had ST elevations in inferior and 427 (98%) in lateral leads. 2/40 (5%) and 22/427 (5%) participants with inferior and lateral ST elevations, respectively, had evidence of scar. 15 (1.0%) had myocardial scar noted in the basal anterior region. In the fully adjusted models, ST elevation was associated with scar in basal anterior region (OR 18.2, $p = 0.031$).
Conclusions: In a community population, ST elevation at baseline in the inferior or lateral leads was associated with myocardial scar in the basal inferior and anterior segments. The previously described association between ST elevation and increased mortality may be mediated by myocardial scar.

Introduction

Cardiac magnetic resonance (CMR) is the most sensitive imaging modality to detect both ischemic and non-ischemic myocardial scar with the presence of late gadolinium enhancement (LGE). A recent study from the multiethnic study of atherosclerosis (MESA) showed that nearly 8% of adults had evidence of myocardial scar, of which 78% were undetected by clinical evaluation or electrocardiogram (ECG) [1]. This suggests a substantial population of individuals with abnormal myocardial substrate of unclear significance.

Clinically unrecognized myocardial scar on CMR has been shown to be associated with major adverse cardiac events in certain populations [2]. While mechanism of this is unknown, these scars may represent silent myocardial infarctions that predispose to re-entrant ventricular arrhythmias or simply reflect substantial burden of undiagnosed cardiovascular disease. It remains unknown whether these scars could be non-ischemic in origin and whether they may be associated with adverse outcomes through alternative mechanisms.

In patients with dilated cardiomyopathy, the presence of scar is strongly associated with sudden cardiac death, regardless of ejection fraction, likely because myocardial scar acts as the substrate for

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potentially fatal ventricular arrhythmias [3,4]. It is possible that clinically unrecognized scar in otherwise normal hearts might increase the risk of sudden cardiac death through the same mechanism.

Although these clinically unrecognized scars on CMR are being increasingly identified, their association between ECG findings, especially ST elevations at baseline has not been completely examined. Some degree of ST elevation, especially in ECG leads V1-V3, can be normal especially in healthy young men [5]. Nevertheless, there is evidence in Brugada Syndrome that abnormal ST segment morphology and elevation is associated both with increased risk of sudden cardiac death and abnormal myocardial substrate in the right ventricular outflow tract [6]. ST elevations at baseline other than those characteristic of Brugada Syndrome could reflect a similarly complex interplay between ion channel abnormalities and an anatomic region of abnormal myocardial substrate.

In this study we sought to examine the association of ST elevation on ECG and the presence of myocardial scar on CMR in individuals without recognized cardiovascular disease.

Methods

Data

Subjects

Between July 2000 and August 2002, men and women who were 45 to 84 years old and free of clinically apparent cardiovascular disease were recruited from 6 US communities: Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan and the Bronx, NY; and St. Paul, MN [7]. Approval was received from Institutional Review Boards at each participating university before the start of the study and protocol modifications were reviewed and approved each year. All participants of MESA, a multiethnic population free of clinically apparent cardiovascular disease, without atrial fibrillation, QRS duration ≥120 ms, QRS axis < −30 or > 90 degrees, ST depression, or pathological Q waves (>40 ms duration), and with a 5th exam (2010–2012) electrocardiogram and gadolinium contrast-enhanced CMR were included in this study ($n = 1365$). The clinical characteristics and prevalence of cardiovascular disease in this population at the time of the 5th year exam has been reported previously [1].

Electrocardiogram

All participants underwent resting 12 lead ECGs during the 5th examination, which were acquired at 10 mm/mV calibration and 25 mm/s speed. ECG reading was performed centrally at the Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, NC. All ECGs were initially inspected visually for technical errors and inadequate quality, and then automatically processed with the GE Marquette 12-SL program 2001 version [GE Marquette, Milwaukee, WI]. The program was used to automatically obtain the amplitude at the J-point, mid-ST, ST-end, and STJ60. The program determined ST levels relative to the QRS onset voltage, which was defined as 0 μV. The J-point was defined at the QRS offset. Mid-ST was at the QRS offset plus 1/16 of the average RR interval. ST-end was at the QRS offset plus 1/8 of the average RR interval [8]. In this study, we defined ST elevation as ≥1 mm (100 μV) ST elevation in any two contiguous non-V1-V3 leads.

Cardiac magnetic resonance imaging

CMR was performed using 1.5-T scanners (Avanto and Espree, SiemensMedical Systems and Signa HD, GE) with a 6-channel anterior phased array coil. CMR protocol was uniform in all centers and all studies were centrally evaluated by readers blinded to all other study data. Myocardial scar was defined as focal LGE either in 2 adjacent short-axis slices or in 1 short-axis and a long-axis image at a corresponding location using QMass (version 7.2, Medis). Myocardial scars that involved subendocardium in a coronary artery distribution were defined as "ischemic" scars. Myocardial scars predominantly affecting midwall or subepicardium without subendocardial involvement in a noncoronary artery distribution were defined as "non-ischemic" scars.

Statistical analysis

Continuous variables were summarized as means and standard deviation, and categorical variables as numbers and percentages. Continuous variables were compared among patients with versus those without ST elevation at each ST point using the Student's *t*-test, and categorical variables were compared using Chi Squared or Fisher's exact tests as appropriate. Multivariable logistic regression was used to examine the association of ST elevation and the presence of regional myocardial scar using a standard 17-segement model of the heart. A parsimonious model was used to examine the association between inferior or lateral ST elevations on ECG and myocardial scar in the 17 segments of the heart. Segments with collinearity were excluded from the model. Multiplicative terms to examine the possibility of interaction between gender, race, body mass index, hypertension, diabetes mellitus, cigarettes smoking status, and the presence of levet ventricular hypertrophy with scar in its association with ST elevation were sequentially introduced to the model. Analyses were performed using STATA version 12 (College Station, TX).

Results

Of 1316 participants who met inclusion criteria, 105 participants had myocardial scar identified by CMR. Of these, the scar in 40 participants followed an ischemic pattern and in the other 65 participants followed a non-ischemic pattern. Table 1 summarizes the baseline demographic variables for all patients that underwent CMR, and for categories after stratification by the presence or absence of myocardial scar, and by ischemic versus non-ischemic pattern of scar. Participants with any myocardial scar were older (61 ±10 vs 58 ±9 years, $p < 0.001$), more frequently male (83 vs 49%, $p < 0.001$) and smokers (56 vs 51%, $p = 0.030$), more likely to use aspirin (38 vs 24%, $p = 0.001$), have hypertension (46 vs 33%, $p = 0.012$), and had lower levels of HDL cholesterol (46 ±13 vs 51 ±15 mg/dl, $p < 0.001$) than those without any myocardial scar on CMR. There were no significant differences in baseline characteristics of those participants with ischemic vs. non-ischemic scars on CMR.

Table 2 summarizes the baseline characteristics by whether ST elevation was present in the lateral, inferior, or either inferior or lateral leads. Of the 435 participants with ST elevations, 22 had evidence of scar on CMR. Participants with ST elevations were younger than those without any ST elevation (56 ±8 vs 59±8, $p < 0.001$. They were also more likely to be male than those without ST elevations (75 vs 39%, $p < 0.001$), less likely to have hypertension (24 vs 39%, $p < 0.001$), and had a lower HDL cholesterol level (48 ±13 vs 51±14 mg/dl, $p < 0.001$). Other cardiovascular risk factors, including cigarette-smoking status, left ventricular hypertrophy on ECG, diabetes, body mass index, and LDL cholesterol levels were found to be similar between those with and without ST elevations regardless of their distribution.

The multivariable logistic regression using the 17-segment model of the heart revealed an association between presence of lateral ST elevation and basal anterior scar on CMR (OR 14.8, $p = 0.017$). An additional model was then examined including potentially confounding cardiovascular risk factors (Table 3). This demonstrated an association between the presence of ST elevation on ECG and basal anterior myocardial scar on CMR (OR 18.2, $p = 0.031$). In this model, age, non-Caucasian race, male gender, HTN, and BMI were also associated with the presence of lateral ST elevations on ECG. No significant association was found with myocardial scar in other regions. On unadjusted analysis, there was a trend toward patients with lateral ST elevations being more likely to have scar in the basal anterior region although this result was

Table 1
Baseline participant characteristics.

	All participants ($n = 1365$)	Scar ($n = 105$)	No scar ($n = 1260$)	*p*-value	Non-ischemic Scar ($n = 65$)	Ischemic scar ($n = 40$)	p-value
Age, yrs	58 ±9	61 ±10	58 ±9	*<0.001*	61 ±11	63±9	0.192
Female (%)	655 (48)	17 (16)	638 (51)	*<0.001*	9 (14)	8 (20)	0.936
Caucasian (%)	628 (46)	57 (54)	571 (45)	*0.019*	32 (48)	25 (63)	0.246
Never cigarette smoker (%)	669 (49)	46 (44)	623 (49)	*0.030*	30 (46)	16 (40)	0.795
Aspirin use (%)	341 (25)	40 (38)	301 (24)	*0.001*	16 (25)	24 (60)	0.088
Left ventricular hypertrophy on ECG (%)	8 (0.6)	1 (0.9)	7 (0.6)	*1.000*	0 (0)	1 (1.7)	0.472
Diabetes (%)	96 (7)	9 (9)	87 (7)	*0.673*	5 (8)	4 (10)	0.861
Hypertension (%)	464 (34)	48 (46)	416 (33)	*0.012*	22 (34)	26 (65)	0.217
Body mass index, kg/m^2	29 ± 6	28 ±5	29±5	*0.428*	29 ±5	28±4	0.189
HDL cholesterol, mg/dl	49 ± 15	46 ±13	51 ±15	*<0.001*	48±13	45±11	0.229
LDL cholesterol, mg/dl	120 ± 29	116 ±26	120 ±30	*0.131*	115 ±25	117 ±27	0.343

Abbreviations: ECG electrocardiogram; HDL; high density lipoprotein; LDL low density lipoprotein.

insignificant (OR 2.5; 95% CI 0.79–8.81; $p = 0.65$). There was no evidence of multiplicative interaction between scar and gender or ethnicity ($p = 0.285$, and $p = 0.327$, respectively).

Of the 1365 participants, 15 (1.0%) had myocardial scar noted in the basal anterior region. There were no significant differences in the baseline cardiovascular risk factors between participants who had basal anterior myocardial scar and those with scar noted in other regions.

Discussion

Elevation of the ST segment at baseline is a common finding with an unclear mechanism and incompletely established clinical significance. Multiple population based CMR studies have identified clinically unrecognized myocardial scar, which may represent the substrate for abnormal ST segments on ECG. This scar could act as a substrate for fatal arrhythmias and may be associated with as much as an 8% increase in mortality [1,9]. In this study we examined the association between ST elevations and myocardial scar in a population free of clinical recognized cardiovascular disease.

In our multiethnic population of 1365 participants, 105 had myocardial scar identified by LGE on CMR. Participants with myocardial scar had more traditional cardiovascular risk factors, regardless of whether the scar was identified as following an ischemic pattern. There was a strong association between myocardial scar in the basal inferior or anterior segments and inferior or lateral ST elevations. Baseline characteristics of participants with evidence of myocardial scar in these regions were similar to those with myocardial scar in other regions and they had otherwise structurally normal hearts, raising the biologically plausible possibility that the presence of scar in this segment may have been causally associated with the ST elevations.

In the normal heart, a flat ST segment with voltage equal to that of the TP segment is observed because of homogeneous repolarization of the myocardium. In contrast, myocardial scar causes heterogeneity in regional action potential duration, repolarization currents, and resultant ST elevation in corresponding anatomic leads. Thus, ST elevations at baseline may be associated with abnormal function and structural myocardial substrate following a similar pattern as Brugada syndrome, which may be associated with an arrhythmogenic substrate in the right ventricular outflow tract epicardium in addition to abnormal ion channel function [10–12].

While the population size and event rates were insufficient to investigate a potential association between ST elevations and mortality, these findings support the idea that ST elevations at baseline could be a marker of structural abnormalities. Specifically, the fibrotic changes that are likely reflected by LGE on CMR are known to be substrates for ventricular arrhythmias [13]. Such sites appear to provide the heterogeneous myocardial tissue necessary for unidirectional block, slow conduction, and thus the initiation and perpetuation of reentrant ventricular arrhythmias. The presence of myocardial scar has been shown to be associated with risk of sudden cardiac death even in those without severely reduced LV function but its significance is less well characterized in those with normal cardiac function [3,14–17].

Historically, early repolarization (ER) with associated ST elevations at baseline has been considered a benign variant of interest for its distinction from ST elevations associated with acute myocardial infarction. In the past two decades, this pattern has been shown to be associated with increased risk of sudden cardiac death [18–20]. The association of ER with increased mortality remains incompletely understood and, although suggestive of heterogeneity in repolarizing currents, the physiologic or anatomic correlation with the surface electrocardiogram has not been clarified. The possibility that ER may represent structural abnormalities has been considered [21–23].

Inconsistent use of various definitions for ER has led to discordance in reported prevalence ranging from 2 to 31% [24]. Initial descriptions focused on the presence of an elevated ST-segment followed by a tall, symmetric T-wave in addition to end-QRS notching or slurring.

Table 2
Baseline participant characteristics among patients who had CMR with gadolinium and inferior or lateral ST elevations. Characteristics of participants with inferior or lateral ST elevations compared to participants with no ST elevations using student's t-test, chi squared or Fisher's exact tesets.

	No ST elevation ($n = 930$)	Inferior or lateral STE ($n = 435$)	p-value	Lateral STE ($n = 427$)	Inferior STE (n = 40)	Inferior and lateral STE ($n = 32$)
Age, years	59 ± 8	56 ± 8	*<0.001*	56± 8	56 ±9	56 ±8
Female (%)	567 (61)	109 (25)	*<0.001*	107 (25)	*10 (25)*	8 (25)
Caucasian (%)	465 (50)	161 (37)	*<0.001*	154 (36)	12(30)	5 (16)
Never cigarette smoker (%)	464 (50)	200 (46)	*0.672*	194 (45)	17 (43)	11 (34)
Aspirin use (%)	298 (32)	114 (26)	*0.146*	111 (26)	9 (23)	6 (19)
Left ventricular hypertrophy on ECG (%)	6 (0.6)	1 (0.2)	*0.589*	1 (0.2)	0 (0)	0 (0)
Diabetes (%)	65 (7)	22 (5)	*0.165*	21 (5)	2 (5)	1 (3)
Hypertension (%)	363 (39)	104(24)	*<0.001*	102 (24)	6 (16)	4 (13)
Body mass index, kg/m^2	28 ± 6	27 ± 5	*0.849*	27 ± 5	25±5	26±6
HDL cholesterol, mg/dl	51 ± 14	48 ± 13	*<0.001*	48 ± 13	56 ± 17	53 ± 16
LDL cholesterol, mg/dl	118± 31	116 ± 31	*0.628*	116 ±31	117±33	113 ± 30

Abbreviations: CMR cardiac magnetic resonance imaging; HDL high density lipoprotein; LDL low density lipoprotein.

Table 3
Association of lateral ST elevations with scar distribution in a multivariable model including cardiovascular risk factors and the presence of scar by myocardial segement.

	Unadjusted odds ratio (95% confidence interval)	p-value	Adjusted odds ratio[a] (95% confidence interval)	p-value
Mid Anterolateral Scar	0.9 (0.1–28.2)	0.739	0.6 (0.1–36.3)	0.858
Mid Anteroseptal Scar	3.1 (0.1–110.1)	0.836	2.0 (0.2–78.1)	0.592
Mid Inferoseptal Scar	0.8 (0.2–12.8)	0.241	0.6 (0.1–30.9)	0.637
Mid Inferior Scar	1.0 (0.1–27.4)	0.493	0.8 (0.1–61.0)	0.914
Mid Inferolateral Scar	0.9 (0.1–86.3)	0.890	0.7 (0.4–42.6)	0.473
Basal Anterior Scar	14.8 (3.1–37.8)	0.017	18.2 (2.6–31.4)	**0.031**
Basal Anteroseptal Scar	0.4 (0.8–18.6)	0.098	0.2 (0.9–16.5)	0.058
Basal Inferoseptal Scar	2.1 (0.1–61.7)	0.849	0.8 (0.2–46.4)	0.467
Basal Inferior Scar	1.9 (0.9–12.0)	0.063	3.5 (0.6–18.6)	0.132
Basal Inferolateral Scar	1.3 (0.5–17.9)	0.132	0.9 (0.3–18.7)	0.560
Basal Anterolateral Scar	3.6 (1.3–43.7)	0.047	2.5 (0.3–45.2)	0.509
Apical Inferior Scar	0.3 (0.2–6.7)	0.374	0.2 (0.2–6.3)	0.318
Apical Lateral Scar	2.2 (0.1–206.3)	0.791	2.4 (0.1–201.1)	0.746
Apical Scar	3.7 (0.2–17.9)	0.646	1.3 (0.3–15.6)	0.304

Bold represents $p<.05$.
[a] Variables used for adjustment: Age, Race, Left Ventricular Hypertrophy, Low Density Lipoprotein, Gender, Cigarette Smoking Status, Diabetes Mellitus, Hypertension, Body Mass Index.

Additional components that have been considered include the degree of J-point elevation and the ST-segment slope. While we were unable to analyze the morphology of the QRS or QRS termination, J-wave, and ST segment, which are essential in the identification of true ER pattern [25]. Recently methods have been developed for automated J-wave detection that may allow this analysis [26,27].

This study provides evidence that ST elevation, one of the features of ER, may be associated with a regional myocardial scar. Additional conclusions are limited by low frequency of scar in this population and further investigation is necessary to confirm this association and determine whether myocardial scar may represent the structural abnormality predisposing patients to ventricular arrhythmias and sudden cardiac death.

Limitations

Our study is limited by several factors. Participant numbers were insufficient for subgroup analyses and for examination of the association of ST elevation as a surrogate of ER with cardiovascular events and mortality or the mediation of this association by myocardial scar. All included patients survived to the 5th exam, raising the potential of survival bias. Our definition of ischemic and non-ischemic scar is based on patterns identified in animal studies and patients with clinically overt disease though this may represent over simplification of scar etiology in this population. While CMR is the best non-invasive strategy for the detection of myocardial scar, it is unable to detect small scar <1 g of tissue, so the role of these scars could not be evaluated. Importantly, on unadjusted analysis, the odds ratio of patients with lateral ST elevation having basal anterior scar was insignificant suggesting that our results should only be interpreted as hypothesis generating.

Conclusions

In a multiethnic population free of any clinically recognized cardiovascular disease, there is an association between the presence of ST elevations in the lateral leads and myocardial scar in the basal anterior and inferior segments. Additional research is necessary to determine whether the previously described association between ST elevation and increased mortality is mediated through myocardial scar.

Disclosures

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The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

The remaining authors have nothing to disclose.

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