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The relationship between subclinical atherosclerosis and electrocardiographic abnormalities as biomarkers of cardiovascular risk

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Abstract

Electrocardiographic findings indicating myocardial disease, such as left ventricular hypertrophy or ST-T wave abnormalities, or the presence of coronary artery calcium, indicating atherosclerotic coronary artery disease, are both biomarkers of future cardiovascular (CV) risk. Although the risk factors for myocardial and coronary artery disease are similar, their concomitant expression has implications for CV disease screening and prevention programmes. The relationship between the resting 12-lead ECG and subclinical atherosclerosis measured as coronary artery calcium (CAC) with electron beam tomography was examined in 937 healthy participants (aged 40–50 years) enrolled in a CV risk screening study. Electrocardiograms and CAC were interpreted in blinded fashion, using standard criteria. An abnormal ECG was coded in 268 (28.6%) participants, most commonly left ventricular hypertrophy (3.1%), delayed precordial R wave transition (5.7%), T-wave abnormalities (10.0%) and intraventricular conduction delay (10.4%). Although abnormal ECG findings were associated with CV risk variables, the prevalence of any CAC was similar in subjects with any ECG finding (43 of 268, 16.0%) compared with those with normal ECGs (125 of 669, 18.7%, p = NS). In a logistic model controlling for CV risk factors including systolic blood pressure, low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), glycosylated haemoglobin, race, age and gender, significant associations with CAC were found for LDL-C, race and BMI. There was no significant relationship between CAC and ECG abnormalities (odds ratio 0.80, 95% confidence interval 0.54–1.20). In conclusion, electrocardiographic abnormalities and subclinical calcified atherosclerosis were not significantly associated with each other in this middle-aged screening population. This suggests these two biomarkers may be complementary towards broader detection of latent CV risk.

Keywords: *Risk factors, calcium, tomography, atherosclerosis, electrocardiography*

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Introduction

The identification of asymptomatic people at risk for cardiovascular disease (CV) is a major focus of preventive cardiology practice. Electrocardiographic findings such as left ventricular hypertrophy or ST-T abnormalities suggest underlying myocardial disease, and have been associated with a several-fold increased coronary heart disease (CHD) mortality (Liao et al. 1987, 1988) Since then, newer modalities to detect latent cardiovascular risk have emerged. Among these are tests of subclinical atherosclerosis burden, such as with the non-invasive measurement of coronary artery calcium (CAC) using coronary computed tomography (CT). Increasingly, the presence of CAC is also recognized as an independent predictor of coronary heart disease risk (Pletcher et al. 2004) even among younger individuals (Taylor et al. 2005). Coronary calcium is a unique variable, one that is generally related to CV risk factors such as blood pressure, low-density lipoprotein cholesterol (LDL-C), a family history of heart disease and body mass index (BMI), as previously shown in the Prospective Army Coronary Calcium (PACC) Project (Taylor et al. 2004, 2005, 2006). However, through all of the work relating CAC to CV outcomes, electrocardiographic abnormalities have not been included as covariates.

Although the risk factors for myocardial disease and atherosclerosis are similar, their expression has implications for primary screening and prevention programmes. American Heart Association statistics indicate that a large proportion, as much as 1/3, of CHD mortality arises from myocardial disease such as the consequences of hypertensive heart disease and congestive heart failure. Thus, consideration of both subclinical atherosclerosis, identified as CAC, and subclinical myocardial disease, identified as silent electrocardiographic abnormalities, could provide enhanced detection of CHD prognosis. However, a prerequisite to such data considerations is that these two variables are independent – thereby avoiding or limiting overlap in their identification of CHD risk. The purpose of this study was to determine whether a relationship exists between the resting ECG and subclinical atherosclerosis measured as CAC with electron beam tomography (EBT) in 937 healthy (aged 40–50 years) participants enrolled in a CV risk screening study.

Methods

The Walter Reed Army Medical Center Department of Clinical Investigation Human Use Committee approved this study, for which the methods have previously been described (O'Malley et al. 1999). Briefly, the PACC Project cohort consists of US Army personnel, aged 40–50 years old who voluntarily participated in the research study under informed consent at the time of a periodic army-required, physical evaluation. All subjects were asymptomatic and free of known CV disease at the time of enrolment. Among the 2000 participants enrolled between October 1998 and February 2003, the first 937 consecutive participants underwent paired ECG analysis and EBT testing. The characteristics of the 937 subjects in this analysis are representative of the 2000 subjects in the study (Taylor et al. 2006)

Each participant provided details of their medical history, including a history of hypertension, diabetes mellitus, hyperlipidaemia, and a family history of CV disease. Smoking was self-reported as current, never, or ex-smoker and categorized by years of use and average daily use. A family history of CHD included a history of sudden death, myocardial infarction, or coronary revascularization in a first-degree relative

prior to the age of 55 (males) and 65 (females). Height and weight were measured and BMI was calculated as weight/height^2 (kg m^{-2}). Resting blood pressure was measured using an automated sphygmomanometer, and was recorded as the average of three seated measurements taken 5 min apart. Hypertension was defined as either a systolic blood pressure of >135 mmHg, a diastolic blood pressure of >85 mmHg, or a history of hypertension (treated or untreated). Fasting blood was collected for the measurement of serum glucose, glycosylated haemoglobin, and lipids. LDL-C was measured using a direct assay.

Electrocardiography

Standard 12-lead ECGs were recorded at 25 mm s^{-1} and 1 mV cm^{-1} standardization with equipment (Marquette Electronics Corp.) whose frequency response characteristics met American Heart Association recommendations. Duration was measured to the nearest 2 ms and amplitudes to the nearest microvolt. ECGs were independently interpreted (without knowledge of the CAC score or other risk factors) by authors from the cardiology service at Walter Reed Army Medical Center each with extensive experience in ECG interpretation. ECGs were comprehensively evaluated using agreed-upon criteria for all abnormal findings including rhythm, vector axis, heart block and intervals. Criteria for the detection of left ventricular hypertrophy included QRS duration, Sokolow–Lyon voltage, gender-specific Cornell voltage, and a Point-Score System (Romhilt-Estes). Criteria for ST-T wave abnormalities were based on the Minnesota Code Manual of Electrocardiographic findings, codes 5–1 and 5–2. An approximate 10% subset of tracings ($n=117$) were randomly selected for paired analysis by two separate reviewers to determine the concordance of the coding procedures. This analysis showed no significant differences between the prevalence of any of the major ECG findings between interpreters.

EBT scanning and analysis

For the measurement of CAC, EBT was performed using an Imatron C-150 LXP scanner (Imatron Corp., South San Francisco, CA, USA) calibrated daily with air and water phantoms, and twice-monthly with contrast and resolution phantoms. Images were obtained using a 40–50 slice (3 mm thickness) protocol with image acquisition triggered to 60–80% of the electrocardiographic RR interval while respirations were held. Scans were interpreted in a blinded manner by an experienced radiologist (I.M.F.) using the Agatston scoring method (Agatston et al. 1990) A focus of coronary calcium was defined as the presence of 4 or more contiguous pixels with >130 Hounsfield units. A total CAC score was determined from the sum of individual scores of the four major epicardial coronary arteries. A scan was considered positive for CAC when the total CAC score was >0 (Mahoney et al. 1996, Taylor et al. 2001).

Statistical analysis

The primary analysis was the comparison of electrocardiographic abnormalities and the presence of any detectable coronary calcium (CAC score >0). Continuous variables were compared using a *t*-test for independent groups. Categorical variables, such as the prevalence of CAC among subgroups of ECG findings, were compared using the χ^2 test or ANOVA as appropriate. The relationship between multiple CV

risk factors and the presence of CAC was assessed using stepwise logistic regression analysis. Risk factor variables with a univariate relationship ($p \leq 0.05$) to CAC were entered into the model. All statistical analyses were performed using SPSS for Windows (v. 13, Chicago, IL, USA). Data are presented as mean $\pm$ SD. A two-tailed p-value of $p \leq 0.05$ was considered significant. The statistical power of this study was analyzed using SamplePower v. 2.0 (SPSS Inc., Chicago, IL, USA).

Results

Table I displays the baseline demographics and CV risk variables of the study participants. Overall, a majority of the participants were Caucasian (70.9%), males (82.7%) with at least one CV risk factor. Although risk factors were prevalent, the absolute 10-year CHD risk was low, consistent with the generally younger age of the study group.

An abnormal ECG was coded in 268 subjects (28.6%) participants. Specific findings are shown Table II and most commonly were T-wave abnormalities and intraventricular conduction delays, although other specific findings in decreasing order of prevalence included delayed precordial R-wave transition, left ventricular hypertrophy, atrial abnormality, ST segment depression, ST elevation and possible right ventricular hypertrophy. Single ECG abnormalities were present in 14.1%, with multiple abnormalities (two or more) present in 14.7%. The presence of any ECG finding was associated with higher levels of several CV risk variables including BMI, waist girth, systolic and diastolic blood pressure and glycosylated haemoglobin (Table III). Lipid values were similar between the two groups.

Table I. Demographics of PACC participants in the ECG substudy.

Variable	Value ($n = 937$)
Male gender, *n* (%)	775 (82.7)
Age (years)	42 $\pm$ 2
Caucasian, *n* (%)	664 (70.9)
Cardiac risk factors	
Total cholesterol (mg dl^{-1})	202 $\pm$ 36
LDL cholesterol (mg dl^{-1})	129 $\pm$ 33
HDL cholesterol (mg dl^{-1})	52 $\pm$ 15
Hypertension, *n* (%)	241 (25.7)
Systolic blood pressure (mmHg)	122 $\pm$ 13
Diastolic blood pressure (mmHg)	76 $\pm$ 9
Tobacco use within 6 months, *n* (%)	74 (7.9)
Diabetes mellitus, *n* (%)	9 (1.1)
Blood glucose (mg dl^{-1})	91 $\pm$ 11
Family history of coronary artery disease	315 (33.6%)
Body mass index (kg m^{-2})	27.4 $\pm$ 3.3
Waist girth (cm)	92 $\pm$ 10
10-year Framingham predicted coronary heart disease risk (%)	3.9 $\pm$ 2.2
Coronary artery calcification score	
Mean	13 $\pm$ 87
Median	0
CAC score >0, *n* (%)	168 (17.9)

Values are mean $\pm$ standard deviation unless otherwise indicated.

Table II. Prevalence of specific ECG findings.

	n (%)
Any ECG finding	268 (28.6)
QRS prolongation	97 (10.4)
T-wave abnormalities	94 (10)
Delayed precordial transition	53 (5.7)
Left ventricular hypertrophy	29 (3.1)
Q waves	21 (2.2)
Atrial enlargement	20 (2.1)
ST segment depression	16 (1.7)
ST elevation	8 (0.9)
Findings suggestive of right ventricular hypertrophy	5 (0.5)

The prevalence of CAC in study participants was 17.9% ($n=168$) and was associated with traditional cardiac risk factors such as higher BMI (28.2 ± 3.2 vs 27.25 ± 3.3 kg m^{-2}, $p<0.001$), higher blood pressure (125 ± 13 vs 122 ± 13, $p=0.003$), higher LDL-C (139 ± 34 vs 126 ± 33, $p<0.001$), and lower high-density lipoprotein (HDL)-C (50 ± 15 vs 53 ± 15, $p=0.047$), as noted within other reports from the PACC Project focused on clinical CV risk factors (Taylor et al. 2006). Overall, the prevalence of any CAC in subjects with any ECG finding (43 of 268, 16.0%) was similar to those with normal ECGs (125 of 669, 18.7%, $p=$NS). There were no univariate associations with any specific ECG abnormalities including ST segment or T-wave findings, Q waves, conduction delays, left ventricular hypertrophy or left atrial enlargement (Table IV). Electrocardiographic intervals (PR, QRS and QTc) were also similar in groups with and without CAC. There also was no significant bivariate relationship between the Framingham risk score (a CV risk scale based on the number and severity of risk factors) and the number of major ECG abnormalities ($r=0.012$, $p=0.71$).

In a logistic model for the prediction of CAC, there was no significant relationship between CAC and ECG abnormalities (odds ratio 0.80, 95% confidence interval [CI] 0.54–1.20) after controlling for CV risk factors including systolic blood pressure,

Table III. Relationships between major ECG abnormalities and cardiovascular risk factors.

	Any major ECG abnormality		
Variable	Positive ($n=268$)	Negative ($n=669$)	*p*-Value
Age (years)	42 ± 2	42 ± 2	0.61
Body mass index (kg m^{-2})	28.1 ± 3.5	27.2 ± 3.2	<0.001
Waist girth (cm)	93.7 ± 9.4	91.9 ± 9.9	0.012
LDL cholesterol (mg dl^{-1})	129 ± 33	128 ± 33	0.75
HDL cholesterol (mg dl^{-1})	53 ± 16	52 ± 14	0.31
Triglycerides (mg dl^{-1})	123 ± 72	127 ± 94	0.53
Systolic blood pressure (mmHg)	124 ± 14	121 ± 12	0.007
Diastolic blood pressure (mmHg)	77 ± 9	76 ± 10	0.029
Tobacco use, *n* (%)	22 (8.2)	52 (7.8)	0.82
Glycosylated haemoglobin (%)	5.62 ± 0.84	5.48 ± 0.52	0.002
10-year Framingham risk index (%)	4.0 ± 2.8	3.9 ± 2.8	0.52
Family history of coronary artery disease, *n* (%)	52 (19.4)	128 (19.1)	0.91

Values are mean $\pm$ standard deviation unless otherwise indicated.

Table IV. Relationships between coronary artery calcification and specific ECG abnormalities.

Variable	EBT results		*p*-Value
	CAC negative ($n=769$)	CAC positive ($n=168$)	
Any major ECG abnormality, *n* (%)	225 (29.3)	43 (25.6)	0.34
Left atrial abnormality, *n* (%)	19 (2.5)	1 (0.6)	0.12
Left ventricular hypertrophy, *n* (%)	25 (3.3)	4 (2.4)	0.56
ST depression, *n* (%)	15 (2)	1 (0.6)	0.22
T wave abnormalities, *n* (%)	8 (10.4)	14 (8.3)	0.42
QRS prolongation, *n* (%)	81 (10.5)	16 (9.5)	0.70
Q waves, *n* (%)	15 (2)	6 (3.6)	0.20
Delayed precordial R wave progression, *n* (%)	44 (5.7)	9 (5.4)	0.85
ECG intervals (mean $\pm$ SD)			
Heart rate (beats per min)	62 ± 12	61 ± 11	0.19
P axis	52 ± 17	54 ± 18	0.29
QRS axis	57 ± 26	59 ± 25	0.38
T axis	47 ± 19	47 ± 19	0.95
PR interval (ms)	165 ± 28	161 ± 35	0.20
QRS duration (ms)	93 ± 9	92 ± 12	0.39
QTc interval (ms)	412 ± 28	409 ± 40	0.33

LDL-C, BMI, glycosylated haemoglobin, race, age and gender. Similar analyses restricted to either Caucasian or African-American subjects showed similar results to the main cohort.

The studied sample of 937 subjects including 168 with CAC had a statistical power to detect an absolute 10% difference in the rate of major ECG abnormalities between groups with and without CAC.

Discussion

We found that among healthy, middle-aged asymptomatic men and women participants of the PACC Project, there was no relationship between the results of screening EBT and resting ECG, including multivariable analysis controlling for the effects of CV risk factors. Additional screening tests such as EBT and the 12-lead ECG have been advocated to improve the detection of latent CV risk, as each test has been shown to have an independent association to CHD outcomes. In theory, whereas the detection of coronary calcium is a sensitive test for the detection of subclinical atherosclerosis and thus principally ischaemic heart disease outcomes, the ECG may be more globally indicative of myocardial disease thereby providing the rationale to consider the tests as incremental in the evaluation of total CV disease risk. In this analysis, we sought to examine this potential by determining the extent of overlap between these two methods. These data have implications for the use of the 12-lead ECG and coronary calcium scanning as potentially complementary in the detection of latent CV risk in screening populations without known CHD.

The growing worldwide burden of CV disease includes substantial morbidity and mortality from both CHD and other aetiologies such as hypertensive heart disease, congestive heart failure, and other CV diseases according to the American Heart Association. The detection of cardiovascular risk in the population begins with the measurement of traditional cardiovascular risk factors such as blood pressure, BMI and lipid concentrations which are a common link between many different forms of

CV disease. However, because most risk prediction tools, such as the Framingham risk score, are primarily focused on the detection of CHD (non-fatal myocardial infarction and coronary death) risk, they generally do not include ECG findings as a component.

Previous epidemiologic surveys have shown that an abnormal 12-lead ECG is associated with increased CV mortality. For example, data from the Chicago Heart Association Detection Project in Industry revealed a relative risk for CV mortality of 2.6 ($p < 0.0001$) independent of other risk factors in men with minor ECG abnormalities including abnormalities of the ST-T wave (Liao et al. 1987, 1988). Although the Chicago Heart Association Detection Project suggested a limited relationship between ST-T wave abnormalities and CV outcomes in women, several other studies have shown that an abnormal resting ECG carries the same prognostic value for CV mortality in men and women. For example, in the Belgian Interuniversity Research on Nutrition and Health Study, asymptomatic women with ischaemic ECG findings were found to be at the same increased risk for CV mortality as men (De et al. 1998). In this large observation study of 4797 men and 4320 women aged 25–74 years, CV deaths attributable to an ischaemic ECG were estimated at 19.3% for men and 22.4% for women with the multivariate adjusted risk ratios of 2.45 (95% CI 1.7–3.53) for men and 2.16 (95% CI 1.30–3.58) for women.

Similar to abnormalities in 12-lead electrocardiography, the presence and extent of CAC has also been related to the risk for incident CHD outcomes. Data from multiple independent studies supports such a relationship, as summarized in a recent Clinical Expert Consensus Document from the American College of Cardiology (Greenland et al. 2007) and as also shown (Taylor et al. 2005) as a major prespecified aim (O'Malley et al. 1999) of the PACC Project. However, incident CHD outcomes in such studies of coronary atherosclerotic burden are uniformly limited to those arising from ischaemic heart disease – specifically non-fatal myocardial infarction, coronary death and coronary revascularization procedures.

In the setting of such similar relationships to CHD outcomes for ECG findings and CAC, it is notable that none of the available studies on CAC and CHD outcomes have adjusted for electrocardiographic abnormalities. Based on the findings from the current study suggesting no relationship of CAC with electrocardiographic abnormalities in healthy middle-aged individuals, future studies on the relationship between CAC and CV outcomes should examine whether the inclusion of ECG abnormalities improves the predictive power of models from such studies. Also notable is the absence of ECG findings in risk screening algorithms in widespread clinical use for predicting CHD including the Framingham risk score (Wilson et al. 1998) guidelines of the National Cholesterol Education Program (ATP III) (NCEP 2001) and PROCAM (Assmann et al. 2002).

Yet, broader clinical prediction tools, for example the Framingham risk algorithm that include outcomes beyond ischaemic heart disease such as congestive heart failure (Kannel et al. 1987) have included electrocardiographic variables such as left ventricular hypertrophy based upon its independent contribution to CV disease prognosis. The present study is a call to remain broad in our approach to screening for CV event risk, being mindful of the combined impact of myocardial and ischaemic heart disease on CV morbidity and mortality.

Limitations

The present data are derived from a healthy, middle-aged and predominantly male screening cohort and thus may not be generalizable across other populations. However, CV risk factors and a broad spectrum of potential abnormal ECG findings are prevalent in this cohort, as they are in general clinical populations. It is probable that the relationships between CAC and ECG findings would vary in older populations with more prevalent CV abnormalities, and more prolonged exposure to common risk factors (e.g. hypertension) as precursor conditions for both myocardial and ischaemic heart disease. However, a specific advantage of the PACC cohort is the narrow age range, thus effectively removing age as a confounding variable with collinear relationships to both CAC and ECG abnormalities. Lastly, the number of ethnic minorities in this study is low, among whom the prevalence and severity of coronary calcium can differ (Bild et al. 2005, Lee et al. 2003). Thus, broader study among ethnic groups of the relationship between CAC, ECG abnormalities and CV events is warranted.

Conclusions

This study in a middle-aged screening cohort found no significant relationships between electrocardiographic abnormalities and subclinical calcified atherosclerosis, both established biomarkers of CV risk. This finding suggests that the early expression of the effects of CV risk factors on either the myocardium or the coronary arteries may be distinct thereby enabling a complementary relationship in the prediction of CHD risk. Prevention programmes and prospective cohort studies should individually consider both the myocardial and coronary effects of risk factors in order to more fully identify their long-term relationships with CV morbidity and mortality.

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