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Association of Isolated Minor Non-specific ST-Segment and T-Wave Abnormalities with Subclinical Atherosclerosis in a Middle-Aged, Biracial Population: Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Abstract

Aims—Isolated minor non-specific ST segment and T wave abnormalities (NSSTTA) are common and known to be independent electrocardiographic risk markers for future cardiovascular disease (CVD) events. The association of NSSTTA with subclinical atherosclerosis is not well defined, but has been postulated as a potential mechanism of association with future clinical events.

Methods and Results—We studied participants from the Year 20 examination of the middle-aged, biracial CARDIA cohort. This examination included measurement of traditional risk factors, 12-lead electrocardiograms (ECG), coronary artery calcium (CAC) measurement and common carotid intima-media thickness (CCIMT). ECGs were coded using both Minnesota Code (MC) and Novacode (NC) criteria. Isolated minor STTA was defined by MC as presence of MC 4-3, 4-4, 5-3, or 5-4, and by NC as presence of NC 5.8. ECGs with secondary causes of STTA (i.e. LVH) were excluded. Multivariable logistic regression was used to determine the cross-sectional association of isolated minor NSSTTA with CAC and CC-IMT. The study sample consisted of 2175 participants with an average age of 45 years (57% women and 43% black). No association was observed between NSSTTA and CAC. After multivariable-adjustment for traditional CVD risk factors, the presence of isolated minor NSSTTA remained significantly associated with the extent of CCIMT (OR 1.25 (1.06 – 1.48), $p < 0.01$). This association remained significant after further adjustment for CAC.

Conclusions—Isolated minor NSSTTA were associated with the extent of CCIMT, but not with CAC, in this middle-aged biracial cohort. Further study is needed to elucidate potential mechanisms for these findings.

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CONFLICTS OF INTEREST: none

Keywords

Electrocardiography; Atherosclerosis; Risk factors

INTRODUCTION

Isolated minor non-specific ST and T wave abnormalities (NSSTTA) represent very minor or up-sloping ST segment depression and flat or minimally inverted T-waves. (1) They are among the most common electrocardiographic abnormalities with an estimated prevalence of 4–10% in middle-aged white men and occur more frequently among African-Americans, the elderly, and women. (1) A large number of epidemiologic studies to date have established an association between isolated NSSTTA and clinical cardiovascular (CVD) and coronary heart disease (CHD) mortality, independent of traditional coronary risk factors. (1–6) The magnitude of increased risk associated with isolated NSSTTA is similar to that associated with elevated levels of traditional CVD risk factors such as smoking, diabetic status, hypercholesterolemia, and hypertension. (7, 8) However, the mechanism through which isolated NSSTTA are associated with increased risk is unclear; several investigators have postulated that it may be mediated through an association with subclinical atherosclerosis but there have been few studies to date examining this association. (5, 9)

Coronary artery calcium (CAC) and common carotid intima-media thickness (CC-IMT) are two widely used measurements of subclinical CVD that are known to be highly correlated with atherosclerosis and prospectively associated with incident CVD events. (10–13) We sought to examine the cross-sectional association of isolated NSSTTA with these measures among the younger adult and middle-aged participants in the Year 20 examination of the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. The CARDIA cohort is uniquely suited for the purposes of our study in that it is a large, healthy, middle-aged cohort with similar numbers of black and white men and women, and with current data that reflect contemporary exposures to CVD risk factors (e.g., the obesity epidemic). Further elucidation of the cross-sectional association of subclinical atherosclerosis with isolated NSSTTA could provide insight into the mechanism through which these ECG abnormalities confer increased risk for CVD and CHD mortality. Moreover, in contrast to CAC and CC-IMT, the ECG is a widely available and inexpensive clinical tool that could potentially be used to screen for subclinical atherosclerosis and inform decisions regarding treatment of risk factors for clinicians and patients.

METHODS

Study Sample

The CARDIA cohort was initiated to investigate the development of heart disease risk factors in young age. Details about the study design have been previously published. (14) Briefly, 5,115 men and women aged 18 to 30 years with approximate balance in distribution of sex, race (black and white), and education were enrolled in 1985 and 1986 from 4 field sites: Birmingham, AL (University of Alabama at Birmingham); Chicago, IL (Northwestern University); Minneapolis, MN (University of Minnesota); and Oakland, CA (Kaiser

Permanente Northern California). Participants were examined at baseline (Y0) and at follow-up examinations in year 2 (Y2), Y5, Y7, Y10, Y15, and Y20. Follow up has been maintained on 91% of all baseline participants. For the present analysis, we used data from participants attending the most recent (Y20) examination. All participants signed informed consent at each examination, and the institutional review boards at each site approved study protocols.

Clinical Assessment and Measurement

Demographic, anthropometric, physiologic, and hematologic measurements for each participant were obtained according to previously published standardized protocols. (14) Current medication data were also obtained at the Y20 examination. ECGs were obtained in conjunction with the CARDIA Fitness Study, an ancillary study of the main CARDIA cohort during examination Year 20. (14) Participants who declined to participate in the CARDIA Fitness Study, therefore, did not undergo routine ECG ascertainment. As a result, 2,585 of the 3,548 participants attending the Year 20 examination underwent ECG ascertainment and were included in the study. In addition, 410 participants were excluded for missing covariates and hence there are 2,175 participants in the present analysis.

ECG Analysis and Exclusions

For resting electrocardiography, all participants had standard limb and precordial ECG leads placed, with use of the Heartsquare device(15) to determine appropriate placement of the precordial leads (V_1 – V_6). Identical electrocardiographs (GE MAC1200 Marquette Electronics, Milwaukee, WI) were used in all clinical centers. After acquisition, ECG recordings were transmitted via modem and a phone line to the Central ECG Laboratory (EPICARE Center, Wake Forest University, Winston-Salem, North Carolina) for reading using Marquette 12SL (GE Marquette, Milwaukee, Wisconsin). All ECGs received were inspected visually to detect technical errors, missing leads, and inadequate quality, and such records were rejected from electrocardiographic data files. Because of the automatic measurement of the CARDIA ECGs, the repeatability of ECG waveform measurements is 100%. ECGs were read using both Minnesota Code (MC)(16) and Novacode (NC)(17) criteria.

We focused on isolated minor non-specific ST-segment and T-wave changes described by Minnesota codes (MC) 4-3, 4-4, 5-3, and 5-4, defined, briefly, as follows: ST junction depression less than 0.5 mm (MC 4-3); ST junction depression over 1 mm and ST segment ascending, i.e. “up-sloping” (MC 4-4); T-wave flat, diphasic, or inverted less than 1 mm (MC 5-3); and T-wave amplitude positive and T- to R-wave amplitude ratio of less than 1:20, i.e. flattened T-wave (MC 5-4). (16) A visual representation of isolated minor NSSTTA is displayed in Figure 1. In order to study *isolated* NSSTTA, we next excluded, in a hierarchical fashion, participants with ECG findings typically associated with secondary ST-T changes: MC 1-1 and 1-2 (pathologic Q waves, n=38); MC 3-2 with STTA (left ventricular hypertrophy with STTA, n=19); MC 7-1 (left bundle branch block, n=0); MC 7-2 (right bundle branch block, n=9); MC 7-4 (other intraventricular block with QRS duration 120 msec, n=7); and MC 8-3 (atrial fibrillation, n=2). Next, we excluded 60 participants with major STTA (MC 4-1, 4-2, 5-1 or 5-2) and 20 participants who were either receiving

digitalis glycosides or stated that they were taking medications for a previous heart attack at the Y20 examination. Therefore, there were 155 ECGs excluded from the *isolated* minor NSSTTA MC analysis. Participants were free of clinical CVD at baseline (Year 0). In addition to MC isolated minor NSSTTA, we also examined minor STTA (Novacode 5.8), defined, briefly as ST depression or T wave negativity more than or equal to 10 points in any lead group. (17)

CAC and CC-IMT measurement

CAC was measured with an electron-beam computed tomography scanner or a multidetector computed tomography system in accordance with standard protocols, as described previously. (18) The prevalence of coronary calcium was treated as a categorical variable (CAC=0 or CAC >0) using the Agatston score. (19) Prior analyses of CARDIA have demonstrated the presence or absence of CAC to be a reliable measure, with observed agreement of 96%. (18) Carotid IMT was measured at the year 20 examination in CARDIA with high-resolution B-mode ultrasound, in accordance with standard procedures. (20) Briefly, maximal IMT of the internal and common carotid sites was measured as the mean of the maximum IMT of the near and far walls of the right and left sides. A composite Z score for overall maximal IMT was created by summing the two carotid IMT sites (if both were measured) after standardization (subtraction of the mean and division by the standard deviation of each measure), and then dividing by the standard deviation of the sum. If only one of the two measures was available, it was used. The Z score maximum IMT has a mean of zero and a standard deviation of one.

Statistical Analysis

All analyses were performed using SAS version 9.1 (SAS institute, Cary, NC). Baseline characteristics were described, after stratification by race and sex, using means and standard deviations (SDs) or percentages. Differences in means or percentages were compared between race-sex subgroups using general linear models (t-test) for continuous variables and chi-square tests for categorical variables, as appropriate. To determine the cross-sectional association of ECG abnormalities with CAC+ (defined as CAC > 0 and $\ln(\text{CAC} + 1)$), logistic regression models were fitted with the presence of CAC as the predictor and the presence of isolated minor NSSTTA as the outcome variable. For the association of ECG abnormalities with common carotid IMT, we used logistic regression models with mean maximal CC-IMT as the predictor (standardized to a 0.1 mm difference) and isolated minor NSSTTA as the outcome. All regression models were adjusted for demographic and clinical covariates including; age, sex, race, blood pressure, body mass index, total cholesterol level, high density lipoprotein, diabetes, smoking status, creatinine, medication of hypertension and medication for hyperlipidemia (Model 1) as well as CC-IMT or $\ln(\text{CAC} + 1)$ (Model 2). Secondary analyses were conducted in race-sex subgroups. To address missing ECGs from the Y20 examination all analyses were repeated using multiple imputation for participants without an ECG record at Y20. The imputation for missing ECG record was performed using Imputation and Variance Estimation software (IVEware) to obtain 5 imputed data sets. Results were combined using SAS Proc Mianalyze procedure. Variables used to impute data sets included all the covariates fitted in the models. A p value < 0.05 was considered statistically significant.

RESULTS

Study Sample

The study sample consisted of 2,175 participants, of whom 57% were women and 43% were black, with a mean age of 45 years. Characteristics of the study cohort at Exam Y20, stratified by race and sex, are shown in Table I. Compared to whites, black men and women had higher systolic and diastolic blood pressures, higher rates of diabetes and smoking, and were more likely to be treated for hypertension. CAC > 0 (%) was most prevalent among white men and mean CC-IMT (mm) was greatest in black men and women.

Frequency of isolated minor NSSTTA by race and sex

As shown in Figure 2, black men and women had a significantly higher prevalence of isolated minor NSSTTA.

Cross-Sectional Association of CAC with isolated minor STTA

As shown in Table II and III, isolated minor NSSTTA was not associated with the presence of CAC in unadjusted or multivariable models. This lack of association remained after further adjustment for CC-IMT. Similarly, the lack of association was consistent across all race-sex strata (not shown in tables) and by Novacode.

Cross-sectional Association of CC-IMT with isolated minor NSSTTA

Isolated minor NSSTTA was significantly associated with CC-IMT. As shown in the logistic regression analysis in Table IV, participants with isolated minor NSSTTA had 25% greater odds (OR 1.25 per 0.1 mm higher CC-IMT, 95% CI 1.06 – 1.48) of having a greater burden of CC-IMT than those without NSSTTA. This association remained, without any attenuation, after further adjustment for presence of coronary artery calcium (ln CAC +1). In secondary analyses by sex-race strata, the association between isolated minor NSSTTA and CC-IMT appeared to be driven largely by black men (multivariable-adjusted OR 1.37, 95% CI 1.04–1.79) and white women (OR 1.47, 95% CI 0.92–2.35).

Internal Validity of Study Sample

Only 2,585 (73%) of the 3,548 Year 20 participants had resting ECGs available for inclusion. In addition, 1,567 participants did not attend the Year 20 examination. These missing data may have biased the internal validity of the sample by selecting for participants that are more likely to pursue follow up. To further examine this possibility we compared the baseline characteristics of participants who did not attend the Year 20 examination with those who attended and did not receive an ECG, and those who attended and did receive an ECG. The participants who did not attend the Year 20 examination were more likely to be male (non-attendees 51% male, attendee/no ECG 43% and attendee with ECG 43%, respectively), black (63%, 52% and 45%) and smokers (40%, 30% and 25%). Other cardiovascular risk factors including age, systolic and diastolic blood pressure, body mass index, total cholesterol, LDL and HDL-cholesterol, were similar across the three groups. In secondary analyses, we performed multiple imputation to include the 963 participants who attended Exam Y20 but did not have ECGs performed. In these analyses, the association of

isolated NSSTTA with CAC remained non-significant, whereas the multivariable-adjusted association of isolated NSSTTA with CC-IMT was similar (data not shown).

DISCUSSION

Principal Findings

Isolated minor NSSTTA are common and known to be associated with incident CVD and CHD events. Their association with subclinical atherosclerosis is not well defined. In this cross-sectional analysis of a large, asymptomatic, biracial cohort composed of men and women with a mean age of 45, isolated minor NSSTTA were associated with the extent of CC-IMT independent of traditional coronary risk factors, but not associated with CAC. These findings suggest that isolated minor NSSTTA may be a marker for subclinical “sclerosis” and hypertrophy of the arterial media but perhaps not *coronary* plaque burden. This apparent contradiction may indicate differing underlying mechanisms of association or common underlying risk factors such as hypertension. Thus, the strong prognostic association of these ECG abnormalities with incident CVD and CHD events may be mediated through subclinical atherosclerotic disease. Further prospective and mechanistic studies are warranted to investigate this association.

Potential Mechanisms

Measurement of the carotid intima-media thickness by high-resolution ultrasound has been widely used in epidemiologic studies as a marker of subclinical atherosclerosis. In multiple studies to date, it has been shown to correlate with vascular risk factors and incident CVD events across age and sex. (21, 22) Among adults < 50 years of age from the Carotid Atherosclerosis Progression Study (CAPS), (22) every 0.1 mm Hg increase in the measurement of CC-IMT (as used in our analysis) increased the risk of a combined end-point of MI, stroke or death by 26% (HRR 1.26, 95% CI (1.06 – 1.49). While CC-IMT and CAC are both widely used markers of subclinical atherosclerosis and endpoints of CVD, they differ in the mechanisms underlying their development, and they are only moderately correlated within individuals. (23) While CAC shows a strong association with overall burden of coronary atherosclerosis ($r=0.52$, $p<0.0001$) (24), CC-IMT is associated with hypertrophy of the arterial media and global atherosclerotic burden. Hence our results suggest that the mechanism underlying the cross-sectional association between isolated minor NSSTTA and CC-IMT but not CAC may be related to their preferential association with global hypertrophy of the arterial media as opposed to coronary plaque burden. Alternatively, NSSTTA and CC-IMT may share some common underlying risk factor or substrate that is also associated with fatal CVD, but less associated with CAC. Indeed, data from the Cardiovascular Health study and elsewhere have shown that both isolated NSSTTA and increasing IMT are highly correlated with hypertension as well as incident stroke. (6, 21, 25) This common endpoint for these CVD risk markers may suggest that each represents an intermediate phenotype of subclinical CV disease brought on by hypertension that ultimately manifests in incident CVD events. As opposed to CC-IMT, the ECG is a widely available and inexpensive clinical tool that could be used as a risk marker for atherosclerosis and subclinical CVD in seconds. Furthermore, isolated minor NSSTTA are very common

and easily identifiable by clinicians (as shown in Figure 1). Further prospective analyses are necessary to provide insight into the longitudinal association of these risk markers over time.

Although the observed lack of association between isolated NSSTTA and CAC is consistent with previous studies³¹, both subclinical CVD measures have been consistently shown to be associated with fatal CHD (6). This discrepancy could be explained by the younger age of the participants in CARDIA. While CC-IMT has been suggested as an early risk marker for atherosclerosis (26, 27), the men and women of CARDIA may not have had enough time to develop calcified plaques at a mean age of 45.

Current Study in Context

To our knowledge this is one of the largest studies to date to examine the association of subclinical atherosclerosis with minor NSTTA in younger adults, at a time when significant atherosclerosis may be developing. It is also the first study to date to show an association between CC-IMT and minor NSSTTA. Lee et al (28) measured ECG abnormalities and CAC in 893 white and black US Army personnel between the ages of 40 and 45. In this study, black men and women had significantly higher prevalence of STTA (18% vs. 4%, $p<0.001$) compared with whites. However, as in the current study, STTA were not associated cross-sectionally with CAC. We recently reported⁽²⁹⁾ on the cross-sectional association of both CAC and CC-IMT with isolated minor NSSTTA, minor and major ECG abnormalities among 6,710 older men and women (mean age 62) from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. We found that minor NSSTTA (NC) were not associated with the presence of CAC (Agatston score > 0), extent of CAC in those with CAC, or amount of CC-IMT. This study benefitted from a large, multiethnic group of middle-aged and older men and women with high quality ECGs and multiple measures of subclinical atherosclerosis. The CARDIA cohort, however, represents a much younger group of individuals (mean age 45 years) with a lower burden of risk factors than the MESA participants. Moreover, the CARDIA cohort provides the first analysis of a biracial group of men women with both Minnesota (not available in the previous MESA analysis) and Novacode during a critical age period when these ECG changes are most likely to develop. Our secondary findings regarding potential sex-race differences in the association between isolated minor STTA and CC-IMT should be regarded as hypothesis generating. Further longitudinal analysis is warranted to investigate the strong association between minor NSSTTA and CC-IMT among black men (specifically examining hypertension's contribution).

Limitations

The cross-sectional nature of this analysis limits its ability to determine the temporal nature of an association between isolated NSSTTA and CC-IMT. The clinical implications, however, remain valid, as clinicians are concerned with the immediate association of easily interpretable ECG abnormalities with risk markers of atherosclerotic burden. Another potential limitation is selection bias, as there were a large number of participants who did not attend or did not have ECGs obtained from the Year 20 examination of CARDIA. However, as discussed above, the participants who did not attend the year 20 examination or attended but did not have ECGs obtained demonstrated generally similar baseline

characteristics to the study sample with few exceptions (more likely to be male, black and smokers) and the association remained after multiple imputation was performed on the Year 20 participants without ECGs. Also, more direct markers for atherosclerotic disease (e.g., computed tomographic angiography, intra-vascular ultrasound) might be more ideal for quantification of coronary plaque burden, but they would be less feasible for a healthy observational cohort, given that they are invasive or involve significant radiation exposure. Finally, the non-randomized nature of this study makes it subject to residual confounding.

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Isolated Non-Specific ST-Segment and T-Wave Abnormalities (NSSTTA)

MN Codes Definition

4-3

- ST junction depression
< 0.5 mm

4-4

- ST junction depression
 ≥ 1 mm and ST segment
“up sloping”

5-3

- T-wave flat, diphasic, or
inverted < 1 mm

5-4

- Positive, low-amplitude T-
wave

Figure 1.
Minnesota Code Definitions for Minor ST-Segment and T-wave ECG Abnormalities

Figure 2.

Frequency of participants with isolated minor ST and T wave abnormalities by race and sex for CARDIA Year 20*

* $p < 0.05$ across race and sex

Table I

Characteristics of CARDIA Participants by Race and Sex at Year 20

	White Men (n=576)	Black Men (n=359)	White Women (n=665)	Black Women (n=575)
Age, years *	45.7 ± 3.3	44.6 ± 3.5	45.9 ± 3.3	44.6 ± 3.8
Systolic BP, mm Hg	117 ± 12	123 ± 14	109 ± 13	119 ± 17
Diastolic BP, mm Hg	72 ± 10	76 ± 11	68 ± 10	76 ± 12
Body mass index, kg/m ²	29 ± 6	29 ± 6	27 ± 6	32 ± 8
Total cholesterol, mg/dL	188 ± 37	184 ± 35	188 ± 32	185 ± 34
HDL-cholesterol, mg/dL	46 ± 13	49 ± 16	62 ± 17	58 ± 16
LDL-cholesterol, mg/dL	115 ± 33	112 ± 34	106 ± 29	110 ± 31
Triglycerides, mg/dL	141 ± 102	110 ± 72	97 ± 61	88 ± 50
Diabetic †	5.6 %	7.2%	6.8%	13.6%
Current Smoker	14.2%	25.6%	12.2%	18.8%
Treated for Hypertension	12.0%	15.9%	8.1%	28.5%
Treated for Dyslipidemia ‡	14.2%	6.7%	5%	7.6%
Creatinine (mg/dl)	0.98 ± 0.14	1.09 ± 0.71	0.78 ± 0.14	0.82 ± 0.33
CAC>0, %	31.2%	22.3%	9.3%	10.1%
Median CAC score if CAC>0	28.6	19.3	15.1	31.0
IMT, mm	0.80 ± 0.11	0.85 ± 0.14	0.74 ± 0.10	0.81 ± 0.11

Abbreviations: BP = Blood Pressure, HDL = High density lipoprotein, LDL = Low density lipoprotein, CAC = Coronary Artery Calcium

* Means ± Standard deviation unless otherwise indicated

† Defined as self-reported “yes” or fasting glucose ≥ 126 mg/dL

‡ Any lipid lowering medication

Table II

Multivariate-Adjusted Cross-Sectional Association of Minor ST segment and T wave Abnormalities (NSSTTA) with Coronary Calcium (CAC > 0) *

	N	Odds Ratio (95% CI)	p-value
Isolated Minor STTA (Minnesota Code)	116	0.91 (0.77 – 1.08)	0.30
Minor STTA (Novacode)	279	0.95 (0.86 – 1.04)	0.27

* Adjusted for age, sex, race, smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood pressure med, total cholesterol, high-density lipoprotein, cholesterol med, diabetes, body mass index, and creatinine

Table III

Multivariate-Adjusted Cross-Sectional Association of Minor ST segment and T wave Abnormalities (NSSTTA) with Coronary Calcium (ln CAC +1) – adjusted for CC-IMT[†]

	N	Odds Ratio (95% CI)	p-value
Isolated Minor STTA (Minnesota Code)	116	0.89 (0.75 – 1.06)	0.20
Minor STTA (Novacode)	279	0.93 (0.84 – 1.03)	0.18

[†]ln (CAC +1) adjusted for variables in Model 1 plus CC-IMT (per 0.1 mm)

Table IV

Multivariate-Adjusted Cross-Sectional Association of Minor ST segment and T wave Abnormalities (NSSTTA) with Carotid Intima-Media Thickness (logistic regression per 0.1 mm of CC-IMT)

	Model 1 [*]			Model 2 [†]		
	N	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	p-value
Isolated Minor STTA (Minnesota Code)	116	1.25 (1.06 – 1.48)	< 0.01	1.27 (1.07 – 1.50)	< 0.01	< 0.01
Minor STTA (Novacode)	279	1.20 (1.07 – 1.34)	< 0.01	1.21 (1.08 – 1.35)	< 0.01	< 0.01

^{*} Model I: Adjusted for age, sex, race, smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood pressure med, total cholesterol, high-density lipoprotein, cholesterol med, diabetes, body mass index, and creatinine

[†] Model II: Adjusted for variables in Model 1 plus ln (CAC + 1)