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Sudden death: Causes, epidemiology, and associations in cardiology

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ABSTRACT

The largest challenge in modern cardiology is certainly sudden death (SD). Sudden death is described as an unanticipated, nontraumatic death that occurs within an hour of the development of new or worsening symptoms, within 24 hours of the last time the person was seen alive. Genetic, environmental, or acquired factors may all play a role in SD. In this review, we evaluated the factors related to both sudden cardiac death and sudden non-cardiac death and we explained the epidemiology of SD and the disorders that are associated with SD.

Keywords: Epidemiology, risk factors, sudden cardiac death, sudden non-cardiac death.

Sudden deaths (SD) often appear as unexpected deaths. The basis of SDs lies in traumatic events. The World Health Organization (WHO) defines SD as "deaths that occur within 24 hours of the onset of symptoms";[1] while the Association for European Cardiovascular Pathology defines SD as "a natural death that occurs within six hours of the onset of symptoms in a seemingly healthy subject or in a person whose disease is not as severe as expected of a lethal outcome".[2]

In sudden unexpected deaths, the cause can be an acute-serious complication of a systemic disease, an acute or late complication of previous trauma or a late complication of a forgotten or ignored trauma, or intoxications. A person who does not have a known illness is found dead or dies within a short time without understanding the cause of death or a person with a known disease but does not show a clinical cause of death is usually considered an unexpected death by the relatives of the person. In these cases, an autopsy is required to explain the cause of death.[3]

During the external examination, crime scene investigation, and autopsy, several significant pieces of evidence are collected to help identify the causes of SD. Also, anamnesis and clinical data should be collected to identify the exact cause of death.[4]

Sudden death may have many different etiologies, however, it is most commonly related to ischemic heart disease. In general, a person with sudden cardiac death (SCD) cannot survive. When the patient survives, the event is referred to as a canceled SCD or sudden cardiac arrest.[5]

EPIDEMIOLOGY AND RISK FACTORS

The most prevalent cause of death in the case of SD is related to cardiovascular diseases. In the US, the annual incidence of SCD is 60 per 100,000 people. Accordingly, between 300,000 and 400,000 SCDs happen in the United States (US) every year. Men (76 per 100,000) have a higher incidence than women (45 per 100,000).[6]

The incidence of SCD rises with age. Younger populations have a 100-fold lower incidence of SCD than older people do. Women are generally protected from SCD until the menopausal years when the incidence rises to approach that of men. However, conventional coronary artery disease (CAD) risk factors can predict SCD events in younger women as well. Sudden cardiac death is related to genetic factors at multiple points along the pathophysiological pathway. Mutations and polymorphisms influence the risk

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of SCD connected with both CAD and non-CAD etiologies. Additionally, studies have shown a familial tendency for SCD to be the first sign of CAD. Some studies have shown that African Americans had a higher risk of SCD than whites, although Hispanics may have a lower risk.[7]

Almost half of the people with SCD had no previous diagnosis of a cardiac disorder. In this population, risk categorization is especially difficult. Additionally, 40% of SCDs happen in people with known heart diseases who also have a left ventricular ejection fraction (LVEF) of more than 40%. The remaining (about 10%) incidence of SCD affects people with known structural heart disease and LVEF is less than 40%. Only 2% of all SCDs are caused by genetic arrhythmias. Sudden cardiac death risk factors are similar to those of ischemic heart disease and include smoking, hypertension, dyslipidemia, and diabetes. Additionally, patients with CAD who are obese have a higher risk of SCD.[8] The risk of SCD increases (about 17-fold) in non-sedentary people after vigorous physical activity, particularly in those who are generally sedentary (approximately 74-fold).[9]

The risk of SCD is also increased by psychosocial stressors. Significant disasters like earthquakes and war raise the prevalence of SCD in the affected populations.[10] The risk of SCD is increased by binge drinking and heavy alcohol use (six drinks or more per day).[11] Additionally, a higher level of serum C-reactive protein has been linked to a higher risk of SCD.[12] However, not all diseases linked to SCD have a cardiac origin; some of them are non-cardiac conditions. Based on this knowledge, SD can be classified by the involved anatomical system.

CARDIOVASCULAR DISEASES AND SUDDEN DEATH

Cardiovascular diseases are the primary cause of SD globally, accounting for over 90% of such cases. Coronary artery disease is the most common cause of the so-called SCDs. Age and sex are two key risk factors for SCD that have been identified. Age certainly has an impact on the risk of SD, which is higher in males than females. In middle age, especially from 45 to 64 years old, the death rate rises significantly.[13]

Previous CAD is another major consideration. Sudden death is four times as common in patients who had known CAD. Furthermore, myocardial infarction from coronary disease is the most prevalent cause of SCD. Cardiomyopathy with or without left ventricular dysfunction, as well as a variety of arrhythmogenic disorders (most notably the Wolff-Parkinson-White syndrome and inherited channelopathies such as congenital long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome), are also relatively common primary cardiac causes of SCD. According to estimates, only 5 to 10% of SCD instances, include people who do not have heart failure or coronary disease.[14]

Also, hypertension may be a significant indirect risk factor for the rise in SCD events. Especially, the incidence of SD is three times higher in males with systolic blood pressures >160 mmHg than in those with systolic pressures 140 mmHg.[15] Sudden cardiac death and obesity are connected. According to reports, the probability of this deadly event rises gradually with weight.[16] In addition, cigarette smoking and alcohol/drug addiction are two more key indirect factors to consider. Smokers have a threefold higher prevalence of SD than nonsmokers.[17]

Sudden death can occur in young individuals during athletic activities. Hypertrophic cardiomyopathy was the most common cardiovascular cause of SD in major postmortem research studies of athletic populations in the US.[18] Congenital coronary artery abnormalities are the second most common cardiovascular cause of SD in athletes.[19]

NEUROLOGICAL DISORDERS AND SUDDEN DEATH

Epilepsy, ischemic stroke, intracranial hemorrhage, drugs, and traumatic head injury are among the diseases of the central nervous system that can directly (or indirectly through cardiac involvement) cause SD.[20] Epilepsy is a common chronic neurological condition marked by seizures. Individuals diagnosed with epilepsy have a much higher mortality rate. The most prevalent type of seizure-related mortality is sudden unexpected death in epilepsy

(SUDEP).[21] It often occurs during sleep, often going unnoticed. Risk factors for SUDEP include nighttime seizures, generalized tonic-clonic seizures, early onset of epilepsy, longer duration of epilepsy, the presence of asthma, dementia, male sex, symptomatic etiology of epilepsy, and alcoholism.[22] Intracerebral hemorrhage (ICH) can result from hypertension or various other factors and constitutes approximately 10% of all stroke cases. The primary and most significant risk factor associated with ICH is hypertension.[23] About 5% of strokes are caused by subarachnoid hemorrhage, which has associated risk factors including smoking, high blood pressure, becoming older, and probably female sex.[24] Reduced heart rate variability (HRV) is suspected to be caused by brain infarction. Furthermore, there is a significant positive correlation between SD and decreased HRV.[25]

RESPIRATORY DISEASE AND SUDDEN DEATH

Acute pulmonary embolism is the most significant cause of death in the respiratory system.[26] Fatal pulmonary embolism (PE), a consequence of deep vein thrombosis, is the most common cause of SD affecting the respiratory system.[27] High mortality rates are associated with PE. The severe acute respiratory syndrome coronavirus-2 is what causes the coronavirus disease 2019 (COVID-19).

Analysis of the available data reveals a probable link, even if the direct causal relationship between SCD and COVID-19 has not yet been established. Sudden cardiac death incidence has been observed to be rising in both community and hospital settings.[28]

According to data from the Houston Fire Department, the number of cardiac arrest calls that resulted in patient death increased by 45% during the COVID-19 epidemic.[29] Data from Italy indicates a significant positive correlation between the spread of COVID-19 and a 58% increase in out-of-hospital cardiac arrests compared to the previous year.[30]

Acute pneumonia is one of the natural causes of SD. It could be caused by bacterial and viral agents, leading to a variety of diseases such as sepsis-related cardiomyopathy, and myocardial ischemia.[31] Hypoxia resulting from pulmonary conditions such as minor and major airway obstruction (bronchospasm, aspiration, foreign body, edema) is a significant additional cause of SD.[32]

GASTROINTESTINAL DISEASE AND SUDDEN DEATH

In comparison to other disorders, gastrointestinal problems are a less prevalent cause of sudden unexpected death. This is because to the fact that gastrointestinal disorders usually exhibit symptoms that demand early medical intervention. Various congenital and acquired gastrointestinal abnormalities are among the causes of sudden unexpected death. It might be associated with several disorders such as duodenal ulcer, gastric ulcer, ulcerative colitis or diverticulitis, cancer, duodenal obstruction, gastric heterotopia, gastric dilatation, and abdominal hernias. Furthermore, reflex vagal cardiac inhibition caused by distension of the upper gastrointestinal tract has been characterized as another quick cause of mortality due to duodenal obstruction.[33]

ENDOCRINE (METABOLIC) DISEASE AND SUDDEN DEATH

The metabolic disease known as diabetes mellitus (DM) is characterized by hyperglycemia despite having a diverse spectrum of etiologies and clinical manifestations.[34]

However, diabetics frequently experience heart failure; CAD or left ventricular dysfunction is common in these individuals. Researchers from the Rochester Diabetic Neuropathy Study discovered that significant CAD or left ventricular dysfunction was present in every event of SD with diabetes.[35] Diabetes is reported to be the most common reason that puts people at risk for cardiac events in the US. Additionally, people with DM have a higher risk of ventricular arrhythmia.[36]

Hypoglycemia (HoG) is one of the metabolic diseases that causes SD and remains uncertain. One hypothesis for HoG-related SD is that hypoglycemia produces direct abnormalities in cardiac electrophysiology, which can lead to malignant tachydysrhythmias. Premature ventricular contractions, atrial arrhythmias, and ischemia electrocardiogram abnormalities

have all been reported to occur during hypoglycemia.[37] Testing for glucose levels in the blood, spinal fluid, or vitreous fluid can confirm the postmortem diagnosis of HoG as the cause of SD. In circumstances when hypoglycemia is suspected, the measurement of the ketone body-hydroxybutyrate may also be helpful.[38]

Also, undiagnosed chronic thyroiditis has been linked to cases of SD. According to reports in the literature, thyroid diseases, particularly silent (painless) thyroiditis, can be one of the causes of SD.[39] For example, a young woman who was found unconscious in a sauna recently died from unusual heatstroke, and an autopsy showed she had Hashimoto's thyroiditis previously.[40]

HEMATOLOGICAL DISORDERS AND SUDDEN DEATH

A genetic condition called hemoglobinopathy causes one of the globin chains in the hemoglobin molecule to have an irregular shape. A sickle-cell disorder is the most common hemoglobinopathy.[41] Infection/sepsis, acute chest syndrome (ACS), which is clinically defined by a new pulmonary infiltrate on chest radiography and is accompanied by fever, chest pain, and a range of respiratory symptoms, including wheezing, coughing, and tachypnea, are the most frequent causes of death in the sickle cell population.[42-44] A significant fraction of unexpected deaths in sickle-cell patients is caused by acute pulmonary sequelae, which include ACS, thrombosis, lung edema, fat/bone marrow embolism, and vaso-occlusive crisis.[45,46] In summary, data from the literature show that a significant proportion of the patients who report SD have pulmonary symptoms (fat embolism, pulmonary hypertension, and cardiac right ventricular hypertrophy).

A neoplastic disease called leukemia causes the bone marrow and other blood-forming tissues to create an excessive amount of blood cells, which then enter circulation. The most typical malignancies causing sudden unexpected death in adults are acute leukemia, bronchogenic carcinoma, stomach adenocarcinoma, and adenocarcinoma of the urinary bladder.[47]

Symptoms of acute leukemia develop fast and worsen swiftly. As with chronic leukemia, unexpected mortality has been observed in both adults and children.[48] Sudden unexpected death due to neoplastic disease in infancy and childhood (SUDNIC) is exceedingly rare. Tumors affecting essential tissues, such as the heart and brainstem, are the most prevalent causes of SUDNIC.[49,50] Finally, it has lately been acknowledged that several leukemia treatments may result in sudden unexpected death. Nowadays, acute promyelocytic leukemia is frequently treated with arsenic tetroxide, which seems to be a successful medication. However, its usage can result in rapid death as arsenic impairs the normal function of potassium channels, causing QT prolongation.[51]

MORBID OBESITY AND SUDDEN DEATH

Being overweight and obese are both explained as having an excess of body fat that may be harmful to one's health. Body mass index (BMI), which is calculated by dividing a person's weight (in kilograms) by their height squared, is a basic population measure of excess fat (in meters). A BMI of 25 or above indicates being overweight, while a BMI of 30 or higher indicates being obese, according to the WHO. Obesity and being overweight have negative effects on health. Risk gradually rises as BMI rises.[52]

As a result, both are associated with hypertension, diabetes, heart failure, CAD, and cerebrovascular accidents. Obesity is also linked to premature death and higher mortality after cardiovascular events.[53] Even in the absence of cardiac dysfunction, obese people are more likely to have arrhythmias and SD, and both genders are at an elevated risk for SCD as their weight increases.[54] Overall, due to its effects on the circulatory system, being overweight or obese increases one's risk of developing a variety of cardiac issues, including coronary heart disease, heart failure, and SD.

In conclusion, the incidence of SD described in the literature varies from 10 to 32% of all deaths from natural causes. This range is mostly a result of the definition's variability, the population's age and sex distribution, and the varying severity of the disease. The distribution of SD causes in a community depends on the population at risk's

age, race, and other socioeconomic demographic factors. Analytical studies have continued to attempt to identify the specific risk factors related to SD. The major known risk factors, such as cholesterol, blood pressure, smoking, behavior type, and other system diseases are associated with all clinical manifestations of SD. The heart is the primary cause of sudden unexpected death, accounting for more than 400,000 unexpected SCDs per year. A deeper knowledge of the molecular pathways behind sudden unexpected death will help us to identify and prevent the tragic result, keeping in mind that the best approach to treat a disease is to prevent it.

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