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THE IMPORTANCE OF THE CORRELATION OF THE MACROSCOPIC AND MICROSCOPIC EXAMINATION OF LESIONS FROM SUDDEN CARDIAC DEATH IN THE CLUJ INSTITUTE OF LEGAL MEDICINE, 2014-2018 CASE REPORT

Daniela Cristina Pavel (Mironescu)[1,2,*], Costel Siserman[1,2], Daniel Ureche[1,2], Alexandra Șonfălean[2], Denisa Jurje[2], Denisa Lucian[2], Horea Matei-Vladi[1,2]

[1]"Iuliu Hatieganu" University of Medicine and Pharmacy, Legal Medicine Department, [2]Institute of Legal Medicine, Cluj-Napoca, Romania

Abstract: Sudden cardiac death is a major public health problem; special attention is paid to the thanatogenesis of sudden cardiac death to identify the causes of many patients at risk and to administer effective prophylactic treatment. The evolution to death after cardiac arrest is the result of a complex interaction of so-called fate factors (eg age, underlying conditions, comorbidities, toxic consumption) and influenceable factors (eg time interval to BLS and defibrillation). Although cardiovascular mortality has decreased in high-income countries in recent years, cardiovascular diseases are responsible for approximately 17 million deaths each year of which approximately 25% are sudden cardiac deaths. The risk of sudden cardiac death is higher in men than in women, and increases with age due to the higher prevalence of ischemic heart disease in old age (1).

Keywords: Sudden cardiac death (SCD), forensic cases, acute death, macroscopic and microscopic examination.

INTRODUCTION

The "Original Contributions" chapter is based on the study of autopsies performed in the years 2014-2018 at the Institute of Forensic Medicine in Cluj-Napoca, in cases that were classified as suspicious deaths following the on-site investigation. Later, the correlation of the results of the on-site investigation with the macroscopic and microscopic results, as well as with the complementary medico-legal examinations of the medico-legal autopsy, showed that in these cases of suspicious deaths there were objective conditions that led to the consideration of these deaths as sudden deaths of cardiac cause. Next, the gender and age group distribution of sudden cardiac deaths, the influence of external and internal risk factors, as well as the correlation of macroscopic and microscopic data of autopsy lesions in sudden cardiac deaths are studied (2). We have assessed based on the theoretical and practical study that the current legislative provisions in our country, regarding the mandatory autopsy in suspicious or suspected suspicious deaths, correspond to those in most countries, because only the medico-legal autopsy can fully clarify the type and cause of the suspicious death, thus bringing useful evidentiary data not only to the investigative body, but also to clinicians as well as to the relatives of the deceased.

Definition

From the definition of sudden death, it appears that it is of pathological cause, but due to the circumstances and the suddenness with which it appears, it often takes young individuals, in full apparent health (the only sign of the disease being death itself) and different places of occurrence, it awakens numerous suspicions. That's why the medico-legal autopsy is mandatory to delimit it from violent death. At the same time, sudden death raises problems related

*Correspondence to: Daniela Cristina Pavel (căs. Mironescu) MD, "Iuliu Hatieganu" University of Medicine and Pharmacy, Legal Medicine Department Cluj-Napoca, Romania, E-mail: dana_pvl@yahoo.com

to tan prophylaxis, applicable to the whole population. All the characteristics that define it were incorporated by the Anglo-Saxon authors in the formula SUUD (sudden, unexpected, unexplained, death) (3). Accurately determining the cause of an unexpected death helps the family in a more rational understanding of the tragedy and, moreover, allows other family members, first-degree relatives, to assess the risk of sudden cardiac death for an early diagnosis and to take measures to necessary prevention. It is important to carry out a specialized medico-legal examination that includes a molecular autopsy, in these cases of sudden cardiac death, especially for people in whom there is a high suspicion of genetic diseases that affect the integrity of the muscle fiber or its functions electrical (4). Sudden death is a non-traumatic, unexpected fatal event occurring within less than 1 hour of the onset of symptoms in an apparently healthy individual. If the death occurs in the absence of witnesses, the definition applies if the victim was in apparent health 24 hours before the event (5). The term sudden cardiac death (SCD) has been used for several centuries, and during this time different authors have had controversies about the most appropriate definition. MSC is defined as follows: "Natural death due to cardiac causes, announced by the sudden loss of consciousness within one hour of the onset of acute symptoms; pre-existing heart disease may be known but the time and manner of death are unexpected (6).

Etiology

The leading and unrivaled cause of death in the adult population of the industrialized world is sudden cardiac death from coronary artery disease. The most common rhythm recorded in patients who are brought in with sudden cardiovascular collapse is ventricular fibrillation (in 75 – 80% of cases), while bradyarrhythmia's are credited as determinants for a minority of SCD cases (7). In approximately 5–10% of cases, SCD occurs in the absence of ischemic heart disease or congestive heart failure, as a result of valvulopathy, cardiac tamponade, or hypertension. MSC can also occur as a result of an inherited genetic abnormality that affects key proteins in the heart. Heart disease associated with SCD differs depending on the age – young or old – of the individuals. In the young, there is a predominance of cardiomyopathies, myocarditis and substance abuse, while in the elderly, chronic degenerative diseases are dominant (CI, valvular disease, HF) (8). About 50% of cardiac arrests occur in patients without known cardiac involvement, but the majority have undiagnosed BCI. An autopsy is recommended to investigate the causes of SCD and to determine whether it is secondary to an arrhythmic or non-arrhythmic mechanism (eg, rupture of an aortic aneurysm). Whenever an autopsy is performed, a standard histological examination of the heart, including labeled myocardial blocks from representative cross-sections from both ventricles, is also recommended. Toxicological and molecular analysis of collected blood and other body fluids is recommended for all victims of SCD (9).

Anatomopathological data

The histopathological analysis was performed on representative transverse sections of myocardial tissue, collected from both ventricles and/or from areas with macroscopically evident pathological changes, fixed in 10% formalin (kept ~ 24-48 hours) and embedded in paraffin for staining standard HE histopathology and light microscopy examination. The histopathological parameters followed were: coronary atherosclerosis, myocardial necrosis, fibrosis (interstitial, perivascular, subepicardial and subendocardial), lipomatosis, interstitial edema, vascular stasis and coronary bridging (10). The aim of the study was to determine if there is a correlation between the macroscopic diagnoses of myocardial ischemia, coronary atherosclerosis and interstitial fibrosis made during the autopsy with the histo-pathological microscopic diagnoses.

Macroscopically, the atheroma plaque appears as a raised, buttoned, circular lesion of a whitish-yellow appearance (due to lipid deposits and fibrous tissue deposits) with a variable diameter between 5 and 15 mm. At the level of arteries, atheroma plaques appear isolated or confluent and in different stages of development. In evolution, atheroma can be accompanied by ulcerations, calcifications, thrombosis. Microscopically, the earliest changes corresponding to the lipid stria consist in the accumulation of lipids in the myocyte cells of the intima (with their transformation into foamy macrophages) and between the cells in the deep layer of the intima, in relation to the elastic fibers and the internal elastic lamina (11). The macroscopic aspects of myocardial infarction depend on its age. In order for the lesions to be visible, it is necessary to have a survival interval of at least 6-8 hours. During the first 15 hours, the necrotic area has a homogeneous appearance, with lost structure, the color is dirty gray, low consistency, it forms a triangle with irregular edges, represented by a hemorrhagic lyserium. At this stage the lesion may protrude on the surface of the epicardium. After about 35 hours after the occurrence,

the myocardial infarction has a yellow-gray center and the periphery is hemorrhagic; in the next 3 days the center turns brown, and after 7 days it retracts. After 2-3 weeks, the center of the lesion is yellowish, with a perifocal leukocyte infiltrate, everything being delimited on the periphery by a red area, corresponding to the hemorrhage; granulation tissue can be visualized as a red line. If death has not occurred by the 6th - 8th week, the healing stage follows. This consists in healing the injury through the appearance of a fibrous tissue. In the area of necrosis, the proteolytic enzymes released by the leukocytes around the focus show their lytic activity, which results in the resorption of cellular detritus. The remaining fibrin network organizes as a scar (12). Microscopic aspects of myocardial infarction. Experimental research has signaled the rapid changes following hypoxia. In the first 5 minutes after the occlusion, the disappearance of glycogen was highlighted, and after 15 minutes the nucleus homogenizes, the chromatin is arranged at the periphery, the sarcoplasm evaporates, the number of lysosomes increases; between 15-30 minutes the mitochondria swell and the myofibrils lose their striations, after 30 minutes the myocytes begin to lose transaminases, and after 6 hours many of the myocytes have disappeared (11,12). Recent lesions are manifested microscopically after 6 hours by the necrosis of the myocytes, which take on a hyaline appearance, become eosinophilic, the striations become more and more smooth and disappear, the sarcoplasm vaporizes and karyolysis occurs. Inframicroscopic support of sarcoplasmic vaporization is given by mitochondrial afflictions. The intercalated discs undergo cystic dilatation, which is partly responsible for the conduction disturbances. A fine granular, eosinophilic detritus and an edema rich in leukocytes and acidic mucopolysaccharides appear between the myocytes. Specific reactions for highlighting ischemic type lesions are positive. The developing infarction consists in the appearance of hyperemia and neutrophilic infiltrate in the area of necrosis, neutrophils will release lytic enzymes. In the second week, the neutrophils are replaced by macrophages that are loaded with pigment that comes from the disintegration of the muscle fibers and the hematic hemoglobin. During this period, complications such as heart ruptures and interventricular septum perforations may occur. If the necrosis does not affect the entire thickness of the heart wall, then aneurysmal dilatations of the ventricular wall or rupture of the papillary muscles occur (13) . The evolution can be towards cicatricial infarction or death. Cicatricial infarction is established starting from the third week. It is characterized by the formation of a granulation tissue with neocapillaris and collagen-producing fibroblasts. In week 4-6, the healing is definitive, the place of the destroyed muscle fibers being taken by the dense fibrous connective tissue, among its cells cells loaded with hemosiderin pigment can be highlighted. Myocardiosclerosis occurs against the background of chronic coronary obstruction. Macroscopically, we can see frames and whitish areas arranged on the surface of the section. Microscopically, there is atrophy and dystrophic lesions of the cardiac myocytes, as well as replacement fibrosis but no necrosis. Myocardosclerosis progresses to cardiac dilatation, with a progressive decrease in the force of contraction (13).

Working hypothesis

There is a tendency to consider all sudden non-traumatic deaths in senescent and middle-aged individuals to be due to cardiac disease, autopsy studies in unselected patients suggest that approximately 2/3 of these deaths are of cardiac cause, ischemic heart disease and its complications being responsible for the overwhelming majority of these deaths. The accuracy of certifying ischemic heart disease as the cause of out-of-hospital deaths was assessed by forensic examination and review of autopsies. In industrialized countries the main risk factors for sudden cardiac death are older age, male sex, history of heart disease, changes in lipid metabolism, hypertension, smoking, alcohol consumption and diabetes (14). In the study under consideration, we aimed to highlight the sudden cardiac deaths from the 2014-2018 case report of IML Cluj, these risk factors as well as the correlation of the macroscopic and microscopic diagnosis of the necropsy lesions that led to the establishment of the cause of death.

MATERIAL AND METHOD

The study undertaken is retrospective, observational and descriptive. The data were collected from the consultation of the Forensic Autopsy Reports located in the Cluj-Napoca IML Archive recorded over a period of 5 years (2014-2018). The collected data were entered into a database organized in the form of a Microsoft Excel 365 table and processed for statistical analysis. Forensic necropsy reports performed in non-violent deaths from causes other than cardiac and those in violent deaths were not taken into account. For each individual case, a series of variables/parameters were followed for statistical elaboration, namely:

Demographic variables – age, sex, background. Parameters – consumption of toxic substances, sudden deaths from coronary and non-coronary cardiac causes, the presence of heart failure, the association of diabetes and hypertension, the presence of liver, lung or cerebral pathology. The importance of the associated pathology as a risk factor in the occurrence of sudden cardiac death was also studied. In this sense, sections harvested from organs with macroscopically visible pathology were examined, the results were correlated with those from microscopy, and it was aimed to highlight their role in the occurrence of a sudden cardiac death. All these parameters were tracked and organized and for their descriptive statistical presentation the Pivot Table function from the Microsoft Excel program was used. They were used for graphing the graph parameters of type: graphs of type: 3D radial structure (Pie), Columns, Bars and radial ring structure (sunray type).

RESULTS AND DISCUSSIONS

From the total of 3438 medico-legal autopsies within IML Cluj from 2014-2018, 1201 were sudden cardiac deaths and 2237 were other causes. Regarding the total number of expert cases each year, the graphs show a tendency to maintain the percentage between 30-40%. Because heart disease is often asymptomatic or unrecognized, there will be an unknown proportion of individuals with advanced ischemic heart disease in the general population. However, they may be identified if screening for ischemic heart disease risk factors is performed in a systematic or targeted manner (Figs 1, 2).

The presence of risk factors: The medico-legal expertise is interested in knowing the risk factors, to be able to appreciate their role in thanatogenesis and sometimes to be able to mark with more certainty and scientific documentation the difference between a sudden non-violent death and a violent death. The presentation of risk factors for ischemic heart disease and myocardial infarction will be done following Mscarey's classification (15). I have chosen this classification because it seems to me the most appropriate and usable for the purposes and requirements of the medico-legal expertise. According to this author, the risk factors are divided into: (1) non-evaluable factors (age, sex, heredity); (2) non-influential factors (arterial hypertension, hypercholesterolemia, hyperlipoproteinemia, diabetes, stress, hyperuricemia) and (3) avoidable factors (smoking, food excesses, obesity, sedentary lifestyle) (14). There are also risk factors that may specifically prognosticate the occurrence

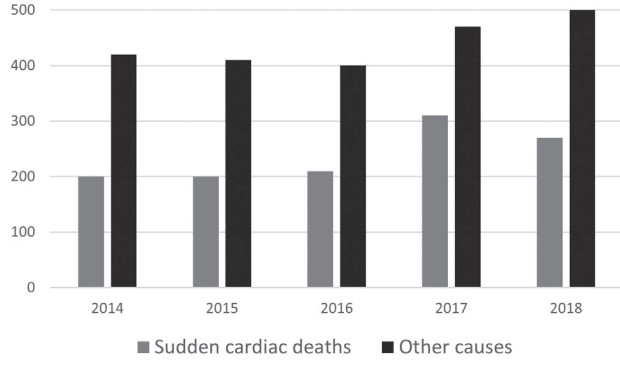
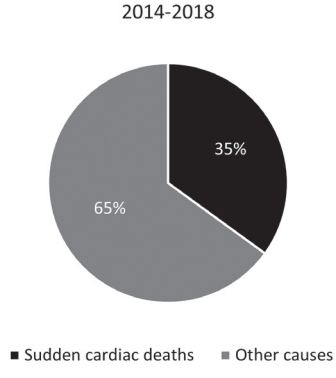


Figure 1.



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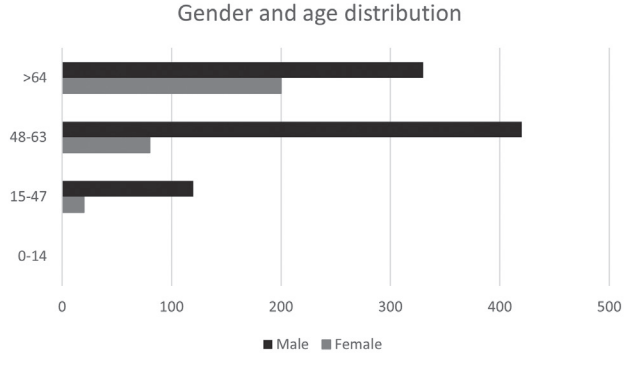

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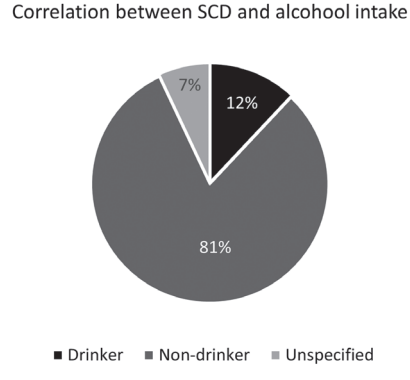
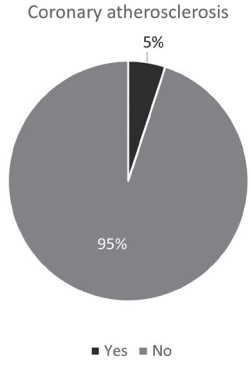


Figure 4.

of SCD distinct from the occurrence of myocardial infarction or other manifestations of ischemic heart disease in subgroups without diagnosed heart disease. Of these, the most studied were alcohol consumption and increased heart rate. Age: all authors are unanimous in appreciating that ischemic heart disease has the highest frequency in the period 50-60 years, although especially in recent years, cases under the age of 50 and over 60 are also frequent. For the period under study, most cases (551 cases) were aged over 64, closely followed by those in the 48-64 age range (507 cases). This confirms that the age range for the occurrence of sudden cardiac death has been decreasing necessitating screening and prophylaxis. Gender: classic research has shown that cardiopathy with its various forms is more common in men. Thus, angina pectoris is more common in men than in women up to the age of 50, so that between 50-60 years the proportions between the two sexes are almost equal and equalize after this age (14). The Framingham study adds to the above, showing that women usually have uncomplicated angina pectoris, and sudden cardiac death is 4 times more common in men with myocardial infarction than in women. Regarding our study 902 cases were male and 299 cases were female, which confirms a 3 times higher percentage of sudden cardiac deaths in males compared to females. An important role in these cases is possibly represented by the estrogenic protection of women until menopause, although myocardial infarctions in women with hyperestrogenism have also been highlighted (Figs 3, 4).

Regarding the environment of origin, it can be observed that the difference between the rural and urban environment is significant, an important role in these results is the possibility and degree of addressability of the patients to the hospital. There is a correlation between toxic and alcohol consumption, especially excesses that increase the risk of sudden cardiac death, although the literature states that in fact moderate alcohol consumption is a protective factor for acute coronary events. Regarding smoking as a risk factor in our study no predilection effect of smoking on SCD was demonstrated. The most important and unequaled cause of death in the adult population of the industrialized world is sudden cardiac death due to coronary heart disease. The frequency of active coronary lesions observed during the autopsy in victims with sudden coronary death with coronary dissection or thrombosis were highlighted in 27 and 21 cases respectively, although chronic coronary lesions were highlighted in 1143 cases (Figs 5-7).



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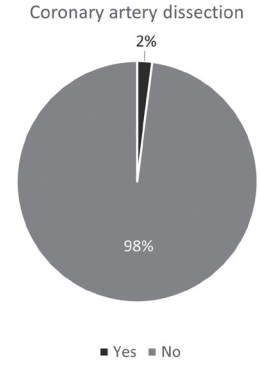

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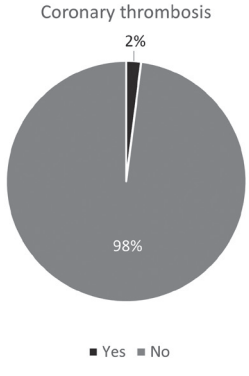

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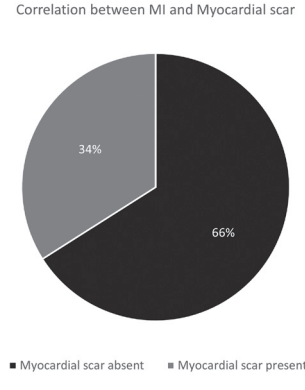


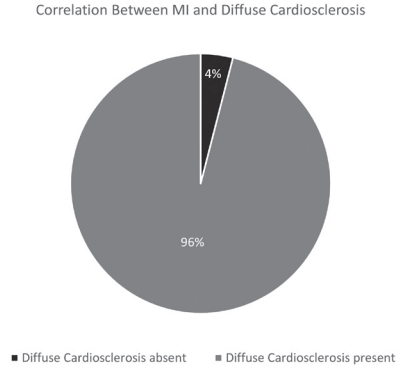
Figure 8.

Although the definitive terminal event of sudden cardiac death after myocardial infarction is usually a cardiac arrhythmia, this may be due to a new ischemic episode or another infarction in the presence of scarred myocardial infarction or the combination of these factors and the presence of diffuse myocardial sclerosis (Figs 8, 9).

In addition to coronary causes, cases of sudden death were also associated with non-coronary cardiac pathology that had a direct or indirect contribution to the cause of death. Cases of cardiomegaly (52 cases), dilated cardiomyopathy (184 cases), hypertrophic cardiomyopathy (344 cases), myocarditis (9 cases) and myocardial fibrolipomatosis (30 cases) were studied (Figs 10, 11).

Hypertrophic cardiomyopathy (HCM) is an inherited heart muscle disorder caused by mutations in genes encoding cardiac sarcomeric proteins. MHC has a highly characteristic anatomopathologic appearance (myocardial hypertrophy, myocyte disarray, and fibrosis) that contributes to a spectrum of functional abnormalities including myocardial ischemia, diastolic dysfunction, and LV ejection obstruction, resulting in congestive heart failure and sudden cardiac death(16). Because most sudden deaths occur in asymptomatic (or mildly asymptomatic) young individuals, the main effort in the management of CMH is to identify those individuals at increased risk of SCD. Myocyte disarray, myocardial ischemia and subsequent myocardial scarring contribute decisively to the underlying substrate responsible for MSC. Dilated cardiomyopathy (CMD) is a chronic disease of the heart muscle characterized by ventricular dilatation with impairment of systolic function. MCS can occur in those with advanced CMD but also in those with minor involvement or in those who appear clinically and paraclinically improved. The most severely affected patients will most likely die of progressive heart failure (17) (Figs 12, 13).

Myocarditis is an inflammatory disease of the heart muscle associated with cardiac dysfunction. Myocarditis can be the consequence of a systemic infectious disease (viral or bacterial) or a silent infection. It is a major cause of SCD through arrhythmias especially in young people. MSC can occur in the initial phase or in the healing phase, the arrhythmias being precipitated by the inflammatory infiltrates and the accompanying interstitial edema(18). Heart failure in SCD occurs in a small population group that may include post-infarction patients as well as those with primary or



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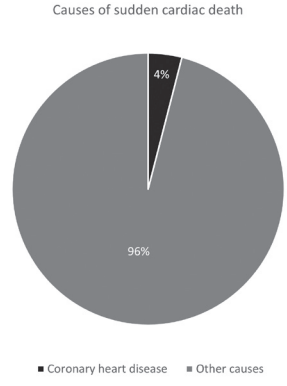

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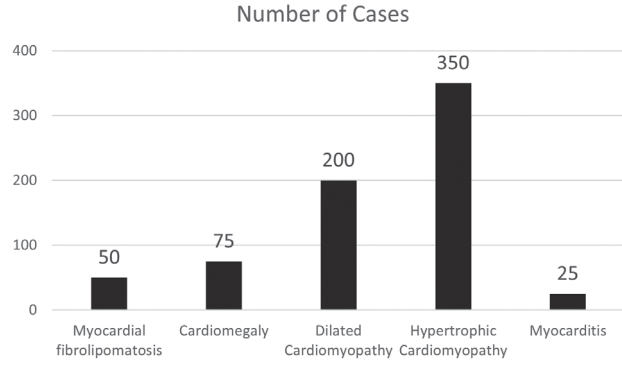

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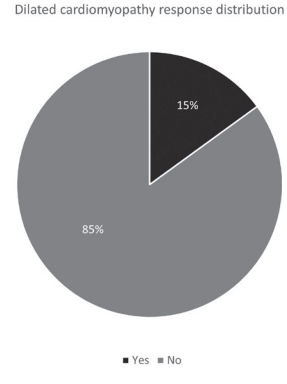
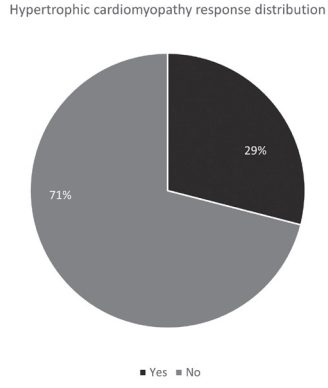


Figure 12.

post-infarction CMD or heart failure of other cause. Diabetes mellitus and impaired glucose tolerance are independent risk factors for SCD. They may be risk factors for those who have ischemic heart disease, but it is not a specific risk factor for sudden versus non-sudden death (19). Hypertension is a known risk factor for ischemic heart disease and plays an important role in SCD. The association of diabetes and hypertension were additional risk factors in SCD (20) (Figs 14, 15).

Considering that we did not find a statistic or a more recent report regarding the association of other organic pathologies present in these cases with MSC, we decided to correlate the presence of other pathologies both macroscopically and microscopically with MSC. We looked for correlations of brain, lung, liver and kidney pathologies that could favor the precipitation of some mechanisms that later led to MCS without these pathologies directly causing the death of the patient. From our study it emerged that there are correlations between the increased level of LDL-cholesterol which can also be highlighted by liver changes (steatosis) and the risk for all manifestations of ischemic heart disease including MSC. The reduction in risk for MCS occurs in parallel with the reduction in LDL-cholesterol. Our study showed a significant correlation between the presence of emphysema-type lung pathology associated with sudden cardiac death. The study did not show a significant correlation between the presence of cerebral pathology (cerebral contusion, cerebral hemorrhages) associated with sudden cardiac death. Our study showed that there is a significant correlation between the presence of chronic kidney disease associated with sudden cardiac death.



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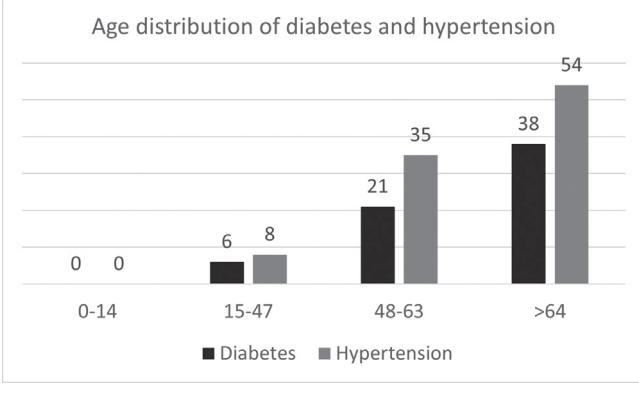

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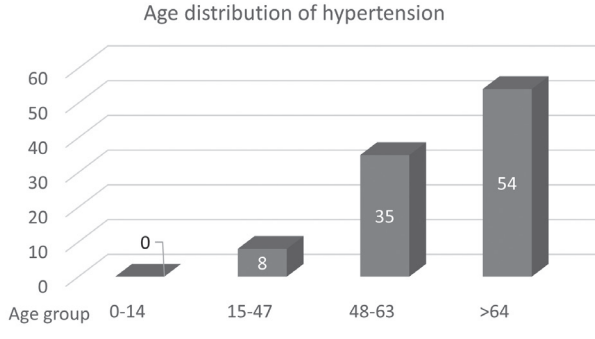

Figure 15.

The conclusions of the study: From the statistical analysis presented on the occasion of this study, the following conclusions can be drawn:

1. In the IML Cluj case study, sudden cardiac deaths represented approximately 1/3 of all medico-legal autopsies in the period studied.

2. Basic demographic factors are strong predictors of sudden cardiac death although generally neglected.

3. The consumption of toxic substances represents factors that can be risk factors and precipitants for sudden cardiac death, especially in those who have associated underlying cardiac pathology.

4. Coronary heart disease is the main cause of death in sudden cardiac deaths, this being represented mainly by coronary atherosclerosis, thrombosis and coronary dissection.

5. Among the non-coronary causes, the most important as risk factors for sudden cardiac death were: cardiomegaly, hypertrophic and dilated cardiomyopathy.

6. Acute myocardial infarction was the leading cause of death in cases of sudden cardiac death.

7. The existence of a myocardial scar is a major risk factor for the occurrence of a new acute myocardial infarction leading to sudden cardiac death.

8. Diffuse myocardial sclerosis has been

associated with increased risk of sudden cardiac death.

9. Arterial hypertension represented a major risk factor in the occurrence of sudden cardiac death, especially through left ventricular hypertrophy.

10. In most of the sudden cardiac deaths studied, the presence of diabetes was highlighted, especially in association or not with hypertension.

11. Liver pathology seen at macroscopic necroptic examination and confirmed histopathologically was also present in approximately half of the cases of sudden cardiac death.

12. There is a significant correlation between the presence of pulmonary pathology such as emphysema associated with sudden cardiac death.

13. Brain lesions were not identified in a significant number of cases.

14. About 60% of cases of sudden cardiac death also have associated chronic kidney disease

Final conclusions: The logical conclusion of these statistics is that the most important chance of decreasing the social impact of sudden cardiac death is represented by reducing the prevalence of ischemic heart disease in the general population. Asymptomatic individuals with multiple risk factors for ischemic heart disease have an increased risk of sudden cardiac death compared to the general population.

Conflict of interest

The authors declare that they have no conflict of interest.

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