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Review

REVIEW ON SUDDEN DEATHS DUE TO CARDIAC ABNORMALITIES

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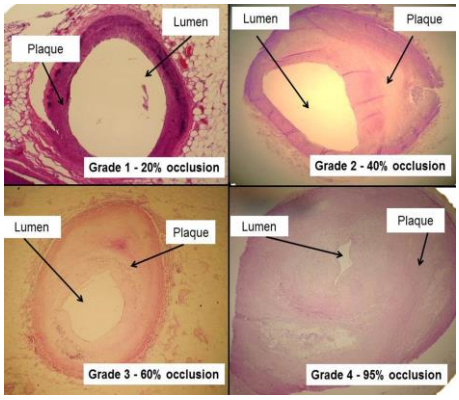
Graphical abstract



Abstract

Sudden death is an unexpected natural death within the one-hour onset of a symptom or unwitnessed death that occurs within 24 hours. This definition is most often used to describe death caused by cardiac failure as it is one of the well-known causes of natural death. Various aetiologies are leading to sudden death, and myocardial infarction is reported to be one of the leading causes either due to coronary atherosclerosis and/ or thrombosis. An autopsy is a procedure routinely performed by the pathologist to determine the cause and manner of death which provides valuable information such as, demographic factors comprises gender, age, ethnic and lifestyle that were strongly linked to sudden deaths. This article review will discuss on autopsy in sudden death, as well as the aetiology of sudden death associated with cardiac abnormalities. Further, the contribution of demographic factors to sudden death will also be discussed and highlighted.

Keywords: Autopsy, atherosclerosis, myocardial infarction, sudden death, cardiac abnormalities

Abstrak

Kematian mengejut adalah merujuk kepada kematian yang tidak dijangka dan semulajadi dalam masa sejam setelah menunjukkan simptom atau kematian tidak bersaksi dalam masa 24 jam. Definisi ini acap kali dikaitkan dengan kematian yang berpunca dari kematian jantung akibat kegagalan fungsi jantung dan ianya merupakan punca utama kematian semulajadi. Jenis-jenis kegagalan jantung yang mengakibatkan kematian mengejut adalah miokardial infaksi, samada berpunca daripada ateroskelrosis dan/atau trombosis. Pemeriksaan autopsi adalah pemeriksaan rutin yang dijalankan oleh pakar patologi untuk mengenalpasti punca kematian. Merujuk kepada laporan autopsi, faktor demografik seperti jantina, umur, etnik dan gaya hidup mempunyai hubungkait dengan kematian mengejut. Manuskrip ini akan membincangkan definisi kematian mengejut dan autopsi, juga etiologi kematian mengejut yang berkait dengan ketaknormalan jantung. Pengaruh faktor demografik di dalam kes kematian mengejut juga akan dibincangkan.

Kata kunci: Autopsi, aterosklerosis, miokardial infaksi, kematian mengejut, forensik

1.0 INTRODUCTION

Sudden death (SD) is defined as natural death in which the duration between the onset of symptoms and time of death is not more than 24 hours. Most cases occurred not in the hospital and usually more likely to be happening at home [1]. According to the World Health Organization (WHO), it is stated that any natural death that occurred within 24 hours from onset of symptoms is considered as sudden death. The similar definition is being used in previous studies by researchers [2-5]. However, some researchers shorten the duration of death between the onset of symptoms and time of death to less than 1 hour [6, 7] or even 2 hours [8]. Some even defined it as 6 hours from symptoms onset [9].

In the same study, 10.8% of cases involved the victims who died without any complication of painfulness on body parts or any potential fatal diseases [4, 9]. About 20.1% of cases in which patients found to have ischemic heart disease but remain healthy before the event occur. Thus some sudden death which occurred unpredictably on those who always look healthy whether from the aspect of time or health status especially considered as sudden death despite the patients may have been diagnosed for any cardiovascular disease such as coronary heart disease [10]. However, an exception is taken for any death cases caused by trauma or violent incidence of homicidal, suicidal or accidental nature despite its sudden occurrence. Cases would only be categorised as sudden death if the person died by any other natural causes or manner than expected [4].

However, sudden cardiac death (SCD), a significant cause of sudden death is an unanticipated natural cardiac death that occurs within an hour onset of a symptom or unwitnessed death within 24 hours. Autopsy, toxicology and other evidence were collected and examined to determine the cause of death [11]. The pathologist or forensic scientist plays a significant role in determining the cause and manner of sudden death. This complex task was highlighted in many books, professional guidelines and articles including the procedure for an autopsy performed by pathologists in the investigation of sudden death [12-16].

Following a report on a sudden death case, a doctor will notify the police officer, who will classify the death as natural death prior to an autopsy [4]. The forensic pathologist will gather relevant information such as age, gender, occupation, lifestyle, circumstances of death, medical and family health history to help to conclude the cause and manner of death [12]. Autopsy comprise external and internal examination. During an external examination, the pathologist will examine the body externally to determine identity, cause and manner of death and collection of evidence. For internal examination, the pathologist will collect blood samples and tissues to be analysed in the laboratory. The most common laboratory tests are histological, biochemical and toxicological analyses [17, 18]. In some cases of sudden death, further investigation is required to identify potential substances such as drugs and alcohol that might be involved in triggering the death. Therefore, a toxicological analysis is vital for forensic investigation to determine its contribution to the cause of death.

Histopathologic examination is the primary diagnostic tool to determine histomorphological changes in a normal and/ or diseased organs such as lung, liver, brain and heart. The heart sample will be examined macroscopically by following a standard procedure [12] as shown in Table 1. Toxicology examination is a quantitative analysis that detects the presence of toxic substances in the body that might lead to death. In the presence of abnormalities of the heart detected either grossly and/ or microscopically, other causes that might contribute to the death should also be evaluated. As demonstrated in Table 2, specimens sampled for toxicology analysis include blood from the heart and femoral veins, urine and bile (particularly, when urine is not available) [14, 15]. Also, strands of hair will be removed from the back of the head or pubic hair when head hair is not available (Basso *et al*. 2008). If there is suspicion of toxicity, the post-mortem report will be reserved until the laboratory results are confirmed [17].

Table 1 The standard procedure of gross heart examination during post-mortem [12]

Number	Procedure
I	Examine the pericardium and pericardial cavity
II	Examine the anatomy of arteries and transect
III	Examine the pulmonary veins and transect
IV	Anatomize the right atrium from inferior vena cava to the apex of appendage. Similarly, with the left atrium that opens up between pulmonary veins and atrial appendage.
V	Examine the aorta, pulmonary artery, aortic and pulmonary valves
VI	Examine the structure of coronary arteries
VII	Perform a complete transverse cut of the heart at the mid-ventricular level
VIII	Measurements of variables as follows: a. Total heart weight b. The thickness of heart wall c. Heart dimensions
IX	Anatomize basal half of the heart.

Table 2 Types and quantity of samples according to the Guidelines of the Society of Forensic Toxicologists and the American Academy of Forensic Sciences[12]

Number	Types of sample	Quantity
I	Blood from heart	25 ml
II	Peripheral blood from femoral veins	10 ml
III	Urine	30-50 ml
IV	Bile (if urine is not available)	20-30 ml
V	Strands of head hair	100–200 mg

2.0 OVERVIEW OF SUDDEN DEATH

2.1 Epidemiology of Sudden Death

Epidemiological reports revealed that both sudden death and sudden cardiac death were strongly associated with age, gender, lifestyle, ethnicity and family medical history [19]. Hence, all of the demographic factors should be taken into consideration in an autopsy to assist in the determination of the cause of death. Approximately 17 million deaths annually or 30% of all global mortality is caused by cardiovascular diseases (CVD). Studies predicted that 40% to 50% of cardiovascular deaths are sudden cardiac death (SCD) [20]. In America, 200 000 to 400 000 cases of SCD were reported annually, which means around 950 cases were reported daily. This condition includes the formation of atheroma and thrombus in the artery that leads to coronary artery occlusion resulting in myocardial infarction (MI) [21]. Studies are exhibiting 80% of SCD occurring in developing countries, which are due to ventricular tachyarrhythmia [20]. Reports by [22, 23] stated that the number of cardiac diseases had increased among females at the age of 45 to 54 years old.

Sudden death caused by cardiac abnormalities in the youngsters has a more significant impact than cancer and other deadly diseases, which created an enormous impact and burden to the public health system [24, 25]. This shocking finding revealed that cases involving male are higher than the female with a ratio of 10.5:1 [26]. Approximately 90% cases of SD in developing and developed countries are commonly associated with CVD. Furthermore, evidence proved that prevalent and mortality rates due to CVD in developing countries were higher than those in the developed countries [27]. In addition, patients with metabolic syndrome (Mets) exhibited a higher risk of developing CVD [82, 83]. Mets is a condition comprising obesity, elevated blood pressure, atherogenic dyslipidaemia and high plasma glucose or insulin resistance as defined by the World Health Organization (WHO) [84, 85].

2.2 Etiology of Sudden Death Due to Cardiac Abnormalities

Numerous factors were linked to the aetiology of SD with the cardiac disease being the primary cause of death worldwide [28]. There are a few diseases related to cardiac abnormalities such as myocardial infarction (MI), cardiomyopathy, myocarditis and congenital disabilities.

2.2.1 Atherosclerosis

Atherosclerosis is also known as a pathological and multifactorial chronic condition, which characterized by narrowing and hardening of arteries contributing to CVD [9]. The most prominent features of atherosclerosis are the presence of plaque or fuel of fats, cholesterol, lipophages, leukocytes and deposition of calcium in arteries [29, 30]. Hardening of the arteries happens due to accumulation of cholesterol and fat in the blood vessel walls. When the cholesterol specifically LDL being engulf by macrophages it will turned to be foam cells which then formed plaques. Over time, these plaques potentially narrowing or completely obstruct the arteries which lead to various cardiovascular disorders. Atherosclerosis is one of the most common causes of SD among coronary artery diseases (CAD), mainly in adults and elderly persons [26]. Studies by Virmani *et al*. and Luqman *et al.* [3, 31] stated that coronary atherosclerosis is the most common findings in the autopsy. Formation of plaque will block the blood flow, which then restricts blood supply to major organs such as brain, heart, arms, legs and kidney. A decrease in blood circulation to the major organs may be caused by peripheral artery disease, coronary heart disease, chronic kidney disease and angina [19].

Clinical features in an individual with atherosclerosis include chest pain, sudden collapse, dyspnoea, cold sweating and vomiting. The systemic indicators include elevation of cholesterol level in plasma [32]. Other causes that play an essential role in the development of atherosclerosis comprise hypertension, diabetes, and smoking. It is also characterised by the presence of inflammatory markers (interleukin 8) that are associated with atherogenic lipoprotein, low-density lipoprotein (LDL) [30]. On the contrary, there are also protective factors against atherosclerosis implicating apolipoprotein and apoA-I. The presence of apoA-I promotes the modification of LDL to prevent atherogenic and induces reverse cholesterol transport. Concomitantly, the progression of plaque will slow down and promote rapid regression [33].

2.2.2 Thrombosis

The association of acute coronary syndrome and athero-thombotic has been well-defined, which further describes the formation of blood clot in an

artery and ischaemia. A healthy endothelium modulates vasodilation of vessel, inhibits platelet aggregation, activate clotting factor, and defends against inflammation and repair mechanism. However, endothelial dysfunction may culminate in vasoconstriction, thrombus formation, inflammation, and proliferation of smooth muscle may generate the formation of atherosclerotic plaque, [34] a significant cause of mortality worldwide [35]. Formation of unstable plaque that is prone to rupture will lead to exposure of injured endothelium to blood circulation, which then triggers the activation of the extrinsic coagulation pathway. Circulatory platelet will adhere to the sub-endothelial matrix and damaged endothelial cells. Activated platelet release intermediaries such as serotonin, adenosine diphosphate (ADP), thromboxane A2, endothelin, free radicals and platelet activating factor will be released that is followed by platelet aggregation and vasoconstriction. The aggregated platelet named white thrombus will be formed, but it is unstable and will cause reduced blood flow [36]. The activation of coagulation system will promote deposition of fibrin and strengthen the platelet aggregation whereby, vasoconstriction will produce impaired blood flow resulting in pooling of blood and formation of red thrombi [37].

2.2.3 Myocardial Infarction

Myocardial Infarction (MI) can also be considered as a significant contributor to morbidity and mortality globally [38], particularly in sudden deaths [39]. Approximately 90% cases of SCD developed from MI, the most frequent cause of coronary artery disease (CAD) [40, 41]. MI is characterised by irreversible necrosis of myocardium tissue resulting from decreased blood flow in arteries, which leads to a lack of oxygen supply. This condition is suggested to be due to the formation of atheroma and coronary thrombosis in an artery [21]. Atheroma will cause reduced blood flow in an artery that leads to ischemia and death of myocardial tissue [42].

A patient, who suffers from myocardial ischemia can be diagnosed from medical history and electrocardiographic record (ECG). Symptoms of myocardial ischemia include the combination of chest pain, upper extremity discomfort, mandibular and epigastric discomfort, dyspnoea and/ or fatigue. These symptoms are related to acute MI, which will last about 20 minutes. The feeling of discomfort is not localised or positional, which might present along with diaphoresis and nausea. Atypical symptoms of MI are palpitation or asymptomatic and increase or decrease of cardiac markers [43]. There are five classes of MI comprise Type I spontaneous MI, Type 2 MI secondary to an ischaemic imbalance, Type 3 MI resulting in death when biomarker values are unavailable, Type IVa MI related to percutaneous coronary intervention (PCI), Type 4b MI related to stent thrombosis and Type 5 MI related to coronary artery bypass grafting (CABG). All types of MI are classified based on the value of biomarker, clinical history of patient and angiographic results [43].

3.0 OTHER ETIOLOGIES ON CARDIAC ABNORMALITIES

Moreover, cardiac abnormalities that are often reported in association with SD are ventricular tachycardia and fibrillation. According to a study, the fatal arrhythmia is caused by electric irritation of myocardium induced by ischaemia [44]. Ventricular tachycardia is a condition, where three or more consecutive ventricular beats at a rate of 120 beats/min that last for 30 seconds [45]. Besides, ventricular fibrillation can be defined as a heart contractile behaviour on visual inspection [46], which is also known as primitive practice [47].

A well-defined post-mortem report will be helpful to determine the cause of death, especially in some cases that are complex to the forensic pathologist when the heart appears to be healthy to the naked eye [48]. Research by [47, 49] stated that electrocardiogram is a primary test used to determine ventricular tachycardia and ventricular fibrillation. Other non-cardiac causes that contribute to sudden deaths are cerebral haemorrhage, bronchial asthma, Waterhouse–Friderichsen syndrome (WFS) and acute haemorrhagic shock [12] as shown in Table 3.

Table 3 Non-cardiac causes of sudden death [12]

Etiology	Example
Cerebral or Central Nervous System	Sub-arachnoid or intra-cerebral haemorrhage
Respiratory System	Asthma, Anaphylaxis
Acute haemorrhagic shock	Ruptured aortic aneurysm, peptic ulcer
Septic shock (Waterhouse–Friderichsen syndrome)	*Neisseria meningitides* infection

4.0 ASSOCIATION BETWEEN DEMOGRAPHIC FACTORS AND SUDDEN DEATH

Various demographic factors have been associated with sudden death that related with cardiovascular disorders. The factors are include age, gender, lifestyle, ethnic and family history [50, 51]. The risk factor increased with age and this is dependent on gender as well. Ethnicity and family history which are related demonstrated that selected groups of people are more susceptible to experience SD due to their heath conditions. Factors mentioned above will be well explained in this section.

4.1 Gender

Cardiovascular disease is the leading cause of mortality in both male and female. Women are believed to have a higher risk of MI compared to men as females will experience endothelial dysfunction and deposition of fat in blood vessels at menopause. This is due to declining of estrogen level in their later years. Production of estrogen will decline during menopause, hence menopause females have a higher risk of cardiovascular diseases compared to premonopausal [52]. The mechanisms of estrogen influencing CHD are not entirely understood. However, the general function of estrogen on the vascular system include the release of nitric oxide and vasodilation [53, 54], regulation of prostaglandin production, which is a potent vasodilator [55] and inhibit smooth muscle proliferation [56]. Circulating estrogens protects the vascular endothelium by enhancing the release of vasodilators [55]. Hence, reduced oestrogen level was believed to be the primary cause of MI in menopausal females [19]. Moreover, CVD is the leading cause of mortality in menopausal women [19]. Interestingly, in both genders, SCD is the most common cause of death compared to cancer and disease-related death [25].

4.2 Age

As age increases, there is a high risk of contracting MI. It was an evidenced that female with an average age 71.8 years old posed a high risk of MI compared to a 65-year-old male [19]. This condition is due to the physiological changes that occur in female such as hormonal changes, unhealthy lifestyle and reduction of body metabolic rate [38, 57]. Research exhibited that frequency of MI between different sexes was more prevalent among women in an age less than 55 years old based on hospital information [58]. Reports by the National Centre For Health Statistics in 2015 stated readmission due to cardiac disease in female was higher than male at the age of 65 and above [22]. The American Heart Association Statistics Committee and Stroke Statistics Subcommittee reported that the average age for women presenting with the first MI was 71.8 years old, while for men, it was 65 years old [19].

4.3 Ethnicity

Additionally, a comparison between distinctive ethnics (Table 4) on the risk of MI was documented by several researchers. Studies have shown that CVDs present differently across ethnics [59, 60]. Black women have a higher number of incidence of SCD compared to white women [41, 61]. According to studies by INTERHEART, Asian Indian have higher CVD risk factor with MI presentation compared to non-Hispanic white women, black and Hispanic women at the age as young as 69 years old [62]. Besides, SD often happens in non-Hispanics than Hispanics, which was demonstrated by a high prevalence among Indian women, who have diabetes from their clinical history [63-65]. Studies in Singapore by Wong *et al* also concluded that Indians have a higher risk of developing MI before the age of 46 compared to Malays and Chinese [38]. Correspondingly, the researchers pointed out that Indians were most likely to present with new-onset diabetes with the highest HBA1C values for those with pre-existing diabetes compared to other ethnics. However, most Malays in the study were diagnosed with the new onset of hypertension compared to others.

Table 4 Cardiovascular disorders related condition according to ethnicity

Nationality	Ethnic	Health Problem	References
American	Indians	Hypertension	[66]
American	Whites, Blacks and Asians higher	Hypertension	[66]
American	Whites and Blacks higher	Obesity	[66]
Pennsylvania	White and Hispanic youth	Obesity	[67]
Malaysia	Malay	Obesity	[68]

4.4 Lifestyle

Healthy lifestyle such as physical activity is known to have benefits over cardiovascular health [69]. However, research has proven that regular sports activities and vigorous activities may contribute to some risks of SD too[70, 71]. Strenuous activities can lead to SD and MI [72], this happens by an increase platelet adhesiveness and aggregation, whilst moderate exercise may have the advantage to the heart by decreasing platelet adhesiveness and aggregation [73]. A study stated that male athletes have a higher risk of SD than female athletes while black athletes also showed a higher risk compared to white athletes. [74].

Research in 2012 presented that unhealthy lifestyle such as smoking, unhealthy diet intake and obesity are contributors to CVD in males and females of all ethnicities [23]. Wong *et al.* [38] stated that tobacco is the most critical risk factor in triggering MI [75-77]. Prevalence of tobacco usage among men was higher compared to women, and studies showed a strong relationship of tobacco with MI development [78-80].

5.0 CONCLUSION

There is a variety of SD definition which includes natural death with an interval between onset of symptoms, which is not more than 24 hours excluding poisoning and trauma. Cardiovascular disease,

especially MI remain as the most common causes in men and women leading to SD worldwide apart from atherosclerosis and coronary thrombosis. Menopausal women have a higher risk of developing MI. The average age of women presenting with MI is around 71.8 years old and 65 years old in men. Indians are more prone to develop MI due to the presence of diabetes. Unhealthy lifestyles such as cigarette smoking and history of hypertension have a strong correlation with MI. Although the benefits of active physical activity were well established, there is strong evidence of enhancing platelet aggregation and adhesions during vigorous activity that will contribute to MI and SD.

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