

Autopsy and sudden death

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KEYWORDS

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Our story dates back in the late 70s, when a series of juvenile sudden death (SD) occurred in the Veneto region, north east of Italy. A successful application for a prospective study on young people dying suddenly (<35-year-old, sudden infant death syndrome excluded) was submitted to the regional health authorities, thus implementing a network of collaboration with local anatomic and forensic pathologists, to collect all such events and to gather demographic data. The project is still in progress, and since then, we studied hundreds of consecutive juvenile SD cases, allowing to identify the culprit diseases in the various organs and cardiac structures (aorta, coronary arteries, myocardium, valves, and conduction system). The long-standing Veneto region experience clearly shows that autopsy still plays a pivotal role in the study and prevention of SD and should be carried out regularly. With time, the investigation of SD moved from the classic post-mortem study to molecular autopsy, especially in cases of SD with structurally normal heart. Sudden death prevention in the young has to be faced by an interdisciplinary team, including pathologists, cardiologists, sport physicians, and geneticists, the clinicopathologic correlation method still being the polar star. The game in the fight against SD is still played in the anatomical theatre, the place where 'death enjoys to save lives'.

Definition

The role of autopsy, to establish the cause of disease and death, was first stated by Giovanni Battista Morgagni in 1712, when delivering his professorship inaugural lecture at the University of Padua entitled 'Nova institutionum medicarum idea'. He said «*We will state that it is impossible to pursue the nature and cause of any disease without dissection of the respective cadavers*». ¹ And, as far as cases of sudden death, it is astonishing to realize how much actual was his definition «*...And here, with the name of sudden death we mean the death that, expected or unexpected, kills the man abruptly...*», ² compared with the current one «*Sudden death is defined as a natural, unexpected fatal event occurring within 1 hour from symptoms onset in an apparently healthy subject or one whose disease was not so severe enough as to predict such an abrupt outcome*». ³

The previous definition of sudden death by Giovanni Maria Lancisi in his book 'De subitaneis mortibus libri duo' includes not only cardiac but also respiratory and brain arrest, due to a natural event. Indeed, he defined SD «*Natural death with sudden cessation, expected or unexpected, of blood, air and nerve fluid*». ⁴ At that time 'animal spirit' was believed to be a fluid travelling along the nerves.

When nowadays we dissect a young who died suddenly, the aim is the same, namely: ⁵⁻¹⁶

- whether the death is ascribable to **cardiac or extracardiac disease**;
- if cardiac, to establish the **nature of underlying disease**, and the **mechanism**, either mechanical or arrhythmic;
- whether the underlying cardiac morbid entity is **inherited**, thus requiring screening and counselling of the next of kin;
- excluding **toxic or illicit drug** abuse and other unnatural deaths.

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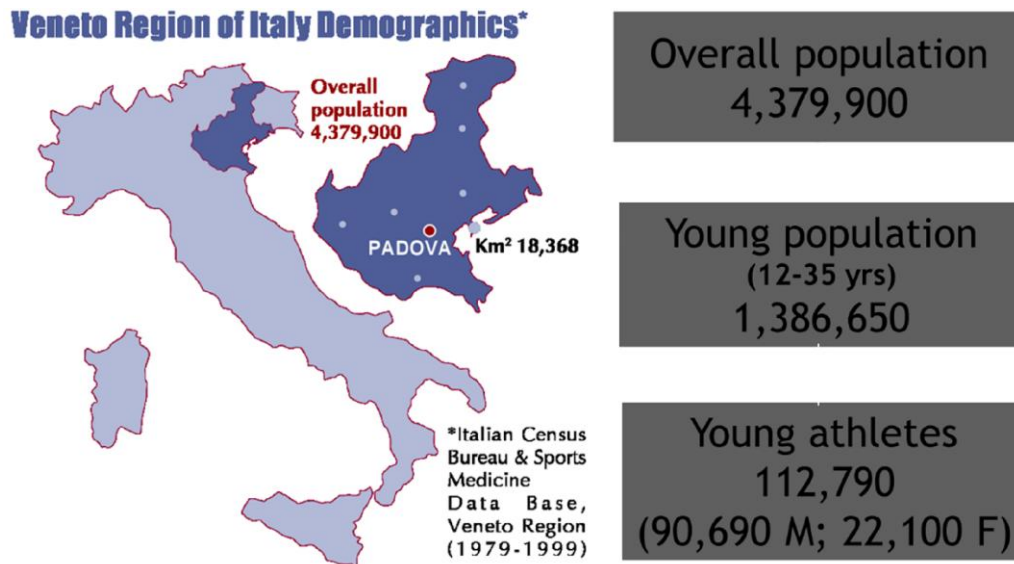


Figure 1 Veneto Region of Italy demographics (Italian census bureau & sports medicine data base, Veneto Region 1979-1999).



Figure 2 Ruptured berry aneurysm in the Willis circle: berry aneurysm of a middle cerebral artery.

Demographics of sudden death in the young: the Veneto Region experience

Sudden death in the young is a devastating event. It occurs unexpectedly in apparently healthy people, often during vigorous cardiac performance.

In 1980 we observed a series of cases and perceived that an investigation covering all the victims in the Veneto Region of Italy might help to clarify the matter.

Then we set up a Registry of sudden death in the young (age 2-35-years-old, sudden infarct death syndrome excluded). The overall population in 1999 was 4.379.900, young people (2-35-years-old) were 1.386.650, young athletes 112.790 up to 1999 (*Figure 1*). Sudden death occurred in 300 young people. Cumulative incidence was 1/100.000/year: 0.9/100.000/year in non-athletes and 2.3/100.000/year in athletes.^{8,9} Clearly the 2.5-fold incidence of SD in athletes vs. non-athletes means that effort by sport activity may unmask concealed diseases, triggering mechanical or arrhythmic cardiac arrest.

In the time interval 1980-2013, we studied 650 consecutive sudden death (SD) cases in the young and athletes. The method of investigation was autopsy with gross, histologic and, later, molecular investigation, together with clinical correlations. Since in Italy eligibility for sport activity requires ECG, the review of ECG records plays a fundamental role by detecting even subtle abnormalities, which could be of help to improve sensitivity and specificity of *in vivo* diagnosis and disqualify the subjects from strenuous sport activity.

Back to the **cause** of SD in the first 300 consecutive young people, 5% were cerebral, due to rupture of berry aneurysm of Willis circle (*Figure 2*), 4% respiratory due to allergic asthma attack (*Figure 3*) and 91% cardiac.

As far as the mechanism of cardiac sudden death, it was mechanical (aortic rupture, pulmonary embolism) in 7% and arrhythmic in 93% of cases. Thus, sudden cardiac arrest was mostly due to electrical abrupt disorders, namely ventricular fibrillation or electro-mechanical dissociation.

When SD in the young is cardiac, the villain should be searched in each structure of the heart: aorta, coronary arteries, myocardium, valves, conduction system, ion channels or receptors.¹⁰

Aorta and pulmonary artery

Only one SD due to pulmonary embolism was observed in a young lady who was under progesterone therapy.

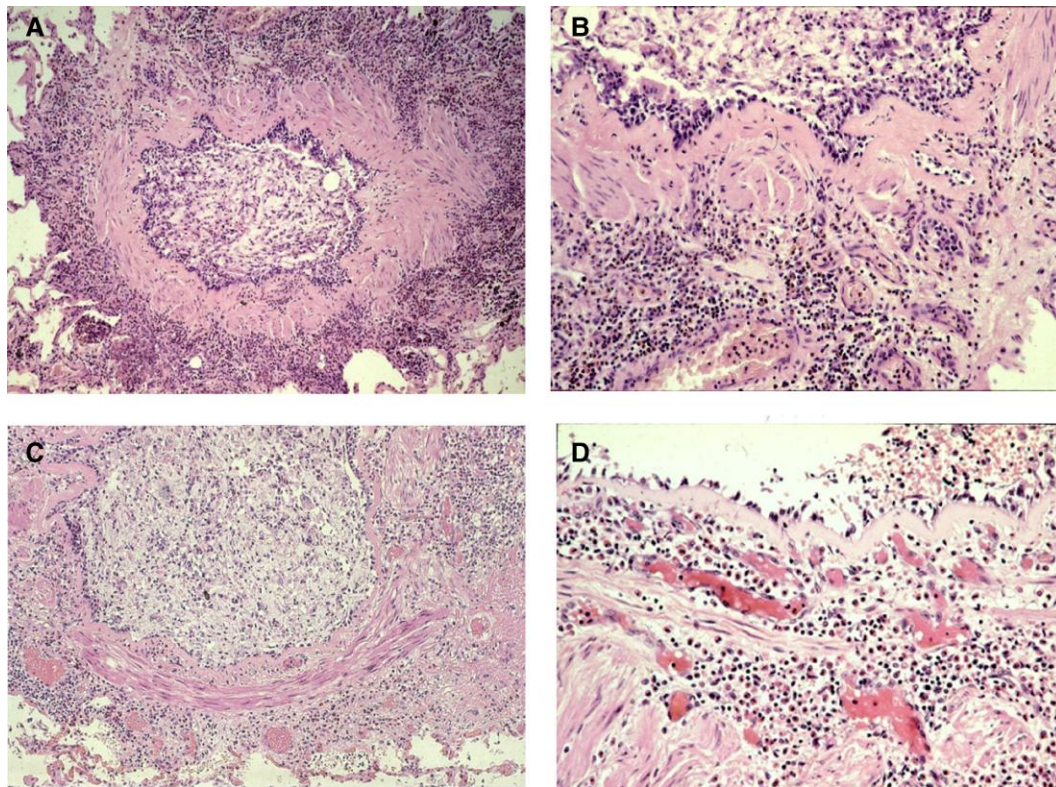


Figure 3 (A-D) Sudden death during asthma attack: histology of peripheral bronchi with eosinophils infiltrates.

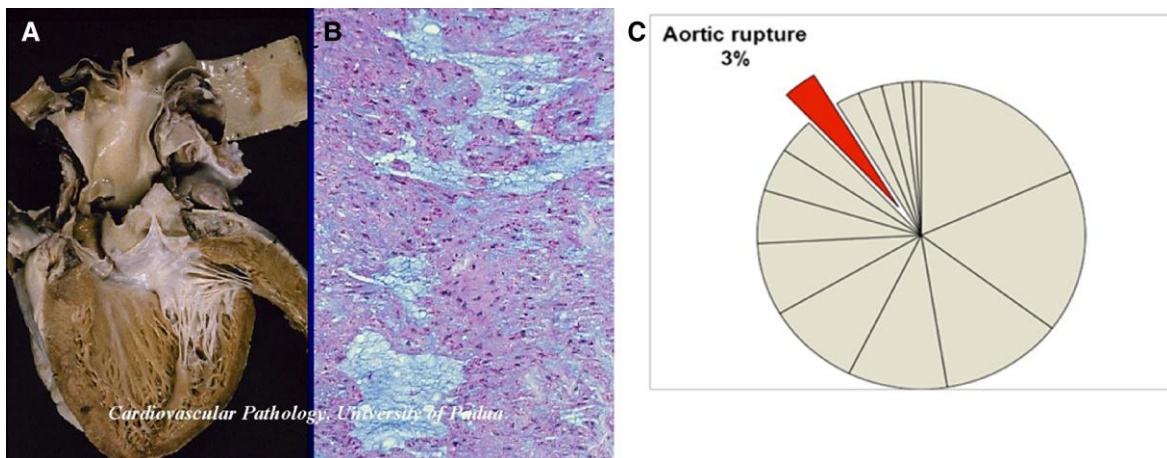


Figure 4 (A) Spontaneous aortic rupture in marfan syndrome of a 22-year-old basket male player; (B) at histology, cystic medial necrosis; (C) aortic rupture accounts for 3% of all sudden cardiac deaths.

Rupture of the aorta occurred in two cases with Marfan syndrome (*Figure 4*) and eight cases of bicuspid aortic valve, with or without aortic coarctation and a diameter of the ascending aorta even less than 5 cm (*Figure 5*), which is considered the critical threshold for surgical indication of ascending aorta replacement.

Altogether, aortic rupture accounted for 3% of all sudden deaths. Aortopathy causes progressive disappearance

of elastic lamellae in the tunica media with cystic medial necrosis (*Figure 4B*).

Coronary arteries: atherosclerosis and congenital anomalies

Among 690 cases (2-40 years-old) studied in the time interval 1980-2016, an obstructive coronary atherosclerotic disease was the main cause of sudden death by 18% (*Figure 6A*).

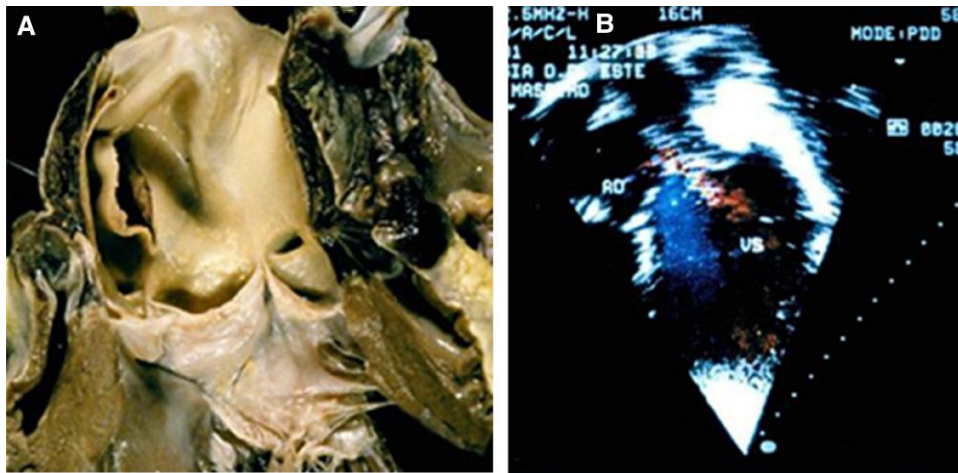


Figure 5 (A) BAV and aortic dissection in 31-year-old male; (B) last echo in the follow-up: mild aortic incompetence and ascending aorta with only 38 mm diameter.

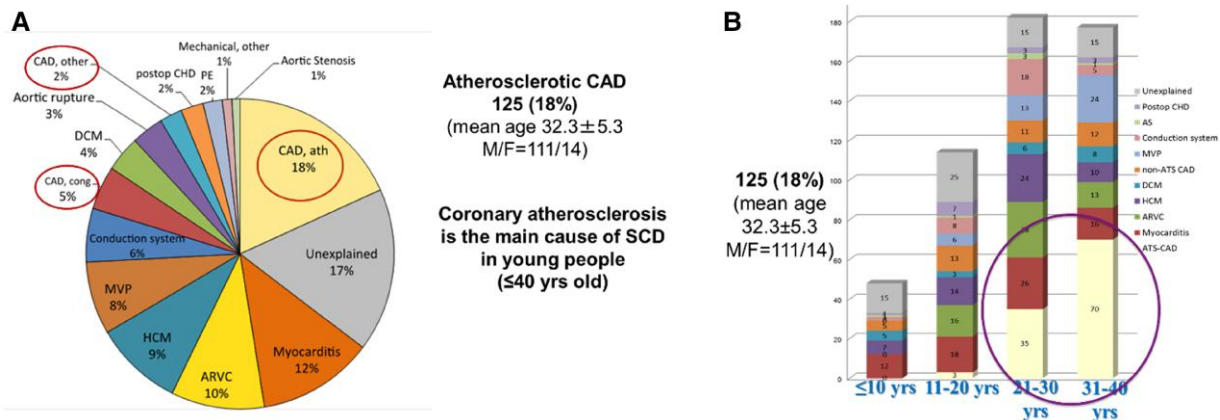


Figure 6 (A) Causes of SCD in the young (1-40 years) at autopsy: total n. 690 (1980-2016). Coronary atherosclerosis is the main cause; (B) The incidence increases with age. ARVC = Arrhythmogenic Cardiomyopathy; ath = atherosclerosis; ATS-CAD = atherosclerotic coronary artery disease; CAD = coronary artery disease; CHD = congenital heart disease; DCM = dilated cardiomyopathy; F = female; HCM = hypertrophy cardiomyopathy; M = male; MVP = mitral valve prolapse; PE = pulmonary embolism; SCD = sudden cardiac death.

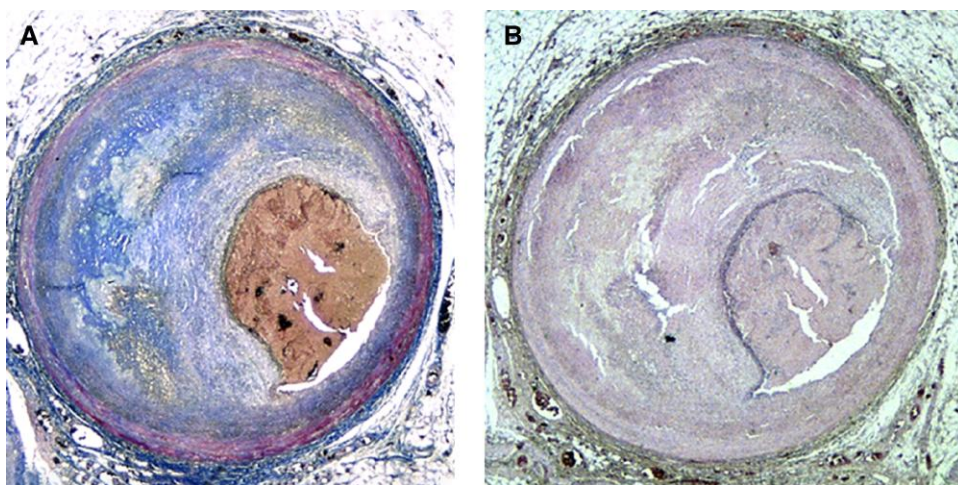


Figure 7 Young sudden cardiac death victim (male 32 years) with single coronary artery disease and thrombosis due to plaque erosion. (A) Thrombotic occlusion of the anterior descending coronary artery; (B) The thrombosis was due to endothelial erosion by inflammation.

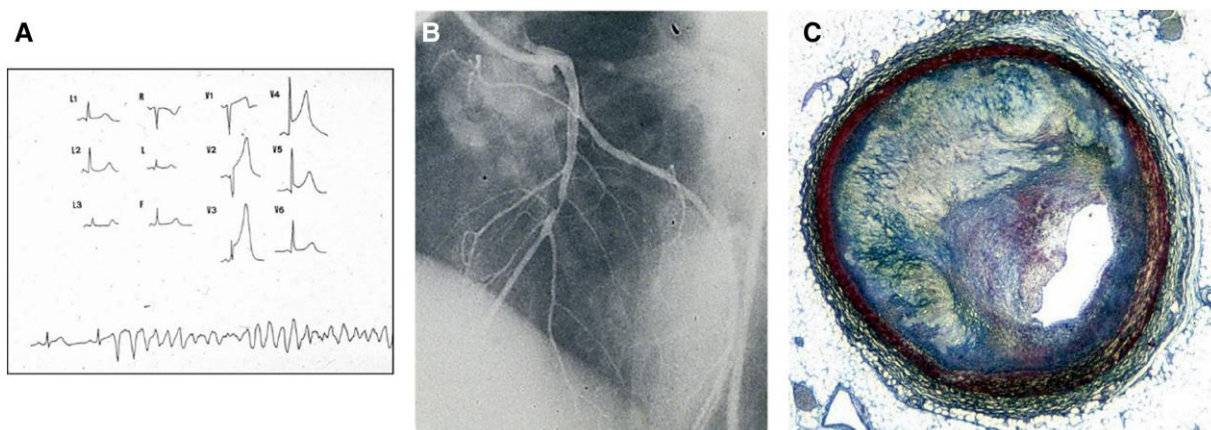


Figure 8 (A) The 12-lead electrocardiogram, recorded during the first episode of resting angina, shows a transient marked ST-segment elevation in the anterior precordial leads. The eeg tracing at the time of cardiac arrest shows ventricular fibrillation occurring during return of ST-segment to baseline; (B) selective angiography of the left coronary artery reveals a focal 90% stenosis in the middle tract of the anterior descending coronary artery; (C) the culprit eccentric atherosclerotic plaque: no atheroma, recent intimal proliferation, well preserved tunica media. From Thiene, G.; Corrado, D.; Basso, C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3,⁷ with permission.

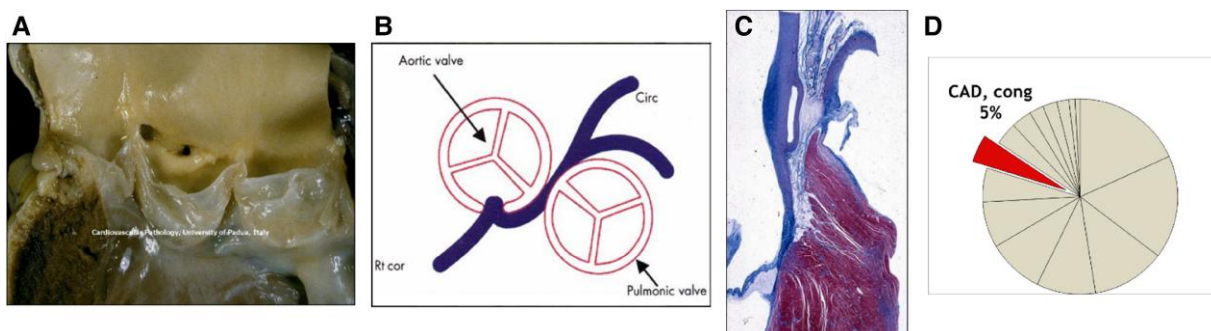


Figure 9 (A) Both coronary artery ostia are in the right sinus of aortic valve; (B) the first course of the left coronary artery travels between the aorta and the pulmonary artery (C) intramural aortic course; (D) coronary artery abnormalities account for 5% of juvenile sudden deaths. CAD, cong = coronary artery disease, congenital. RTcor = right coronary artery.

Incidence progressively increased from 11-20 to 31-40 years intervals. In the latter age group, the rate of sudden death victims was 33% (Figure 6B), as to indicate that coronary atherosclerosis is a nightmare also in the young.

All victims presented a single critical stenotic plaque, located in the descending coronary artery.¹¹

However, thrombotic occlusion was observed only in 49 (39%) of 125 cases. The majority (61%) had a critical obstructive stenosis (>75% lumen reduction). As far as thrombosis, endothelial erosion was the prevalent precipitating factor, due to intimal inflammation (Figure 7). Fibrous cap rupture, which is a regular occurrence in adult-elderly, was rare. As worrisome aspect, thrombotic occlusion of the coronary arteries by endothelial erosion was seen to occur even upon non obstructive plaque, suggesting that the effort eeg may be unable to suspect the existence of an atherosclerotic coronary disease at sport eligibility screening.

The intriguing question is how the prevalence of cases, with isolated obstructive plaque and without thrombotic occlusion, may undergo sudden death. We had the serendipity to record the electrocardiogram during cardiac arrest in a couple of cases with transient ST-segment elevation.¹² Post-mortem revealed a single obstructive plaque located

at the anterior descending coronary artery, previously seen at coronary angiography, which at histology appeared an eccentric atherosclerotic plaque without atheroma and with recent intimal proliferation on the side of the lumen (Figure 8) and well preserved tunica media. The case was in keeping with vasospasm (Prinzmetal's angina) and immunohistochemistry revealed an intimal proliferation upon the plaque consisting on contractile smooth muscle cells,¹³ most probably deriving from endothelial to mesenchymal transformation or by circulating stem cells.

As far as congenital coronary artery malformations, anomalous origin from the wrong sinus was the main cause of SD (Figure 9A).¹⁴ The abnormal localization of the first tract, in between the aorta and the pulmonary artery (Figure 9B) and intramural aortic course (Figure 9C) were both responsible of myocardial ischaemia during effort. It accounted for 5% of all SDs (Figure 9D).

Myocardial disease

Arrhythmogenic right ventricular cardiomyopathy (ARVC), a myocardial disorder with fibrofatty replacement of the ventricular myocardium, accounted for 10% of cases of

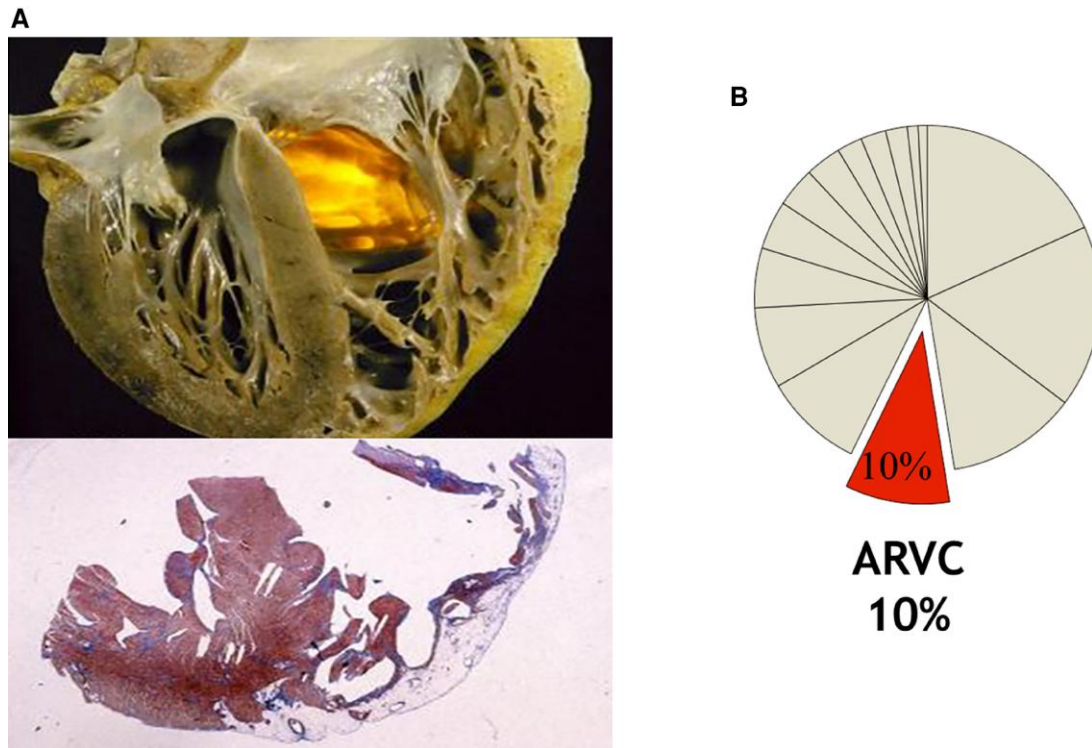


Figure 10 (A) Arrhythmogenic right ventricular cardiomyopathy (ARVC) with fibrofatty replacement of the right ventricle; (B) it accounted for 10% of SD in the young.

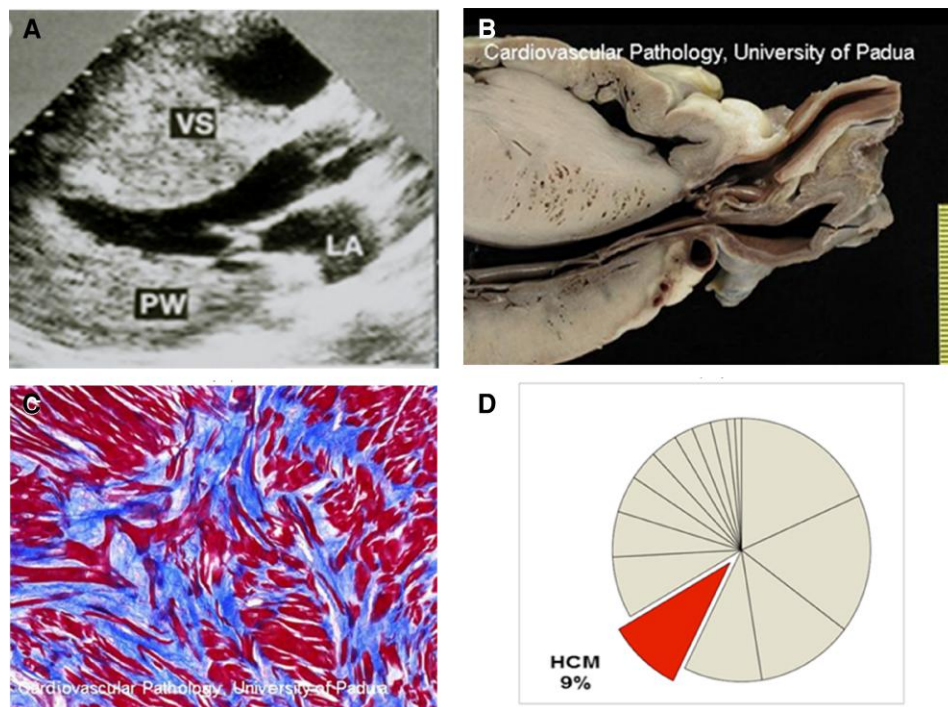


Figure 11 Hypertrophic cardiomyopathy (HCM) and sudden death in a 17-year-old male athlete. (A) Eco long axis view of the left ventricular outflow tract with hypertrophy of the ventricular septum (VS), asymmetric when compared with the posterior left ventricular free wall (PW). LA = left atrium; (B) Heart specimen with long axis tomographic section; (C) myocardial disarray at histology; (D) HCM accounted for 9% of SD in the young. SD = sudden death.

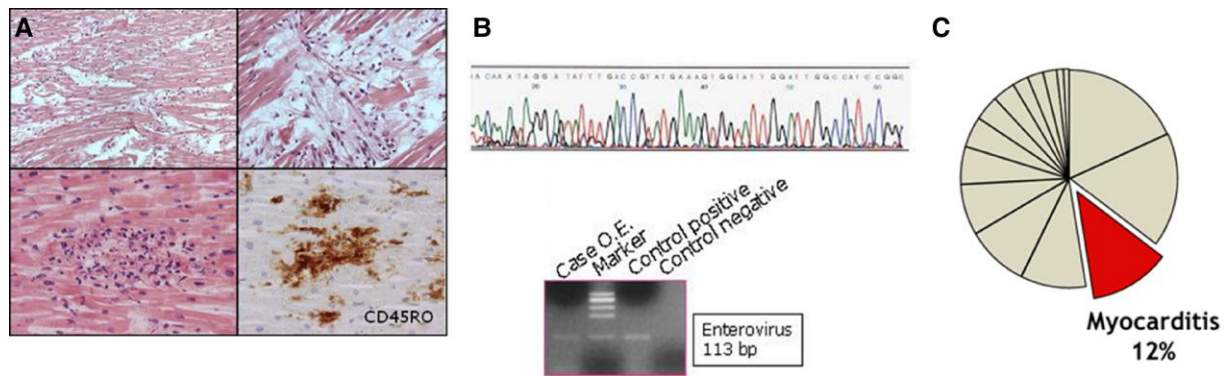


Figure 12 Molecular autopsy of coxsackie virus myocarditis in a 6-year-old boy who died suddenly. (A) Histology and immunohistochemistry. Note the lymphocytic inflammatory infiltrates with cardiomyocyte necrosis; (B) genetic sequence of an enterovirus at molecular analysis; (C) myocarditis accounted for 12% of SDs in the young. SD=sudden death.

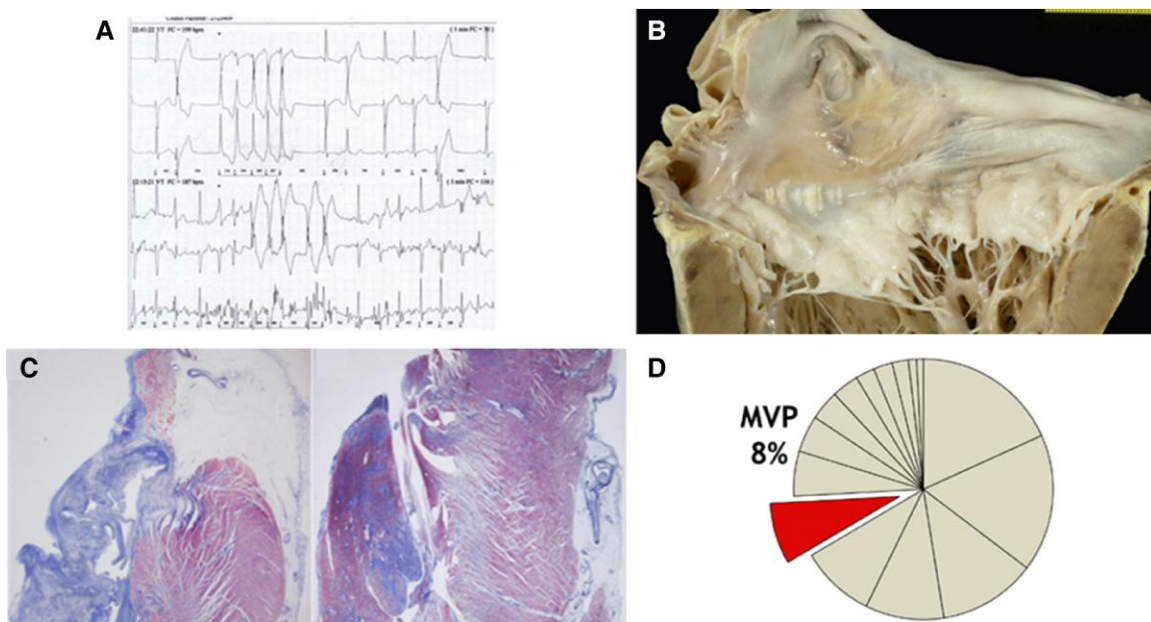


Figure 13 (A) Young lady with ventricular tachyarrhythmias; (B) she died suddenly and mitral valve prolapse (MVP) was found; (C) at histology disjunction of the posterior leaflet attachment from the ring and fibrosis of the posterior wall of the left ventricle and the postero medial papillary muscle of the mitral valve; (D) MVP accounts for 8% as sudden death in the young. From Thiene, G.; Corrado, D.; Basso, C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan, X, 190. ISBN 978-88-470-5775-3,⁷ with permission.

sudden death.^{15,16} Incredibly enough, the right ventricle may be the killer (Figure 10), being the source of ventricular tachyarrhythmias merging into ventricular fibrillation and cardiac arrest during effort. ARVC is the main cause of sudden death of athletes in Italy accounting for 18% of cases.

Molecular genetics investigation revealed that AC is a dominant hereditary disease, due to mutations of the genes coding proteins of mechanical cell junction (desmosome).¹⁷

As far as hypertrophic cardiomyopathy, a heart muscle disease with asymmetric hypertrophy and myocardial disarray at histology (Figure 11) it accounts in the Veneto Region—Italy for 9% of SD in the young but only 2% among the athletes, because the carriers

are easily identified at the screening for sport eligibility and disqualified from sport activity.⁸ Myocardial scarring, due to ischaemia induced by myocardial hypertrophy compression of intramural small coronary arteries, is a source of even lethal ventricular tachyarrhythmias.¹⁸ Genetic investigation revealed HCM to be a sarcomere disease due to mutation of genes encoding proteins of the contractile apparatus.¹⁹

Myocarditis, namely inflammation of the myocardium, is mostly viral in origin and not so minor cause of sudden death in the young and athlete.²⁰ Molecular investigation at autopsy ('molecular autopsy') may discover the culprit virus (Figure 12A)²¹. Myocarditis account for 12% of juvenile sudden death, especially in children and mostly due to coxsackie virus (Figure 12B, C).

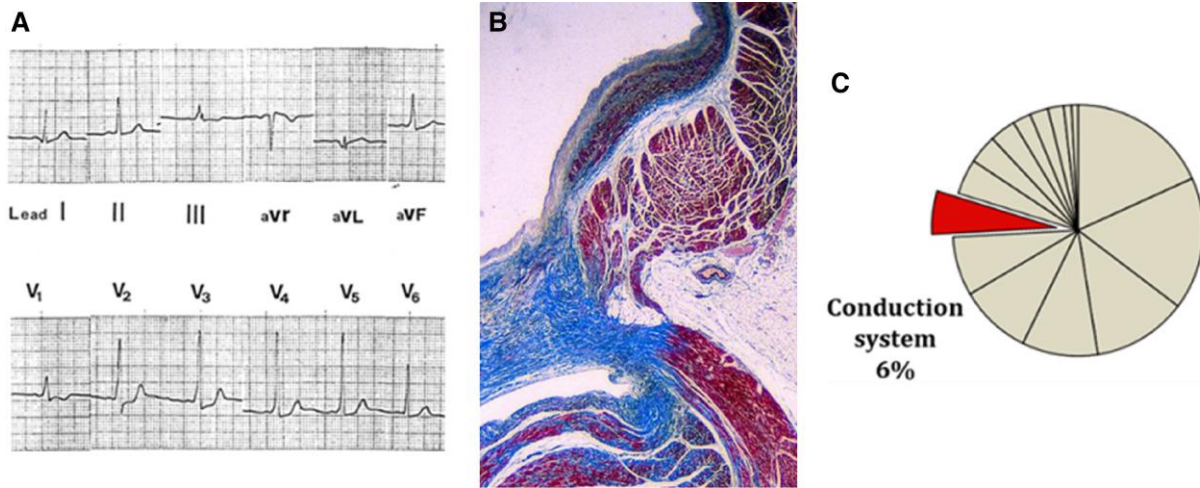


Figure 14 Sudden death in a young student affected by pre-excitation syndrome. (A) ECG with short QT and delta wave; (B) An anomalous fascicle ('Kent fascicle') is laterally connecting the left atrial to the left ventricular myocardium; (C) conduction system congenital abnormalities accounted for 6% of SCDs in the young. From Thiene, G.; Corrado, D.; Basso, C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3,⁷ with permission.

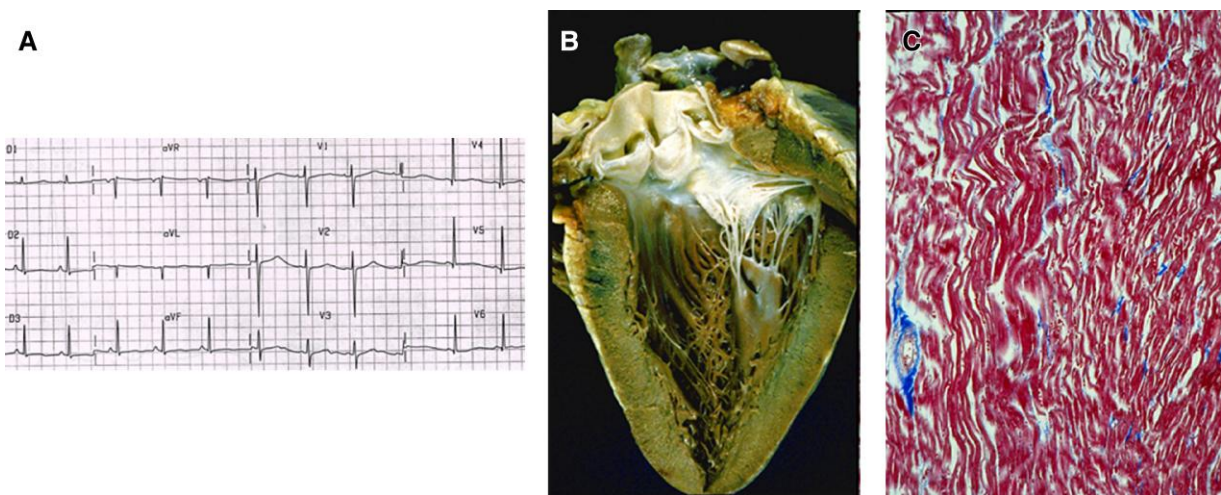


Figure 15 (A) Sudden death in a 20-year-old young male with long QTc (480 msec); (B) normal heart gross examination and (C) only wavy fibers at histology, due to prolonged cardiac arrest. From Thiene, G.; Corrado, D.; Basso, C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3,⁷ with permission.

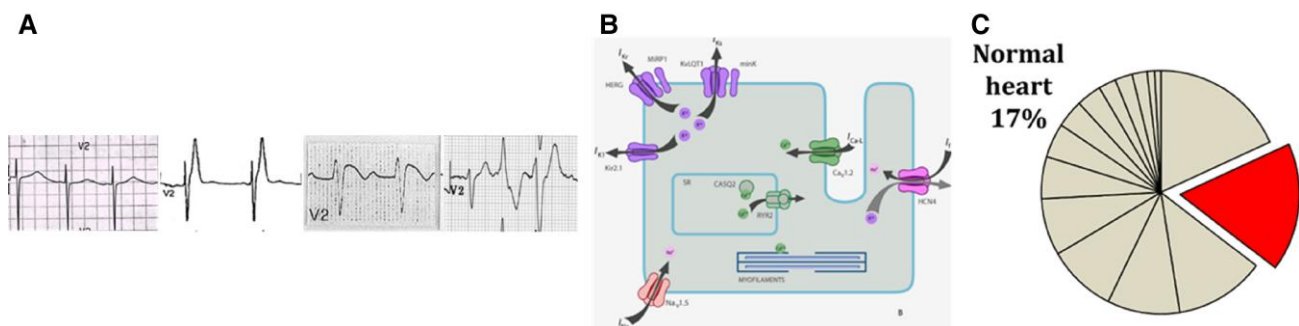


Figure 16 Sudden cardiac death and normal heart: «mors sine materia». (A) Long QT; Short QT; Brugada syndrome; catecholaminergic polymorphic VT; (B) drawing of ion channels and ryanodine receptor; (C) grossly and histologically normal heart was found in 17% of sudden deaths.

Table 1 Main causes of SD in the young and/or athletes (autopsy-proven)

Country (Ref. #)	N, Age (yrs)	Incidence n/100'000/year	CAD (%)	CAA (%)	Myocarditis (%)	HCM (%)	AC (%)	MVP	Normal heart (%)
Denmark	314, 1-35	1.9	13	1	7	0.6	5	2.5	43
United Kingdom	258, ^a 7-35	NA	1.4	6	2	7.4	11.6	NA	47.6
Australia/New Zealand	490, 1-35	1.3		24	7		16	NA	40
USA	842, ^a 14-23	NA	4	19	7	36	5	4	3
Italy	650, 1-40	1	18	5	14	10	10	8	17

Values are % unless otherwise indicated.

AC = arrhythmogenic cardiomyopathy; CAA = coronary artery anomaly; CAD = atherosclerotic coronary artery disease; HCM = hypertrophic cardiomyopathy; MVP = mitral valve prolapse; NA = not available.

^aOnly competitive athletes.

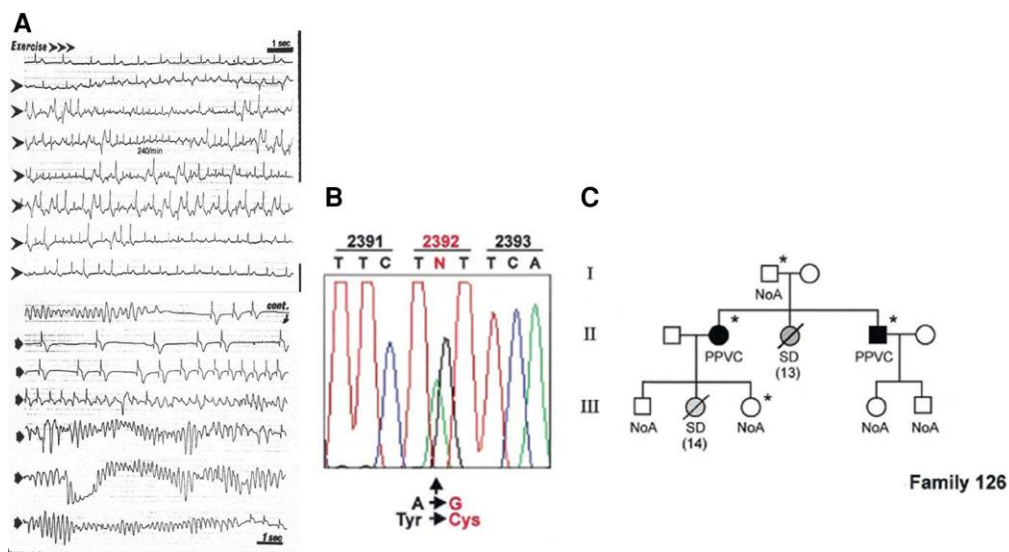


Figure 17 (A) Ecg of catecholaminergic polymorphic ventricular tachycardia merging into ventricular fibrillation; (B) missense mutation of the ryanodine receptor gene; (C) family tree, in keeping with dominant hereditary disease: sudden death occurred in the proband and in an aunt. A = adenine; G = guanine; Cys = cysteine; Tyr = tyrosine.

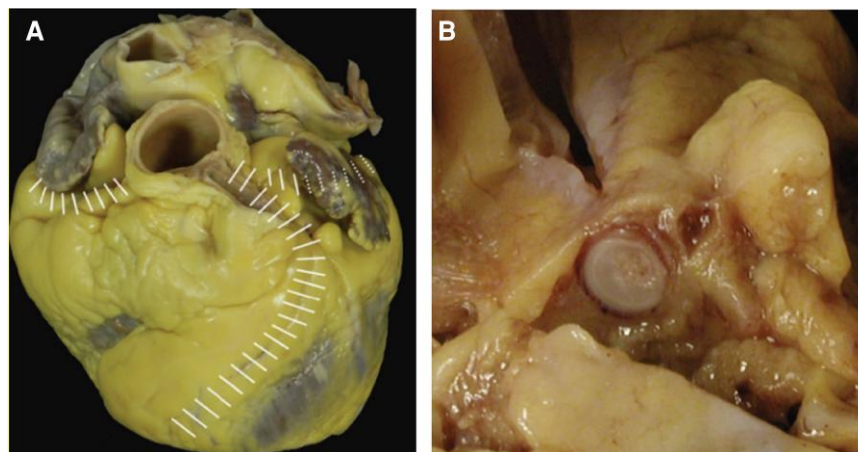


Figure 18 Post-mortem examination of the heart. (A) Cross sections of the subepicardial coronary arteries; (B) Gross appearance of a coronary thrombus in the proximal descending coronary branch at cross section. From Thiene, G.; Corrado, D.; Basso, C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3,⁷ with permission.

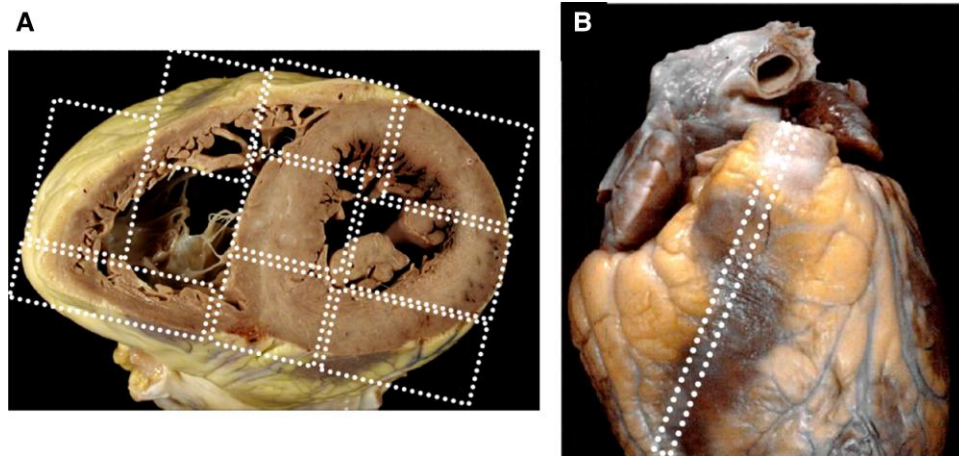


Figure 19 (A) Heart cross sections and myocardium sampling; (B) longitudinal sampling of the pulmonary infundibulum. From Thiene, G.; Corrado, D.; Basso, C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan, X, 190. ISBN 978-88-470-5775-3,⁷ with permission.

Valve disease

As far as bicuspid aortic, see aorta above.

Mitral valve prolapse may be arrhythmic and a significant cause of sudden death, accounting for 8% in our experience (Figure 13). The arrhythmic substrate is a fibrosis of the mitral papillary muscles and the posterolateral wall of the left ventricle, most probably due to traumatic stress of billions ventricular systoles during life, in the presence of congenital disjunction of the mitral ring from posterior leaflet attachment.²²

Conduction system

Abnormalities of the conduction system account for 5% of SD in the young (Figure 14). The main culprit is the pre-excitation syndrome due to an accessory microscopic bundle of working myocardial joining the atrial to the ventricular myocardium ('Kent fascicle') outside the regular conduction system. Lack for refractory action accounts of supraventricular tachycardia and even ventricular fibrillation in case of atrial fibrillation with 1 to 1 conduction.²³

Ion channels and receptors diseases

They correspond to the so called SD with 'mors sine material'. The heart grossly and histologically appears normal, the defect being purely functional and invisible (Figure 15), even at the light microscopy and ultrastructure. 17% of sudden cardiac victim present with a 'normal heart' (Figure 16).

The culprit diseases are long and short QT, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia,²⁴ all dominant hereditary diseases (Figure 16).

Molecular autopsy²¹ is mandatory, otherwise SD cannot find an explanation and the kin remains at risk of the same fatal outcome.

Different rates have been published²⁵⁻²⁷ up to 47.6% (Table 1). The reported data are frequently unreliable because they come from referral centres, where only unexplained deaths are submitted.

The gene of ryanodine receptor is quite long and time consuming to be checked. It is astonishing that just a

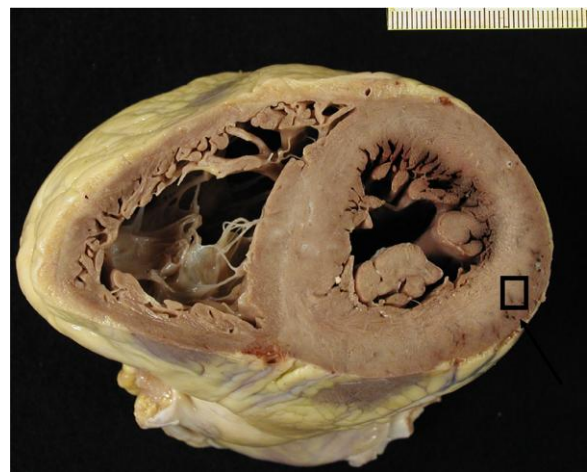


Figure 20 Myocardial sampling for molecular investigation (virus and genetic mutations), to be frozen -80° together with blood and spleen sampling. From Thiene, G.; Corrado, D.; Basso, C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan, X, 190. ISBN 978-88-470-5775-3,⁷ with permission.

missense mutation of the DNA may account for the change of an aminoacid of a so long protein, enough to trigger life threatening arrhythmias on effort (Figure 17).

How to perform autopsy of sudden death victims

The European Association for Cardiovascular Pathology²⁸ has published strict guidelines on how to perform the examination of the cardiac specimens in case of SD (Figures 18 and 19) and when to perform molecular autopsy (Figure 20).

Preservation of the heart and request of a second opinion, by submitting the specimen to a skilled cardiovascular pathologist, is highly recommended.

Autopsy with molecular pathology investigation includes both detection of viral genomes in inflammatory

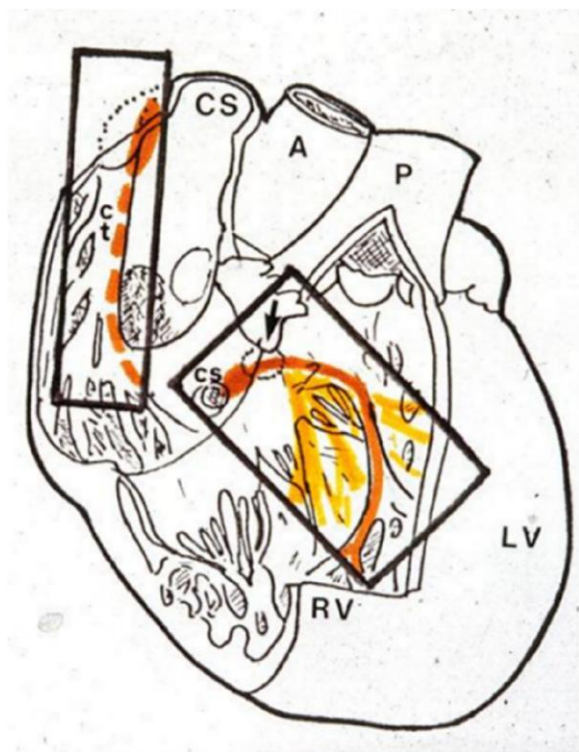


Figure 21 (A) How to remove blocks with sinus node and av conduction system. A = Aorta; CS = superior vena cava; LV = left ventricle; P = pulmonary artery. From Thiene, G.; Corrado, D.; Basso, C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3,⁷ with permission.

cardiomyopathy and genetic analysis in both structural and non-structural genetically determined heart disease. Clinicopathologic correlation with the clinician in charge of the patients is considered mandatory.²⁸

When and how to perform the study of the conduction system and toxicological analysis

Histological investigation of the conduction system (Figure 21) and accessory pathways should be performed only if an ecg tracing is available. The serial histologic section is mandatory.²⁸

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Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

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