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Original communication

Sudden adult death: An autopsy series of 534 cases with gender and control comparison

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ABSTRACT

The aim of our study was to highlight the epidemiological difference in adult sudden death between males and females. The type of pathologies found in adult victims of sudden death was compared to control cases in order to determine the most significant pathologies involved in sudden death.

Among all autopsies performed between 1995 and 2009, 534 adult cases of sudden death and 154 cases who violently died were respectively selected. For each case, a complete autopsy was carried out, including systematic histological examination of all major organs.

The sudden death population was composed of 369 males and 165 females. There was no statistical difference regarding age between males and female. Sudden death took place more often at home in women than in men ($p < 0.0001$). A stressful event was more frequently found in men than in women ($p = 0.03$). Deaths caused by cardiovascular diseases were more frequent in males than in females, especially Coronary Artery Disease (CAD) ($p < 0.0001$). Cardiomyopathy was more often the cause of death in women, particularly Arrythmogenic Right Ventricular Cardiomyopathy (ARVC). Cardiac pathologies were found in 45% of the control cases. CAD and ARVC were statistically more frequent in the sudden death group than in the control group.

According to our study, profile of sudden death is different between males and females. Those data seem to be important for clinicians involved in prevention programs of sudden death, as they can adapt their screening according to the gender.

1. Introduction

Sudden death of a young and healthy person is a devastating event for his/her family and relatives. Sudden adult death mainly gets media attention when it strikes elite athletes collapsing during a match or a training. Several definitions of sudden death can be found in medical literature. Sudden death has been defined as “a natural, unexpected fatal event occurring within one hour of the onset of symptoms in an apparently healthy subject or whose disease was not so severe as to predict an abrupt outcome”.[1] This time interval is useful for identifying the deaths arising from cardiovascular pathologies such as arythmia. It is difficult to apply such short interval in forensic cases, for which death circumstances are often imprecise: deaths may occur without witnesses, sometimes while the victim is asleep. As a consequence, the time interval of 24 h as determined in the WHO (World Health Organization) definition is used in most of the forensic autopsy studies.[2] Moreover a sudden death is by definition a natural death. Studies on sudden death should exclude toxic death cases. Indeed, lethal acute alcohol intoxication or drug overdose can give the appearance of sudden death, but are not natural deaths.

It is difficult to compare studies dealing with sudden adult death, because of the frequent variability of the inclusion criteria. Sudden cardiac death is the most studied entity, and studies

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dealing with all the causes of sudden death are fewer. The aim of our study was to highlight the main epidemiological data on sudden adult death in France. On the same time, we tried to compare the profile of victims according to gender. Finally, the type of pathologies found in adult victims of sudden death was compared to control cases who died violently in order to determine the most significant pathologies involved in sudden death.

2. Material and methods

2.1. Inclusion criteria

Between 1985 and 2009, 10,691 forensic autopsies were performed in the Department of Forensic Medicine and Pathology of Raymond Poincaré Hospital in Garches. Among these autopsies, 534 cases were selected according two inclusion criteria:

- Age ≥18 years old.
- Case victim of sudden death. The definition of sudden death applied in this study was the WHO definition: a death that occurs within 24 h of the onset of symptoms.

All of the selected cases died in the same geographical area (Yvelines and Val d'Oise in the west of Paris).

2.2. Exclusion criteria

All cases with putrefaction, or under the age of 18 years, or with drug intoxication as found by toxicological analyses were excluded.

2.3. Control group

A total of 154 control adult autopsy cases were selected. All had died violently (manner of death was respectively suicide, accident and homicide).

2.4. Data collection

For each case included in the study, the following parameters were reported: age, sex, place where the death occurred, notion of a physical or psychical stress previous to the death, delay between the onset of symptoms and the death, cardiopulmonary resuscitation, time of death, heart weight and cause of the death.

A complete autopsy was performed for each case. It included systematic histological examination of all the organs, neuropathological study of the brain and toxicological analyses for both alcohol and drugs. The heart was dissected following the method described by Oliva and al[2]: coronary arteries were transversally sectioned every 5 mm, from their origin to their distal portion, looking for thrombosis or atherosclerosis. High grade atherosclerosis, possibly responsible for the death, was defined by an occlusion of more than 75% of the artery. Heart chambers were opened in the direction of blood flow. The hearts were weighed after dissection and the chambers were washed to remove blood clots.

2.5. Statistical analysis

Data were summarized using mean (sd) for continuous variables and n (%) for categorical variables. Comparisons respectively between men and women, and between sudden death group and control group, were performed using Student test for continuous variables (age, heart weight) and using a Chi 2 test or exact Fisher test (when the expected values are below 5) for categorical variables. For all analyses, a two-tailed p-value <0.05 was considered statistically significant. Analyses were conducted using SAS 9.2 (Statistical Analysis System, Cary, NC, USA).

3. Results

3.1. Characteristics of the sudden death population

The mean age of the population was 44.4 years (ranging from 18 to 89 years). The sex ratio (male/female) was equal to 2.24. Sudden death took place at home in the majority of the cases (about 57%). Fig. 1 shows the distribution of place of death for the cases.

A relevant physical or psychical stress was found in 63 cases (11.8%). It was a psychical stress in 33 cases and a physical stress in 30 cases. Four deaths occurred during delivery (considered as a physical stress). In 88.2% of the cases, death occurred at rest or during weak physical activity (such as walking). In 32.8% of the cases, the death occurred while the victim was asleep. The time interval between the onset of symptoms and the death was one hour or less in 129 cases (24.2% of the cases). Attempts at resuscitation were carried out in 51.9% of the cases (276 cases).

Cardiovascular causes were the major cause of death, in 66.1% of the cases. Non-cardiac causes included respectively respiratory causes in 12.2%, neurological causes in 12.2% and abdominal causes in 3.2% of the cases. No cause was found in 4.3% of the cases. The proportion of cardiovascular causes was more important when age of the deceased increased. Conversely, the proportion of brain causes was less important when age was greater. Undetermined causes of death were more frequently found in younger patients (Fig. 2).

3.1.1. Cardiovascular findings

The mean heart weight (male and female cases) was 411 g (ranging from 160 g to 920 g).

The most frequent cause of death was Coronary Artery Disease (CAD) accounting for 189 deaths (35.4% of the cases). In 119 of these 189 deaths, acute myocardial infarct was the underlying cause of death. Recent thrombosis was found in 45 cases. Cardiomyopathy was the cause of death in 15.5% of the cases: there were 48 cases (9%) of right ventricular arrythmogenic cardiomyopathy (ARVC), 14 cases (2.6%) of dilated cardiomyopathy, 14 cases (2.6%) of hypertrophic cardiomyopathy and 7 cases (1.3%) of undetermined

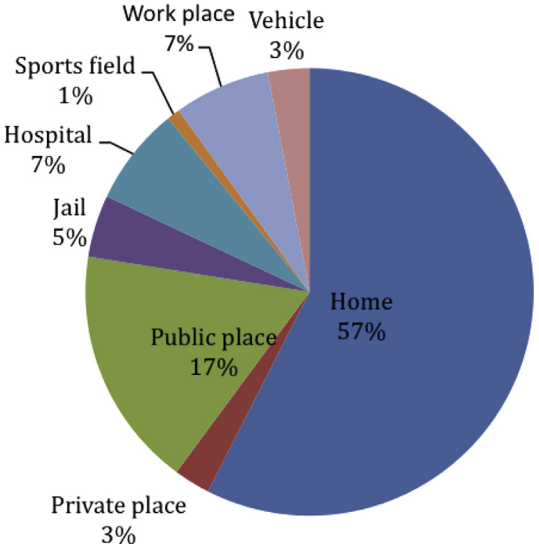

Fig. 1. Distribution of place of death in the sudden death population.

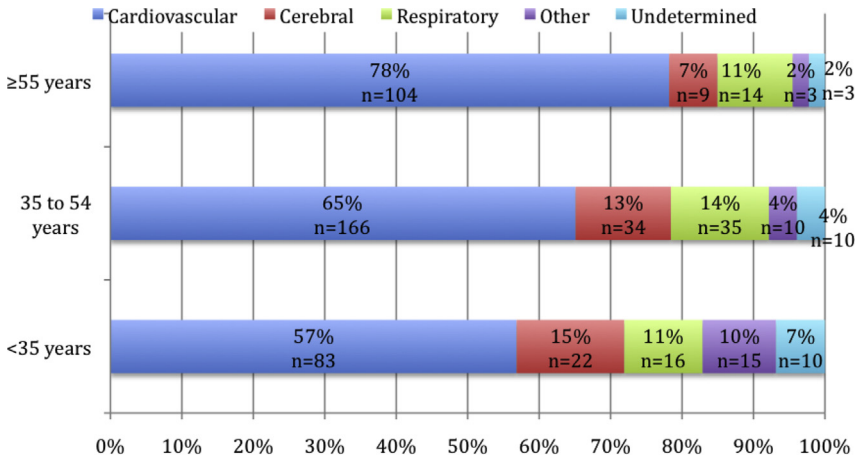

Fig. 2. Causes of sudden death according to the age.

cardiomyopathy. Hypertrophic cardiomyopathy was found in 14 male cases aged 21 to 56 (mean age 38.1). The mean cardiac weight was 545 g, ranging from 400 g to 740 g. In 50% of the cases, cardiac weight was more than 500 g. Heart weight was significantly higher in the hypertrophic cardiomyopathy group than in the group showing other pathologies ($p < 0.0001$).

Infectious cardiac causes represented 6.4% of the causes of sudden death: the most frequent was myocarditis (5.4%, i.e. 29 cases), followed by pericarditis (3 cases) and endocarditis (2 cases). In 11 cases (2.1% of the cases), acute heart failure was responsible for the sudden death but the cause was undetermined. The other cardiac causes were myocardial bridge (2 cases), mitral valve prolapse (3 cases), long QT syndrome (1 case), Steinert disease with associated cardiac lesions (1 case). There were 2 categories of aortic vascular causes of death: aortic dissections (3.4% of the cases) and ruptured aortic aneurysm (1.7% of the cases).

3.1.2. Extra-cardiovascular findings

A neurological pathology was the cause of death in 65 cases (12.2%): the most frequent cause was Sudden Unexplained Death in Epilepsy (SUDEP), related with 32 cases (6%). Among these 32 cases, a structural brain lesion was found in 3 cases. Central Nervous System (CNS) hemorrhage was responsible for 28 deaths (5.2%), among which a stressful event could be found in 2 cases (1 after sexual intercourse, 1 after a fall). 19 ruptured cerebral aneurysms were found. The other neurological causes were 4 cases of acute meningitis and 1 case of cavernous sinus thrombosis.

Respiratory causes were found in 65 deaths (12.2%). The most frequent respiratory cause was pulmonary embolism, found in 32 cases (6%). Origin of the thrombus was found in 9 cases: deep venous system of the lower extremity ($n = 3$), right atrium ($n = 1$), inferior vena cava ($n = 2$), kidney vein ($n = 1$), prostatic venous plexus ($n = 1$), hypogastric vein ($n = 1$). Two cases of pulmonary embolism occurred in a context of neoplasia (kidney and lung). Among the other respiratory causes, there were 16 cases of acute pneumonia (3%), 11 cases of asthma (2.1%), 2 cases of aspiration, 2 amniotic embolisms, 1 pneumothorax and 1 pulmonary arterial hypertension.

Abdominal causes were responsible for death in 17 cases (3.2%): 7 cases of digestive hemorrhage, 2 cases of acute pancreatitis, 2 cases of peritonitis, 2 cases of ischemic colitis and 4 cases related to obstetrical causes (2 ruptured ectopic pregnancies, 1 ruptured uterus and 1 postpartum hemorrhage). The origin of the digestive haemorrhages was esophagus ($n = 1$), stomach ($n = 2$), duodenum ($n = 3$), small intestine with hemorrhagic necrosis ($n = 1$).

The other causes of sudden death were respectively 4 cases of sickle cell crisis, 3 cases of anaphylaxis, 3 cases related to diabetes complications (hypo or hyperglycemia), 1 case of hypokaliemia. No cause of death was found in 4.3% of the cases.

3.2. Results according to gender

The population was composed of 369 males (69.1%) and 165 females (30.9%). Sex ratio was equal to 2.24:1. The average age of the females was 43 years old. The average age of the males was 44.9 years old. There was no statistically significant difference. Sudden death took place more often at home in women than in men ($p < 0.0001$); it occurred more frequently in a public place in men than in women ($p < 0.0001$). A stressful event was found more often in men than in women ($p = 0.03$): it was found in 12 women (7.3% of women) and 51 males (13.8% of men). Sudden death followed physical exertion for 5 women (4 deliveries and 1 running to catch a bus). In women, none of the deaths were related to a sport activity. In men, 25 sudden deaths occurred in a context of physical exertion: 16 deaths during or after a sport activity (cycling, tennis, boxing, rugby, kendo, body building), 9 deaths during another physical exertion than sports (moving house, working on a building site, running). Sudden death occurred while the victim was asleep in 30.9% of females and 33.3% of males.

There was no statistically significant difference when comparing the time interval between the onset of the first symptoms and the death according to gender. Cardiopulmonary resuscitation was performed in 53.7% of males and 47.3% of females. There was no statistically significant difference ($p = 0.17$).

Fig. 3 shows the distribution of the causes of death in males and females. Statistically significant differences were observed in the gender-wise distribution. The deaths caused by cardiovascular diseases were more frequent in males than in females ($p < 0.0001$). The deaths caused by neurological diseases were more frequent in females ($p = 0.048$), as for the deaths caused by pulmonary diseases ($p = 0.01$) Deaths of cardiovascular origin were more frequent in men than in women in the age range 35–54 years old ($p = 0.0005$) and in the age of more than 55 years old ($p = 0.008$).

Table 1 shows the distribution of the causes among the sudden cardiac deaths, according to the gender. This distribution was statistically different. CAD as a cause of death was more frequently found in men than in women ($p < 0.0001$). Cardiomyopathy was more often responsible for the sudden death in women ($p = 0.001$).

CAD was more frequent in men in the age range of 35–54 years old ($p = 0.0005$) and in the age of more than 55 years old ($p = 0.01$).

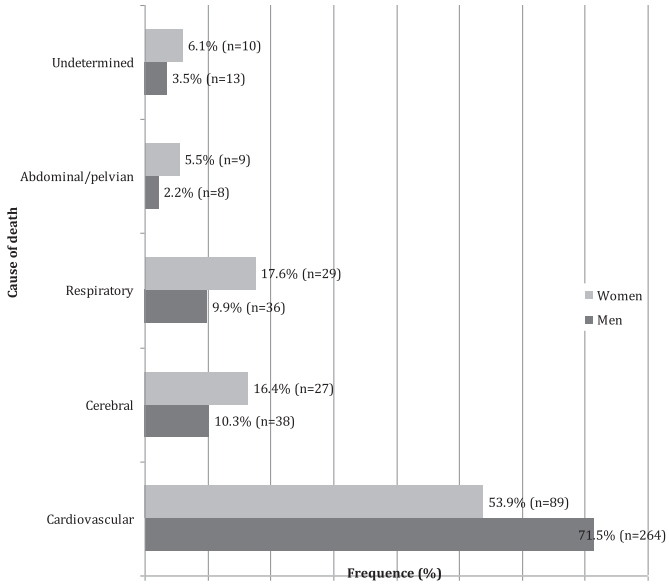

Fig. 3. Distribution of the causes of sudden death in men and women.

Table 1
Distribution of causes of sudden death according to gender.

	Women	Men
Coronary Artery Disease (CAD)	28 (35.4%)	161 (65.2%)
Cardiomyopathy	31 (39.2%)	52 (21.1%)
Myocarditis	10 (12.7%)	19 (7.7%)
Other cause	10 (12.7%)	15 (6.1%)
Total sudden cardiac deaths	79 (100%)	247 (100%)

Cardiomyopathies were more frequent in women in the age range of 35–54 years old ($p = 0.002$) and in the age of more than 55 years old ($p = 0.048$).

ARVC was more frequent in females than in males ($p < 0.0001$). No case of hypertrophic cardiomyopathy was observed in females, while this type of cardiomyopathy was responsible for more of the quarter of the cardiomyopathies in men ($p = 0.001$). Dilated cardiomyopathy was more frequent in males ($p = 0.01$).

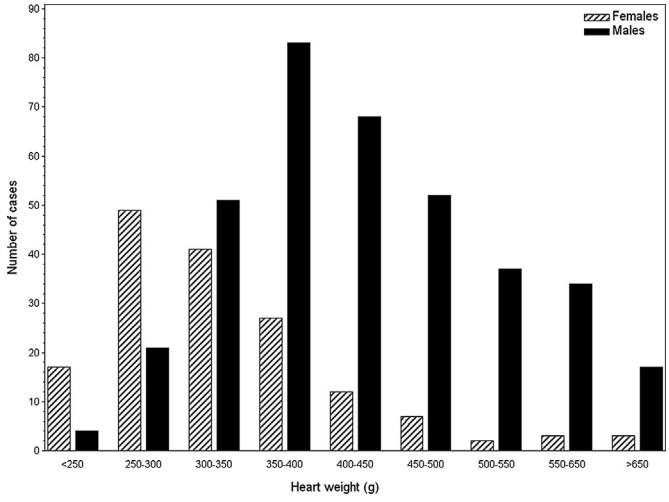

Fig. 4. Distribution of heart weight in the sudden death population according to the gender.

Fig. 4 shows the distribution of heart weight in the sudden death population according to the gender.

No statistically significant difference was found between males and females concerning non-cardiac causes of sudden death.

3.3. Comparison of the sudden death group with the control group

The control group was composed of 112 men and 42 women. The sex ratio (male/female) was equal to 2.6. The mean age was 45.9 years old. There was no statistically significant difference when comparing the proportion of men and women and the mean age in the control group and in the sudden death group.

Cardiac pathologies were found in 45% of the control cases. The most frequent cardiac pathology was CAD, found in 20.8% of the cases ($n = 32$). High-grade stenosis was found in 4 cases. Old infarction was found in 7 cases. CAD was statistically less frequent in the control group than in the sudden death group ($p < 0.0001$). Left ventricular hypertrophy was found in 15.6% of the cases ($n = 24$). Cardiomyopathy was found in 6.5% of the cases. There were 6 cases showing ARVC, 4 cases of dilated cardiomyopathy and one case of hypertrophic cardiomyopathy. ARVC was statistically more frequent in the sudden death group than in the control group ($p = 0.03$). Focal lymphocytic myocarditis was found in 4.5% of the cases ($n = 7$). Other cardiac pathologies included one case of atrial septal defect, 4 cases of myocardial bridge and one case of mitral insufficiency after rheumatic heart disease.

Heart weight was higher in the sudden death group (mean heart weight = 411.2 g) than in the control cases (mean heart weight = 360.2 g, $p < 0.0001$). This difference was also found in men (442.1 g vs. 381.8 g, $p < 0.0001$) and in women (340.7 g vs. 302.8 g, $p = 0.005$).

4. Discussion

The comparison of published autopsy studies on sudden death is difficult because studies vary respectively in their definition of sudden death, in their inclusion criteria of gender and age and in the causes of death analyzed (limited to cardiac causes or not). In Anderson's series,[3] the unexpectedness of the death was determined according to the answer to the following question: “if you were the primary physician of record, would you have been surprised by a phone call from a pathologist informing you that your patient had died of “X” illness or the complications thereof?” Medical information was not always available from forensic material to answer such a question with certainty. Sudden death may involve homeless people without medical care. In the same way, the time between the onset of symptoms and the death is not always clearly determined, especially for deaths without witnesses.

In our series, sudden death took place at home in the majority of the cases (57% of the cases). The greatest frequency of sudden death at home is found in other series.[4–6] We also found that sudden death occurs more frequently at home in women than in males. This might be explained by a longer time spent at home by women, or by a higher psychical stress in women at home than in men.

Nearly a third of the sudden deaths in our series occurred during sleep. Few deaths occurred in a context of psychical stress. However, stress is known as a contributing factor of sudden death. An English study evaluated the circumstances attending 100 sudden deaths due to CAD.[7] In 23 cases, a significant psychological stress occurring in the 30 min preceding the death was reported. In 40 cases, a significant psychological stress had occurred in the 24 h preceding the death. In our series, a psychological stress was less often reported. This can be explained by the fact that sudden deaths may be unwitnessed leading to forensic investigations and causes of death other than CAD were found. According to our results,

strenuous physical activity was rarely involved in sudden death, including sudden death linked with sport activity. However, it has been shown that sport as a physical stress is a significant risk factor for sudden death.[8–10]

In the great majority of the published series, most frequent cause of death is sudden cardiac death, mostly caused by CAD.[3–5,11–14] In our series, cardiovascular cause was found in 66.1% of the cases. The frequency varies from 28.2% in the Mexican series of Anderson et al.[3] to 83% in the Finnish study of Särkioja and Hirvonen.[11] Our series also shows that sudden cardiac deaths are more frequent in males. Epidemiology of sudden cardiac death is closely linked with CAD: Incidence of sudden cardiac death increases with age because the prevalence of cardiac ischemia increases with age.[15] In our series, CAD was the cause of death in 35.4% of the cases, corresponding to 58% of the cardiac sudden deaths, higher than in other countries, where CAD is responsible for sudden death in 13.7%–49.3% of the cases.[3,11,14] Rates are higher in the USA, where CAD is responsible for 80% of the sudden cardiac deaths according to Chugh et al.[16] Sudden cardiac death has a higher incidence in men than in women, reflecting the differences of CAD incidence according to age[17]: in Chugh's series concerning women aged 35–44 years old,[18] CAD was responsible for the death in sudden cardiac death in 22% of women and 40% of men. A study by Framingham concerning 5209 men and women showed that CAD was responsible for the death of 46% of men and 34% of women dying from sudden cardiac death.[2] Our series showed a higher difference: Death was caused by CAD for 35% of women and 65% of men dying from sudden cardiac death. According to Rizzo et al.,[15] incidence of sudden cardiac death is the same in women and in men after 80 years old, because of the higher incidence of coronary atherosclerosis in women after menopause.[15] These data could not be confirmed in our study because there were too few cases older than 80 (only six men and two women). When atherosclerosis was the main cause of death in men, it was the first cause of death only in women older than 55.

One of the difficulties encountered in forensic pathology is to determine the pathologies which played a significant role in the death of the subject. Indeed, autopsy can reveal a pathology which is only incidental.[19] This is very important to take into account for highly prevalent pathology such as atherosclerosis. According to our study, CAD and ARVC seem to be the most significant pathologies involved in sudden death. CAD can explain death only with a certain probability when there is a high-grade stenosis (>75%) of at least one segment of a major epicardial coronary artery.[2,20] However, according to Langlois,[21] the degree of coronary atherosclerosis is not more severe in subjects who died from sudden cardiac death than in non-cardiac deaths. Information given by witnesses about the circumstances of the death can help for the *post mortem* diagnosis which can be difficult as a myocardial infarct is grossly detectable only after 12–24 h.[21] A large sampling of the heart for microscopic examination is required to increase the sensitivity of *post mortem* diagnosis.[2]

Some causes of sudden cardiac death, classically reported in the literature, were not found in our series. Coronary arteries spontaneous dissection is a rare but well-known cause of sudden death, mainly described in young adults, especially in women in postpartum. Histological examination is necessary for the diagnosis, after a meticulous gross examination of the heart and coronary arteries.[22] No cases of aortic stenosis, or abnormal origin of a coronary artery, were identified either.

In our series, the cause of 4.3% of the deaths remained undetermined. The rates reported in the literature vary between 4% and 10%.[21,23,24] According to Chugh et al.,[18] origin of the sudden cardiac deaths remains undetermined in 50% of the women aged 35–44. This notion was not found in our series. In order to minimize the number of undetermined deaths, further investigations are needed, especially molecular analyses. In some cases, especially in young victims, a cardiac channelopathy is responsible for the death: long QT syndrome, short QT syndrome, Brugada syndrome (known as "nocturne sudden death syndrome" in southeast Asian countries) and catecholaminergic polymorphic ventricular tachycardy. In these pathologies, the heart can be normal at gross and also histologically.[25] An American study searched, in 49 cases of sudden unexplained death, for mutations causing long QT syndrome.[26] A cardiac channelopathy was found in 35% of the cases. The mutations associated with catecholaminergic polymorphic ventricular tachycardy are more frequently observed in men, whereas the mutations associated with long QT syndrome are more frequent in women. The Association for European Cardiovascular Pathology has recommended the use of molecular biology techniques.[25] Actually, molecular autopsies are mainly practiced in the field of scientific research. The genetic tests used are expensive and time-consuming, and remain limited to selected cases. Anyway, the role of molecular biology will probably grow in the future, so the preservation of DNA samples is of major importance. Cryopreserved tissues and blood samples in EDTA are the best alternative, rather than formalin-fixed, paraffin-embedded samples.[27] Guidelines will also be necessary, to define the legal and ethical data of molecular autopsy in sudden death.[28]

5. Conclusion

We studied 534 cases of sudden death with a systematic autopsy protocol including histologic and toxicological examination. Despite the differences of inclusion criteria between the published autopsy series, our series confirmed the data of the main epidemiological studies: sudden death is more frequent in men. It is mostly of cardiac origin, mainly caused by CAD. Our study also underlined the gender-linked differences: the main cause of sudden death is CAD in men, whereas it is cardiomyopathies in women. ARVC is more frequent in women, whereas hypertrophic and dilated cardiomyopathies are more frequent in men. Those data seem to be important for clinicians involved in prevention programs of sudden death, as they can adapt their screening according to the gender. Cardiac pathologies involved in sudden death can be frequently found in control population. So, morphological findings must be carefully assessed by the forensic pathologist to avoid the risk of overdiagnosis.

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None.

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None.

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