European Heart Journal Supplements (2023) **25** (Supplement B), B16–B20
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad077

ESC
European Society
of Cardiology

Causes of sudden death

Monica De Gaspari, Stefania Rizzo, Gaetano Thiene, and Cristina Basso *

Cardiovascular Pathology, Padua Hospital, Department of Cardiology, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy

KEYWORDS
Sudden cardiac death;
Cardiac arrest;
Ion channel diseases

Sudden cardiac death (SCD) pathophysiological point of view can be either mechanical or electrical. In case of mechanical SCD, the most frequent causes are pulmonary thromboembolism and cardiac tamponade due to intrapericardial rupture (aortic dissection, heart rupture). This distinction is important because cardiac arrest retains survival potential through cardiopulmonary resuscitation and defibrillators only if the rhythm is shockable. The heart diseases that can cause SCD vary according to the age of the individual. In young people, primary electrical diseases ('ion channel diseases') and cardiomyopathies (particularly hypertrophic and arrhythmogenic), both genetically determined and therefore potentially recurred in the proband's family, as well as myocarditis and coronary anomalies prevail; in adult–elderly populations, coronary atherosclerosis with its complications and degenerative valve diseases (aortic stenosis and mitral valve prolapse) predominate. In this short text, the main structural heart diseases characterized by electrical instability at risk of SCD will be recalled, with a focus on coronary, myocardial, and valvular diseases.

Sudden death (SD) is a natural event that interrupts life instantly. The time interval between symptom onset and death has been the subject of various interpretations, but the widely accepted definition is that of a death that occurs unexpectedly, within 1 h of symptom onset, in healthy even vigorous people or in people with whose pre-existing morbid conditions did not predict such a sudden outcome.[1,2] This temporal definition refers to witnessed SD, while the interval is extended to 24 h for victims of unwitnessed SD, but known to be alive and in a non-exiting condition 1 day before being found dead. Since up to a third of SDs are not witnessed, the exclusion of these cases would prejudice the data, underestimating too much the extent of the phenomenon. In almost two-thirds of cases, SD is the first cardiac event as there are no previous signs or symptoms in the anamnesis, while in one-third, it is predictable because they are patients at risk.

Sudden death can occur throughout life and even in the prenatal period: up to 50% of stillbirths die suddenly *in utero* (unexplained sudden intrauterine death, i.e. SIUD). Sudden infant death (SUID) affects newborns with an incidence of up to 1.5% and can find an explanation at autopsy in unrecognized malformations, infections, or, not infrequently, as a result of abuse. Within the SUID grouping, sudden infant death syndrome (SIDS) refers to SUID infants, aged 1–12 months, found dead ('cot death'), in which an underlying cause is not discovered at autopsy. Today, the incidence of SIDS varies from 0.3% to 1% and is declining, following preventive measures with the supine position during sleep.

Sudden cardiac death: definitions

When it comes to SD, it should be specified that international scientific societies have introduced various definitions to differentiate the various contexts. Below are the definitions, as also reported in the recent guidelines of the European Society of Cardiology.[2]

Sudden cardiac arrest: sudden interruption of normal cardiac activity with haemodynamic collapse.

Cardiac SD: sudden natural death presumed to be of a cardiac cause occurring within 1 h of the onset of symptoms in assisted cases and within 24 h of the subject being

*Corresponding author. Tel: +39 049 827 2286, Fax: +39 049 821 2284, Email: cristina.basso@unipd.it

last seen alive when not witnessed. In the case of the subject undergoing autopsy, cardiac SD is defined as the unexpected natural death of unknown or cardiac cause.

Unexplained SD: sudden unexplained death occurring in an individual older than 1 year of age.

Sudden infant death syndrome: sudden unexplained death occurring in an individual <1 year of age with a negative pathological and toxicological evaluation and a negative forensic examination of the circumstances of death.

Sudden arrhythmic death syndrome (SADS): sudden unexplained death occurring in an individual older than 1 year of age with negative pathological and toxicological evaluation.

Epidemiology of cardiac sudden death

Any epidemiological analysis of cardiac SD must recognize that very few studies report estimates from primary data sources and that the stated definitions of cardiac SD and cardiac arrest are not standardized in the medical community.[3] Ideally, although impractical, all suspected cases of cardiac SD should undergo an autopsy, which is necessary to reliably rule out extra-cardiac causes of SD.[4]

The incidence of cardiac SD increases markedly with age, mainly due to coronary atherosclerosis (CAD) but also to degenerative diseases, such as valvulopathy, primarily mitral valve prolapse, and aortic valve stenosis. The incidence is very low during infancy and childhood (1/100 000 person-years), it is about 50/100 000 person-years in individuals between the fifth and sixth decades of life; and in the eighth decade of life, it reaches an annual incidence of at least 200/100 000 person-years.[5]

At any age, males have higher cardiac SD rates than females, even after adjusting for CAD risk factors.

In the Western world, the epidemiology of cardiac SD is closely related to CAD, which accounts for up to 75–80% of cases.

Obviously, the risk increases in high-risk subgroups. For example, the incidence of SD is 1–2%/year in people with a coronary risk profile, 5%/year in those with a prior coronary event, and 15%/year in those with congestive heart failure, and ejection fraction (EF) < 35%, 25%/year in cardiac arrest survivors. The combination of prior myocardial infarction, low EF, and ventricular tachycardia represents a risk of nearly 35%/year.[6]

Pathophysiology and causes of cardiac sudden death

From a pathophysiological point of view, cardiac SD (or cardiac arrest) can be mechanical or electrical.[1] In the first case, when cardiac function stops for mechanical reasons, the most frequent causes are pulmonary thromboembolism, with blood circulation being interrupted by the sudden occlusion of the pulmonary artery, or cardiac tamponade from intrapericardial rupture (aortic dissection, heartbreak). This distinction is important because within minutes of cardiac arrest, irreversible brain damage occurs due to the arrest of circulation. Cardiac arrest retains survival potential with prompt cardiopulmonary resuscitation and defibrillators, but only if the rhythm is shockable.

Heart disease associated with myocardial ischemia (MI) varies with the age of the individual (*Figure 1*). In young people, primary electrical diseases ('channelopathies') and cardiomyopathies prevail, as well as myocarditis and coronary anomalies.[5] In older populations, chronic structural diseases predominate (CAD either from acute coronary events or from chronic coronary stenosis and post-infarction chronic ischaemic heart disease and valvular heart disease), while potentially hereditary electrical diseases or non-ischaemic structural diseases can cause more than 50% of cardiac SD in individuals younger than 50 years of age.

From an anatomical-pathological point of view, these diseases, acquired or congenital, can involve the coronary arteries, the myocardium, the valves, the large arteries, and exceptionally the conduction tissue (pathologies of the specialized tissue causing atrioventricular blocks or abnormal pathways ventricular pre-excitation substrate).[1]

There is also a variable slice of SD with a 'structurally healthy heart' (mors sine materia), especially in youth but sometimes overestimated. In fact, this group includes SDs caused by ion channel disease (long QT syndrome, short QT syndrome, Brugada syndrome, and polymorphic catecholaminergic tachycardia from exertion), but also dysemias, occult diseases of the conduction system, up to idiopathic ventricular fibrillation.[7] The availability of the ECG trace and the genetic and cardiological study of the family members are essential to reach the diagnosis.

The main structural cardiac diseases at risk of electrical instability are briefly discussed below.

Coronary arteries

Coronary atherosclerosis is the most prevalent of SD in individuals older than 35 years. In adults and the elderly, thrombotic occlusion of a main subepicardial coronary artery is the rule, and diffuse, multi-vessel involvement is typically found.[8] The culprit lesion typically displays the classic features of a vulnerable atherosclerotic plaque (necrotic core covered by a thin fibrous cap, rich macrophage infiltration, and frequent calcifications) (*Figure 2A*). Obstructive atherosclerotic plaque (>75% of the stenotic lumen) is most often located in the proximal portion of the anterior descending branch of the left coronary artery.

Conversely, in juvenile age, only 25–30% of cases present a recent occlusive thrombosis and the atherosclerotic plaque is often fibrocellular or, if fibroatheromasic, often with a fibrous cap and a small lipid core.[9] It is common to observe an abundant presence of smooth muscle cells indicating a recent accelerated proliferative phenomenon (*Figure 2B*), while calcification is mostly absent. The atherosclerotic disease is mostly focal, with single-vessel involvement, preferentially in the anterior descending branch.

When a thrombotic occlusion is observed, if in the adult and in the elderly, this is almost always precipitated by the rupture or fissuring of the atherosclerotic plaque in the presence of a thin fibrous cap, in the young, the phenomenon of endothelial erosion is observed more frequently, with or without superficial inflammation of the intima ('endothelialitis'). To explain plaque instability in the absence of thrombosis in young SD victims with critical atherosclerotic stenosis, the coronary vasospasm hypothesis has also been advocated. Our group demonstrated that

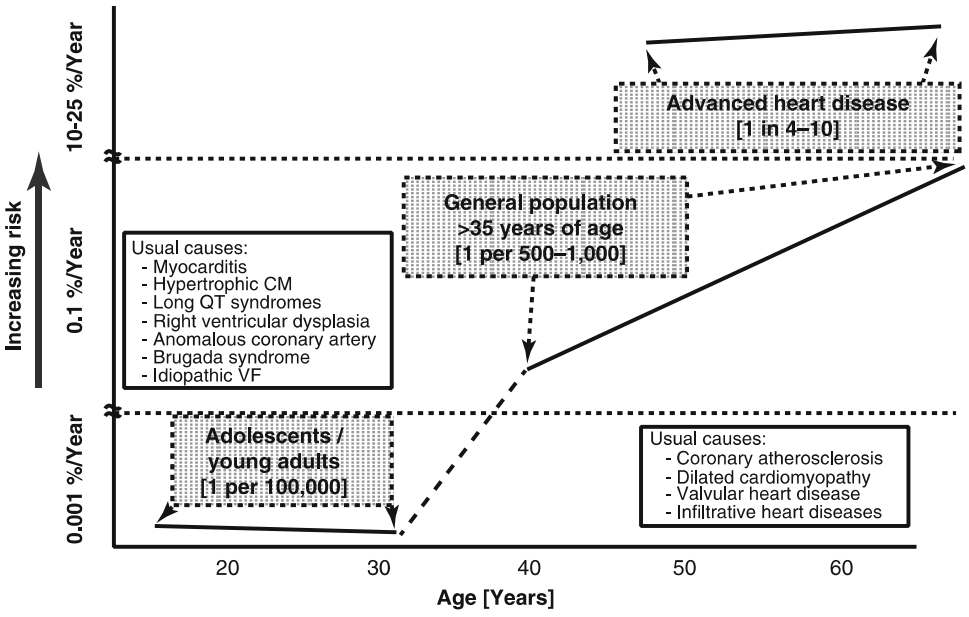

Figure 1 Association between SD incidence and age. The incidence of SD in adolescents and young adults (<35 years) ranges from 0.5 to 8/100 000/year in the reported epidemiological studies. SD is due to different heart diseases throughout life. Cardiomyopathies, myocarditis, premature coronary artery disease, congenital anomalies of the coronary arteries and channelopathies are prevalent in young people in contrast to the adult-old age in which ischaemic heart disease from coronary atherosclerosis dominates (from Myerburg and Vetter[5]).

smooth muscle cells of fibrocellular plate segments, both at the level of the intima and the underlying media, show a contractile phenotype.[10] In the context of critical stenosis, smooth muscle contractility might contribute to transient coronary spasm leading to myocardial ischaemia and arrhythmic SD.

The presence of previous ischaemic damage with post-infarction scar is frequent in the adult-elderly age, while it is exceptional in the youthful age.

Non-atherosclerotic coronary heart disease can also be a cause of ischaemia and SD, especially in the young where they account for one-third of cases of fatal coronary heart disease.[1]

They include congenital and acquired disorders, such as coronary artery anomalies, embolism, arteritis (especially Kawasaki syndrome in children and Takayasu's arteritis or panarteritis nodosa), and spontaneous dissections. Among the congenital anomalies in particular, the anomalies of origin of a coronary artery from the wrong sinus of Valsalva must be mentioned, with a course not only inter-arterial but also intramural aortic in the first section; they are the cause of ischaemia, especially during prolonged physical effort, and the presence of symptoms or signs triggered by physical exercise must always require the exclusion of these anomalies as well.[11,12] Among the non-atherosclerotic coronary diseases, spontaneous dissection is an almost exclusive pathology of the female sex, observed not only in the peripartum, whose etiopathogenesis still remains unknown.

Myocardium

When we speak of cardiomyopathies at risk of SD, we are referring mainly to hypertrophic cardiomyopathies (HCM) and arrhythmogenic (AC) and more rarely to dilated cardiomyopathies as the latter is mostly already diagnosed in symptomatic patients. The first two are also known to cause SD in the young and in the athlete, even as the first manifestation of the disease, as physical effort acts as a trigger of electrical instability.[1]

Hypertrophic cardiomyopathy is the most frequent primary cardiomyopathy, being reported in 0.2–0.5% of the general population. It is characterized by extreme heterogeneity regarding phenotypic expression, pathophysiology, and clinical course. Genetically determined, it is mostly due to mutations of genes coding for sarcomeric proteins.

Arrhythmogenic is a rarer cardiomyopathy, with a prevalence of 0.01–0.05% in the general population. An age- and gender-related penetrance of the phenotype has been demonstrated, with SD typically occurring during adolescence or young adulthood.[13] The most common pattern of inheritance is autosomal dominant with pathogenic mutations mostly in desmosomal genes.

The histopathologic feature of AC is progressive loss of ventricular myocardium and fibrofatty replacement that usually begins in the epicardium. The traditional variant with prevalent involvement of the ventricle almost always sees a transmurality of the fibro-adipose replacement, with the possible development of aneurysms in the so-called triangle of dysplasia. The clinical diagnosis of this variant is well established and rarely escape electrocardiographic and subsequent echocardiographic examination. With the advent of magnetic resonance imaging and genotype–phenotype correlations, the variant with dominant involvement of the left ventricle has emerged, in which the fibro-adipose process, with a prevalent fibrous component, can remain confined to the subepicardial or mediomural layers, in the absence of transmurality and maintaining conserved ventricular volume. This variant

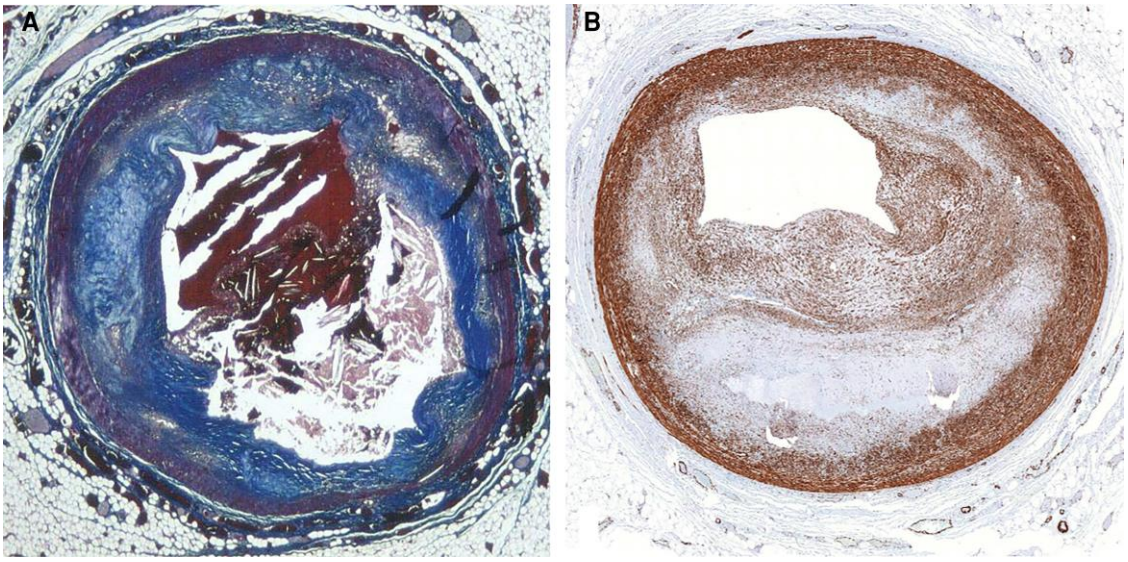

Figure 2 Cases of SD due to coronary atherosclerosis in adults and young people. (*A*) Occlusive coronary thrombosis due to rupture of fibrous cap of fibro-atheromasic atherosclerotic plaque; (*B*) critical stenosis due to uncomplicated fibroatheromasic plaque with exuberant proliferation of intimal smooth muscle cells and preserved media.

is more difficult to identify clinically, so that new criteria have been proposed and cardiac magnetic resonance with contrast is fundamental in the diagnostic process. The morphological substrates of the electrical instability of the AC can be identified in the fibroadipose replacement with impaired conduction of the electrical stimulus in the ventricular wall and in the developmental 'poussees' with cardiomyocyte necrosis and myocarditis-like inflammatory reaction.[14]

Myocarditis, of any etiopathogenesis (infectious, immune, toxic, iatrogenic, etc.), is an inflammatory disease characterized by cardiomyocyte necrosis, inflammatory infiltrates (generally lympho-monocytic but also eosinophilic or granulomatous) and interstitial oedema. It is also counted among the causes of electrical instability and SD and must be excluded in cases of SD or cardiac arrest with unaffected coronary arteries, especially in children and youth. Magnetic resonance imaging is useful for the diagnosis even if the 'gold standard' remains the histological documentation via endomyocardial biopsy to define the inflammatory histotype and proceed with the molecular examination for the search for the viral genome.

Valves

Valvular diseases that can cause arrhythmic SD involve the aortic and mitral valves.[1]

Aortic valve stenosis is generally a degenerative disease of the elderly usually resulting from calcific dystrophy of a morphologically tricuspid valve. If bicuspid, the process can be anticipated with the appearance of stenosis as early as 50–60 years of age. At a young age, it can be congenital aortic valve stenosis, both unicuspid and bicuspid with dysplasia. Sudden death is arrhythmic and the AC substrate is left ventricular hypertrophy and subendocardial ischaemia, in terms of myocytolysis and replacement fibrosis.

Sudden death that occurs in people with mitral valve prolapse is arrhythmic, rarely mechanical from ruptured cords with acute pulmonary oedema. It is a mitral valve prolapse with gross deformation of the leaflets, which appear thickened due to myxoid degeneration, in the absence of relevant mitral insufficiency. The posterior leaflet is usually involved, but the anterior leaflet may also be affected. Several hypotheses have been put forward to explain the electrical instability at risk of SD, such as endocardial friction of the tendon cords, associated right ventricular cardiomyopathy, or abnormalities of the specialized conduction system. Our pathological studies of patients with mitral valve prolapse who die suddenly have shown the presence of patchy replacement-type fibrosis in the papillary muscle of the mitral valve as well as in the posterobasal free wall, with or without endocardial plaque, a finding that represents a AC substrate detectable *in vivo* by cardiac magnetic resonance with contrast.[15]

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

References

1. Thiene G, Corrado D, Basso C. *Sudden Cardiac Death in the Young and Athletes*. Milan: Springer Verlag; 2016.
2. Zeppenfeld K, Tfelt-Hansen J, de Riva M *et al*. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126.

3. Kong MH, Fonarow GC, Peterson ED. Systematic review of the incidence of sudden cardiac death in the United States. *J Am Coll Cardiol* 2011;**57**:794–801.
4. Basso C, Aguilera B, Banner J *et al*. Association for European Cardiovascular Pathology. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. *Virchows Arch* 2017;**471**:691–705.
5. Myerburg RJ, Vetter VL. Electrocardiograms should be included in preparticipation screening of athletes. *Circulation* 2007;**116**:2616–2626.
6. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation* 2012;**125**:1043–1052.
7. Thiene G, Rizzo S, Schiavon M. Structurally normal hearts are uncommonly associated with sudden deaths in athletes and young people. *J Am Coll Cardiol* 2019;**73**:3031–3032.
8. Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *N Engl J Med* 1984;**310**:1137–1140.
9. Corrado D, Basso C, Poletti A, Angelini A, Valente M, Thiene G. Sudden death in the young. Is acute coronary thrombosis the major precipitating factor? *Circulation* 1994;**90**:2315–2323.
10. Rizzo S, Coen M, Sakic A *et al*. Sudden coronary death in the young: evidence of contractile phenotype of smooth muscle cells in the culprit atherosclerotic plaque. *Int J Cardiol* 2018;**264**:1–6.
11. Basso C, Maron BJ, Corrado D, Thiene G. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. *J Am Coll Cardiol* 2000;**35**:1493–1501.
12. Rizzo S, De Gaspari M, Frescura C, Padalino M, Thiene G, Basso C. Sudden death and coronary artery anomalies. *Front Cardiovasc Med* 2021;**8**:636589.
13. Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. *Hum Pathol* 2000;**31**:988–998.
14. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? *Circulation* 1996;**94**:983–991.
15. Basso C, Perazzolo Marra M, Rizzo S *et al*. Arrhythmic mitral valve prolapse and sudden cardiac death. *Circulation* 2015;**132**:556–566.