Relationship between Resting Electrocardiographic Parameters and Estimated 10-Year Risk for Coronary Heart Disease in Healthy Adults in the USA

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Background: Little is known about the relationship between resting electrocardiogram (ECG) parameters and the incidence of coronary heart disease (CHD). We sought to establish the association between ECG parameters and estimated 10-year risk for CHD.

Methods: We applied the risk prediction algorithm used by the National Cholesterol Education Program Adult Treatment Panel III guidelines to data from 6399 individuals in the Third National Health and Nutrition Examination Survey (aged 40–79 years) who had sinus rhythm, no previous heart disease, and no evidence of prior myocardial infarction according to the 12-lead Minnesota Code. We used multiple linear and logistic regression models to determine the relationship between 10-year risk for CHD and levels of resting ECG parameters.

Results: After adjusting for age, gender, race, and body mass index, individuals with high risk had higher heart rate (HR), left ventricular mass index (LVMI), and cardiac infarction injury score (CIIS), and longer HR-corrected QT (QTc) interval than those with low risk. In models fully adjusted for coronary risk factors, individuals in the highest quintile of HR, PR, and QTc interval were 2.2, 0.7, and 1.8 times, respectively, more likely to have a high 10-year risk as those in the lowest quintiles. There are dose-dependent associations between HR, LVMI, CIIS, and QTc interval and the 10-year risk group.

Conclusions: These findings indicate that high HR, LVMI, and CIIS and prolonged QTc interval are positively and prolonged PR interval is negatively associated with high 10-year risk for CHD in a general population.

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Risk prediction models for coronary heart disease (CHD) have been developed to help clinicians estimate patients' absolute risk for developing CHD. The National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) guidelines adopted a modification of the risk prediction algorithm from the Framingham Heart Study that incorporates a patient's age, total cholesterol (TC) concentration, high-density lipoprotein

(HDL)-cholesterol concentration, smoking status, and systolic blood pressure (SBP) to estimate a person's 10-year risk for developing CHD.¹ Selected resting electrocardiogram (ECG) parameters, especially heart rate (HR)-corrected QT (QTc) interval, independently predict risk of and mortality owing to CHD in U.S. adults at high risk.² Prolonged QTc interval was associated with an increased risk of cardiovascular mortality and sudden death in the

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general population^{3–5} and in coronary artery disease.² However, little is known about the relationship between parameters in the resting ECG and the estimated 10-year risk for CHD. We sought to establish the relationship between ECG and the estimated 10-year risk for CHD to analyze whether ECG analysis may yield information that is independent from or additive to traditional risk factors in a general population.

METHODS

Data Source

We applied the risk prediction algorithm used by NECP/ATP III guidelines to data³ from 6399 participants in the Third National Health and Nutrition Examination Survey (NHANES III) (aged 40–79 years) who had sinus rhythm, no previous heart disease, and no evidence of prior myocardial infarction by 12-lead Minnesota Code. This study was conducted in 81 counties in the United States between 1988 and 1994, and subjects were selected to obtain a representative sample of the civilian, non-institutionalized population of the United States greater than 2-month old.^{3,4}

ECG Data

Resting 12-lead ECGs were obtained for the NHANES cohort with the Marquette MAC 12 system (Marquette Medical System, Inc., Milwaukee, WI, USA). An ECG coding scheme was then applied to the data to calculate a cardiac infarction injury score (CIIS) for each participant.^{5,6} The QT interval was corrected for HR using the Bazett method.^{7,8} NOVACODE ECG classification procedures were used to estimate the left ventricular mass index (LVMI) of study participants, and an LVMI of >150 g/m² for men and >120 g/m² for women, respectively, were used as cutoff points to define left ventricular hypertrophy (LVH).⁹

Covariates

We classified parameters used in 10-year risk status assessment for CHD as follows. Race was divided into three categories: white, black, and other. Smoking status was divided into three strata: current, former, and those who had never smoked. The presence of comorbidities was determined by participants' responses to the question: "Has the

doctor ever told you that you had diabetes, congestive heart failure, or chronic bronchitis?"

Statistical Analyses

The baseline characteristics of the study participants with moderate or high 10-year risk were compared to those of individuals with low 10-year risk group with a chi square test for binary variables and a *t*-test for continuous variables. To assess whether there was a gradient in various baseline demographic and clinical factors across the 10-year risk of CHD, we used a Mantel-Haenszel test for trend. For determining changes in ECG parameters by 10-year risk, we performed a weighted multiple linear regression analysis, with one degree of freedom, as a test for trend. We used a multiple logistic modeling technique to determine whether the 10-year risk of CHD was associated with various ECG parameters. In all of these models, we adjusted for age, gender, body mass index (BMI), race, and coronary risk factors. All tests were 2-tailed. Statistical analyses were carried out in STATA version 8.0 (StataCorp LP, College Station, TX, USA) using methods that accounted for the complex sample design of NHANES III. Continuous variables are shown as mean $\pm$ standard deviation unless otherwise indicated.

RESULTS

The baseline characteristics and laboratory profiles, based on the estimated 10-year risk, are summarized in Table 1. Compared with the low-risk group, patients in the high-risk group were older, more obese, and with increased SBP, diastolic blood pressure, glucose, TC, triglyceride, and low-density lipoprotein (LDL)-cholesterol levels.

ECG parameters according to estimated 10-year risk status are presented in Table 2. Compared with the low-risk group, levels of HR, PR interval, QTc interval, LVMI, and CIIS in the high 10-year risk individuals were significantly increased.

The beta coefficients and 95% confidence interval (CI) for the HR, QTc interval, LVMI, and CIIS levels are presented in Table 3. After adjustments for age, gender, BMI, and race, individuals in the high 10-year risk had HR, QTc interval, LVMI, and CIIS levels of 4.0 beats per minute (95% CI 3.2–4.8, $P < 0.0001$), 8.6 ms (7.0–10.3, $P < 0.0001$), 5.2 g/m² (3.7–6.8, $P < 0.0001$), and 1.77 (1.24–2.31,

Table 1. Baseline Characteristics and Laboratory Profiles

Variable	Total (n = 6399)	Estimated 10-Year Risk		
		Low (n = 2252)	Moderate (n = 2947)	High (n = 1200)
Age, years	57.0 ± 11.5	52.1 ± 10.0	57.2 ± 11.1*	63.5 ± 10.5*
Male sex, %	47.0	40.4	53.9*	42.6
White, %	71.9	71.3	73.2*	70.1
Current smoker, %	24.6	22.7	27.1	22.3
BMI, kg/m ²	27.9 ± 5.6	27.2 ± 5.5	27.8 ± 5.4*	29.3 ± 5.8*
DM, %	10.6	—	—	56.5*
SBP, mmHg	130.9 ± 18.8	117.4 ± 15.2	136.4 ± 14.6*	142.7 ± 19.8*
DBP, mmHg	76.9 ± 10.0	73.6 ± 9.0	79.4 ± 9.8*	76.6 ± 10.7*
Glucose, mmol/L	5.6 ± 1.12	6.1 ± 2.5	6.2 ± 2.5*	6.8 ± 3.3*
TC, mmol/L	5.62 ± 1.12	5.45 ± 1.07	5.66 ± 1.11*	5.84 ± 1.22*
Triglyceride, mmol/L	1.82 ± 1.48	1.60 ± 1.10	1.81 ± 1.32*	2.31 ± 1.02*
LDL-cholesterol, mmol/L	3.53 ± 0.99	3.43 ± 0.98	3.54 ± 0.98*	3.73 ± 1.02*
HDL-cholesterol, mmol/L	1.32 ± 0.40	1.29 ± 0.42	1.32 ± 0.46	1.33 ± 0.43*

Continuous variables are shown as mean ± standard deviation.

*P < 0.05 compared with low-risk group.

BMI = body mass index; DBP = diastolic blood pressure; DM = diabetes mellitus; SBP = systolic blood pressure; TC = total cholesterol.

P < 0.0001); these were higher, respectively, than those of individuals with low 10-year risk.

Table 4 shows the odds ratio (OR) and 95% CIs for having high 10-year risk by the quintile groups of ECG parameters. HR was categorized into the following quintiles: ≤59, 60–64, 65–70, 71–77, and ≥78 beats per minute. After adjustment for age, race, gender, BMI, SBP, smoking, and TC level, individuals in the highest two HR quintiles (fourth and fifth) were 1.65 and 2.20 times as likely to

have a high 10-year risk as those in the lowest quintile (95% CI 1.22–2.22, P = 0.001 and 1.65–2.92, P < 0.0001). PR interval was categorized into the following quintiles: <140, 140–154, 155–167, 168–182, and ≥ 183 ms. After adjustment, individuals in the longest PR interval quintiles (fourth and fifth) were 0.53 and 0.70 times more likely to have a high 10-year risk as those in the lowest quintile (95% CI 0.39–0.71, P = 0.001 and 0.52–0.94, P = 0.019). QTc interval was categorized into the

Table 2. Resting Electrocardiographic Parameters

Variable	Total (n = 6399)	Estimated 10-Year Risk		
		Low (n = 2252)	Moderate (n = 2947)	High (n = 1200)
Heart rate, beats per minute	68.7 ± 11.4	67.1 ± 10.8	69.2 ± 11.0*	70.6 ± 12.7*
PR interval, ms	162.2 ± 25.8	161.9 ± 25.2	161.1 ± 25.1	165.7 ± 27.7*
QRS duration, ms	97.0 ± 13.4	98.1 ± 12.4	99.1 ± 13.0*	97.9 ± 15.6*
QTc interval, ms	431.0 ± 23.7	427.1 ± 23.0	430.9 ± 23.2*	438.5 ± 24.7*
LVMI, g/m ²	104.8 ± 22.8	100.6 ± 21.0	106.5 ± 21.8*	108.5 ± 26.8*
LVH	9.3	6.6	8.6*	16.0*
CIIS	5.81 ± 7.39	4.76 ± 6.6	5.76 ± 7.24*	7.90 ± 9.63*
Left axis deviation	15.0	11.1	16.2*	23.8*

Continuous variables are shown as mean ± standard deviation.

*P < 0.05 compared with low risk group.

†Defined as LVMI of >150 g/m² for men and >120 g/m² for women.

CIIS = cardiac infarction injury score; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; QTc = heart rate-corrected QT.

Table 3. Crude and Adjusted Changes in ECG Parameters by 10-Year Risk Status

	Crude	P value	Adjusted	P value
Heart rate, bpm				
Moderate	1.9 (1.3, 2.5)	0.000	2.5 (1.9, 3.2)	0.000
High	3.4 (2.6, 4.1)	0.000	4.0 (3.2, 4.8)	0.000
P for trend	0.000		0.000	0.000
PR interval, ms				
Moderate	-0.6 (-0.2, 0.8)	0.376	-3.1 (-4.5, -1.7)	0.000
High	3.9 (2.2, 5.7)	0.000	-0.2 (-2.0, -1.7)	0.863
P for trend	0.001		0.136	
QRS duration, ms				
Moderate	0.2 (-0.4, 0.9)	0.469	-0.4 (-1.2, 0.4)	0.305
High	1.8 (0.8, 2.8)	0.000	0.7 (-0.3, 1.7)	0.180
P for trend	0.000		0.002	
QTc interval, ms				
Moderate	3.7 (2.5, 5.0)	0.000	4.4 (3.1, 5.6)	0.000
High	11.2 (9.6, 12.8)	0.000	8.6 (7.0, 10.3)	0.000
P for trend	0.000		0.000	
LVMI, g/m ²				
Moderate	6.2 (4.9, 7.4)	0.000	2.9 (1.7, 4.1)	0.000
High	7.8 (6.3, 9.4)	0.000	5.2 (3.7, 6.8)	0.000
P for trend	0.000		0.000	
CIIS				
Moderate	1.01 (0.60, 1.39)	0.000	0.34 (-0.06, 0.74)	0.000
High	3.10 (2.59, 3.60)	0.098	1.77 (1.24, 2.31)	0.000
P for trend	0.000		0.000	

Each cell contains the β -coefficient (95% CI) of each variable, adjusted for age, gender, body mass index, and race. Reference group: low-risk group.

CIIS = cardiac infarction injury score; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; QTc = heart rate-corrected QT.

following quintiles: ≤ 409 , 410–423, 424–435, 436–450, and ≥ 451 ms. Individuals in the highest QTc quintiles were 1.75 times more likely to have a high 10-year risk as those in the lowest quintiles (95% CI 1.29–2.37, $P < 0.0001$).

DISCUSSION

Using a large representative sample of the U.S. population, this study showed that individuals with high estimated 10-year risk for CHD by the

Table 4. Odds Ratios of Having High 10-Year Risk by Quintiles of ECG Parameters

Variable	Age, Race, Sex, and BMI Adjusted	P Value	Multivariate Adjusted*	P Value
Heart rate, beat per minute				
Q4, 71–77	1.68 (1.30–2.18)	<0.0001	1.65 (1.22–2.22)	0.001
Q5, 78–	2.67 (2.09–3.42)	<0.0001	2.20 (1.65–2.92)	<0.0001
PR interval, ms				
Q4, 168–182	0.81 (0.62–1.04)	0.101	0.53 (0.39–0.71)	<0.0001
Q5, 183–	0.98 (0.76–1.27)	0.894	0.70 (0.52–0.94)	0.019
QTc interval, ms				
Q4, 436–450	1.81 (1.39–2.38)	<0.0001	1.26 (0.92–1.71)	0.149
Q5, 451–	3.10 (2.38–4.05)	<0.0001	1.75 (1.29–2.37)	<0.0001

Each cell contains the relative odds (95% CI) for each variable.

*Adjusted for age, race, gender, BMI, SBP, smoking status, and TC.

Q4 = fourth quintile; Q5 = fifth quintile.

BMI = body mass index; QTc = heart rate-corrected QT; SBP = systolic blood pressure.

NCEP/ATP III guideline had higher HR, LVMI, and CIIS, and shorter PR interval and longer QTc interval than those with low risk. There are dose-dependent associations between HR, LVMI, CIIS, and QTc intervals and the 10-year risk group after multivariate analysis, including conventional coronary risk factors.

Our results correspond with data suggesting that a prolonged QTc interval is a strong predictor of incident CHD.² In the Zutphen prospective cohort study in the general population, men with QTc of 420 ms or higher had an elevated risk for myocardial infarction and even greater risks for CHD mortality and sudden death.¹⁰ In the Rotterdam Study, an abnormally prolonged QTc interval was associated with a more than twofold increased risk of sudden cardiac death during an average follow-up period of 6.7 years.³ In the present study, the highest quintile of QTc interval was also associated with a two- to threefold increased 10-year risk (an age, race, gender, and BMI-adjusted OR of 3.10; 95% CI 2.38–4.05; and a multivariate-adjusted OR of 1.75, 95% CI 1.29–2.37).

The CIIS and LVH are associated with risk of CHD, and are also predictors for long-term mortality in apparently healthy individuals.^{6,11,12} According to the Zutphen study, in both middle-aged and elderly men with a CIIS >20, 5-year relative risks were 2.2 (95% CI 1.2–4.1) for angina pectoris, 2.4 (1.4–4.0) for myocardial infarction and 5.8 (3.4–9.9) for death by CHD relative to men with CIIS <5.¹¹ In the present study, CIIS and LVMI in the high-risk group were higher than those in the low-risk group, and after adjustment there were dose-dependent differences across risk groups, as shown in Table 3.

Although the importance of resting HR as a prognostic factor has not been recognized, recent epidemiologic studies have confirmed resting HR as an independent predictor of cardiovascular and all-cause mortality in men and women with and without cardiovascular disease.¹² Excess cardiovascular deaths in those with more rapid HRs, excluding those with interim development of overt cardiovascular disease, were noted, suggesting an effect independent of preexisting cardiac damage.¹³ It was also reported that the minimum HR was faster in the patients with marked progression than in those with regression of focal coronary atherosclerosis.¹⁴ It has been reported that the average 24-hour HR measured with 24-hour ambulatory ECGs in patients with heart disease and sinus rhythm is an

independent risk factor for new coronary events.¹⁵ In the present study, the HR of individuals with high 10-year risk was faster than that of individuals with low 10-year risk and after adjustment, high HR was positively associated with high 10-year risk for CHD in a general population. Conversely, prolonged PR interval is negatively associated with high 10-year risk group. This may be related to the observation that the high-risk group had a high HR, which would be associated with increased sympathetic tone.

This study used data from a nationally representative sample, so the results can be generalized to the entire U.S. population. Our results are also consistent with data suggesting that some resting ECG parameters are independently associated with a high 10-year risk for CHD. Although we adjusted for potential confounders, unknown or residual confounders may possibly exist.

In conclusion, these findings indicate that some resting ECG parameters such as HR, LVMI, CIIS, and QTc interval are associated with the estimated 10-year risk for CHD, which suggests that the assessment of resting ECG parameters may potentially yield information that is additional to the analysis of traditional coronary risk factors in a general population.

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