Relation of Minor Electrocardiographic Abnormalities to Cardiovascular Mortality

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Although minor electrocardiographic (ECG) abnormalities are common findings in clinical practice, their prognostic significance remains unclear due to inconsistent reports. We hypothesized that this inconsistency is due to the traditional focus on examining their prognostic significance as a binary variable (i.e., presence vs absence of any abnormality) ignoring the number of abnormalities. We tested this hypothesis in 6,467 participants (mean age 59 years, 53% women) from the Third National Health and Nutrition Examination Survey who were free of baseline cardiovascular disease (CVD) and major ECG abnormalities. ECG abnormalities were defined from digitally recorded and centrally processed standard electrocardiograms using the Minnesota ECG Classification. CVD mortality was ascertained using National Death Index. About 38% of participants (n = 2,438) had at least 1 minor ECG abnormality at baseline. During a median follow-up of 13.9 years, 755 CVD deaths occurred. In a multivariable Cox model, presence of at least 1 minor ECG abnormality was marginally associated with increased risk of CVD mortality (hazard ratio (95% confidence interval):1.15(1.00,1.34), p-value = 0.04)). However, as the number of ECG abnormalities increases, the association with CVD mortality showed a dose-response relation (event rate per 1,000 person-year of 7.3, 10.1, and 16.7 in participants with 0, 1, and ≥2 ECG abnormalities, respectively; p-value for trend <0.01). Also, each additional minor ECG abnormality was associated with a 13% increased risk of CVD mortality (hazard ratio (95% confidence interval): 1.13(1.04, 1.24)). In conclusion, the number, not only the mere presence of minor ECG abnormalities should be taken into account to understand the prognostic significance of these common findings. **(Am J Cardiol 2019;123:1443−1447)**

Asymptomatic minor abnormalities are common findings on screening electrocardiogram (ECG).[1] Although studies have shown consistent associations between major ECG abnormalities and cardiovascular disease (CVD) mortality,[2−6] the prognostic significance of minor ECG abnormalities remains unclear. While multiple studies have shown a significant association between minor ECG abnormalities and CVD mortality,[7−12] several others have shown no association.[2,13,14] Although these studies used a comparable standard ECG classification method to define ECG abnormalities. Notably, however, these studies focused only on examining the prognostic significance of minor ECG abnormalities as a binary variable, ignoring the quantitative aspect of these abnormalities. That is to say, previous studies focused on the prognostic significance of presence versus absence of minor ECG abnormalities[8,15,16] alone, while ignoring the contribution of the number of abnormalities, which may explain some of the inconsistent findings in studies. Therefore, we examined the association between the number as well as the presence (vs absence) of minor ECG abnormalities and CVD mortality.

Methods

The Third National Health and Nutrition Examination Survey (NHANES-III) is a periodic survey of a representative sample of the noninstitutionalized US civilian population designed to characterize the health of the population and inform estimates of disease prevalence. The NHANES-III protocol was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board. Written informed consent was obtained from all participants for the original study.

Of the 8,561 participants enrolled in the NHANES-III survey who had a 12-lead screening ECG, we excluded those with baseline CVD (heart failure, stroke, and coronary heart disease) defined by self-reported medical history, any major ECG abnormalities defined by Minnesota ECG Classification,[17] or missing covariates. A total of 6,467 participants met the inclusion criteria and were included in this analysis.

NHANES-III baseline data was collected between 1988 and 1994 during an in-home interview followed by a mobile examination center. The data collected included a complete medical history, demographic information, and social history. A physical exam was conducted, from which

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body mass index was calculated. Obesity was defined as body mass index >30 kg/m^2. Blood pressure readings were averaged from measurements obtained during the in-home evaluation and again at the mobile examination center. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of blood pressure lowering medications. Serologic testing included total serum cholesterol level, hemoglobin A1c, and fasting glucose. Diabetes was defined as fasting plasma glucose ≥126 mg/dl, a hemoglobin A1c ≥6.5%, or a history of using glucose-lowering medication.

Twelve-lead ECGs were obtained for each participant at their mobile examination center visit. ECGs were recorded by trained technicians using Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, Wisconsin). In a central ECG core laboratory, the 12-lead ECGs underwent computerized automated analysis followed by visual inspection of outlier values by a trained technician. The ECGs were then analyzed at the Epidemiological Cardiology Research Center of Wake Forest School of Medicine (Winston-Salem, North Carolina) for abnormalities. The Minnesota Code for ECG classification was used to classify minor ECG abnormalities. Minor ECG abnormalities included minor isolated Q-wave abnormalities (MC 1.3.x), minor isolated ST/T-wave abnormalities (MC 4.3, MC 4.4, MC 5.3, MC 5.4), high R waves/increased QRS voltage denoting left or right ventricular hypertrophy without strain pattern (MC 3.1, MC 3.2, MC 3.3, MC 3.4), nonischemic ST segment elevation (MC 9.2), incomplete bundle branch block [incomplete left bundle branch block (MC 7.6), incomplete right bundle branch block (MC 7.3), and left anterior hemiblock (MC 7.7)], minor QT prolongation (QT index> 112% but <116%), short PR interval (MC 6.5), left axis deviation (MC 2.1), right axis deviation (MC 2.2), ventricular premature beats (MC 8.1.2, MC 8.1.3), and other minor abnormalities (low QRS voltage [MC 9.1], premature atrial ectopic beats [8.1.1], wandering atrial pacemaker [8.1.4], abnormal P-wave amplitude [MC 9.3], prolonged PR interval/first-degree atrioventricular block [MC 6.3], marked sinus bradycardia [MC 8.8], and marked sinus tachycardia [MC 8.7]).[17]

Mortality data for NHANES-III participants was obtained through December 31, 2006. The National Death Index in conjunction with a probabilistic matching algorithm based on 12 identifiers, which included social security, gender, and date of birth, was used to link death information from the National Death Index with participants. The follow-up interval was defined as the time between the NHANES-III examination and whichever of the following came first: December 31, 2006, date of death, or date of censoring. CVD mortality was defined using the International Classification of Diseases, Tenth Revision codes 100-178. Those participants who were unable to be matched with a death record were considered to be alive throughout the follow-up period. Further details about matching methodology and ascertainment of mortality in NHANES-III are available at the Centers for Disease Control and Prevention website (http://www.cdc.gov/nchs/data/datalinkage/matching_methodology_nhanes3_final.pdf).

Participant characteristics for those with normal ECG, 1 minor ECG abnormality, and 2 or more minor ECG abnormalities were compared using the analysis of variance for continuous variables and chi-square test for categorical variables. The CVD mortality rates per 1,000 person-year in participants with normal ECG, 1 minor ECG abnormality, and 2 or more minor ECG were calculated and Kaplan-Meier plots were generated to graphically describe the probability of event-free survival over time. Three separate sets of multivariate-adjusted Cox proportional hazard models were constructed to examine the risk of CVD mortality associated with: (1) presence of 1 minor ECG abnormality, and presence of ≥2 minor ECG abnormalities versus presence of 0 minor ECG abnormality (i.e., normal ECG); (2) per each one additional ECG abnormality; and (3) individual minor ECG abnormalities (presence vs absence of each individual ECG abnormality). Models were initially adjusted for age, sex, and race (Model 1) then further adjusted for hypertension, diabetes, current smoking, obesity, chronic obstructive pulmonary disease and dyslipidemia (Model 2). The analysis of individual minor ECG abnormalities (presence vs absence of each individual ECG abnormality) was additionally adjusted for other minor ECG abnormalities (Model 3). Statistical significance was defined as $p \leq 0.05$. Data was analyzed using SAS, version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

A total of 6,467 participants (mean age 58.9, 53% women, 49% non-Hispanic whites) were included in this analysis. At baseline, 2,438 (37.7%) of the participants had at least 1 minor abnormality, of whom 1,758 (27.1% of the total sample) had only 1 abnormality, and 680 (10.5% of the total sample) had 2 or more abnormalities (558 participants had 2 abnormalities, 110 had 3 abnormalities and 12 participants had 4 abnormalities). Table 1 shows the baseline characteristics stratified by presence (1 minor ECG abnormality, and 2 or more minor ECG abnormalities) and absence of ECG abnormalities; normal ECG). As shown, participants with normal a baseline ECG compared with those who had minor ECG abnormalities were more likely to be younger, women, non-Hispanic white and with less prevalent CVD risk factors (hypertension, diabetes, current smoker).

During a median follow-up of 13.9 years, 755 participants died from CVD. In a multivariable Cox model, presence of at least 1 minor ECG abnormally was marginally associated with increased risk of CVD mortality (p-value = 0.04). However, as the number of ECG abnormalities is taken into account, the association with CVD mortality becomes more apparent in a dose-response relation (Table 2). As shown in Table 2, the CVD mortality rates were exponentially increasing from 7.3 to 10.1 to 16.7 events per 1,000-person-years as the number of ECG abnormalities increased from 0 to 1 to ≥2 ECG abnormalities, respectively. Similar dose-response associations were observed in the Cox models where the reference group was normal ECG (i.e., no ECG abnormalities), and each additional minor ECG abnormality was associated a 13% increased risk of CVD mortality (p-value = 0.002). Figure 1

Table 1
Baseline characteristics stratified by ECG abnormalities

Characteristics (% or mean ± SD)	Normal ECG n = 4,029	1 minor ECG abnormality n = 1,758	≥2 minor ECG abnormalities n = 680	p value*
Age (years)	56.9 ± 12.8	59.8 ± 13.1	62.5 ± 13.5	<0.001
Women	55.2%	50.2%	48.8%	<0.001
Non-Hispanic white	50.7%	47.0%	45.8%	0.007
Hypertension	27.6%	37.6%	46.6%	<0.001
Diabetes mellitus	8.9%	11.2%	12.9%	<0.001
Current smoker	21.6%	25.2%	24.4%	0.007
Obesity	19.5%	18.1%	17.6%	0.29
Chronic obstructive pulmonary disease	6.1%	5.9%	7.5%	0.34
Dyslipidemia	23.6%	23.9%	18.0%	0.004

* p Value as calculated by ANOVA for continuous and chi-square for categorical variables.Diabetes was defined as fasting plasma glucose ≥126 mg/dl, a hemoglobin A1c ≥6.5%, or use of glucose-lowering medicationsHypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 or use of blood pressure lowering medicationsObesity was defined as body mass index >30 kg/m^{2}Dyslipidemia was defined as total cholesterol >240 mg/dl or low-density lipoprotein (LDL) >160 mg/dl or high-density lipoprotein (HDL) <40 mg/dl or use of cholesterol-lowering medications.

shows the Kaplan-Meier survival probability curves stratified by ECG status over time.

The most common individual ECG abnormality is isolated minor ST/T abnormalities (n = 768; 11.9%), followed by high R wave (n = 583; 9.0%), then incomplete bundle branch block/nonspecific QRS prolongation (n = 332; 5.1%) and minor QT prolongation (n = 331; 5.1%). In these individual ECG abnormalities, only the association of presence (vs absence) of isolated minor ST/T abnormalities with CVD mortality reached and maintained statistical significance in multivariable adjusted models (Table 3).

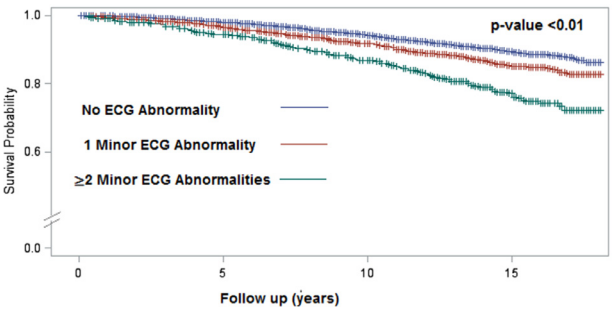

Figure 1. Kaplan-Meier curves for cardiovascular mortality stratified by the number of minor ECG abnormalities. ECG = electrocardiographic.

Discussion

In this analysis of the NHANES-III, we examined the association between the number and the presence of minor ECG abnormalities, separately, with the risk of CVD mortality. The key findings are: (1) At least 1 in every 3 participants (37.7%) of our study population who were free of CVD had at least 1 minor ECG abnormality; (2) presence versus absence of minor ECG abnormality was marginally associated with CVD mortality; (3) When the number of minor ECG abnormalities was taken into account, the association with CVD mortality showed a dose-response relation; (4) There are marked differences in the prevalence of individual minor ECG abnormalities, with the most common abnormality showing the strongest association with CVD mortality.

These findings suggest that the number of minor ECG abnormalities, not only their mere presence, should be taken into account to both understand the prognostic significance of these common findings and to enhance the potential role of ECG to identify individuals at risk. Some of the inconsistencies in previous reports may be explained by the lack of accounting for the wide variations in the prevalence of individual minor abnormalities, which seems to impact their prognostic significance, rather than solely focusing on the marginally significant risk of CVD mortality associated with presence versus absence of specific minor ECG abnormalities. That is to say, slight changes in the prevalence of

Table 2
Association between number of minor ECG abnormalities and cardiovascular mortality

ECG abnormalities (n)	Event rate (per 1,000 person-years)	Model 1* HR (95% CI)	p value	Model 2† HR (95% CI)	p value
No abnormalities (normal ECG)	7.3	Reference	–	Reference	
Presence of any ECG abnormality	8.89	1.24 (1.07-1.43)	0.003	1.15 (1.00-1.34)	0.04
0 abnormality (normal ECG)	7.3	Reference	–	Reference	
1 minor ECG Abnormality	10.1	1.11 (0.95−1.31)	0.17	1.06 (0.89−1.25)	0.49
≥2 minor ECG Abnormalities	16.7	1.53 (1.25−1.86)	<0.001	1.38 (1.13−1.69)	0.001
Per each one additional abnormality	–	1.19 (1.09−1.29)	<0.001	1.13 (1.04−1.24)	0.002

* Model 1 adjusted for age, sex, and race.
† Model 2 adjusted for model 1 plus hypertension, diabetes, current smoking, chronic obstructive pulmonary disease, obesity, and dyslipidemia.

Table 3
Association between individual minor ECG abnormalities with cardiovascular mortality

ECG abnormality*	Event/participant (n)	Model 1†	*p value*	Model 2‡	*p value*	Model 3§	*p value*
Isolated Q/QS waves	37/180	1.31 (0.94,1.83)	0.10	1.26 (0.90,1.76)	0.16	1.23 (0.88-1.73)	0.21
Isolated ST/T	144/768	1.35 (1.13-1.63)	0.001	1.25 (1.04-1.50)	0.01	1.22 (1.00-1.47)	0.03
High R waves	91/583	1.26 (1.01-1.57)	0.03	1.23 (0.99-1.54)	0.05	1.19 (0.94-1.49)	0.13
ST segment elevation	9/104	1.26 (0.65-2.44)	0.48	1.36 (0.70-2.65)	0.35	1.31 (0.67-2.57)	0.42
Incomplete BBB	39/332	1.01 (0.73-1.39)	0.95	0.90 (0.65-1.25)	0.56	0.89 (0.64-1.24)	0.50
QT prolongation	55/331	1.16 (0.88-1.53)	0.28	1.07 (0.81-1.41)	0.63	1.04 (0.78-1.38)	0.77
Short PR interval	18/157	1.29 (0.80-2.06)	0.28	1.36 (0.84-2.17)	0.20	1.34 (0.8-2.16)	0.21
Left axis deviation	45/217	1.16 (0.86-1.58)	0.32	1.15 (0.84-1.56)	0.36	1.14 (0.83-1.55)	0.40
Right axis deviation	21/200	1.33 (0.86-2.05)	0.19	1.12 (0.72-1.75)	0.59	1.19 (0.76-1.88)	0.43
Ventricular ectopic beats	21/86	1.16 (0.75-1.80)	0.49	1.06 (0.68-1.65)	0.77	1.07 (0.68-1.67)	0.75
Other abnormalities	48/291	1.07 (0.79-1.43)	0.65	1.05 (0.78-1.42)	0.70	1.04 (0.77-1.40)	0.76

* Incomplete bundle branch block (BBB) includes incomplete left bundle branch block, incomplete right bundle branch block and left anterior hemiblock. Other abnormalities include low QRS voltage, premature atrial ectopic beats, wandering atrial pacemaker, abnormal P-wave amplitude, prolonged PR interval/first-degree atrioventricular block, marked sinus bradycardia, and marked sinus tachycardia. High R waves denote right ventricular hypertrophy and left ventricular hypertrophy without strain pattern.

† Model 1 adjusted for age, sex, and race.

‡ Model 2 adjusted for model 1 plus hypertension, diabetes, current smoker, obesity, chronic obstructive pulmonary disease, and dyslipidemia.

§ Model 3 adjusted for model 2 plus other minor ECG abnormalities.

the overall minor abnormalities as presence versus absence or the distributions of the individual abnormalities may shift such marginally significant risk in some studies to be insignificant in other studies. This issue would not be of importance if the number of minor abnormalities is taken into account since the strength of association of the number of minor abnormalities will strengthen the power to detect differences.

Our findings regarding the high prevalence of asymptomatic minor abnormalities on screening ECG is in agreement with findings from studies conducted on similar populations using the same ECG classification system.[12,18,19] Also, similar to our study, several studies have shown that minor isolated ST/T abnormalities are the most frequent minor ECG abnormality[19-21] and that they are associated with higher risk of CVD mortality.[8,15,22–25] However, to our knowledge, no previous study has examined the association between the number of minor ECG abnormalities and CVD mortality.

The potential mechanism by which minor ECG abnormalities are predictive of CVD mortality is not entirely clear. However, minor ECG abnormalities are likely markers of subclinical cardiac dysfunction. Subclinical cardiac dysfunction may be secondary to subclinical myocardial ischemia, conduction defects, arrhythmias, structural heart disease, or cardiac remodeling secondary to systemic disease such as hypertension. This idea is supported by previous work which showed that isolated minor ECG abnormalities were associated with higher rates of impaired left ventricular relaxation and left ventricular hypertrophy.[26] Furthermore, isolated ECG abnormalities have also been associated with arrhythmia-related cardiac mortality.[16] Minor ECG abnormalities may also be indicative of systemic disease causing subclinical effects on cardiac function. This idea is supported by a study which showed that minor ECG abnormalities were associated with increased common carotid intima-media thickness.[25] Common carotid intima-media thickness, in turn, has been associated with an increased risk of myocardial ischemia, stroke, and death.[27]

Our study has some limitations. Although we adjusted for potential confounders, residual confounding remains a possibility, as in other studies with similar design. Given the long follow-up, it is possible that participants may have changed their health behaviors, which in turn may have influenced their overall health and mortality. Finally, NHANES did not have serial ECG data during multiple visits, which could be used to examine the natural history of minor ECG abnormalities and the impact of changes over time on CVD mortality. The strengths of our study include the large sample size, community-based population, long-term follow-up, digitally recorded and centrally processed ECG data, use of standard ECG Classification, and use of well-ascertained hard outcomes. These strengths enabled us to show for the first time the importance of the number, not only the presence, of minor ECG abnormalities as predictors of CVD mortality. These findings further add to the potential of ECG to identify individuals at increased risk of CVD. Identifying which combination of minor ECG abnormalities matters most is an important piece of information that could be the subject of further research.

Disclosures

The authors have no conflicts of interest to disclose.

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