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Review Article

Mechanisms of sudden cardiac death

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ABSTRACT

Worldwide, sudden cardiac death (SCD) is a major problem. It is most frequently caused by ventricular tachyarrhythmias: Monomorphic and polymorphic ventricular tachycardia (VT), torsade de pointes (TdP), and ventricular fibrillation (VF). Beta blockade, ACE inhibition, coronary reperfusion and other treatments have reduced the incidence of VT but pulseless electrical activity (PEA) is increasingly seen, particularly in patients with advanced chronic heart disease. From existing data, bradyarrhythmia in the form of asystole (usually complete heart block without escape rhythm) causes only a minor proportion (10–15%) of SCD. In patients aged 50 years and more, coronary artery disease plays a dominant role causing more than 75% of SCD cases, either by acute ischemia and ventricular fibrillation or by chronic scar formation and reentrant VT. In younger patients, SCD may occur in patients with structurally normal hearts. A number of arrhythmogenic disorders with an increased risk of SCD have been detected and better understood recently, such as long and short QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and the early repolarization syndrome. Most importantly, ECG signs and clinical features indicating high risk for SCD have been identified. Knowledge of the exact electrophysiologic mechanisms of ventricular tachyarrhythmias at the cellular level has been improved and mechanisms such as phase 2 reentry and reflection proposed to better understand why and how SCD occurs.

1. Definition of sudden cardiac death

Sudden cardiac death (SCD) has been defined as "natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected".[1] SCD is therefore always non-traumatic and should be unexpected and instantaneous. The delay between onset of symptoms and (sudden) death has been defined differently over time, from "within 24 hours" to "within 6 hours" and "within 1 hour", which is the currently preferred definition.[2]

The term SCD is usually applied in cases where a patient dies suddenly without any symptoms that indicate an imminent risk of natural death within the next minutes. In fact, 25% of patients treated for out-of-hospital cardiac arrest had literally no symptoms before the abrupt onset of SCD.[3]

It has been argued that in many cases of sudden death, the cause is unknown and SCD due to an arrhythmic event is only assumed, thus overestimating cardiac causes of sudden death. However, autopsy studies in patients with sudden

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death showed approximately three quarters of cases due to cardiac disease and only approximately a quarter due to non-cardiac causes, predominantly due to pulmonary embolism (18%) aortic rupture (4%), and intracranial bleeding (3%).[4]

The term "arrhythmic death" has been used instead of SCD, and the Hinkle-Thaler classification distinguishes only arrhythmic and non-arrhythmic cardiac death.[5] However, these terms are not identical with SCD because patients may die non-suddenly due to arrhythmias and not all sudden deaths are due to arrhythmias. The term "sudden death" will be replaced by SCD in this review to clarify that only cardiac mechanisms are considered. In some instances, the term "cardiac arrest" or "aborted SCD" will be used to clarify that survivors of SCD are included.

2. Causes of sudden cardiac death: arrhythmias and underlying pathology

2.1. *Underlying arrhythmias*

If an ECG documentation is available at the time of sudden loss of consciousness, it shows ventricular fibrillation (VF) in 75%–80%, only rarely (10%–15%) bradyarrhythmia; in 5%–10% the ECG does not show an arrhythmia (Fig. 1).[2,6]

Bradyarrhythmias lead to sudden death only in rare cases because in most patients, endogenous release of catecholamines generates and sustains an escape rhythm that is sufficient to keep the patient alive. In contrast, endogenous catecholamine release triggered by circulatory collapse due to ventricular tachyarrhythmias rather deteriorates the situation.

In patients with an implantable cardioverter-defibrillator (ICD), up to 80% of all device-treated ventricular tachyarrhythmias are monomorphic ventricular tachycardia (VT).[7] Ventricular tachycardia (VT) is presumed to represent the typical initial arrhythmia in patients with a myocardial scar after infarction. However, monomorphic VT usually does not

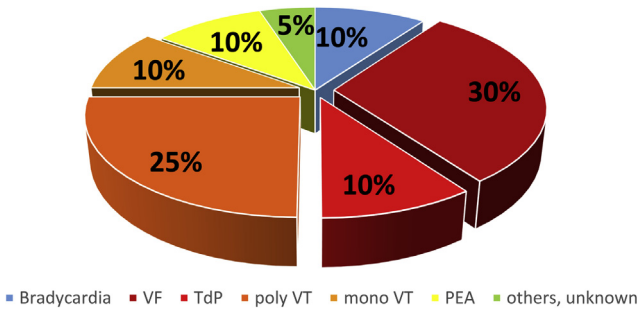

Fig. 1 – Synopsis of the type of arrhythmia documented as the first rhythm at the time of out-of-hospital SCD. The published prevalence ranges widely in different studies and registries. Different forms of VT/VF taken together (four red to orange slices) account for 75% of documented rhythms. Mono VT: monomorphic ventricular tachycardia, PEA: pulseless electrical activity, poly VT: polymorphic ventricular tachycardia, TdP: torsade de pointes, VF: ventricular fibrillation.

lead to loss of consciousness or SCD. In 100 patients with stable VT, systolic blood pressure remained at 110 mmHg despite a mean VT duration of 41 minutes at a rate of 188 bpm and the fact that patients had a mean left ventricular ejection fraction of 27%.[8] Monomorphic VT leads to SCD only if other special conditions contribute to an insufficient circulation or if it degenerates into polymorphic VT or ventricular fibrillation (VF).

Polymorphic VT is a very rare finding on Holter tapes (prevalence 0.15%[9]) but caused up to 40% of SCD that occurred in-hospital during rhythm monitoring.[10,11] Polymorphic VT was inducible in 15–20% of survivors of SCD who underwent an electrophysiological study.[12,13]

Polymorphic VT is estimated to be the cause of SCD in approximately 25% of the cases and is particularly frequent in acute myocardial ischemia. Additionally, it is the typical arrhythmia in catecholaminergic polymorphic VT (CPVT), an inherited arrhythmogenic disorder characterized by adrenergically mediated polymorphic ventricular tachyarrhythmias.

Torsade de pointes (TdP) tachycardia is a form of polymorphic VT characterized by a gradual change in the QRS amplitude and twisting of the QRS vector around the isoelectric line. TdP is frequently associated with a prolonged QT interval. It can terminate spontaneously; recur in non-sustained spells, or degenerate into VF. It may be caused by QT-prolonging drugs, ischemia, or may be due to inherited long QT syndromes. It is 2–3 times more frequent in women; advanced age, bradycardia, hypokalemia, hypomagnesemia, left ventricular systolic dysfunction, renal and liver disease (both leading to elevated plasma concentrations of causative drugs) represent risk factors for drug-induced TdP. Patients with advanced heart failure and a history of drug-induced TdP had a significantly higher SCD risk during therapy with amiodarone.

Ventricular flutter and VF are responsible for 23% of out-of-hospital cardiac arrests treated by the emergency medical system.[14] VF can result from an initial VT that degenerated into less organized rhythms. However, SCD may also result from primary VF caused by acute myocardial ischemia or due to inherited channelopathies such as Brugada or long QT syndrome.

Pulseless electrical activity (PEA) is usually defined as the presence of spontaneous organized cardiac electric activity in the absence of blood flow sufficient to maintain consciousness and (to distinguish it from e.g. vasovagal syncope) absence of a rapid spontaneous return of adequate organ perfusion and consciousness.[15] Clinically, PEA is characterized by the absence of a palpable pulse in an unconscious patient with organized electric activity other than ventricular tachyarrhythmia on the ECG. The definition of PEA does not include the agonal pattern of slow, very wide QRS complexes at the end of a prolonged cardiac arrest. The incidence of PEA as the first documented rhythm in patients with SCD is increasing, potentially due to the ICD therapy, beta blockers and other drugs in heart failure that reduce the risk of VT and VF while not changing the risk of PEA. Additionally, patients with very advanced heart disease may be more likely to develop PEA than VT/VF which is supported by the observation of a higher incidence of PEA in nursing homes compared to public locations.[15] Even in patients with PEA who survived