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Electrocardiogram as a predictor of sudden cardiac death in middle-aged subjects without a known cardiac disease ☆

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ABSTRACT

Background: Abnormal 12 lead electrocardiogram (ECG) findings and proposing its ability for enhanced risk prediction, majority of the studies have been carried out with elderly populations with prior cardiovascular diseases. This study aims to denote the association of sudden cardiac death (SCD) and various abnormal ECG morphologies using middle-aged population without a known cardiac disease.

Methods: In total, 9511 middle-aged subjects (mean age 42 ± 8.2 years, 52% males) without a known cardiac disease were included in this study. Risk for SCD was assessed after 10 and 30-years of follow-up.

Results: Abnormal ECG was present in 16.3% (N = 1548) of subjects. The incidence of SCD was distinctly higher among those with any ECG abnormality in 10 and 30-year follow-ups (1.7/1000 years vs. 0.6/1000 years, P < 0.001; 3.4/1000 years vs. 1.9/1000 years, P < 0.001). At 10-year point, competing risk multivariate regression model showed HR of 1.62 (95% CI 1.0–2.6, P = 0.05) for SCD in subjects with abnormal ECG. QRS duration ≥ 110 ms, QRST-angle > 100°, left ventricular hypertrophy, and T-wave inversions were the most significant independent ECG risk markers for 10-year SCD prediction with up to 3-fold risk for SCD. Those with ECG abnormalities had a 1.3-fold risk (95% CI 1.07–1.57, P = 0.007) for SCD in 30-year follow-up, whereas QRST-angle > 100°, LVH, ER ≥ 0.1 mV and ≥0.2 mV were the strongest individual predictors. Subjects with multiple ECG abnormalities had up to 6.6-fold risk for SCD (P < 0.001).

Conclusion: Several ECG abnormalities are associated with the occurrence of early and late SCD events in the middle-age subjects without known history of cardiac disease.

1. Introduction

The annual incidence of sudden cardiac death (SCD) in the United States is estimated to be as high as 450,000 cases (which accounts approximately 63% of all cardiac deaths) and the majority of SCD events occur in asymptomatic subjects considered to be at low- or intermediate risk for SCD [1–3]. Thus, improvements in risk stratification are urgently required and as SCD is primarily a result of electrical disturbance of the normal cardiac rhythm, 12 lead electrocardiogram (ECG) is still an attractive non-invasive tool beyond clinical factors. In ideal circumstances, health care professionals would have simple tools for overall SCD risk evaluation combining genetic and demographic information to clinical data, such as12 lead electrocardiogram (ECG) and echocardiography.

Risk prediction models for SCD and individual ECG abnormalities associated with SCD have been described earlier in numerous papers, but they have mainly been carried out in elderly populations and/or with patients with cardiovascular disease [4–10]. We aimed to clarify the prognostic significance of abnormal ECG findings in middle-aged subjects without known cardiac disease.

2. Methods

The Finnish Mobile Health Examination Survey, a large nationwide study was carried out in Finland between 1966 and 1972 [11]. As a

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[2] Authors have contributed for gathering the data used in this study.

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Table 1
Characteristics of subjects at baseline.

	Normal ECG (N = 7963)	Any ECG abnormality (N = 1548)	P value
Males (%)[a]	50.8	63.0	<0.001
Age (years)[b]	42.8 ± 8.1	44.5 ± 8.6	<0.001
Current smoker (%)[c]	33.9	38.2	0.001
Diabetes (%)[c]	1.3	1.9	0.369
Cholesterol (mmol/l)[c]	6.46 ± 1.3	6.49 ± 1.3	0.695
BMI (kg/m^2)[c]	25.8 ± 3.7	25.2 ± 3.6	0.001
Systolic blood pressure (mmHg)[c]	135 ± 19	144 ± 23	<0.001

[a] Adjusted for age.
[b] Adjusted for gender.
[c] Adjusted for age and gender.

part of this, The Coronary Heart Disease study (CHD study) was performed using 12 different geographical regions in Finland. Men and women aged 31 to 61 were invited to participate (N = 12,310, participation rate 89%). Age, body mass index (BMI), cholesterol, blood pressure, 12 lead ECG as well as health questionnaire concerning current and prior health status (smoking, medications used, pain, chronic diseases etc.) were obtained as described earlier [12]. Overall, 10,904 ECGs were available for this study. Study was carried out following ethical guidelines and principals of the Declaration of Helsinki.

As this study focused on abnormal ECG findings in subjects without a known cardiac disease, exclusion was based on reported information and certain ECG findings. The exclusion criteria were identical to our previous study [12]. In brief, unreadable or missing ECGs, patients with atrial fibrillation, Wolf-Parkinsonson-White ECG pattern or pacemaker rhythm were excluded. Subject with a known cardiac disease (N = 895, information based on self-reported history of cardiac symptoms or medication, national registries using International Classification of Diseases (ICD) as well as the National Drug Reimbursement Registry maintained by the Finnish National Social Insurance Institution), symptoms of cardiac disease (N = 245) and those using cardiac medication (N = 253) were discounted from the analysis. The total of 9511 subjects (77.3% of the original population) were included in this study.

All participants had 12 lead ECG recordings at baseline (paper speed 50 mm/s). Abnormal ECG findings were defined as: 1) QRS duration over 110 ms (interpreted from leads II or V5); 2) QRST angle over 100°; 3) QTc interval over 440 ms/460 ms (men/women); 4) left ventricular hypertrophy ([LVH] defined by Sokolow-Lyon criteria or Romhilt-Estes point score ≥ 5); 5) early repolarization (ER ≥ 0,1 mV and ER ≥ 0,2 mV) in inferior/lateral leads with descending or horizontal ST-segment; 6) T-wave inversions (≥1.0 mm deep in other leads than aVR, Minnesota codes 5.1 to 5.2).

The death certificate diagnoses, assigned by the physician responsible for the care at the time of death, was obtained from the Causes of Death Registry which is maintained by the Statistics of Finland. These certificates were manually studied by a committee of experienced cardiologists unaware of the data analysis. Events of SCD were defined as arrhythmic according to the Cardiac Arrhythmia Pilot Study, criteria being described earlier in detail [13,14]. The primary endpoint was SCD during a follow-up of 30 years and secondary endpoint was SCD in 10 years of follow-up.

Continuous variables are presented as means ± standard deviation (SD). We used the Fine and Gray competing risk model for assessment of adjusted and unadjusted hazard ratios (HR) and 95% confidence intervals (95% CI). Adjustments in multivariate model included age, gender, systolic blood pressure, smoking, body mass index (BMI), diabetes, blood cholesterol and smoking. In baseline, diabetes was screened with a one-hour glucose tolerance test and urine sample, if not diagnosed earlier. For further assessment of risk prediction value, we used the Integrated Discrimination Increment (IDI) analysis and C-statistics. The log-rank test was used in our Kaplan-Meier graphs. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, version 24, IBM SPSS Statistics, Armonk, NY) and R Statistics (3.4.1, The R Foundation for Statistical Computing, Vienna, Austria). Two-sided P-values < 0.05 were considered significant.

3. Results

The demographic comparison of the groups is presented in Table 1. After exclusions, a total of 9511 subjects included in the analyses. A total of 1548 had at least one ECG abnormality present (test group). A total of 73 subjects suffered SCD in 10-year follow-up and 641 in 30-year follow-up. The incidence of SCD in the test group at 10-year point was 1.7/1000 years compared to 0.6/1000 years in the reference group. Incidences were 3.4/1000 years and 1.9/1000 years during the 30-year follow-up, respectively. The negative predictive value of normal ECG in 10-year follow-up was 99.4%.

3.1. 10-year analysis

The competing risk regression model (adjusted and unadjusted) for 10-year events is presented in Table 2. In the 10-year analysis the univariate yielded a 2.86 HR (95% CI 1.77–4.62, P < 0.001) and the multivariate 1.62 (1.00–2.62, P = 0.052) for those with abnormal ECG. The strongest predictors of SCD in multivariate analysis were QRS ≥ 110 ms (HR 3.09, 95% CI 1.27–7.52, P = 0.013), QRST-angle > 100° (HR 3.4, 95% CI 1.37–8.44, P = 0.009), LVH (HR 2.67, 95% CI 1.42–5.01, P = 0.002) and T-wave inversions (HR 2.98, 95% CI 1.30–6.79 P = 0.010). Subjects with ER ≥0.2 mV had no SCD events during this period, furthermore prevalence being only 40. The survival curves for SCD events is presented in Fig. 1. For predicting non-sudden cardiac death, abnormal ECG did not increase the risk in multivariate adjusted regression model (HR 1.10, 95% CI 0.87–1.38, P = 0.440).

To determine the risk prediction value of abnormal ECG further, we used the C-index and IDI analysis. Original model included known risk factors of cardiac disease: age, gender, systolic blood pressure, diabetes and smoking. After adding abnormal ECG variable to the original model, the C-index showed no significant improvement in risk prediction for SCD, whereas the IDI analysis showed a minor improvement in risk prediction (IDI 0.0033, P = 0.032).

Table 2
Competing risk regression model and hazard ratios (HR), 10-year follow-up.

	Univariate HR	P-value	Multivariate HR[a]	P-value
Normal ECG (N = 7963)	1.0	1.0	1.0	1.0
Any ECG abnormality (N = 1548, 16.3%)	2.86 (1.77–4.62)	<0.001	1.62 (1.00–2.62)	0.052
QRS duration > 110 ms (N = 110, 1.2%)	6.44 (2.59–16.00)	<0.001	3.09 (1.27–7.52)	0.013
QTc (N = 534, 5.6%)	2.68 (1.38–5.22)	0.004	1.26 (0.64–2.48)	0.500
QRST-angle > 100° (N = 125, 1.3%)	5.61 (2.26–13.90)	<0.001	3.40 (1.37–8.44)	0.009
LVH (N = 395, 4.2%)	5.07 (2.78–9.23)	<0.001	2.67 (1.42–5.01)	0.002
ER ≥ 0,1 mV (N = 351, 3.7%)	1.12 (0.35–3.55)	0.850	0.86 (0.27–2.72)	0.800
ER ≥ 0,2 mV (N = 40, 0,4%)	0.00 (0–0)	N/A	0.00 (0–0)	N/A
T-wave inversion (N = 284, 3,0%)	4.05 (1.94–8.45)	<0.001	2.98 (1.30–6.79)	0.010

[a] Adjusted for age, gender, systolic blood pressure, diabetes, BMI and cholesterol. ECG = electrocardiogram, ER = early repolarization, HR = hazard ratio, LVH = left ventricular hypertrophy, QTc = heart rate corrected QT interval. HRs for ER > 0.2 mV were not possible to analyze as no events occurred in this group during the 10-year follow-up.