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 1.0-1.100 years vs. 1.57, P = 0.007) for SCD in 30-year follow-up, whereas 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.

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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 as 12 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
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-Parkinson-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° (interpreted from lead V1); 3) QTc interval over 440 ms/460 ms (men/women); 4) 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.

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 1.5/1000 years during the 30-year follow-up, respectively. The negative predictive value of normal ECG in 10-year follow-up was 99.4%.

### 3. Results

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 2.62, 95% CI 1.30–5.42, 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 IDA analysis showed a minor improvement in risk prediction (IDI 0.0033, P = 0.032).

### 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)d | 6.46 ± 1.3 | 6.49 ± 1.3 | 0.695 |
| BMI (kg/m²)d | 25.8 ± 3.7 | 25.2 ± 3.6 | 0.001 |
| Systolic blood pressure (mmHg)d | 135 ± 19 | 144 ± 23 | -0.001 |

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

### Table 2

| Competing risk regression model and hazard ratios (HR), 10-year follow-up. | Univariate HR | P-value | Multivariate HR* | 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 |

* 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.
and subjects with ≥2 ECG abnormalities, the C-index showed a minor but not significant improvement for SCD risk prediction (10-year analysis: 0.821 vs 0.823, P = 0.662; 30-year analysis: 0.755 vs 0.758, P = 0.153, respectively).

In addition, when prolonged QRS complex (QRS ≥ 110 ms) was accompanied by any of the measured ECG abnormalities (N = 110), the risk for SCD was 6.6-fold (95% CI: 2.6–16.3; P < 0.001) in the 10-year follow-up and 2.9-fold (95% CI: 1.7–5.0) in the 30-year follow-up. After adjustments for clinical covariates these risks decreased to 2.9-fold (95% CI: 1.2–7.4; P = 0.022) and 1.8-fold (95% CI: 1.1–3.1; P = 0.029), for 10-year and 30-year follow-ups, respectively.

4. Discussion

In this study setting of middle-aged subjects without a known cardiac disease, several ECG abnormalities were found to possess predictive value for SCD events. The predictive power of various ECG markers was variable during 10-year and 30-year follow-up periods. In summary, results suggest abnormal QRS-angle, LVH and ER ≥ 0.2 mV having the highest predictive value for SCD events, and cumulative impact of multiple ECG risk variants markedly improves the risk prediction of SCD events in subjects with no history of cardiac disease. The IDI analysis showed a minor enhancement in risk prediction with abnormal ECG for SCD. However, abnormal ECG did not improve the risk prediction model in C-statistics, probably due to strong variables in the original model (age, gender, BMI, high blood pressure, cholesterol, diabetes, smoking).

Sudden cardiac death is considered as a multifactorial event and it is vital to understand the various causes and mechanisms known to increase the risk of SCD [2,15,16]. Majority (80%) of SCD events occur in elderly patients with coronary arterial abnormalities, and minority of SCD cases derive from to cardiomyopathies, valvular/congenital heart diseases and electrophysiological abnormalities. However, stroke, aortic rupture, intoxication and pulmonary embolism are also known triggers of SCD. In 2004, The Framingham Heart Study examined the current trend of SCD, if the mortality rates were in line with notably decreased number of fatal coronary heart disease (CHD) events [17]. They concluded that the incidence of SCD events has decreased by 49% during the past 5 decades. This confirms the importance of primary and secondary intervention of CHD to reduce the incidence of SCD. This phenomenon is also seen in the incidence rates of SCD according to age. The age-related incidence of SCD is demonstrated to form a peak among children under the age of five, remaining low for the age groups of 5 to 44 years, and increasing rapidly from the age of 45 indicating the importance of CHD prevention in effort to decrease SCD events [2].

4.1. ECG risk markers for SCD

In a recent study, ECG risk variants were evaluated in the context of left ventricular ejection fraction (LVEF) for better prediction of future SCD events [18]. They utilized data from the community-based Oregon

Table 3
Competing risk regression model, 30-year follow-up.

| ECG Abnormality                      | Univariate | P-value       | Multivariate | P-value |
|--------------------------------------|------------|---------------|--------------|---------|
| Normal ECG (N = 7963)                | 1.0        | 1.0           | 1.0          | 1.0     |
| Any ECG abnormality (N = 1548, 16.3%)| 1.67       | <0.001        | 1.30 (1.07–1.57) | 0.007 |
| QRS duration ≥ 110 ms (N = 110, 1.2%)| 2.20       | 0.003         | 1.57 (0.91–2.72) | 0.110 |
| QTc (N = 534, 5.6%)                  | 1.56       | 0.002         | 1.06 (0.79–1.43) | 0.670 |
| LVH (N = 395, 4.2%)                  | 2.01       | 0.001         | 1.79 (1.08–2.95) | 0.020 |
| ER ≥ 0.1 mV (N = 351, 3.7%)          | 1.81       | <0.001        | 1.52 (1.12–2.05) | 0.007 |
| ER ≥ 0.2 mV (N = 40, 0.4%)           | 3.29       | 0.001         | 2.60 (1.28–5.29) | 0.009 |
| T-wave inversion ≥ 0.4 mV (N = 284, 3.0%) | 1.41 (0.948–2.08) | 0.090 | 1.33 (0.88–2.02) | 0.170 |

a Multivariate model included 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. Adjusted for age, gender, systolic blood pressure, diabetes, BMI and cholesterol.
Sudden Unexpected Death Study with 522 cases of SCD and 736 controls studying a total of 8 abnormalities on ECG. Results indicated a progressively greater risk of SCD in subject with multiple ECG abnormalities combined with preserved (LVEF over 35%) LVEF. Subjects with 24 abnormal ECG variants had over a 20-fold risk (95% CI 9.4–47.7, P < 0.001) for SCD. The results suggested that the cumulative effect of ECG risk markers was a strong predictor of future SCD events among subjects with LVEF over 35%. This can be regarded as a marked finding since we lack proper clinical tools and knowledge for decent SCD prediction. From this perspective, our results are parallel for showing remarked elevation of SCD risk for those with multiple risk variants on 12 lead ECG.

In case of prolonged QRS duration (QRSd) and intraventricular conduction delay (IVCD), the consensus as usable risk variable for SCD is not uniform [6,10,19,20]. Aro et al. in 2011 performed a general population study and concluded QRSd ≥ 110 ms and IVCD as a significant risk marker for SCD with 2- and 3-fold risks, respectively [6]. Our results suggested QRS duration as a risk factor for SCD in 10-year analysis, however no value in risk prediction was found in longer follow-up period. Nonetheless, the segregation between QRSd/IVCD being independent markers for SCD or just a manifestation of more proceeded cardiovascular disease remains debatable.

The total electrical activity of the heart including depolarization and repolarization seems to have value in predicting SCD. However, more high quality clinical trials are needed in effort to discover practical and cost-effective means to recognize and treat these patients.

The spatial and frontal QRS-T angle calculated by using vectorcardiography of depolarization and repolarization has been studied for decades and this field research has reemerged in recent years as it has been associated with increased risk of cardiac death and SCD [28]. The definition of an abnormal QRS-T angle varies (from 100° to 135°) depending on the study [28–31]. In selected studies using large general populations, QRS-T angle was regarded as a significant risk factor for adverse cardiac events. The hazard ratio for cardiac mortality varied from 1.9 to 5.2, and the risk for SCD from 2.3 to 5.6. Our study yielded parallel results. The significance was notable in 10-year risk prediction. In addition, T-wave inversions are suggested as isolated risk factor for SCD [32]. This was also noted in our study. T-wave inversions showed a 3-fold risk in 10-year period but had no significance in 30-year follow-up.

Left ventricular hypertrophy on ECG is regarded as a potential trigger of ventricular arrhythmias and therefore regarded as a risk marker for SCD events [33]. This has been established especially among patient with hypertension induced hypertrophy [34]. This increased risk was noted in this setting of middle-aged subjects with no history of cardiac disease, being one of the strongest individual predictors for SCD.

Currently, we obviously lack decent tools for SCD prediction. As recent studies have implied, a 12 lead ECG provides evident benefits for this field of research. Wide availability, simple interpretation and good

**Table 4**

| Number of ECG abnormalities | Number of SCDS/subjects at risk | Univariate | P value | Multivariate* | P value |
|-----------------------------|---------------------------------|------------|---------|---------------|---------|
| 10-year follow-up           |                                 |            |         |               |         |
| 1 ECG abnormality           | 16/1313                         | 2.10 (1.19–3.69) | 0.011   | 1.29 (0.72–2.30) | 0.393  |
| ≥2 ECG abnormalities        | 10/186                          | 7.62 (3.85–15.09) | <0.001 | 3.22 (1.57–6.62) | 0.001  |
| 30-year follow-up           |                                 |            |         |               |         |
| 1 ECG abnormality           | 87/1313                         | 1.55 (1.23–1.96) | <0.001 | 1.12 (0.89–1.43) | 0.334  |
| ≥2 ECG abnormalities        | 37/186                          | 4.57 (3.26–6.41) | <0.001 | 2.97 (2.09–4.20) | <0.001 |

* Adjusted for age, gender, systolic blood pressure, diabetes, BMI and cholesterol. ECG = electrocardiogram.

**Fig. 2.** Cumulative effect of abnormal ECG findings for sudden cardiac death.
cost-effectiveness makes it important for clinicians and researchers. More prospective studies are needed to validate novel risk models for SCD prediction. From electrocardiographic point of view, future studies should focus on both individual and combined ECG risk variants alongside with other clinical factors.

4.2. Study limitations

As retrospective study, a few limitations are obvious concerning this study. For identifying subjects with and without cardiac disease, the definition was based on self-reported information. This information was obtained by using a questionnaire including data of used medications, symptoms (angina pectoris for example), and was performed by a trained nurse. At that time of pre-digitalization and lacking electronic patient report regimes, this was regarded as the most reliable method for obtaining a large amount of data. We cannot rule the possibility of a silent cardiac disease developing during the 30-year follow-up.

After the time of baseline study in 1960s’ to 1970s’, the practice of medicine has gone through major changes. As the general knowledge of diseases, symptoms and risk prevention is being brought to public awareness via internet and public channels, and this information is added to the constantly growing prosperity and well-being, it is apparent that the utilization of health care has increased substantially. This general knowledge combined with more advanced and novel clinical tools have led to early diagnosis and/or intervention to prevent adverse events. Therefore, comparing the past and the present era, the risk profiles are not completely in line for the risk of SCD. More studies are needed using populations of the present time, rather with various ethnic backgrounds.

4.3. Future directions of SCD prevention

As for risk prediction for SCD events, the current consensus and understanding relies on prevention/treating/diagnosing of known risk factors, such as CHD, congenital heart/valvular diseases and LQTS. Improved knowledge of drugs with potency of QT prolongation educates clinical practitioners for reasonable evaluation of medication to prevent redundant SCD events. Since the all mechanisms of SCD are not completely understood, the risk evaluation of those with no clinical symptoms or known risk factors for SCD still remains challenging and more research is needed. As for future innovation in general practice with constantly increasing knowledge for SCD risk markers, considering cost-effectiveness and availability, the development of automated ECG analysis could involve more advanced algorithms to detect those subjects with multiple known risk factors. This initial risk assessment could lead to further diagnostic inspection with traditional methods such as echocardiogram, magnetic resonance imaging and Holter monitoring. For example, patient with numerous risk variables on ECG combined with low (<35%) left ventricular ejection fraction (LVEF) on ECHO imaging, could benefit primary prevention with ICD therapy, thus improving the “number needed to treat” rate compared to risk assessment using only LVEF values [35]. As genetic testing has grown dramatically over the past decades with decreasing expense, this field of research probably improves the future risk assessment for SCD.

5. Conclusion

Electrocardiograph is a valuable and inexpensive tool for predicting SCD events in middle-aged subjects with no history of cardiac disease. There seems to be an obvious correlation between the risk of SCD and the number of observed abnormal ECG findings. The prediction of SCD should include multiple clinical risk factors (age, gender, diabetes, smoking, blood pressure, cardiac function) in addition to observed ECG abnormalities. Future clinical studies on predictive value of ECG should be performed using both traditional and novel statistical methods. Studies providing more exact information about the high-risk combination of ECG variants could offer medical professionals means to prevent majority of SCD events.

Conflict of interest

None.

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