Improvement in Diagnosis of Sudden Cardiac Death

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Zhenzhen Gao, Fang Zhang, Changxiao Yu, and Ziren Tang

Abstract

Sudden death (SD) is often the first clinical manifestation of an underlying disease in previously asymptomatic, apparently "healthy" subjects. Various criteria have been used to define sudden cardiac arrest and sudden cardiac death in the medical literature. The 2006 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS Writing Committee to establish data standards for electrophysiology) included definitions to guide documentation in research and clinical practice. "[Sudden] cardiac arrest is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden death. Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing. Sudden cardiac death should not be used to describe events that are not fatal." Correct identification of future SCD victims is especially important as there is an effective treatment, namely, defibrillation via an external or internal (implanted) defibrillator. Currently, the commonly used SCD risk score based on left ventricular ejection fraction can only predict some cardiac arrest events. There is an urgent need for more effective and reliable SCD risk early warning methods. The rapid development of ECG signals, genetic markers, and a combination of multiple index risk scoring models, including the foregoing two, have opened new paths for SCD early warning diagnosis.

Keywords

Sudden cardiac death (SCD) · Sudden cardiac arrest (SCA) · Definition · Genetic markers · Risk score

Z. Gao · F. Zhang · C. Yu · Z. Tang (✉)
Emergency Department, Beijing Chao-Yang Hospital, Beijing, China

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Sudden cardiac death (SCD) refers to sudden accidental death within 1 or 24 h after the onset of symptoms and to exclude death caused by arrhythmia or hemodynamic reasons [1]. Epidemiological investigations have shown that SCD is still a serious public health issue, although significant progress has been made in high-risk patients with implantable cardioverter-defibrillator (ICD) implantation and coronary heart disease prevention. Cardiac arrest and its main outcome, SCD, account for 50% of cardiovascular deaths, causing serious health threats and huge social burdens worldwide [2]. Survival analysis shows that the survival rate of patients with cardiac arrest outside the hospital is less than 10%, and even if the cardiac arrest occurs in the hospital, the incidence of survival to hospital rescue is less than 25% [3]. Therefore, the early diagnosis of SCD is particularly important, and a reliable and effective early diagnosis method of SCD is urgently needed to improve the severe social health status of SCD diagnosis and treatment.

Left ventricular ejection fraction (LVEF) is an important indicator for clinical evaluation of left ventricular systolic function and has been widely used as an indication criterion for ICD treatment. The latest US SCD prevention management guidelines released in September 2018 have once again emphasized the importance of LVEF as an early warning indicator of SCD and an indicator of whether or not to implant CD [1]. However, there is evidence that more than 50% of patients with high-risk SCD after myocardial infarction often do not show a decrease in LVEF or show only a slight decrease in LVEF [4]. In addition, even in high-risk SCD populations with significantly reduced LVEF, only 10–30% of patients can benefit from ICD treatment [5]. Therefore, the results of more and more large clinical studies show that the effectiveness of LVEF as an indicator of SCD risk stratification faces major challenges. The direct cause of SCD is mainly malignant arrhythmia events, which are mostly manifested as ventricular tachycardia, ventricular fibrillation, cardiac arrest, etc., and the cardiac function index LVEF is not sufficient to sensitively reflect changes in the patient's ECG activity. Because SCD mainly comes from malignant arrhythmias, the SCD warning value of ECG signals has great potential.

At present, the field of ECG detection technology continues to develop, and a variety of ECG characteristics have played an important role in predicting sudden cardiac death in the clinic.

8.1 Heart Rate

1. Resting heart rate is a simple indicator commonly used in clinical practice. High-level resting heart rate has been reported by many studies to be related to the risk of sudden cardiac death. A prospective study in Paris showed that those with a high level of resting heart rate (75 beats/min) had a risk of sudden cardiac death approximately four times as high as those with low resting heart rate (<65 beats/min) [6].
2. Heart rate turbulence: Heart rate turbulence describes a short-term change in heart rate caused by ventricular premature beats (VVTs). It usually manifests as a significant acceleration of the heart rate (T0) followed by a gradual heart rate

deceleration (TS). Abnormal heart rate turbulence has been reported to be significantly associated with all-cause death and sudden cardiac death, especially in patients with heart failure after myocardial infarction [7]. Similarly, some studies have shown that heart rate turbulence is significantly related to cardiovascular death and can effectively predict the occurrence of sudden cardiac death in patients after acute myocardial infarction, and its prediction efficiency has significantly improved after combining with other ECG characteristics [8].

3. Heart rate variability: Heart rate variability refers to the frequency variation between heart beats, which reflects the state of cardiac autonomic nerve function, and can predict the occurrence of sudden cardiac death in patients with chronic heart failure [9].

8.2 12-Lead ECG

8.2.1 Deep Negative of P Wave in Lead V1

Deep terminaI negativity of P wave in V1 (DTNPVl) is a marker of atrial abnormality, defined as biphasic P wave detected by resting 12-lead ECG, and negative P wave amplitude>1 mm. DTNPV1 is closely related to all-cause death, cardiovascular disease death, and ischemic heart disease death in the adult population. It is a simple but effective prognostic indicator [10, 11].

8.2.2 QT Interval

Corrected QT interval (QTc) is a classic indicator for the diagnosis of cardiac ion channel diseases (such as long QT syndrome and short QT syndrome, etc.), but its clinical value is not limited to the diagnosis of cardiac ion channel disease. It can be extended to the risk diagnosis of heart failure, diabetes, and other diseases [12]. The prolongation of the QT interval reflects the prolongation of the action potential of cells, which in turn leads to the activation of L-type calcium ion channels, which eventually leads to cardiovascular events [13].

8.2.3 QRS Wave

1. In a follow-up study in Finland, the risk of sudden cardiac death in patients with QRS duration (QRSd) ≥110 ms was 2.5 times higher than in patients with QRSd <96 ms [14]. QRSd is an independent risk factor for cardiovascular death, and an increase in QRSd every 10 ms results in an 18% increase in the risk of cardiovascular death [15].
2. QRS dispersion (QRS dispersion) refers to the maximum QRSd and minimum QRSd in a 12-lead ECG. Difference. QRSd has been reported as an independent predictor of sudden cardiac death in arrhythmic right ventricular cardiomyopa-

thy populations [16]. In patients with heart failure, QRSd is significantly associated with left ventricular systolic dysfunction and can effectively predict sudden cardiac death [17].

3. Fragmented QRS (fQRS) refers to a multiphase QRS wave that appears in two or more adjacent leads of a 12-lead ECG and complete or incomplete bundle branch block and complete right bundle branch block. Studies have reported that fQRS can be used as a predictor of myocardial scars and also predict arrhythmic events in non-ischemic cardiomyopathy [18].
4. QRS. The QRS-T angle refers to the angle between the QRS wave and the T-wave electrical axis and can be divided into a space angle and a frontal angle. A case-control study showed that the positive QRS-T angle was significantly associated with sudden cardiac death and that its predictive value was independent of the left ventricular ejection fraction [19–21].
5. QRS points are scores composed of the Q, R, and S wave amplitude, time history, and notch of each lead. In ischemic cardiomyopathy, QRS scores are still highly reliable in the evaluation of myocardial scars compared to the myocardial nuclear magnetic resonance that is currently prevalent [22]. Increased QRS scores have been shown to be closely related to ventricular arrhythmias, the occurrence of ICD discharges, and decreased left ventricular inverse remodeling [23].

8.2.4 T Wave

T wave alternans (TWA) refers to the phenomenon in which the shape, amplitude, and polarity of T waves alternately change step by step in an electrocardiogram. TWA is mainly produced by the alternating repolarization of a single myocardial cell. Other possible mechanisms include calcium imbalance, myocardial memory, and mechanical-electrical feedback [24]. TWA can be observed in various disease states, such as myocardial infarction, heart failure, long QT syndrome, and Brugada syndrome. TWA is highly consistent with intracardiac electrophysiology in predicting sudden cardiac death and can be used as a predictor of sudden cardiac death [25].

8.2.5 Others

(1) Index of cardiac electrophysiological balance (iCEB) is calculated from the ratio of QT interval to QRSd (iCEB = QT/QRSd), which can effectively predict arrhythmia events caused by multiple drugs [26]. (2) Ventricular ectopic QRS interval (VEQSI) refers to the maximum interval between ventricular ectopic fluctuations. A health-based study in Italy found that VEQSI is significantly associated with structural heart disease and can help predict all-cause mortality [27]. (3) Waveform heterogeneity is the rapid development of computer image recognition technology, which makes the digitization of ECG and more complicated calculation indicators possible. Some studies have used the residual algorithm to evaluate the

heterogeneity of R waves and T waves on each lead and provided a better predictive model for the risk of arrhythmia than conventional ECG [28]. There are also studies that used the second-order central moment analysis method to process the electronic 12-lead ECG of 5618 adults, and the results show that the increase in R wave, J wave, and T wave heterogeneity is significantly related to the occurrence of sudden cardiac death, and even after adjusting for conventional risk factors, the heterogeneity of J wave and T wave is still significantly associated with sudden cardiac death, suggesting that waveform heterogeneity can provide more ECG information and help assess the risk of sudden cardiac death [29].

In recent decades, with the rapid development of high-throughput sequencing technology, more and more whole-genome association studies (GWAS) have been implemented, and the genetic markers of SCD have gained more recognition. For example, in hypertrophic cardiomyopathy, mutations in the myocardial sarcomere gene can explain about 60% of the etiology of hypertrophic cardiomyopathy, with MYBPC3 and MYH7 being the most common. Studies have confirmed that patients with hypertrophic cardiomyopathy who carry multiple mutations in disease-causing genes will face a higher risk of SCD and a worse disease prognosis [30]. Long QT syndrome often shows autosomal dominant inheritance, and the exact pathogenic genes can be detected in more than 85% of patients. More than 15 gene mutations are closely related to the disease. In familial long QT syndrome, even carriers of genetic mutations who are asymptomatic and have normal ECG examinations have a risk of developing cardiac events about ten times higher than those of non-mutated carriers [31]. Therefore, this increasing evidence suggests that genetic testing can play an extremely important role in SCD risk warning [32].

In addition to the above cardiac function indicators, ECG signals, and genetic markers, there are still many other factors that may be related to SCD risk, such as age, gender, ethnicity, and disease history. Combining multiple predictive factors into a scoring system can more improve the prediction of SCD risk. For example, the CHA2DS2-VASc score that has been used clinically to assess the risk of stroke in patients with atrial fibrillation (AF) has been reported to be significantly associated with SCD events in patients with AF [33]. Based on the well-known ARIC cohort study, some researchers have proposed a SCD risk scoring system that includes a variety of traditional risk factors. The scoring system includes age, gender, total cholesterol, lipid-lowering drugs, hypertension drugs, systolic blood pressure, and diastolic blood pressure. Ten risk factors including smoking status, smoking status, diabetes, and body mass index build an index function prediction model, which predicts the risk of SCD in the community population and the actual observed risk is very close: And this study also used the Framingham cohort to verify the scoring system, suggesting the scoring system can effectively predict community SCD high-risk populations [34].

Obviously, in the routine diagnosis and treatment work, high-risk patients need to get an arrhythmia risk assessment quickly. At the same time, in view of the current SCD risk assessment's complete reliance on LVEF and the high medical costs of ICD treatment, other clinical-based, predictive indicators that are independent of LVEF are urgently needed. Electrocardiogram as a routine examination has the

advantages of being simple, fast, effective, and inexpensive, and it is also very suitable for capturing the electrophysiological abnormalities of patients with high-risk SCD. We have reason to believe that with the rapid development of computer science, next-generation sequencing technology, and big data science, various new types of ECG characteristics, genetic markers, and a scoring system composed of multiple risk factors are likely to provide SCD warnings. More valuable information. In addition, the rapid popularization of wireless signal transmission technology and wearable devices has made it possible to extract and analyze remote ECG features, which will greatly expand the individualization, real time, and effectiveness of SCD risk prevention and control based on ECG monitoring. It is expected that SCD early warning for the general population will be truly realized in the near future.

8.3 The Evolution of Diagnostic Criteria of Sudden Cardiac Death

Sudden death (SD) is usually the first clinical manifestation of an underlying disease in previously asymptomatic, apparently "healthy" subjects [35]. Sudden death is a major problem that has significant impact on public health. Many conditions can predispose to sudden cardiac death (SCD) and sudden cardiac arrest (SCA) [36, 37]. Various criteria have been used to define sudden cardiac arrest and sudden cardiac death in the medical literature [38]. Difficulties in deriving a specific definition include the following:

- Events are witnessed in only two-thirds of cases, which makes the diagnosis difficult to establish in many instances.
- It is too hard to restrict the definition of SCA to documented cases of VF since the cardiac rhythm at clinical presentation is unknown in so many cases.
- The duration of symptoms prior to SCA generally defines the suddenness of death. However, the duration of symptoms is unknown in approximately one-third of cases.

Therefore operational criteria for SCA and SCD have been proposed that do not rely on the cardiac rhythm at the right time of the event. The criteria focus on the out-of-hospital occurrence of a presumed sudden pulseless condition and the absence of evidence of a noncardiac condition (e.g., central airway obstruction, intracranial hemorrhage, pulmonary embolism) as the cause of cardiac arrest.

An international multidisciplinary conference held at the Utstein Abbey near Stavanger in June 1990. The purpose of this meeting was to develop uniform terms and definitions for out-of-hospital resuscitation. The term "Utstein style" is synonymous with consensus reporting guidelines for resuscitation from then on [38, 39]. The original Utstein recommendations focused on patients with non-emergency medical services—witnessed cardiac arrest of presumed cardiac cause, with ventricular fibrillation at the point of first rhythm analysis. At that time, cardiac arrest

was defined as the cessation of cardiac mechanical activity, which confirmed by pulseless, by unresponsiveness, and by apnea (or agonal, gasping respirations). For the purposes of the Utstein style, no comment on time or "suddenness" was recommended [40].

The Utstein definitions were revised in 2004 with the purposes of reducing complexity and updating data elements based on advances in resuscitation science [41]. The Utstein 2004 revision broadened this focus on including all EMS-treated cardiac arrests no matter what the first monitored rhythm is and whether or not the arrests were witnessed. Other changes in 2004 related to the definition of cardiac arrest (transition from carotid pulse to signs of circulation), including defibrillation attempts by bystanders, and extension of the template to include reporting of in-hospital cardiac arrest (IHCA) in adults and children in the same template [41, 42]. The 2004 Utstein resuscitation registry template for out-of-hospital cardiac arrest was updated in 2015, which balances the necessity of uniform collection of evidence-based factors associated with outcome and the challenges of real-life data collection and validation. Because substantial between in-hospital and out-of-hospital epidemiology, process of care, and treatments are different, a decision was made again to use separate reporting templates [43]. And a 2019 update was focused on in-hospital cardiac arrest [44].

The Utstein elements of the latest out-of-hospital cardiac arrest were grouped into five domains. Each domain contained both core and supplemental elements. Some important subgroups are identified which allow an estimate of the specific contribution of rhythm and bystander actions that are the key determinants of outcome [43].

The 2006 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS Writing Committee to establish data standards for electrophysiology) included definitions to guide documentation in research and clinical practice [45].

The following definitions of SCA and SCD were presented:

> "[Sudden] cardiac arrest is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden death. Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing. Sudden cardiac death should not be used to describe events that are not fatal."

Sudden cardiac death is unexpected death within 1 h of symptoms [46]. It is a devastating and tragic outcome of numbers of underlying cardiovascular diseases. While coronary artery disease and acute myocardial infarction are the most probable causes of SCD in older populations, genetic cardiac disorders comprise a substantial proportion of SCD cases aged ≤40. It includes primary arrhythmogenic disorders such as long QT syndromes and inherited cardiomyopathies. In 30% of young SCD, no cause of death is identified at postmortem, which is called autopsy-negative or sudden arrhythmic death syndrome (SADS). Since these disorders rarely cause structural change to the heart, postmortem is often "negative." That

means no cause of death is identified at postmortem, including normal histopathology and normal toxicology analysis [47].

Worldwide, less than 1% of those who experience sudden cardiac arrest can finally survive [48]. Widespread accessibility of automated external defibrillators and effective utilization of public defibrillation programs can improve management of out-of-hospital cardiac arrest [49]. The investigation of sudden death involves five steps:

1. Clinical features, including the history and circumstances of death.
2. Autopsy examination and histology.
3. Further laboratory tests including toxicology.
4. Formulation of a diagnosis.
5. Recommendation for family screening by specialized cardiologists [46].

SCD pressingly requires primary prevention since the first clinical event is always fatal, especially in patients with ventricular tachyarrhythmias. Patients with acute bradyarrhythmias usually retain a basal circulation. Accordingly, the appropriate treatment (such as pacemaker) can be deployed in time to prevent irreversible MODS when a sudden bradyarrhythmia occurs. However, VF often results in a rapid and complete loss of blood circulation. This condition will result in irreversible organ (especially the brain) damage after a few minutes if untreated timely. Only a very small proportion of patients suffering from VF can leave the hospital alive even in the regions with highly developed emergency medical care systems. Despite recent efforts to improve the treatment in the community setting by using semiautomatic external defibrillators, primary prevention of SCD is such a diagnostic challenge that it requires identification of future sudden death victims prior to the first arrhythmia episode. Correct identification of future SCD victims is important, cause there is an effective treatment, which is called defibrillation via an external or internal (implanted) defibrillator [50].

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