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Journal Title: JOURNAL OF THE AMERICAN HEART ASSOCIATION

Volume: Volume 11, Number 5

Publisher: WILEY | 2022-03-01, Pages e021582-e021582

Type of Work: Article | Final Publisher PDF

Publisher DOI: 10.1161/JAHA.121.021582

Permanent URL: <https://pid.emory.edu/ark:/25593/vr6pr>

Final published version: <http://dx.doi.org/10.1161/JAHA.121.021582>

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ORIGINAL RESEARCH

Early Life Trauma Is Associated With Increased Microvolt T-Wave Alternans During Mental Stress Challenge: A Substudy of Mental Stress Ischemia: Prognosis and Genetic Influences

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BACKGROUND: Early life trauma has been associated with increased cardiovascular risk, but the arrhythmic implications are unclear. We hypothesized that in patients with coronary artery disease, early life trauma predicts increased arrhythmic risk during mental stress, measured by elevated microvolt T-wave alternans (TWA), a measure of repolarization heterogeneity and sudden cardiac death risk.

METHODS AND RESULTS: In a cohort with stable coronary artery disease (NCT04123197), we examined early life trauma with the Early Trauma Inventory Self Report-Short Form. Participants underwent a laboratory-based mental stress speech task with Holter monitoring, as well as a structured psychiatric interview. We measured TWA during rest, mental stress, and recovery with ambulatory electrocardiographic monitoring. We adjusted for sociodemographic factors, cardiac history, psychiatric comorbidity, and hemodynamic stress reactivity with multivariable linear regression models. We examined 320 participants with noise- and arrhythmia-free ECGs. The mean (SD) age was 63.8 (8.7) years, 27% were women, and 27% reported significant childhood trauma (Early Trauma Inventory Self Report-Short Form ≥ 10). High childhood trauma was associated with a multivariable-adjusted 17% increase in TWA ($P=0.04$) during stress, and each unit increase in the Early Trauma Inventory Self Report-Short Form total score was associated with a 1.7% higher stress TWA ($P=0.02$). The largest effect sizes were found with the emotional trauma subtype.

CONCLUSIONS: In a cohort with stable coronary artery disease, early life trauma, and in particular emotional trauma, is associated with increased TWA, a marker of increased arrhythmic risk, during mental stress. This association suggests that early trauma exposures may affect long-term sudden cardiac death risk during emotional triggers, although more studies are warranted.

Key Words: psychological stress ■ repolarization heterogeneity ■ sudden cardiac death risk

Epidemiologic studies have associated emotional stress, including acute anger and chronic depression/anxiety,¹ with ventricular arrhythmias.²

Sudden cardiac death (SCD) rates also spike after emotionally devastating natural disasters.³ The psychological and electrophysiological mechanisms underlying

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For Sources of Funding and Disclosures, see page 7.

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CLINICAL PERSPECTIVE

What Is New?

- Exposure to early life trauma was associated with increased repolarization heterogeneity with mental stress challenge, measured by T-wave alternans, in individuals with stable coronary artery disease.
- Increased repolarization heterogeneity is associated with greater risk of ventricular tachyarrhythmias and sudden cardiac death.

What Are the Clinical Implications?

- Providers should consider the implications of early traumatic events on arrhythmic risk during stress when managing their patients with coronary artery disease.

Nonstandard Abbreviations and Acronyms

ETISR-SF	Early Trauma Inventory Self Report-Short Form
TWA	T-wave alternans

the connection between psychological stress and ventricular arrhythmias remain incompletely understood. Studies that examine the potential proarrhythmic mechanisms of psychological stress are needed, given the high prevalence of acute stressors and psychiatric conditions like depression.⁴ SCD is also one of the most widespread causes of mortality.⁵

Early childhood trauma associates with increased stress reactivity⁶ and risk of cardiovascular events.⁷ Childhood trauma is a prevalent (36% of US population)⁸ risk factor for psychological conditions such as depression and cardiovascular disease alike.⁹ Coronary artery disease (CAD) is an established SCD risk factor. In many cases, SCD is the first manifestation of CAD as well.¹⁰ Studies of early trauma and SCD specifically are needed to help guide preventive therapies.

We sought to determine whether arrhythmia risk in the setting of acute emotional stress was influenced by early life trauma in a large cohort with stable CAD. We evaluated arrhythmia risk using microvolt T-wave alternans (TWA), a marker of repolarization heterogeneity and SCD risk.^{11,12} TWA has been found to increase during acute mental stress in both patients with heart failure and those with CAD, even though the increases in heart rate with mental stress are lower than with exercise stress.¹³ Elevated mental stress TWA is associated with an increased risk of future ventricular arrhythmias

and may provide insight into the risk of an acute arrhythmia during acute psychological stress specifically.¹⁴ We hypothesized that patients with CAD and a history of early life trauma demonstrate increased repolarization heterogeneity in response to stress and during the recovery phase, which may help elucidate the role of early trauma in the risk of stress-induced arrhythmia.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for the purpose of reproducing the results or replicating the procedure.

Patient Sample

Individuals between the ages of 30 to 80 with clinically stable CAD were recruited for the study, "Mental Stress Ischemia: Prognosis and Genetic Influences," from the Emory University Hospital and affiliated hospitals; this study's methods were previously described in detail.¹⁵ The study was approved by the Emory Institutional Review Board, and all participants signed an informed consent. Diagnosis of CAD was defined by 1 or more of the following: angiographically proven disease including at least 1 major vessel, prior myocardial infarction as documented by typical chest pain and enzyme elevation or ECG changes, coronary atherosclerosis by angiography, intravascular ultrasound exam, or a history of percutaneous coronary intervention or coronary artery bypass surgery. Individuals with unstable psychiatric conditions, alcohol/substance abuse, end-stage renal disease, human immunodeficiency virus, or permanent atrial fibrillation were excluded. The current study was performed as an ancillary investigation that started ambulatory ECG data collection approximately 2 years after the parent investigation began. Of 695 individuals enrolled in the parent study, we collected ambulatory ECG data on 380 of them.

Trauma Questionnaire

The Early Trauma Inventory Self Report-Short Form (ETISR-SF) is a 27-item questionnaire that evaluates childhood trauma in 4 areas: general, physical, emotional, and sexual. Higher scores indicate a higher cumulative number of traumatic life experiences before 18 years of age.¹⁶ It has good validity and reliability, with the Cronbach's alphas for these 4 domains ranging from 0.7 to 0.87,¹⁷ and showing good face validity in assessing the relationship between a range of cardiovascular variables and early trauma. We calculated the score by summing the unweighted responses of each question.¹⁸⁻²⁰ We defined high trauma exposure based on an ETISR-SF score ≥ 10 based on the criterion that it is 2 SDs above the mean for normal individuals.¹⁷

Medical History

Information regarding previous health conditions was obtained through standard medical history forms completed by participants and supplemented by chart review. Assessment of heart failure included chart review of ejection fraction from recent echocardiogram, left ventriculogram, or, if neither were available, gated myocardial perfusion imaging.²¹ Information regarding symptoms of major depressive disorder and post-traumatic stress disorder were obtained through the Structured Clinical Interview for DSM-IV Disorders.²²

Mental Stress Procedure

Participants were asked to hold all anti-ischemic medications, including beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and nitrates for 24 hours before testing. Participants were also asked to fast for 12 hours before the morning of their test. Upon arrival, participants were taken to a quiet room where a blood pressure cuff and Holter monitor were applied. Vital signs were monitored every 5 minutes while participants rested for a total of 30 minutes. Mental stress was induced by a standardized public speaking task in which they were asked to imagine that a loved one had been mistreated by nursing home staff.^{23,24} They were told to compose a speech and that the speech would be recorded on video for later analysis. Participants were given 2 minutes to prepare a speech and 3 minutes to deliver it in front of a small audience wearing white coats, and during this time, blood pressure and heart rate were recorded at 1-minute intervals with an Omron blood pressure monitor (Matsusaka, Japan) approved by the Food and Drug Administration. The test was administered by personnel unknown to the participant, which reduced possible stress attenuation owing to the staff's relationship with the participant.²⁵

Electrocardiographic Assessments

ECG data were recorded using General Electric SEER Light Holter monitors, which recorded 2 channels at 125 samples per second. TWA was analyzed using a GE MARS 8.0.2 workstation using proprietary commercial algorithms based on the modified moving average method.²⁶ The method divides successive ECG complexes into even and odd beats and averages the even beats together as one complex, and the odd beats together in another complex. TWA is then computed as the maximum difference in amplitude between the odd-beat and even-beat average complexes from the J point to the end of the T wave. All TWA was reported as the maximum value within any 15-second window per 5-minute recording segment.¹² We used an update factor of 1/32 for TWA measurement. Although the algorithm has noise filtering mechanisms to exclude

areas with >20 μV of noise, as an additional cautionary step, we manually reviewed the signals and excluded any ECG 15-second windows in which the T-wave was not discernible because of visible noise. Clinically high TWA was defined as levels ≥ 47 μV .²⁷ We excluded participants with excessive signal artifact and nonsinus arrhythmia in $>20\%$ of recorded time.

Statistical Analysis

Baseline analysis was performed comparing those with high trauma scores (≥ 10) to the others. Continuous variables were compared using the Student *t* test, and binary variables were compared using the chi-square test statistic. The primary outcomes were peak TWA during stress and recovery. The change from rest to stress and rest to recovery was also evaluated. TWA measures were log-transformed to achieve normality. Linear regression models using ETI (both as a continuous and binary predictor) as the primary predictor was used to predict TWA during each phase and the changes from rest to stress/recovery. We adjusted for baseline demographics, medical history, CAD history (myocardial infarction, revascularization, and abnormal stress test), and beta blockers. Depression, PTSD, and antidepressant use were also sequentially evaluated in secondary analyses, as these may be direct consequences of early trauma. We also examined each subtype of trauma (general, emotional, physical, and sexual) in additional secondary analysis, as previous work has shown that the cardiovascular effects of early trauma may differ by type of trauma.²⁸ We also evaluated the effects of stress hemodynamic reactivity by calculating the peak rate pressure product (heart rate \times systolic blood pressure) during mental stress and subtracting the baseline rest rate pressure product. In order to do this, 4 nested multivariable models were constructed to include increasing numbers of covariates, including sociodemographic variables (model 1), CAD risk factors and history (model 2), heart failure related variables (model 3), and psychiatric/stress hemodynamic variables (model 4). We determined significance for each variable in the linear model using the Wald test of the beta coefficient. For all linear regression models, we used SAS 9.4 regression diagnostic plots to examine linear regression assumptions, including linearity, homoscedasticity, and normality.

RESULTS

Baseline Characteristics

Of the 380 participants, we analyzed a subset of 320 participants who had adequate ECG data. Those who had missing data were similar to the study sample without missing data, with the exception of heart failure (12% in the study sample versus 18% in those

with missing data) and hypertension (78% in the study sample versus 69% in those with missing data). A histogram of the total ETISR-SF scores is presented in Figure 1.

Nearly 1 in 4 patients ($n=85$, 26%) had a high trauma level (ETI-SF ≥ 10). Characteristics of those who were exposed to high levels versus others are shown in Table 1. Participants in the high trauma group were more likely to be Black, have a yearly income of \$20 000, have PTSD or depression, and were more likely to take antidepressants. The high trauma group also had a higher body mass index and more often had a history of heart failure and angioplasty, but other clinical factors were similar.

Hemodynamic Reactivity With Mental Stress Challenge

The heart rate increased significantly from baseline to stress for the entire group, with the mean (SD) difference from minimum baseline heart rate to peak stress heart rate of 17.3 (11.6) beats/min. Systolic and diastolic blood pressures also increased, 41.1 (18.5) mm Hg and 23.7 (10.3) mm Hg, respectively. When comparing the early trauma group to the rest, a slightly blunted diastolic blood pressure response (21.4 versus 24.6 mm Hg, $P=0.01$) and heart rate response (14.7 versus 18.2 beats/min, $P=0.008$) were recorded. No differences in resting heart rate or systolic blood pressure reactivity were noted between groups with high and low ETI scores.

Repolarization Heterogeneity With Mental Stress Challenge (TWA)

The mean value of TWA increased from 11.6 μV at baseline to 17.1 μV during the mental stress phase ($P<0.001$),

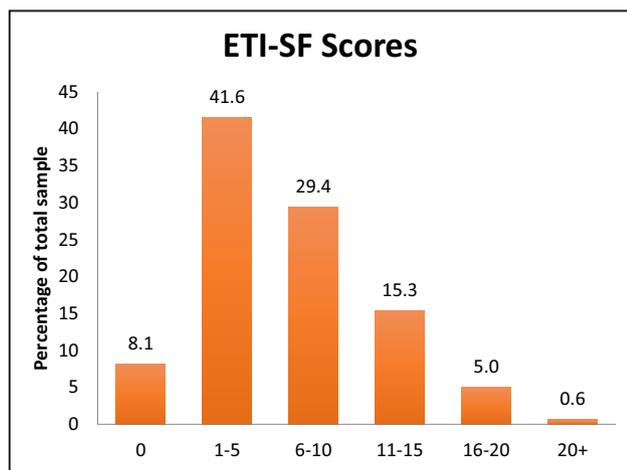


Figure 1. Histogram of ETISR-SF scores in a sample of patients with coronary artery disease.

ETISR-SF indicates Early Trauma Inventory Self-Report-Short Form.

and decreased to 15.9 μV during recovery. Clinically high (≥ 47 μV) TWA was observed in 2.6% ($n=6$) of the low trauma group and 3.5% ($n=3$) of the high trauma group (Fisher exact $P=0.7$). Patients with high trauma exposure exhibited 17% ($P=0.04$) higher TWA during stress compared with those with low trauma, as shown in Figure 2. Tables 2 and 3 show the association of rest, stress, and recovery TWA per 1-point increase in total trauma and emotional trauma scores. Each increased point of total and emotional trauma score associated with a 1.6% and 5.4% increased TWA, respectively, in fully adjusted models ($P<0.05$ for each). These models included sociodemographic, medical, hemodynamic, and psychological factors. No significant findings were noted with the other types of trauma (general, sexual, and physical trauma). Examination of TWA reactivity (stress minus rest) showed similar results as the stress TWA findings. No significant interaction by sex and race were noted.

DISCUSSION

In this study of individuals with stable CAD, we found that early life stress is an independent predictor of repolarization heterogeneity during acute mental stress challenge. Emotional trauma had the most robust associations for both stress and recovery phases, and because it was the only ETI subscale that associated with TWA, was the main driver of the association between the total score and TWA. The association was not explained by other patient characteristics, including depression and PTSD, which are 2 downstream effects of early trauma that are also independent CAD risk factors.^{29,30} These findings suggest that exposure to early life stress is an independent contributor to arrhythmic risk during emotional arousal in patients with CAD. These results may have clinical significance when considering the risk of future ventricular arrhythmias in trauma-exposed patients with CAD.¹⁴ Of note, addition of heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, and ejection fraction did not appreciably change any of the estimates in any of the models. This is likely because the prevalence of heart failure with reduced ejection fraction was low ($<10\%$).

Previous studies have reported early life trauma associations with CAD but have not explicitly evaluated its relationship with arrhythmic markers during emotional stress challenge.³¹ The Adverse Childhood Experiences study established associations between early life trauma and multiple poor outcomes, including obesity, substance abuse, depression, chronic lung disease, liver disease, and ischemic heart disease.^{32,33} Other studies confirmed the link between childhood stressors and cardiovascular disease. However, they

Table 1. Baseline Characteristics of Patients With Coronary Artery Disease With High and Low Early Trauma Exposure

Baseline characteristics	Low trauma (n=235)	High trauma (n=85)	P Value
Socioeconomic			
Age, mean y±SD	64.0±8.8	62.1±8.3	0.10
Female sex, % (n)	27 (63)	27 (23)	0.96
Black, % (n)	26 (61)	39 (33)	0.03
Education, mean y±SD	15.3±3.8	14.8±2.8	0.23
Employed, % (n)	36 (84)	31 (26)	0.39
Income <\$20 000, % (n)	10 (24)	29 (25)	<0.0001
Behavioral			
Current smoker, % (n)	11 (27)	14 (12)	0.53
Past smoker, % (n)	50 (117)	53 (45)	0.62
Psychological			
Depression, % (n)	20 (46)	44 (36)	<0.0001
Posttraumatic stress disorder, % (n)	4 (10)	12 (10)	0.01
Antidepressant use, % (n)	22 (52)	34 (29)	0.03
Medical			
Body mass index, mean±SD	29.3±5.0	30.5±5.7	0.05
History of hypertension, % (n)	76 (179)	82 (70)	0.24
History of hyperlipidemia, % (n)	82 (193)	85 (72)	0.59
History of diabetes, % (n)	32 (75)	38 (32)	0.34
History of heart failure with reduced ejection fraction, % (n)	5 (12)	8 (7)	0.30
History of heart failure with preserved ejection fraction, % (n)	3 (6)	14 (12)	<0.001
History of abnormal stress test, % (n)	9 (20)	14 (12)	0.14
History of myocardial infarction, % (n)	30 (71)	33 (28)	0.64
History of percutaneous transluminal coronary angioplasty, % (n)	57 (133)	40 (34)	0.009
History of coronary artery bypass graft, % (n)	34 (80)	33 (28)	0.85
Beta blocker use, % (n)	73 (171)	78 (66)	0.41
Hemodynamic			
Left ventricular ejection fraction, mean %±SD	59.6±10.8	58.6±11.9	0.29
Min systolic BP at rest, mean±SD	128.9±16.7	127.8±19.7	0.65
Min diastolic BP at rest, mean±SD	73.1±9.9	74.7±9.9	0.20
Min HR at rest, mean±SD	60.5±10.9	61.6±11.0	0.45
Max systolic BP during stress, mean±SD	170.7±23.3	168.1±26.6	0.41
Max diastolic BP during stress, mean±SD	97.7±13.5	96.0±13.4	0.34
Max HR during stress, mean±SD	78.7±16.5	76.3±14.4	0.23
Systolic BP at 5 min recovery, mean±SD	142.1±19.1	140.8±22.8	0.63
Diastolic BP at 5 min recovery, mean±SD	80.2±11.4	81.5±10.7	0.36
HR at 5 min recovery, mean±SD	64.8±12.2	65.0±10.6	0.93

BP indicates blood pressure; and HR, heart rate.

emphasized intermediate conditions, like depression, which is independently associated with cardiovascular morbidity and mortality.^{9,34,35} Our findings highlight potential new risk pathways downstream of CAD that warrant further consideration and possibly arrhythmia-specific therapies.

Early trauma may increase arrhythmia risk through several potential mechanisms. Trauma that occurs early in life while the brain is still developing can leave epigenetic marks that can persist into adulthood.³⁶ These changes may lead to adverse physiologic effects through efferent pathways from the brain.³⁷ Heim et al

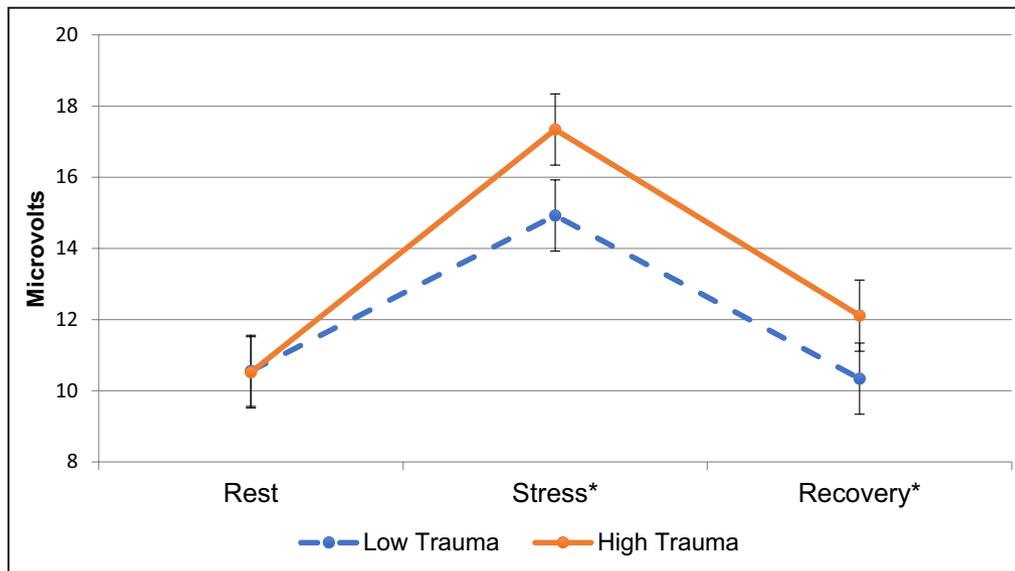


Figure 2. T-wave alternans with rest, stress, and recovery in patients with coronary artery disease with high and low early trauma exposure.

* $P < 0.05$ for the difference between high trauma (solid line) and low trauma (dashed line) groups.

found that a history of child abuse predicted a heightened autonomic response to stress in women, as seen by a 6-fold increase in corticotropin.⁶ This suggests that early trauma exposure may have an exacerbating stress reactivity, although the electrophysiological implications are not clear. Autonomic mechanisms are known to be an important driving force in TWA and SCD. Although adjustment for the heart rate \times blood pressure product in model 4, which indicate autonomic activation, did not significantly mediate the findings,³⁸ other mediating autonomic mechanisms may be possible. For example, pathways involving the stellate ganglion (local cardiac sympathetic activity) have been previously described to influence TWA and SCD risk.³⁹ Inflammation is also associated with childhood trauma and therefore a potential mediator as well, given its associations with SCD.^{18,40}

This study is subject to some limitations. Because the sample included only established patients with CAD, the findings cannot be generalized to patients

without CAD. Nonetheless, CAD is one of the most important risk factors for SCD, and therefore this is an important group to study.¹⁰ Early trauma scores could be affected by recall bias; nonetheless, such misclassification would likely bias the results towards the null, suggesting that the true association is likely stronger. The levels of TWA were lower than previously published in studies that validated a cutoff of 47 μV or increased sudden cardiac death risk; however, in those studies the individuals were higher risk, as they had recent myocardial infarction and left ventricular systolic dysfunction.²⁷

Conclusions

In conclusion, we found that early life trauma is associated with increased TWA during mental stress and recovery in our cohort of patients with CAD. This relationship was strongest for emotional trauma and was not mediated by depression or PTSD. Our results suggest that early trauma may increase vulnerability to

Table 2. Association of Repolarization Heterogeneity With Total Early Trauma Exposure as a Continuous Score During Rest, Stress, and Recovery Phases

	Rest		Stress		Recovery	
	B*	P Value	B*	P Value	B*	P Value
Unadjusted	0.5%	0.46	1.5%	0.02	1.3%	0.048
Model 1	0.1%	0.84	1.4%	0.04	1.3%	0.06
Model 2	0.0%	0.97	1.6%	0.02	1.4%	0.05
Model 3	-0.1%	0.92	1.7%	0.02	1.3%	0.08
Model 4	-0.2%	0.81	1.6%	0.04	1.4%	0.07

*B coefficient expresses the % increase in T-wave alternans per unit higher trauma score.

Table 3. Association of Repolarization Heterogeneity With Emotional Early Trauma Exposure as a Continuous Score During Rest, Stress, and Recovery Phases

	Rest		Stress		Recovery	
	B*	P Value	B*	P Value	B*	P Value
Unadjusted	0.3%	0.89	4.1%	0.03	3.6%	0.07
Model 1	0.1%	0.98	4.6%	0.02	4.4%	0.03
Model 2	0.0%	1.00	5.2%	0.01	5.1%	0.01
Model 3	−0.2%	0.94	5.3%	0.01	5.0%	0.02
Model 4	−0.4%	0.86	5.4%	0.02	5.6%	0.01

Model 1: adjusted for sociodemographic factors—age, sex, Black race, education, employment, and income. Model 2: adjusted for Model 1 variables + smoking history, body mass index, hypertension, hyperlipidemia, diabetes, coronary artery disease history (myocardial infarction, revascularization, and abnormal stress test), other vascular disease history (peripheral vascular disease, cerebral vascular disease, abdominal aortic aneurysm), chronic obstructive pulmonary disease, chronic renal disease, and beta blocker use. Model 3: adjusted for Model 2 variables + heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, and ejection fraction. Model 4: adjusted for Model 3 variables + depression, posttraumatic stress disorder, hemodynamic stress reactivity, and antidepressant use.

*B coefficient expresses the % increase in T-wave alternans per unit higher trauma score.

arrhythmia and possibly SCD triggered by emotional stress.¹⁴ Owing to the high prevalence of early trauma in people with CAD and the high frequency of fatal arrhythmias in this group, these findings suggest that further investigation is warranted into the potential of using early life trauma for risk stratification purposes, as well as the potential benefits of interventions such as positive psychotherapy.⁴¹

ARTICLE INFORMATION

Received September 18, 2021; accepted November 18, 2021.

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Acknowledgments

We acknowledge the MIPS staff for their tireless work in recruiting patients, conducting the study, and assembling the data set. We would also like to acknowledge the Emory Discovery program for its support in providing Ms. Weeks with her protected time. We would like to thank several affiliated institutions, including the Atlanta Veterans Affairs Medical Center, Emory Program in Cardiovascular Outcomes Research and Epidemiology (EPICORE), the Emory Clinical Cardiovascular Institute (ECCRI), and Atlanta Clinical and Translational Science Institute (ACTSI).

Sources of Funding

This work was supported by the National Institutes of Health (K23HL 127251, R03 HL146879, K24HL077506, K24MH076955, KL2TR000455, R01 HL68630, R01 AG026255, R01 HL109413, P01 HL101398, and T32HL130025); and by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR000454.

Disclosures

None.

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