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Prediction of sudden cardiac death based on a 12-lead ECG record

Przewidywanie nagłego zgonu sercowego na podstawie 12-odprowadzeniowego zapisu EKG

Karolina Semczuk-Kaczmarek, Anna Ryś-Czaporowska, Grzegorz Karpiński, Anna E. Płatek, Filip M. Szymański, Krzysztof J. Filipiak

1st Department and Clinic of Cardiology, Medical University of Warsaw, Warsaw, Poland

Lekarz Karolina Semczuk-Kaczmarek jest absolwentką I Wydziału Lekarskiego Warszawskiego Uniwersytetu Medycznego. Obecnie odbywa szkolenie specjalizacyjne w zakresie kardiologii w I Katedrze i Klinice Kardiologii Warszawskiego Uniwersytetu Medycznego. Równocześnie realizuje tam rozprawę doktorską, której promotorem jest prof. dr hab. n. med. Krzysztof J. Filipiak. Rozprawa dotyczy oceny związku występowania objawów ze strony dolnych dróg moczowych z ryzykiem sercowo-naczyniowym. Zainteresowania medyczne skupia na prewencji sercowo-naczyniowej. Wolny czas poświęca górskim wędrówkom.

Abstract

Sudden cardiac death (SCD), which is often the first manifestation of cardiovascular disease, is defined as a non-traumatic, unexpected fatal event occurring within one hour of the onset of symptoms in an apparently healthy subject. According to the current guidelines, implantable cardioverter-defibrillator therapy is recommended for the primary prevention of SCD among patients with a reduced (*i.e.* less than < 35%) left ventricular ejection fraction. The authors of the Oregon Sudden Unexpected Death Study (SUDS) have proposed a new electrocardiographic model of SCD risk assessment including: resting heart rate > 75/min, prolonged QTc interval (> 450 ms for men, > 460 ms for women), QRS-T angle > 90 degrees, delayed QRS transition zone (> V4), prolonged Tpeak-to-Tend (TpTe) > 89 ms and left ventricular hypertrophy (according to Sokolow-Lyon or Cornell criteria). This novel ECG risk score could be particularly effective for patients with left ventricular ejection fraction > 35% where risk stratification is currently unavailable.

Key words: sudden cardiac death, left ventricular ejection fraction, ECG, prevention

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Introduction

According to the guidelines of the European Society of Cardiology (ESC), sudden cardiac death (SCD) is defined as an unexpected fatal incident not related to any trauma, causing death within an hour from the onset of symptoms in an apparently healthy individual. If there are no witnesses to the death, the definition of SCD is used when the deceased individual was in good health for at least a day before the incident. The term SCD is also used if the individual was

Address for correspondence: lek. Karolina Semczuk-Kaczmarek, I Katedra i Klinika Kardiologii, Warszawski Uniwersytet Medyczny, ul. Banacha 1a, 02–097 Warszawa, Poland, e-mail: karolina.semczuk-kaczmarek@wum.edu.pl

diagnosed with a potentially lethal congenital or acquired heart disease during their lifetime, or if an autopsy uncovers a cardiac or vascular anomaly as the most probable cause of death with no other obvious non-cardiac causes, which allows for a high degree of certainty that the cause of death was an arrhythmic incident.

The aetiology of SCD varies with age: in the case of young people, SCD usually occurs due to channelopathies and cardiomyopathies, while in older age groups the dominant causes are coronary artery disease, valve abnormalities and heart failure [1]. Moreover, it has been shown that SCD is the sum of several different risk factors, and is in most cases the first manifestation of cardiovascular disease. It is estimated that 17 million deaths a year in Western countries are caused by cardiovascular diseases, of which SCD accounts for up to 25% of cases [2]. An emphasis has been placed on the role of preventative actions in estimating the risk of SCD.

The aim of this short review is to discuss the changes observed in a 12-lead electrocardiogram (ECG) record that may indicate an increased risk of SCD occurring.

Risk scales of SCD

Current guidelines

The 2016 ESC guidelines for the diagnosis and treatment of heart failure underline that patients with a reduced left ventricular ejection fraction (LVEF) are at higher risk of a sudden and early death. A group of experts recommends the use of an implantable cardioverter-defibrillator (ICD) to prevent sudden deaths in patients with: asymptomatic systolic dysfunction of the left ventricle (LVEF ≤ 30%) with an ischaemic aetiology at least 40 days following a myocardial infarction, or in patients with asymptomatic dilated cardiomyopathy (LVEF ≤ 30%) with a non-ischaemic aetiology who are undergoing optimal pharmacotherapy (class IB recommendation) [3]. The recommendations were developed based on observations of patients after acute coronary syndrome. After analysing more than 14,000 cases, it was concluded that patients with left ventricular systolic dysfunction were in a group of higher risk for SCD, of which the largest proportion (21%) of SCDs were observed in the group of patients with LVEF < 30% [4]. However, it seems that a reduced ejection fraction is not the only factor in predicting the risk of SCD.

Oregon SUDS study

The Oregon SUDS (Sudden Unexpected Death Study) case-control study conducted in 2002–2015 concerned the analysis of out-of-hospital incidents of SCD in the north-western United States. The study group of 522 patients included all cases of cardiac arrest occurring outside of hospital, while the control group included 736 individuals with a similar risk profile, but without a history of ventricular arrhythmia or out-of-hospital cardiac arrest. Aro et al. [5] conducted an analysis of the available electrocardiographic tests performed before cardiac arrest and compared these to ECG records in the control group. It was shown that a few electrocardiographic parameters differed statistically significantly between the groups. The researchers proposed a new electrocardiographic model to assess risk of SCD, assigning one point each to:

- heart rate (HR) > 75/min;
- electrocardiographic features of left ventricular hypertrophy (according to Sokolow-Lyon or Cornell criteria);
- delayed QRS transition zone (in at least lead V5);
- QRS-T angle > 90 degrees;
- prolonged QTc interval (> 450 ms in men and > 460 ms in women), and
- prolonged Tpeak-to-Tend, TpTe > 89 ms.

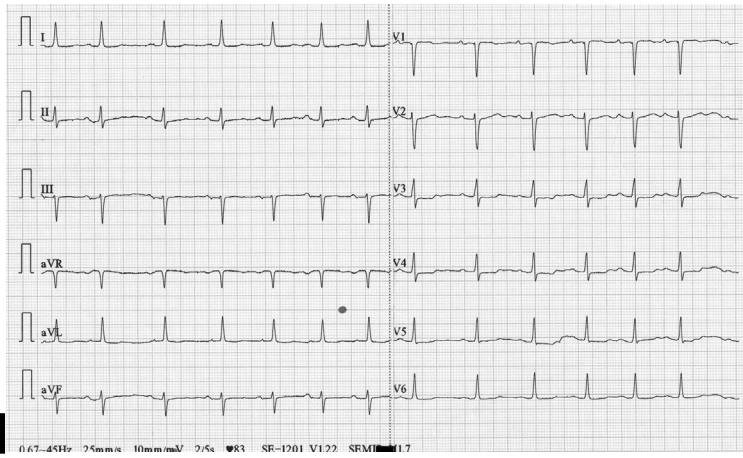
In the study group, around 16% of patients had an ECG record with ≥ 4 of the above electrocardiographic risk factors, while in the control group this proportion was significantly lower, at 3% ($p < 0.001$). It was calculated that scoring ≥ 4 points in the proposed scale was associated with a 21.2% risk of SCD [odds ratio (OR) 21.2, 95% confidence interval (CI) 9.4–47.4, $p < 0.001$]. It was also noted that when narrowing the analysis to the group of patients with an ejection fraction of > 35%, a score of ≥ 4 points in the electrocardiographic scale significantly increased the risk of SCD (OR 26.1, 95% CI 9.9–68.5, $p < 0.001$), which was not observed in the group of patients with a reduced ejection fraction < 35% [5]. Examples of 12-lead ECG analysis according to the Oregon SUDS categories were presented in Figure 1A–C.

ARIC study

The ARIC (Atherosclerosis Risk in Communities) prospective cohort study assessed risk factors, progression and manifestation of atherosclerosis in a group of almost 15,000 inhabitants of four US cities aged 45–64 years, without a prior history of cardiovascular disease [6, 7]. Patient recruitment was started in 1987–89, and they were then observed for 15 years for the occurrence of SCD. The analysis conducted by Deo et al. [7] showed that among the ARIC study participants, 171 SCDs occurred. Based on the interpretation of clinical and laboratory data, a model for SCD risk was developed which included the following parameters:

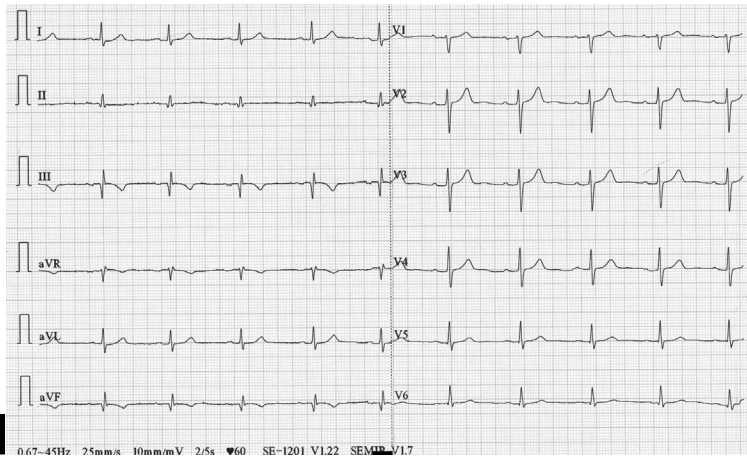
- age > 54 years;
- male sex;
- smoking tobacco;
- elevated systolic arterial blood pressure;
- treatment for hypotension;
- diabetes;
- potassium concentration;
- high-density lipoprotein (HDL) cholesterol concentration;

A



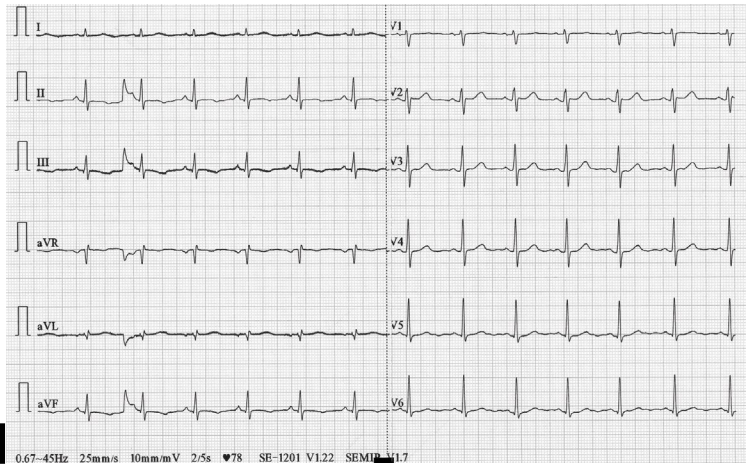
Parameter	Values	Points in Oregon SUDS
Heart rate	83/min	1
LVH parameters:		0
• Sokołow-Lyon criteria	2.0 mV	
• Cornell criteria	1.2 mV	
QRS complex transition zone	V3	0
QRS-T angle	96°	1
QTc interval	490 ms	1
Tpeak-Tend interval	90 ms	1
Total points		**4**

B



Parameter	Values	Points in Oregon SUDS
Heart rate	60/min	0
LVH parameters:		0
• Sokołow-Lyon criteria	1.2 mV	
• Cornell criteria	1.4 mV	
QRS complex transition zone	V4	1
QRS-T angle	13°	0
QTc interval	400 ms	0
Tpeak-Tend interval	85 ms	0
Total points		**1**

C



Parameter	Values	Points in Oregon SUDS
Heart rate	78/min	1
LVH parameters:		0
• Sokołow-Lyon criteria	1.7 mV	
• Cornell criteria	0.7 mV	
QRS complex transition zone	V3	0
QRS-T angle	107°	1
QTc interval	470 ms	1
Tpeak-Tend interval	90 ms	1
Total points		**4**

Figure 1A–C. Examples of 12-lead electrocardiogram analysed according to the Oregon SUDS (Sudden Unexpected Death Study) categories

— estimated glomerular filtration rate (eGFR) and
— prolonged corrected QT (QTc) interval.

This model included pro-arrhythmic factors that are not accounted for in other risk scales (*i.e.* plasma potassium concentration, prolonged QTc). This study emphasised that currently available cardiovascular risk assessment scales may not be sensitive enough in predicting the risk of SCD [8].

Risk factors for SCD in an ECG record

Resting heart rate

The model designed in the Oregon SUDS study showed that resting heart rate > 75/min is one of the risk factors for SCD (OR 3.5, 95% CI, 2.8–4.5). Similar results were found in previously published works, for example in the study by Jouven et al. [9]. Researchers in the years 1967–72 conducted cardiac stress tests in a group of 5,713 men unaffected by clinically detectable cardiovascular disease, and then observed this group for 23 years. The primary endpoint was the occurence of SCD. They noted that the risk of SCD was significantly increased in the patient group with a resting HR > 75/min [relative risk (RR) 3.92, 95% CI 1.91–8.00); with an increase in HR on exertion of less than 89 (RR 6.18, 95% CI 2.37–16.11), and with a decrease in HR of < 25/min after exertion (RR 2.20, 95% CI 1.02–4.74). The registered chronotropic incompetence, *i.e.* inability to achieve 85% of the age-appropriate maximum HR (220 — patient age), reflect impaired autonomic regulation. The inability to achieve the age-appropriate maximum HR can be a result of an impaired ability to increase activity of the sympathetic nervous system, while both increased resting HR and slow drop of HR after exertion appear to be secondary to impairments of the parasympathetic system. An impaired ability to increase activity of both the sympathetic system and the parasympathetic system is associated with disturbances of baroreceptor reflexes, and can lead to cardiac arrest during ventricular tachycardia, which precedes ventricular fibrillation and SCD [10].

QTc interval > 450/460 ms

The QT interval reflects the duration of the action potential of cardiomyocytes, starting from the beginning of the depolarization of subendocardial cells (which depolarize the earliest) to the end of repolarization of M cells (with the longest lasting action potential that determines the length of the QT interval). The QT interval consists of the QRS complex, representing the depolarization of ventricular muscles, and the ST-T wave, which conveys the processes of repolarization. Under physiological conditions, the QT interval undergoes many changes depending on the activation of the autonomic nervous system and heart rate: the higher the heart rate, the shorter the QT interval. Corrected QT interval (QTc) in relation to the heart rate is calculated using Bazett's formula (among others), which can be used in the heart rate range of 50–100/min according to the formula:

$$QTc = QT/\sqrt{RR}$$

where: QTc is corrected QT interval and RR is the interval from the beginning of one QRS complex to the beginning of the following QRS complex measured in seconds.

The limits of normal for the QT interval are not strictly defined, and according to the current standards the upper limit of normal for QTc is accepted to be 450 ms for men and 460 ms for women [11]. It has been proved multiple times that a prolonged QTc interval measured in a standard 12-lead ECG is an independent risk factor for SCD [12]. In the Oregon SUDS study, a prolonged QTc interval was linked to a statistically significantly higher risk of SCD (OR 4.9, 95%CI 3.8–6.4, p < 0.001) [13]. The above observations remain consistent with the previously published Rotterdam QT Project study conducted on 6,000 patients, which showed that a prolonged QT interval is linked to a 2.3-fold higher risk of SCD [14]. A prolonged repolarization time of the ventricles, which is the main reason for a prolonged QTc interval, elongates the activation time of cells, and predisposes to the occurrence of ventricular tachycardia/ /fibrillation, which in many cases will lead to SCD.

QRS-T angle > 90 degrees

A measure of repolarization of the left ventricle is the angle formed between the axis of the QRS complex and the axis of the T wave, called the QRS-T angle. This is defined as the absolute value of the difference between the direction of the depolarization vector (the QRS complex) and repolarization (T wave) between 0° and 180°, and it is classified as normal (≤ 90°) or abnormal (> 90°). An abnormal QRS-T angle is a result of both structural abnormalities affecting the process of depolarization, as well as of regional changes in ion channels changing the sequence of repolarization. In studies published so far, it was observed that patients with an abnormal QRS-T angle have a higher chance of SCD [relative risk (RR) 2.26, 95%CI 1.59–3.21, p < 0.001] [15]. Also, in the Oregon SUDS study, a widening of the QRS-T angle beyond 90° was linked with a 2.3-fold higher risk of SCD (OR 2.3, 95%CI 1.7–3.1, p < 0.001).

QRS transition zone > V4

The conception of the transition zone applies to the ECG in precordial leads, in which there is a transition of QRS complexes from dominantly negative to dominantly positive. In other words, the transition zone is found in the location where the QRS complex is isoelectric. In the case where the transition zone is found before the V3 lead (most cases) — this state is called left axis deviation (early transition zone); when the transition zone is found in lead V4 or later — this state is referred to as right axis deviation (delayed transition zone). In two thirds of cases, the location of the transition zone does not precisely correlate with the position of the heart in the chest. A study conducted on a group of over 10,000 middle-aged Finnish citizens found that the presence of a delayed transition zone is linked to an increased risk of death from any cause (RR 1.15, 95% CI 1.07–1.22, p < 0.001) and an increased risk of SCD (RR 1.23, 95%CI 1.03–1.47, p = = 0.029). Moreover, the presence of the transition zone in lead V5 or later was linked with a more than 60% increased risk of SCD. The authors of the study suggested that the

occurrence of a delayed transition zone may be a marker of subclinical heart disease which, through changes in the geometry of the walls and chamber of the heart, may cause changes in the localisation of the transition zone, which correlates with an increased risk of SCD [16]. The Oregon SUDS study also found that the presence of a delayed transition zone in leads V5 or V6 was associated with a more than two-fold higher risk of SCD (OR 2.14, 95% CI 1.67–2.75, $p < 0.001$), independently of other risk factors. In addition, a correlation was observed between the presence of a delayed transition zone and a greater frequency of myocardial infarction, greater mass and volume of the left ventricle, and a reduced left ventricular ejection fraction [17].

Tpeak-Tend interval > 89 ms

The T wave is associated with a repolarization of the ventricles, a process that proceeds differently in various layers of the ventricular walls. As we know, the depolarization phase spreads from the endocardium to the epicardium, while the repolarization phase proceeds in the opposite direction: from the epicardium to the endocardium. The end of repolarization in epicardial cells is reflected in the peak value of the positive T-wave, known as the Tpeak (Tp), while the Tend (Te) is linked to the end of repolarization in subendocardial M cells. It is accepted that the interval from the peak to the end of the T wave, called the Tpeak-Tend interval, is a measure of transmural dispersion of repolarization. Transmural dispersion of repolarization is a period during which the epicardial cells have aready finished the process of repolarization and are excitable, while the M cells are still repolarizated and are prone to early after depolarizations (EAD). In normal conditions, the Tpeak-Tend interval is short. In pathological situations, such as heart failure, ischaemic heart disease, electrolyte imbalances (especially hypokalemia), use of drugs that prolong QT, and genetic defects in ion channels, a non-homogenous elongation of action potentials occurs, especially in M cells, which significantly increases dispersion of repolarization [18]. Increased dispersion of repolarization is linked with a tendency to develop early after depolarizations, which occur during the *plateau* or repolarization phase, which are associated with a risk of re-entry as well as polymorphic ventricular tachycardia or ventricular fibrillation. A prolonged Tpeak-Tend interval probably corresponds to a prolonged time of sensitivity, and in the suitable conditions, it can increase the risk of ventricular arrhythmias. Due to these reasons, the measurement of the Tpeak-Tend interval has been applied in estimating the risk of SCD. In the Oregon SUDS study, the Tpeak-Tend interval was significantly greater in individuals who experienced SCD during the long-term observation period (87 ± 18 ms in the group of individuals with SCD vs. 81 ± 15 ms in the control group, $p < 0.001$).

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH), defined as enlargement and thickening of the muscle of the left ventricle, changes the electrocardiographic record of the cardiac cycle, causing the occurrence of higher forces of depolarization in left ventricular precordial leads (V5–V6) and exacerbating of the nagative forces in the anterior precordial leads. Most used electrocardiographic criteria of left ventricular hypertrophy are the Sokolow-Lyon criteria (S wave in lead V1 and R wave in lead V5 or V6 greater than or equal to 35 mm) and the Cornell criteria (R wave in lead aVL and S wave in lead V3 greater than 20 mm for women and 28 mm for men). Several epidemiological studies have shown a linear relationship between the mass of the left ventricle with the development of cardiovascular diseases, and recent publications have emphasised the relationship between the presence of electrocardiographic indicators of LVH and the risk of SCD. In the Oregon SUDS study, electrocardiographic features of LVH were present in 16% of patients who had SCD, and in only 8% of the control group. After conducting a multivariate statistical analysis, it appeared that the presence of electrocardiographic features of LVH was linked to an over 2-fold higher risk of SCD (OR 2.2, 95%CI 1.5–3.1, $p < 0.001$). Experimental studies show that in hypertrophic muscles of left ventricular the speed of electrical condution is slowed down, which can be a substrate for the occurrence of cardiac arrhythmias. It appears that LVH causes disturbances in the processes of depolarization and repolarization of the ventricles, atrioventricular conduction, changes in the function of ion channels, cytoskeletal remodelling in cells of the myocardium and impaired calcium balance. The cells of the hypertrophic heart muscle are more prone to ischaemia [19]. In conditions of adenosine triphosphate (ATP) deficiency, potassium channels are opened, sodium-potassium pumps are inhibited, and sodium gradient is reducted. Moreover, it has been observed the upregulation on Na/Ca exchange current and enhanced sarcoplasmic reticulum Ca release, which increase the risk of early and delayed after depolarizations and the risk of ventricular tachycardia and fibrillation.

Summary

According to the current Guidelines of the European Society of Cardiology, the value of the left ventricular ejection fraction should be considered during assessing the risk of SCD. The electrocardiographic risk scale for SCD described in the Oregon SUDS study has a particular use among patients with a preserved or moderately fraction — the group for whom no risk scales of SCD have been developed so far.

Conflict(s) of interest

The authors declare that there is no conflict of interest.

Streszczenie

Nagły zgon sercowy (SCD), będący niejednokrotnie pierwszą manifestacją choroby układu sercowo-naczyniowego, definiuje się jako niespodziewany, śmiertelny incydent niezwiązany z urazem, powodujący zgon w ciągu godziny od początku objawów u pozornie zdrowej osoby. W aktualnych wytycznych w prewencji pierwotnej SCD zaleca się implantację układu kardiowertera-defibrylatora w grupie pacjentów z obniżoną (< 35%) frakcją wyrzutową lewej komory (LVEF). Autorzy *Oregon Sudden Unexpected Death Study* zaproponowali nowy, elektrokardiograficzny model oceny ryzyka SCD uwzględniający: spoczynkową czynność serca powyżej 75/min, wydłużony odstęp QTc (> 450 ms u mężczyzn, > 460 ms u kobiet), kąt QRS-T ponad 90 stopni, opóźnioną strefę przejściową zespołu QRS (> V4), wydłużony czas mierzony od szczytu załamka T do jego końca (TpTe, *Tpeak-to-Tend*) ponad 89 ms oraz elektrokardiograficzne cechy przerostu mięśnia lewej komory (wskaźnik Sokołowa-Lyona lub Cornella). Omawiany model może mieć szczególne znaczenie u pacjentów z LVEF przekraczającą 35% — grupy, dla której nie opracowano zwalidowanej skali ryzyka wystąpienia SCD.

Słowa kluczowe: nagły zgon sercowy, frakcja wyrzutowa lewej komory, EKG, prewencja

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