ETIOLOGY OF SUDDEN CARDIAC DEATH IN FORENSIC MEDICAL PRACTICE AND SELECTION OF CASES FOR POST-MORTEM GENETIC TESTING – 5 YEAR RETROSPECTIVE STUDY

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Abstract

Sudden cardiac death (SCD) is a term used to describe death in a person who has no previously diagnosed heart disease, or is not expected to die at that stage of the disease. SCD is considered a major health problem in the world, accounting for 15-20% of all deaths, and the mechanism of its occurrence includes the development of ventricular tachycardia, which progresses to ventricular fibrillation and finally asystole. SCD is generally seen in the older population; however, a significant mortality rate is also observed in young people with hereditary heart pathology.

The use of substances that can have an effect on cardiac function is associated with many cases of SCD, so toxicological substances should always be considered by forensic doctors and screening tests should always be performed.

The aim of this research is to analyze the causes of sudden cardiac death and to select cases in which post-mortem genetic testing is indicated.

For this purpose, a review was made of the autopsies performed at the Institute of Forensic Medicine between 2018 and 2022, the biochemical and toxicological findings of the various causes of death were analyzed, and the cases where the exact cause of sudden cardiac death was not determined were also analyzed. In the analyzed period of 5 years, the cases with cardiomyopathy dominated, followed by coronary artery heart disease, and in 20 percent of the cases the exact cause of death was not determined. Men dominated with a percentage representation of 80%.

Keywords: Sudden cardiac death, Troponin I, toxicology, post-mortem genetic analysis.

Introduction

Sudden cardiac death (SCD) is defined as death occurring no later than 24 hours after the onset of symptoms, as a result of a cardiovascular event or without present cardiac pathology. Sudden cardiac death accounts for 15-20% of the total number of deaths. The mechanism of sudden cardiac death is associated with the development of ventricular tachycardia (VT) which then progresses to ventricular fibrillation (VF) and finally ends with asystole [1,2].

This disturbance of the heart rhythm also explains the fast occurrence of death. Sudden cardiac death is generally seen in the elderly population, however, a significant rate is also seen in the younger population, in those individuals who have inherited a heart disease [3,4,5].

Clinicians are faced with a difficult task in determining the risk of SCD, especially when it occurs without previous clinical manifestations. Thus, the percentage of patients suffering from heart diseases, which are discovered too late, only when they become the subject of interest of the forensic medical practice, is not small [6,7,8].

The most common cause of sudden cardiac death is coronary artery disease (CAD), followed by diseases of the valvular apparatus, cardiomyopathies, infiltrative diseases of the myocardium, myocarditis, infective endocarditis, hereditary defects of ion channels and congenital heart diseases [9,10,11].

Epidemiologically, CAD is responsible for 80% of SCD cases, cardiomyopathies account for 10-15% of cases, while 5-10% of SCD are caused by inherited cardiac disorders, such as coronary artery anomalies or cardiac channelopathies [12,13].

Coronary atherosclerosis is the most common cause of SCD in people aged 35 years and above, with men at higher risk compared to women, while cardiomyopathies, especially hypertrophic cardiomyopathy (HCM), ion channel defects and coronary artery anomalies are the leading causes for SCD in adults younger than 35 years. In the pediatric population, myocarditis and congenital heart diseases are the main causes of SCD [14,15].

Apart from the underlying cardiac pathology leading to SCD, it has been observed that patients with chronic kidney disease and obstructive sleep apnea also showed a higher risk of SCD [16,17].

Prevention of sudden cardiac death is a field that is continuously studied, however, its rate remains high despite various preventive measures [18,19].

Preventive therapeutic modules include the use of pharmacological therapy and an implantable cardioverter-defibrillator (ICD). A particularly important prevention measure is the identification of people who are at risk of SCD, and the most commonly used method for that purpose is the Framingham risk score, which is recommended as a routine screening method for men in their 40s and for postmenopausal women [20]. This method calculates individual CAD risk based on multiple variables such as age, sex, smoking, blood pressure, LDL levels, body mass index (BMI) and diabetes; and different variations of this method also calculate the risk of sudden cardiac death.

Electrocardiography has its role in people with genetically inherited electrical abnormalities of the heart, especially in long QT syndrome [21, 22, 23]. In fact, the degree of QT prolongation shows a positive correlation with the risk of SCD [24, 25].

Preventive measures also include the screening of young athletes, which is mandatory for people who are actively and professionally engaged in a certain sports discipline. Cases of sudden cardiac death during increased physical exertion such as during sports training and competition are not unknown, and ECG combined with physical examination is one of the most common screening tools in young people before their active involvement in sports activities [26, 27, 28].

Protocol for processing cases of sudden cardiac death in forensic medical practice

The forensic medical expertise of sudden death includes providing data on the health condition of the deceased and his family, life habits, profession, possible abuse of psychoactive substances and drugs, as well as macroscopic and histopathological analysis of the heart and other organs in order to exclude other potential causes of death, followed by genetic testing of a blood sample in those cases where indicated [29, 30, 31].

In case of positive results from the genetic testing, the family members undergo clinical and genetic testing for risk assessment. In general, autopsy protocols for sudden cardiac death begins with a macroscopic study of the heart, if the cause is identified, and no further testing is necessary [32].

In majority of cases, the macroscopic finding is supplemented by histopathological analysis, and in a certain small selected number of cases, there is a need for molecular post-mortem analysis. The protocol for macroscopic examination of the heart includes checking the pericardium for the presence of possible abnormalities, checking the pulmonary arteries for the presence of embolism, checking the coronary arteries and their distribution, as well as the condition of their intima (internal layer) and the lumen. The heart ventricles are examined as well, their size, the thickness of the wall, the condition of the heart valves, the endocardium, and the papillary muscles. Finally, the heart muscle is assessed to determine whether there are signs of acute or chronic distress, such as presence of fibrosis, bleeding, etc. The heart examination includes certain predetermined measurements such as weight of the heart, the thickness of the ventricle walls, and the thickness of the interventricular septum. During the autopsy, tissue samples are taken from various parts of the heart, then they are fixed in formaldehyde, and the tissue samples undergo histopathological analysis after staining with hematoxylin and eosin. A negative autopsy is defined as the absence of any structural change of the heart and negative histological and toxicological tests [33, 34, 35, 36]. The presence of a negative autopsy is a strong indicator of the presence of an inherited electrical abnormality of the heart that sets the indication for genetic testing, a process commonly referred to as molecular autopsy [37, 38].

The identification of genetic risk factors contributes to a better understanding of the basis of diseases that lead to sudden cardiac death and to the development of new therapeutic modules [39, 40, 41, 42].

Aim of the study
The aim of this study was to analyze the causes of sudden cardiac death and to select cases in which post-mortem genetic testing was indicated.
Study objectives:
- To determine the most common causes leading to sudden cardiac death;
- To determine the correlation between troponin I and CK-MB values and the cause of sudden cardiac death;
- To select cases of sudden cardiac death with a negative autopsy finding or cases suspected for genetic hereditary cardiac pathology, which were candidates for molecular testing

Materials and methods
The Institute of Forensic Medicine, Criminalistics and Medical Deontology at the Faculty of Medicine in Skopje provides professional forensic services for at least 70% of the territory of Macedonia, i.e. serves approximately 1,500,000 people. For the purpose of this study, data from the main register of the Institute of Forensic Medicine was analyzed in the period from 2018 to 2022, and an additional, extended analysis was made of the written reports on the autopsies of the cases of sudden cardiac death performed at the Institute in the given period.The complete autopsy protocols were analyzed; they contain operative data on the case, heteroanamnestic data on the deceased, demographic data, data on external and internal autopsy findings, data from histopathological, biochemical and toxicological examinations, pathoanatomical diagnoses and cause of death.The autopsies as well as all biological samples that were the subject of analysis were performed and secured according to the standard, routine protocols for forensic-medical autopsy, processing and storage of a biological sample prescribed by the European Council for Forensic Medicine and the R99 recommendations.
Sudden death was defined as death occurring within 24 hours of the onset of symptoms (the definition used by the World Health Organization).
Histopathological analysis of tissues for all analyzed cases was performed on paraffin-embedded tissues, pre-fixed in 10% formaldehyde, stained with hematoxylin and eosin.
Screening for presence of psychoactive substances and commonly abused drugs for all analyzed cases was done with Fluorescence Polarization/Enzymatic Immunoassay - FPIA/EIA (AxSYM /Architect c4000, Abbott) for urine samples, as well as Biochip Array Technology - BAT (Evidence investigator Randox) for blood samples.
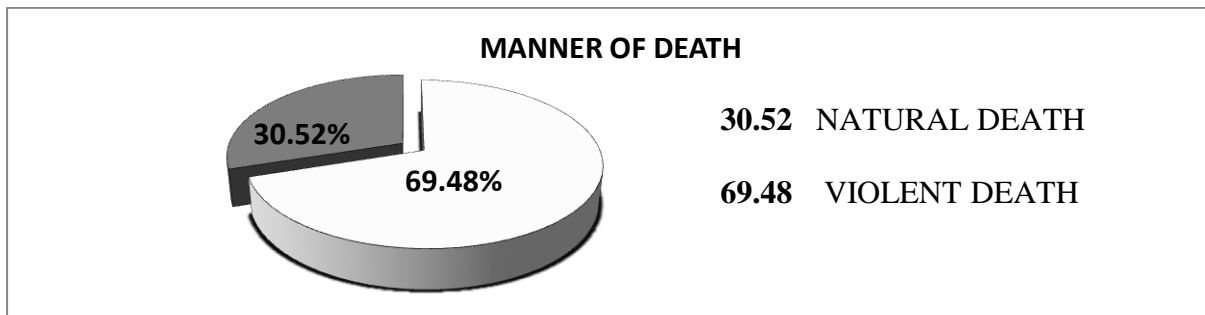Confirmatory tests were carried out by Gas Chromatography with Mass Spectrometry (GC-MS QP2010 Shimadzu, Japan).
Determination of ethyl alcohol was carried out by Headspace Gas Chromatography with Flame Ionization Detection (GC-FID 2010 Plus Shimadzu, Japan).
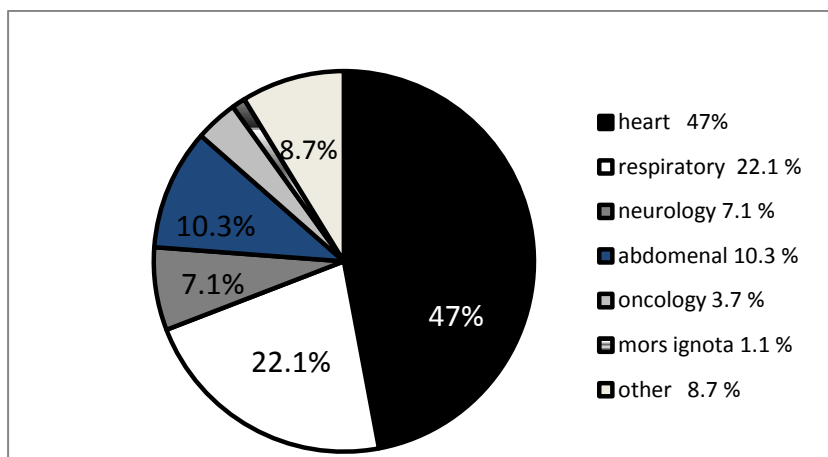The determination of the cardiac enzyme markers Troponin I and CK-MB was performed at the Institute of Clinical Biochemistry of the PHI, Skopje, using immunoenzymatic tests CMIA (Chemiluminescent Microparticle Immuno Assay) for Troponin I and PHO (phosphatase immunoenzymatic test) for CK-MB.

Results
In the analyzed period, 1,720 autopsies were performed, 1,195of which belonged to violent death, according to the manner of death, and 525 to natural death. In the group of natural death, 247 cases were due to cardiac death, 116 cases to death due to pathology of the respiratory system, 54 cases to pathology of the gastrointestinal system, 37 cases with neurological pathology, 19 cases with oncological pathology, 6 cases with an unknown cause of death due to postmortem degradation processes and 46 cases of other pathology that occurred sporadically in practice.

MANNER OF DEATH

30.52% 69.48%

30.52 NATURAL DEATH

69.48 VIOLENT DEATH

Figure 1. Distribution of cases according to manner of death

8.7%

10.3%

7.1%

22.1%

47%

■ heart   47%
□ respiratory 22.1 %
▦ neurology 7.1 %
■ abdomenal 10.3 %
□ oncology 3.7 %
▤ mors ignota 1.1 %
□ other 8.7 %

Figure2. Distribution of natural deaths from the total number of analyzed cases

Respiratory, gastrointestinal, neurological and cardiovascular diseases were responsible for sudden death cases. Among them, the leading role in the occurrence of sudden death was played by cardiovascular diseases, which prevailed with their representation in all the studied years. The representation of cardiovascular pathology was 47% of the total number of cases of natural death, and even 68% of the total number of cases of sudden death.

2018 — 53
2019 — 56
2020 — 45
2021 — 61
2022 — 32

0   20   40   60   80

□ GASTROINTESTINAL
□ NEUROLOGY
■ HEART
▦ RESPIRATORY
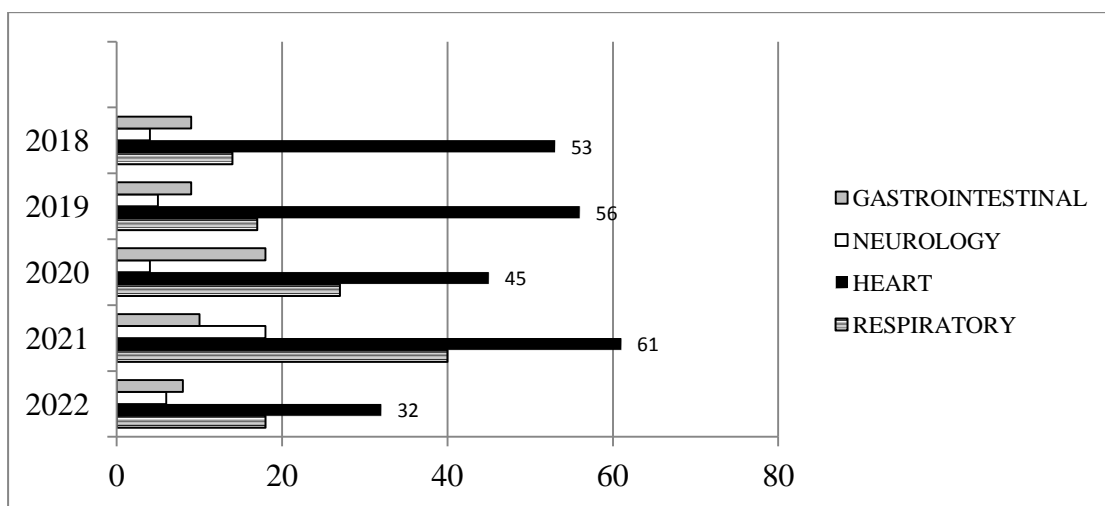
Figure3. Distribution of sudden death according to the underlying pathology – number of cases in each analyzed year
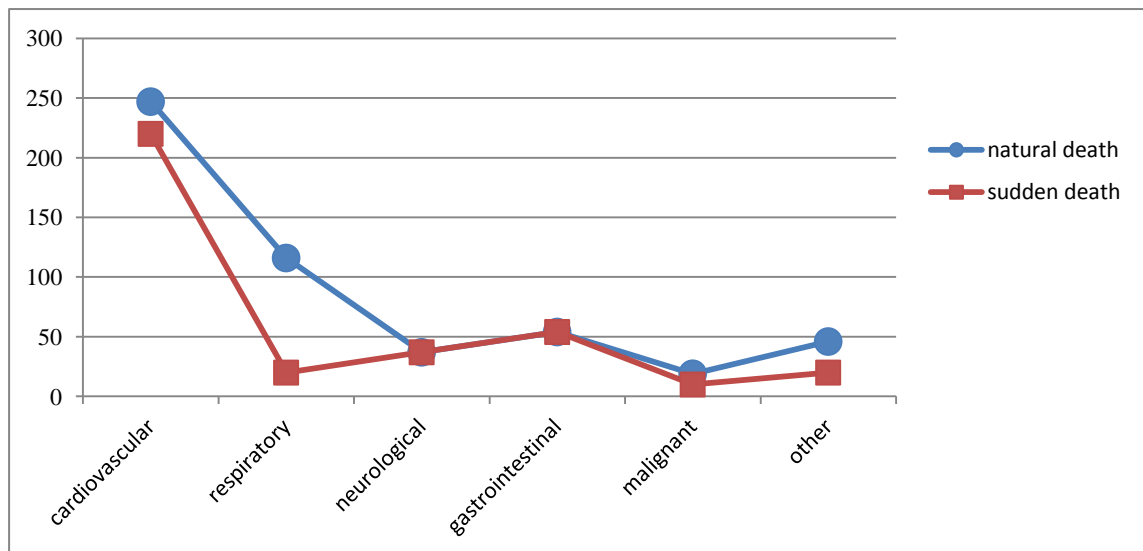
Figure4. Display of the share of cardiovascular cause of death in all natural deaths and against its share in the group of sudden cardiac death

When analyzing the cases of sudden cardiac death, they were grouped into six groups according to the cause of death, while in the sixth group were selected the cases in which there was a strong indication that it was a cardiac death, but because of the negative autopsy finding, they were not closed with a final cause of death.

The most common cause of death in the first five groups in all analyzed years was unspecified cardiomyopathy, except in the last analyzed year, where it equaled the second most common stated cause, which was myocardial infarction. The third most common cause of sudden cardiac death was myocarditis, the fourth was coronary artery disease of the heart, and the fifth cause of sudden cardiac death was cardiac tamponade.
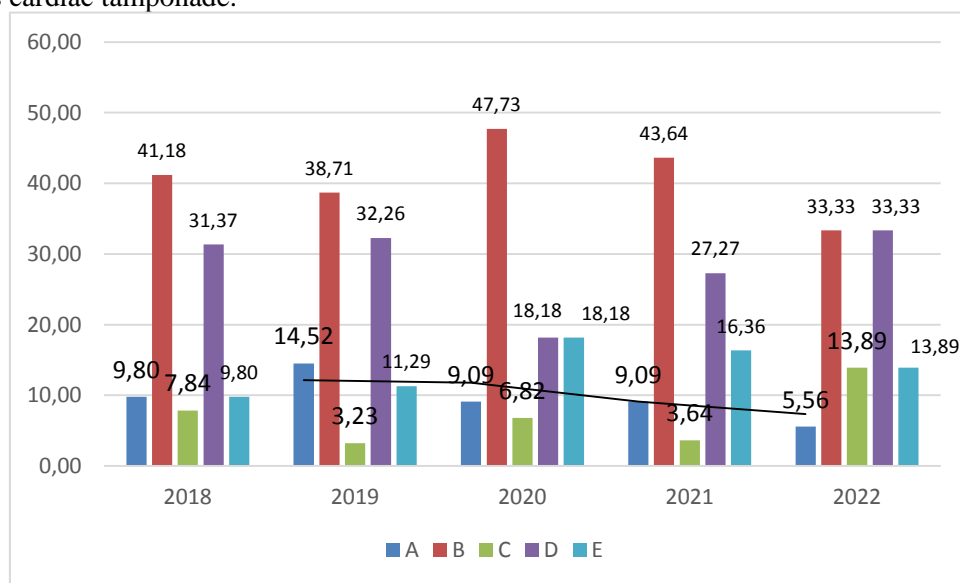
Figure5. Distribution of causes of sudden cardiac death by years A – CAD, C – cardiomyopathy, C – cardiac tamponade, D – myocardial infarction, E – myocarditis

In the age group over 60 years, cardiomyopathy was the most frequently determined cause of death.In this age group, the second in order was cardiac tamponade, the third coronary heart disease, the fourth myocardial infarction and the fifth myocarditis.

In the age group of 50-60 years, there was an approximate equalization of the causes of death, but cardiomyopathy was least representation, while myocardial infarction was the most frequently determined cause of death.

In the group of 41-50 years, the order of representation of causes of SCD is as follows: cardiac tamponade, CAD, myocardial infarction, myocarditis, while not a single case of cardiomyopathy was recorded in this age group.

In the age group of 31-40 years, the most common cause of death was coronary heart disease, followed by myocardial infarction, myocarditis and cardiomyopathy.

In the age group of 21-30 years, almost the only cause was myocarditis, with two cases of myocardial infarction.

In the age group of 11-20 years, in the five analyzed years, no cases were registered in which the cause of sudden cardiac death was determined.

In the age group of 0-10 years, all cases in which the cause of cardiac death was determined were due to myocarditis.
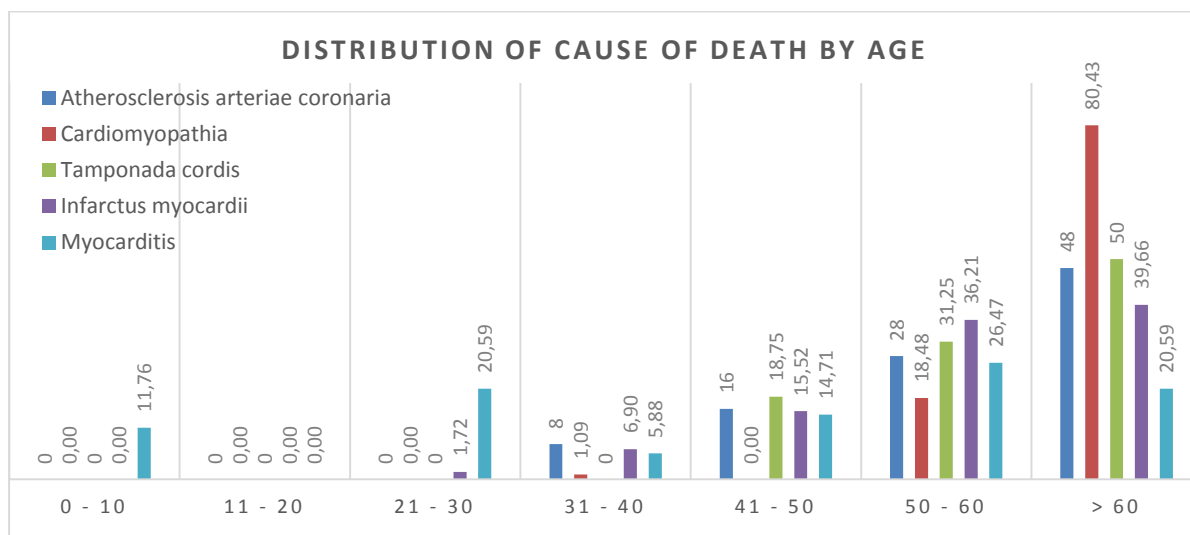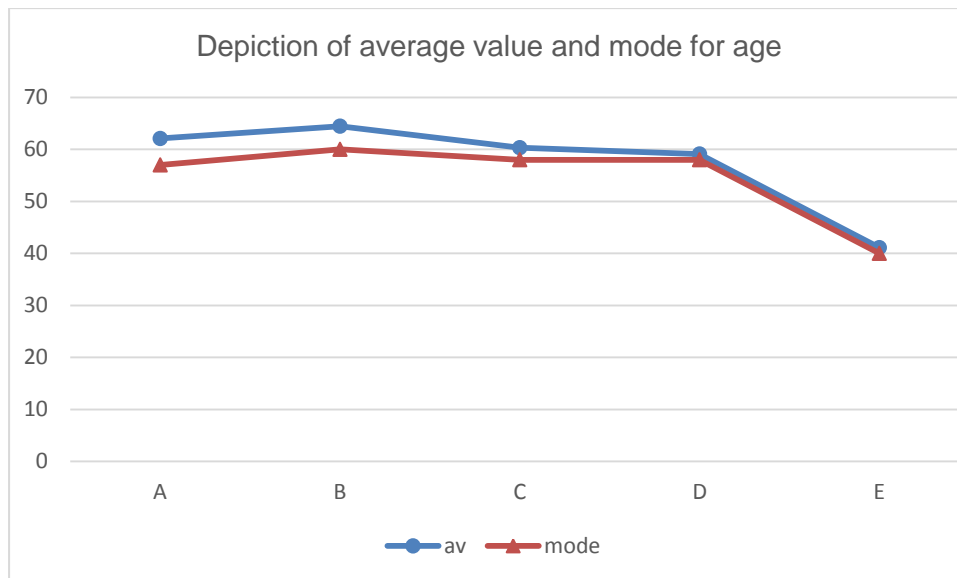

Figure 6. Distribution of causes of death by age

The mean age was lowest in the myocarditis group and highest in the cardiomyopathy group.

**Table 1.** Depiction of middle age and mode for age

Age	CAD	Cardiomyopathy	Tamponade of the heart	Myocardial infarction	Myocarditis
Average value (mean)	62.08	64.45	60.31	59.1	41.09
Mode	57	60	58	58	40

Figure7. Average value (mean) and mode for age by cause of death

The majority of cases of sudden cardiac death was seen in the male population with a representation of 79.35%, while the representation of women was 20.65%.
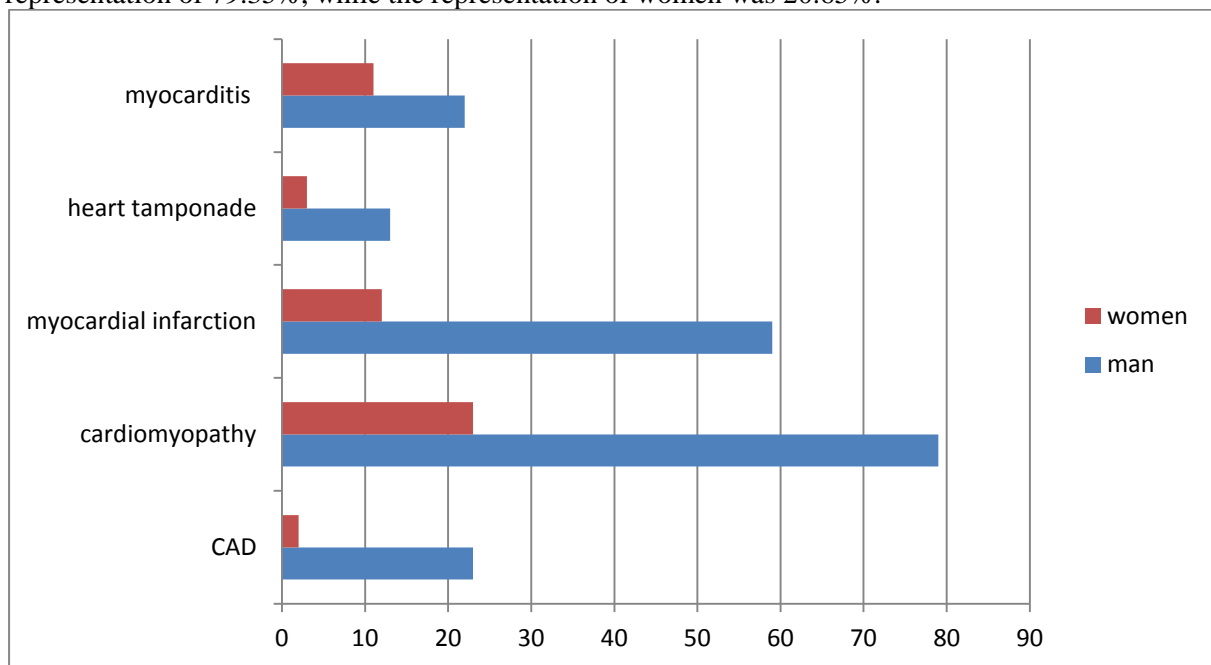
Figure 8. Distribution by gender of the different causes of SCD

The examined cardiac enzyme markers Troponin I and CK – MB were significantly elevated in all cases of sudden cardiac death. A comparison was made between the different groups according to the cause of death and the levels of cardiac enzyme markers.

Regarding Troponin I levels, there were statistically significant differences between the myocardial infarction and myocarditis group (Mann-Witney U Test = 246, Z = 3.04793, p = 0.00114), with the conclusion that the levels in myocarditis were lower compared to those with myocardial infarction. There were no statistically significant differences among the other studied groups. Regarding CK – MB levels,there were statistically significant differences between the group of myocardial infarction and myocarditis (Mann-Witney U Test = 223, Z = 2.43541, p = 0.00734), with

the conclusion that the levels in myocarditis were lower in comparison with those in myocardial infarction. CK – MB had statistically significant differences between both cardiomyopathy and myocarditis group (Mann-Witney U Test = 168, Z = 3.04793, p =0.00114), with the conclusion that the levels in myocarditis were lower compared to those in cardiomyopathy. There were no statistically significant differences among the other studied groups.

Toxicological findings in the analyzed cases showed presence of low concentrations of benzodiazepines in 21% of those who died from sudden cardiac death; presence of ethyl alcohol in 12.6%; presence of opiates in 2.1%; presence of a combination of benzodiazepines and alcohol in 2.1% and presence of tetrahydrocannabinol in . 0.5% of cases.

Table 2. Results of toxicological analyses in the analyzed cases

	Benzodiazepines	Ethyl alcohol	Opiates	Tetrahydrocannabinol
CAD	1	3	/	/
Cardiomyopathy	30	15	4	/
Tamponade of the heart	/	/	/	/
Myocardial infarction	16	10	/	/
Myocarditis	5	3	1	1
Total	52	31	5	1

From all the analyzed cases in the examined period, 25 cases were singled out in which there was a suspicion of sudden cardiac death, and in which there was no possibility to determine the exact cause of death.

Table 3. Presentation of cases in which the exact cause of death was been determined

	Men	Women	Autopsy finding	Total number
Suspect a primary electrical abnormality	18	7	Negative autopsy	25
Hypertrophic cardiomyopathy	2		Macroscopic and histopathological findings support the diagnosis	2
Restrictive cardiomyopathy		3	Macroscopic and histopathological findings support the diagnosis	3
Dilated cardiomyopathy		2	Macroscopic and histopathological findings support the diagnosis	2
WPW Sy (Wolff-Parkinson-White-Syndrome)	4		Macroscopic and histopathological findings support the diagnosis	4

Table 4. Distribution by age groups

	Number of cases with negative autopsy
0-10	5
11-20	10
21-30	7
31-40	3

Discussion

Out of a total of 1,720 autopsies over a five-year period, cases of violent death dominated, which is typical in forensic medical practice worldwide. Respiratory, gastrointestinal, neurological and cardiovascular diseases were responsible for sudden death cases. Among them, the leading role in the occurrence of sudden death was played by cardiovascular diseases, which prevailed with their representation in all the studied years. The representation of cardiovascular pathology was 47% of the total number of cases of natural death, and even 68% of the total number of cases of sudden death.

The most common cause of sudden cardiac death according to the specific causes of death entered in the Institute's registry was cardiomyopathy, followed by myocardial infarction. The third most common cause of sudden cardiac death was myocarditis, and the fourth was coronary artery disease of the heart.These data differ from data reported in Europe and the United States, where the leading cause of sudden cardiac death is coronary heart disease [43,44,45].

In fact, in the largest percentage of cases in which cardiomyopathy was determined as the cause of death, as well as in all cases in which myocardial infarction was determined, the specialists conducting the autopsy chose to state the immediate cause of death in their reports. When reviewing the written reports of those autopsies, it is clear that these cases describe coronary artery disease, which is the underlying cause of ischemic heart disease and is essentially the underlying cause of death. Thus, CAD emerges first as the most common cause of sudden cardiac death in our study population as well.

In the age group over 35 years, coronary heart disease and cardiomyopathies were prevalent, while in the younger population under this age, myocarditis played a dominant role in the occurrence of sudden death, mostly with a viral etiology.

In 36 cases, the exact cause of death was not determined, but in this group of sudden deaths, it was assumed that the cause was of a cardiac nature. In seven cases where there was a suspicious histopathological finding in favor of cardiomyopathy, additional genetic tests were needed to confirm the diagnosis, but considering the hereditary nature of this disease, genetic analyses openthe possibility of screening in living relatives in order to reduce or prevent their risk of SCD. In 25 cases in which there was a negative autopsy finding, i.e. without determined structural, morphological changes of the heart, the toxicological analyses were negative, and the cause of death was probably a primary electrical abnormality of the heart.

In infant deaths attributed to SIDS (sudden infant death syndrome), genetic testing for electrical abnormalities of the heart, most likely long QT syndrome, is absolutely indicated [46].

The same syndrome is determined in victims of the so-called "dry drowning", i.e. drowning people who do not have the typical finding of asphyxia, and spumous emphysema, i.e. there are no signs of drowning [47, 48].

It is interesting that the most commonly reported cause of sudden cardiac death in the United States and most of Europe in the population under 35 years of age is hypertrophic cardiomyopathy, while in our cases the largest number of cases in that age group fell to the group suspected of primary electrical abnormalities of the heart. If structural changes of the heart are responsible for sudden death in the older population, in the younger group myocarditis is dominant, and less often, but not negligible, genetically inherited cardiomyopathies and primary electrical abnormalities [49,50,51].

It should be taken into account that most cardiac genetic disorders that cause sudden death in young people are inherited as an autosomal dominant trait, and 50% of the affected person's offspring carry the risk of developing the same disease. Therefore, identification of such cases by forensic autopsy enables appropriate clinical and genetic screening of surviving family members. Screening in relatives is of particular importance with the advent of preventive therapies for sudden death (e.g., implantable cardioverter defibrillator).

Conclusion

In conclusion, cardiovascular diseases are the main cause of sudden death. Coronary artery heart disease is responsible for mostcases of SCD and is typically seen in the older male population. In the younger population, the risk of sudden cardiac death mainly comes from the inflammatory processes of the heart muscle. In cases that are without a specific cause of death, and the circumstances of the death and the autopsy findings raise a suspicion of cardiac etiology, genetic analyses for genetic hereditary heart diseases should be considered. Determining the etiology and risk

of sudden cardiac death is of great importance for introducing preventive therapeutic modules and reducing the mortality rate in risk groups.

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