Sudden cardiac death – a known unknown?

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Sudden cardiac death (SCD) is a major medical, economic and social problem. The estimated annual number of SCDs is approximately 4 million cases worldwide. Approximately 50% of SCDs are unexpected first manifestations of cardiac disease. The survival rate after out-of-hospital cardiac arrest is low even in countries with the most advanced health care systems. It all emphasizes the importance of prevention, in which implantable cardioverter-defibrillators play a dominant role. However, our ability to recognize high-risk patients remains insufficient. Moreover, a declining rate of shockable rhythm as the initial recording has been reported in the last decades. Despite numerous SCD studies and undisputed progress, there are still many unanswered questions.

Key words: sudden cardiac death, mechanism, prevention, risk stratification, implantable cardioverter-defibrillator

INTRODUCTION

Sudden cardiac death (SCD) is a natural death from cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of an acute change in cardiovascular status. If unwitnessed, subjects should have been observed alive within 24 hours of their death¹. It represents a serious problem due to its incidence and impact on society, especially the victims’ families. The burden of premature death is greater for SCD than for all individual cancers and most other leading causes of death². The aims of this review article are to provide current insights into the causes, mechanism, preventive and management strategies and to point out the gaps in our knowledge.

EPIDEMIOLOGY

The worldwide incidence of SCD is difficult to estimate. Existing SCD registries are highly concentrated in Western Europe and North America, with low-income and middle-income regions of the world lacking surveillance of SCD (ref.³). The annual numbers of SCD cases are derived from various sources and thus range widely, for example, from 184,000 to 462,000 in the United States⁴. Studies using retrospective death certificate-based methodology are likely to significantly overestimate SCD incidence⁴. Autopsies are seldom performed and detailed clinical records are often unavailable. Data collected by first responders to primary cardiac arrest do not include the significant proportion of cases that are unwitnessed. Ambulance-reported data miss cases transported directly to coronial services. Although integrating multisource data seems to be the most suitable approach, comprehensive multisource surveillance registries or studies are few. The most cited data are those reported by the American Heart Association; its 2020 statistical update lists 379,133 SCDs per year in the United States (114/100,000) (ref.⁵). The global annual incidence is calculated to be 100–200 per 100,000 population. The estimated annual burden of SCD would be approximately 4 million cases worldwide.

The incidence has two peak ages. The first in infancy, often associated with complex congenital heart disease (73/100,000 person-years). In adolescents and adults under 30 years of age, the rate decreases to approximately 6/100,000 person-years. From 35–45 years of age, the risk of SCD increases, with the second peak at around 75 years of age. Black people have a higher risk of SCD across all age groups. SCD has a large preponderance in men relative to women during the young adult and early middle-age years because of the protection that women enjoy from coronary atherosclerosis before menopause. Men have a fourfold to sevenfold greater incidence of SCD than women before 65 years of age, at which point the difference decreases to 2:1 or less and continues to decrease with advancing age⁶.

ETIOLOGY

SCD is associated with many causes and contributing factors (Table 1). Preexisting coronary artery disease and its consequences (acute myocardial ischemia, scarring from previous myocardial infarction, heart failure) are manifest in 80% of SCD victims. Dilated nonischemic and hypertrophic cardiomyopathies account for the second largest number of SCDs, whereas other cardiac disorders, including congenital heart defects and the known
Table 1. SCD causes and contributing factors (adapted from Myerburg 2018 (ref.1))

<table>
<thead>
<tr>
<th>SCD causes and contributing factors</th>
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<td>Coronary artery abnormalities</td>
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<tr>
<td>Hypertrophy of the ventricular myocardium</td>
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<td>Myocardial diseases and dysfunction, with or without heart failure</td>
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<td>Inflammatory, infiltrative, neoplastic and degenerative processes</td>
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<td>Diseases of the cardiac valves</td>
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<td>Congenital heart disease</td>
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<td>Electrophysiologic abnormalities</td>
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<td>Electrical instability related to neurohumoral and central nervous system influences</td>
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<td>Miscellaneous</td>
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genetically determined ion channel anomalies, account for 5–10% of SCDs (ref.17,8).

The spectrum of SCD causes varies with age. In the young, there is a predominance of channelopathies, cardiomyopathies and myocarditis; in older populations, chronic degenerative diseases (coronary artery disease, valvular heart diseases and heart failure) predominate. Cardiovascular mortality has decreased in recent decades due to primary and secondary prevention as well as advances in acute treatment. Despite this, cardiovascular diseases remain the leading cause of death in developed countries and approximately 50% of all these deaths are sudden and unexpected, occurring shortly after the onset of symptoms1. The presence of heart failure (HF) increases the incidence of SCD fourfold9. The annual mortality of people with HF with reduced ejection fraction (HFrEF) is around 15%, about half of deaths being sudden. Severe left ventricular dysfunction with an ejection fraction below 35% is the most accurate and independent predictor of SCD. The overall mortality increases with worsening functional capacity, usually expressed using the New York Heart Association functional classification system (NYHA class I–IV). However, patients with HF and better functional capacity (NYHA class II) have a higher risk of dying suddenly than those with worse capacity (NYHA class IV) (ref.1).

RISK FACTORS

As most SCDs are due to coronary heart disease (CHD), it is not surprising that they have similar risk factors such as hypertension, diabetes mellitus, obesity, smoking and psychosocial factors. The association between physical activity and SCD is affected by the intensity and regularity of exercise. Vigorous exercise increases the risk of SCD, particularly in otherwise inactive people. However, regular exercise attenuates this risk10. A positive family history is a significant independent risk factor for SCD. Occurrence of SCD in first-degree relatives led to a 1.6- to 2.2-fold increase in SCD susceptibility after controlling for traditional risk factors of coronary artery disease11-13. Familial patterns of risk for SCD, which result from known or suspected genetic variations, are emerging as important factors for risk profiling. The various genetic associations can be separated into four categories: inherited uncommon primary arrhythmic syndromes (e.g. long QT syndromes (Fig. 1), Brugada syndrome (Fig. 2), catecholaminergic polymorphic ventricular tachycardia or fibrillation), inherited uncommon structural diseases associated with risk for SCD (e.g. hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy), “acquired” or induced risk for arrhythmias (e.g., drug-induced long QT interval or proarrhythmia, electrolyte disturbances) and common acquired diseases associated with risk for SCD (e.g. CHD, nonischemic cardiomyopathies) (ref.1).

MECHANISM

The propensity to die suddenly originates as a “perfect storm” – interaction of a vulnerable substrate (genetic or acquired changes in the electrical or mechanical properties of the heart) with multiple transient factors that participate in triggering the fatal event7. In the past, the most common (80–95%) sequence of events leading to SCD was degeneration of ventricular tachycardia (VT) into ventricular fibrillation (VF), often followed by asystole or pulseless electrical activity (PEA) (ref.14,15). Nowadays, however, the most common initial documented recording
is asystole or PEA. The first recorded rhythm certainly depends on the time from loss of consciousness to the recording of the electrocardiogram, with an increasing number of false-positive asystolic and bradyarrhythmic cases with time. But in the last three decades, a declining rate of VT/VF has been reported despite significant improvements in response time and rates of bystander cardiopulmonary resuscitation\(^\text{17-20}\). Kuisma et al. reported a 48% decrease in the incidence of out-of-hospital VF from 1994 to 1999 in Finland\(^\text{18}\). A study from Seattle, USA, recorded a 43% decline in the incidence of out-of-hospital VF from 1980 to 2000 (ref.\(^\text{19}\)). The exact reasons have not been fully explained. It is probably related to better primary and secondary prevention of cardiovascular disease and to an aging population. Advanced age is associated with non-shockable rhythms during sudden cardiac arrest. The increased prevalence of end-stage heart failure patients may have influenced the rates of non-shockable cardiac arrest, as terminal heart failure is typically characterized by PEA/asystole\(^\text{21}\). It has a powerful impact on patient outcome and treatment. Patients with asystole or PEA at initial contact have worse prognosis. In a prospective multicenter observational study of 36,902 adults with in-hospital cardiac arrest, the prevalence of VF/VT as the first documented rhythm was 23%, asystole 35% and PEA 32% and rates of survival to hospital discharge for first documented rhythms of VF/VT were 36%, asystole 10.6% and PEA 11.2% (ref.\(^\text{22}\)). Similar results were found.
in another prospective study involving more than 50,000 patients\textsuperscript{23}. Research has focused mostly on SCD due to VF/VT. Therapeutic protocols focus on early defibrillation. Great efforts and investments have been made to equip strategic locations with automatic external defibrillators. However, this will not help if the initial rhythm is unshockable. SCD due to PEA and asystole is a challenge for the future.

**TREATMENT**

Continuous cardiopulmonary support and restoring spontaneous circulation as quickly as possible are the main principles in cardiac arrest management. In most communities, the median time from emergency call to emergency medical service arrival is 5-8 min, or 8-11 min to a first shock\textsuperscript{24}. During this time, the victim’s survival depends on bystanders. The immediate initiation of cardiopulmonary resuscitation (CPR) can double or triple survival from cardiac arrest. Defibrillation within 3-5 min of collapse can produce survival rates as high as 50-70\%. Each minute of delay to defibrillation reduces the probability of survival to discharge by 10-12\% without CPR and by 3-4\% with CPR (ref.\textsuperscript{25}).

After 10 and more minutes without defibrillation, 95\% of people die. Even if CPR was started, only 8\% of patients survived for at least 30 days after out-of-hospital cardiac arrest or to hospital discharge\textsuperscript{26}.

After return of spontaneous or stable assisted circulation, focus shifts to the diagnostic and therapeutic elements of post-cardiac arrest syndrome, which include brain injury, myocardial dysfunction, systemic ischemia/reperfusion responses and control of persistent precipitating factors\textsuperscript{1}. Survivors should be admitted to an intensive care unit (cardiac arrest center if available). Management is determined by the specific cause and underlying pathophysiologic process. Finally, a long-term management strategy to prevent recurrent cardiac arrest has to be established according to the causation and patient functional status.

**PREVENTION**

We distinguish between primary and secondary prevention of SCD. Secondary prevention is intended for persons who have already overcome circulatory arrest or life-threatening arrhythmia. Primary prevention is for those who have a higher risk of SCD but have not yet overcome circulatory arrest or life-threatening arrhythmia. In both groups, the treatment is complex and includes pharmacological and non-pharmacological procedures. Effective therapy of underlying heart disease and associated comorbidities is fundamental. Then we can choose and combine various antiarrhythmic strategies (pharmacotherapy, cardioverter-defibrillator implantation, catheter ablation, surgical treatment). High expectations were set for pharmacological treatment. However, the results of studies with class 1 antiarrhythmics were disappoint-
having a reasonable expectation of survival with a good functional status for more than one year undergo implantation of an ICD for secondary prevention. However, they represent only a small percentage of those at risk for SCD. Most people die during their first episode of malignant arrhythmia, which emphasizes the importance of primary prevention. The current European Society of Cardiology recommends ICD implantation as primary prevention in the following cases:

**Left ventricular dysfunction**

The individual’s left ventricular ejection fraction (LVEF) and functional capacity are central to SCD risk stratification. According to the guidelines, ICD therapy is recommended in patients with symptomatic HF (NYHA class II–III) regardless of etiology and LVEF ≤35% after more than 3 months of optimal medical therapy who are expected to survive for at least 1 year with good functional status.

**Coronary artery disease**

Up to 6% of patients with acute coronary syndrome develop VT or VF. However, early ICD implantation does not improve the prognosis and is not indicated. It may be considered in the presence of specific conditions (pre-existing LVEF dysfunction, incomplete revascularization, occurrence of arrhythmias more than 48 hours after the onset of acute coronary syndrome, polymorphic VT or VF). Assessment of LVEF is recommended in all patients with acute myocardial infarction before discharge and 6–12 weeks after myocardial infarction. The majority of patients with severely depressed LVEF immediately after myocardial infarction show significantly improved systolic function after 3 months. If left ventricular dysfunction persists, ICD implantation is recommended.

**Cardiomyopathies**

Besides left ventricular dysfunction, the guidelines recommend primary ICD prophylaxis in some patients with dilated, hypertrophic and arrhythmogenic right ventricular cardiomyopathy. Lamin A/C gene associated cardiomyopathy is a form of dilated cardiomyopathy with poor prognosis, a rapid evolution toward end-stage heart failure and malignant ventricular arrhythmias associated with increased risk of sudden cardiac death. Screening of first degree relatives is useful for the early diagnosis of the disease. ICD implantation should be considered in case of dilated cardiomyopathy with a confirmed disease-causing mutations in lamin A/C and at least two of these risk factors: non-sustained VT during ambulatory electrocardiogram monitoring, LVEF <45% at first evaluation, male sex and non-missense mutations (insertion, deletion, truncations or mutations affecting splicing). The decision to implant an ICD to a patient with hypertrophic cardiomyopathy is based on the 5-year SCD risk calculated using the HCM Risk-SCD model and taking into account the age and general health of the patient. ICD implantation should be considered in patients with arrhythmogenic right ventricular cardiomyopathy and unexplained syncope or hemodynamically well-tolerated sustained VT. It may be considered in patients with one or more recognized risk factors for ventricular arrhythmia following detailed clinical assessment (frequent non-sustained VT, a family history of premature sudden death, extensive right ventricle disease, marked QRS prolongation, late gadolinium enhancement on cardiac magnetic resonance imaging, left ventricular dysfunction and VT induction during electrophysiological study).

**Inherited primary arrhythmia syndromes**

This is a diverse group of inherited syndromes with heterogeneous manifestations, from asymptomatic carriers to SCD. ICD implantation for secondary prevention is generally accepted. Primary prevention recommendations are based on expert opinion and small observational studies. The device implantation should be considered individually. According to the guidelines, it is recommended in patients with long QT syndrome (Fig. 1) who experienced syncope and/or VT while receiving an adequate dose of beta-blockers. It may be considered in high-risk patients such as women with LQT2 and corrected QT more than 500 ms, patients with corrected QT more than 500 ms and signs of electrical instability and those with high-risk genetic profiles. It is also indicated in patients...
with Brugada syndrome (Fig. 2) with documented VT and in those presenting with a spontaneous type 1 electrocardiogram pattern and a history of syncope. Finally, ICD implantation is recommended in patients with catecholaminergic polymorphic VT and recurrent syncope or polymorphic/bidirectional VT despite optimal therapy (beta-blockers or flecainide).

**Limits of current risk stratification**

Secondary ICD prophylaxis is well defined, effective and generally accepted. The situation in primary prevention is more complicated. The current primary preventive strategies are targeted at a preselected population of people with certain characteristics of heart disease. However, only 55% of SCD victims had known heart disease at the time of death (Fig. 3) (ref.47). In almost half of the cases, cardiac arrest is the first symptom of cardiac disease. Our ability to identify individuals at risk for SCD in this group remains poor. It is the primary challenge of the “Myerburg paradox”. As already mentioned, traditional risk factors increase the risk of SCD, but they cannot be used for SCD risk stratification. Traditional risk factors cannot distinguish people at increased risk for SCD from people with other manifestations of CHD. Cardiology examination would reveal some cases but it is not suitable for identifying possible candidates from the general population. Screening is recommended only for athletes who have a higher risk of arrhythmias and worsening of structural or genetic heart disease during intense physical exercise and for first-degree relatives of sudden death victims7. In this case, a comprehensive autopsy examination including macroscopic, histological and toxicology assessment and postmortem genetic testing of SCD victims can be helpful. Palpitations, presyncope and syncope are the three most important symptoms that require taking a thorough clinical history and possibly further investigations. To the rest of the population, we could recommend “only” the control of modifiable cardiovascular risk factors, early diagnosis and adequate treatment of CHD.

Even our ability to recognize future cardiac arrest in the group with known heart disease is limited. Most SCD studies concentrated on people with CHD, especially after myocardial infarction and/or HF. Based on their results, the individual’s LVEF and functional capacity are central to SCD risk stratification. However, the assessment of functional capacity is subjective and can change significantly over time50. Severe left ventricular dysfunction is thus the strongest independent predictor of SCD, but risk stratification based on LVEF alone is not sufficient. It cannot identify a large subset of people without known heart disease and those with heart disease with normal or slightly reduced LVEF (Fig. 3) (ref.47,49,50). Especially women do not benefit from the current risk stratification. They are 50% less likely to have severe systolic dysfunction and, at the same time, they are less likely to have known heart disease before SCD (ref.51).

Moreover, only some patients with an implanted ICD according to the current guidelines receive appropriate ICD therapy. Of 829 patients, 31% received shocks from their device for any cause and 21% received shocks for rapid VT/VF. During five years of follow-up, the average annual rate of appropriate ICD shocks was 5.1% (ref.51). Around 10% of patients with ICD experience an inadequate shock with all its psychosocial consequences52–55. Avoidable ICD shocks can be reduced by evidence-based programming of the detection rate, detection duration, antitachycardia pacing, algorithms that discriminate supraventricular tachycardia from VT, and specific programming to minimize the sensing of noise56,57. ICD programming based on the current guidelines is associated with a significantly lower rate of ICD therapy and shock without changes in mortality, however only one-third of the studied population had an ICD device programmed in concordance with current guidelines58.

Several SCD risk markers have been proposed for patients with myocardial ischemia, including programmed ventricular stimulation, late potentials, heart rate variability, baroreflex sensitivity, QT interval dispersion, microvolt T-wave alternans and heart rate turbulence. Despite the promising outcomes of the early studies, none of these “predictors” has influenced clinical practice5. High expectations are placed on research of genetic markers of arrhythmic risk and magnetic resonance imaging, especially with the application of gadolinium contrast agent, which can distinguish ischemic and non-ischemic myocardial damage.

Nowadays, it seems unlikely that any single measure will have sufficient discrimination to be used in isolation. Combining known measures in a composite score or serial testing need to be evaluated. The personalized approach is exactly the goal of the PROFID project funded by the European Union (https://profid-project.eu/). It is the study for developing and validating a multivariable clinical prediction model for risk of SCD in patients with prior myocardial infarction. This model will be based on a collection of existing highly phenotyped data with the largest number of post-myocardial infarction patients ever in this regard (~1,000,000 patients of both sexes). The databases represent a wide variety of data sources such as national registries, institutional research databases, electronic health records and claims databases. The project will then compare this model against current clinical practice in patients with LVEF<35% and LVEF>35% in two multinational randomised clinical trials - PROFID-Reduced and PROFID-Preserved. All major stakeholders are represented: academic institutions with top expertise in SCD, European Society of Cardiology, patient organizations, large hospital chains, a large statutory health insurance company, policymakers, and state authorities across Europe59.

**CONCLUSION**

SCD represents a serious problem due to its incidence and impact on society, especially the victims’ families. Thanks to better treatment and prevention of cardiovascular disease, cardiovascular mortality and thus the incidence of SCD has decreased. However, SCD is still responsible for more than half of all cardiovascular deaths.
The overall rate of survival from out-of-hospital cardiac arrest remains low. This underlines the importance of primary prevention, with ICDs playing an important role in high-risk patients. Our ability to identify these patients is insufficient. Currently, the risk stratification and prevention of SCD is targeted at a preselected population with certain characteristics of heart disease. Reduced LVEF is the strongest independent predictor, but it has low sensitivity and specificity. Selected patients represent a relatively heterogeneous group with different comorbidities and prognosis. We need other predictors to help us identify subgroups which will benefit from prevention strategies. We also need to improve risk stratification in people without known heart disease as well as in those with a history of heart disease, but with normal or slightly reduced LVEF. More attention should be paid to women who have a lower risk of SCD, but are more likely to have SCD as the first sign of heart disease. They are also less likely to have severe systolic dysfunction before death and benefit from current prevention strategies. SCD is a “perfect storm” – interaction of a vulnerable substrate (genetic or acquired changes in the electrical or mechanical properties of the heart) with multiple transient factors that participate in triggering the fatal event and can change over time. The risk stratification will thus require regular reassessment. At the present time, early defibrillation is emphasized, as in the past, the most common mechanism of SCD was VT degenerating into ventricular fibrillation. In contrast to earlier data, the most common initial recording is asystole or PEA, against which our strategies are ineffective. This represents another challenge for the future.

Search strategy and selection criteria

Our research strategy was focused on the current state of knowledge about SCD. We examined studies and articles from various resources (e.g. PubMed, ResearchGate). The search terms included: sudden cardiac death, sudden cardiac death incidence, sudden cardiac death prevention, risk stratification, implantable cardioverter-defibrillator. Citations from journals with high impact factors were given special weight.

ABBREVIATIONS

ACEi, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II type 1 receptor blockers; ARNI, Angiotensin receptor-neprilysin inhibitor; CHD, Coronary heart disease; CPR, Cardiopulmonary resuscitation; HCM, Hypertrophic cardiomyopathy; HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction; ICD, Implantable cardioverter-defibrillator; LVEF, Left ventricular ejection fraction; PEA, Pulseless electrical activity; SCD, Sudden cardiac death; SGLT2i, Sodium-glucose co-transporter-2 inhibitor; VT, Ventricular tachycardia; VF, Ventricular fibrillation.

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