**The Aetiology of Sudden Death in Sport: Insights from a Large Regional Registry in the United Kingdom**

**Authors:** Gherardo Finocchiaroa MD, Michael Papadakisa MBBS, MRCP, MD, Jan-Lukas Robertusb MD, Harshil Dhutiaa BSc MRCP, Alexandros Klavdios Steriotisa MD PhD, Maite Tomea MD PhD, Greg Mellora MB, BChir, Ahmed Merghania MRCP, Aneil Malhotra MSc, MRCP, Elijah Behra MA, MBBS, FRCP, Sanjay Sharmaa BSc, MBChB, FRCP, MD\*, Mary N.SheppardbMBBCH, BAO, BSc, MD, FRCPath\*

**Institutions:**

a Cardiovascular Sciences Research Centre, St George's, University of London, London, United Kingdom

b Cardiovascular Pathology Department, St George's, University of London, London, United Kingdom

\*Contributed equally

Keywords: sudden death, sport, arrhythmogenic right ventricular cardiomyopathy

Word count: 4375

**Author for correspondence:**

Sanjay Sharma, MD

Professor of Clinical Cardiology,

Cardiovascular Sciences,

St. George’s University of London,

Cranmer Terrace,

London. SW17 0RE. UK.

E-mail: sasharma@sgul.ac.uk

**ABSTRACT**

**Background and aims:** An accurate knowledge of the causes of sudden cardiac death (SCD) in athletes and the role of precipitating factors are necessary in order to establish preventative strategies. The aim of the study was to investigate the causes of SCD and their association with intensive physical activity in a large cohort of athletes.

**Methods:** Between 1994 and 2014, 357 consecutive cases of athletes who died suddenly (age 29 ± 11 years, 92% males, 76% Caucasian, 69% competitive) were referred to our cardiac pathology centre. All subjects underwent detailed post-mortem evaluation including histological analysis by an expert cardiac pathologist. Clinical information was obtained from referring coroners.

**Results:** Sudden arrhythmic death syndrome (SADS) was the most prevalent cause of death (n=149, 42%). Myocardial disease was detected in 40% of cases including idiopathic left ventricular hypertrophy (LVH) and/or fibrosis (n=59, 16%), arrhythmogenic right ventricular cardiomyopathy (ARVC) (13%), and hypertrophic cardiomyopathy (HCM) (6%). Coronary artery anomalies were identified in 5% of cases. Sudden arrhythmic death syndrome and coronary artery anomalies affected predominantly young athletes (≤35 years) whereas diseases of the myocardium were more common in older individuals. Death during intense exertion occurred in 61% of cases and ARVC and idiopathic left ventricular fibrosis were the strongest predictors of SCD during exertion.

**Conclusions:** Conditions predisposing to SCD in sport demonstrate a significant age predilection. The strong association of ARVC and idiopathic left ventricular fibrosis with exercise induced SCD reinforces the need for early detection and abstinence from intense exercise. However, almost 40% of athletes die at rest, highlighting the need for widespread availability of complementary preventative strategies.

**ABBREVIATIONS**

AED: automatic external defibrillator

ARVC: arrhythmogenic right ventricular cardiomyopathy

CAD: coronary artery disease

HCM: hypertrophic cardiomyopathy

LVH: left ventricular hypertrophy

SCD: sudden cardiac death

**INTRODUCTION**

Sudden cardiac death (SCD) is a tragic event which occasionally affects apparently healthy individuals ([1](#_ENREF_1)), including young (≤35 years) athletes ([2-5](#_ENREF_2)). A spectrum of cardiac diseases are implicated with variable prevalence depending on the age and other demographics of the cohort ([6](#_ENREF_6)). A large proportion of reports relating to the causes of SCD in athletes are limited by the lack of a detailed post-mortem examination performed by an experienced cardiac pathologist which, potentially impacts on the precise aetiology of SCD. A recent study comparing the interpretation of autopsy findings between a referring pathologist and a specialist cardiac pathologist, demonstrated a 40% disparity with respect to the actual cause of death ([7](#_ENREF_7)).

Knowledge regarding the precise causes and precipitating factors for SCD may influence national strategies to prevent such events including pre-participation screening methods and widespread availability of automated external defibrillators (AEDs). Pre-participation screening with ECG is useful for detecting quiescent inherited cardiac diseases, particularly the inherited cardiomyopathies and ion-channelopathies, but has limited value in detecting athletes with coronary artery disease (CAD). Conversely, the AED appears to be more effective in the termination of arrhythmias in athletes with CAD or coronary artery anomalies than in athletes with cardiomyopathy ([8](#_ENREF_8),[9](#_ENREF_9)).

The objective of this study was to investigate the causes and circumstances of SCD in a large cohort of athletes with the post-mortem performed by an expert cardiac pathologist.

**METHODS**

**Setting**

The Cardiac Risk in the Young (CRY) center for cardiac pathology was established at the Royal Brompton Hospital and subsequently transferred to St. George’s University of London. The centre is led by an expert cardiac pathologist (MNS) and receives over 400 whole hearts of cases of SCD across the United Kingdom each year. General pathologists are likely to refer when the clinical history is suggestive of inherited cardiac disease, especially when the death affects a young or athletic individual or when the cause of death is uncertain after the initial autopsy.

**Study population**

We reviewed a database of 3684 cases of SCD which were referred to the CRY centre for cardiac pathology between 1994 and 2014. SCD was defined as death occurring within 12 hours of apparent wellbeing. We retrieved a subgroup of 357 (9.7%) cases of individuals who engaged in regular sport activities during life, defined as >3 hours of organised physical training per week. The majority (84%) of referrals were between 2004-2014. Competitive athletes were defined as those who were involved in organized sport requiring participation in regular, formal competition. Circumstances of death were subdivided broadly into death occurring during exercise and death during rest or sleep.

**Post-mortem examination**

All SCD cases underwent a full post-mortem evaluation by the local pathologist. Following the exclusion of extra-cardiac causes, the heart was referred to our centre after written consent of the coroner and the family of the deceased. In 58% of cases the local pathologist also performed an initial cardiac autopsy before referring the heart. A thorough toxicology screen was conducted in all cases in accordance with the usual investigation of sudden and unexpected deaths in the UK. Comprehensive macroscopic examination of the whole heart and histological analysis were performed in accordance with the guidelines on “Autopsy practice for sudden death with likely cardiac pathology” of the Royal College of Pathologists (REF) and the Association for European Cardiovascular Pathology (REF). All cardiac structures were systematically examined. The heart weight was recorded in grams and ventricular wall thickness and internal cavity dimensions were measured at mid-ventricular level excluding the papillary muscles and fat. A minimum of 10 blocks of tissue are taken for histological analysis as reported previously (REF). Sections of myocardium were fixed in formalin, embedded in paraffin and stained with haematoxylin and eosin as well as elastic Van Gieson stain to highlight myocardial fibrosis.

The criteria for defining specific cardiac pathologies have been previously described ([6](#_ENREF_6),[10](#_ENREF_10)) and are summarised in Table 1. Sudden arrhythmic death syndrome (SADS) was a diagnosis of exclusion, defined as a structurally normal heart with no evident abnormality on macroscopic and histological evaluation, and a negative toxicology screen([11-13](#_ENREF_11)).

**Clinical information**

The referring coroner and pathologist were asked to complete a questionnaire inquiring about the demographics of the deceased, past medical history, family history, cardiac symptoms, the nature and level of physical activity and exact circumstances of death. The data were derived from a number of sources including: interview with the family of the deceased, potential witnesses of the SCD and reports from the deceased’s family physician. Data were collected prospectively and stored on an electronic database.

**Statistical analysis**

Statistical analysis was performed using the PASW software (PASW 18.0 Inc, Chicago, IL). Results are expressed as mean ± standard deviation (SD) for continuous variables or as number of cases and percentage for categorical variables. Comparison of groups was performed using Student’s T-test for continuous variables with correction for unequal variance when necessary and Chi-square test or Fisher Exact Test, as appropriate for categorical variables. Univariate and multivariate logistic regression analysis was used to determine the factors associated with death during exertion. Variables that were univariately correlated with the dependent variable, age and sex were selected and entered into the forward stepwise multiple regression model.

**RESULTS**

**Clinical characteristics**

The mean age at death of the 357 athletes was 28 ± 12 years (range 7-67 years; median 27 years), with a large male predominance (n=330, 92%). The average body mass index (BMI) and body surface area (BSA) were 25 ± 5 Kg/m2 and 2.2 ± 0.4 m2, respectively. A significant proportion of individuals were competitive athletes (n=245, 69%), participating in regular training and competition in team (n=155, 43%) or individual (n=90, 26%) sports. The rest of the cohort (n=112, 31%) was comprised of recreational athletes. Sporting disciplines included: running (n=92, 25%; 40 participating in half-marathons and marathons), football (n=91, 25%), cycling (n=30, 8%), gymnastics (n=30, 8%), swimming (n=22, 6%), weightlifting (n=20, 6%), rugby (n=19, 5%), tennis (n=6, 2%), golf (n=6, 2%), boxing (n=5, 1%) and other sports (n=36, 10%).

The majority of the athletes were asymptomatic (n=288, 81%). Of the 69 (29%) symptomatic athletes, 27 (8%) had palpitations, 20 (6%) had chest pain, 18 (5%) had syncope, 4 (1%) complained of decreased exercise tolerance. Five patients suffered from palpitations due to paroxysmal atrial fibrillation, including one in the context of Wolf-Parkinson-White syndrome. One athlete was diagnosed with myocarditis 4 years before death and one athlete was hospitalized 4 months prior to death for suspected myocarditis. There was a family history of premature sudden death (defined as death of a first-degree relative <50 years), in 28 (8%) cases. The main comorbidities were asthma 28 (8%), epilepsy (n=5, 1%) and treated arterial hypertension (n=4, 1%).

**Aetiology**

The main causes of death are illustrated in Figure 1. A normal post-mortem indicative of sudden arrhythmic death syndrome (SADS) was the most common finding and accounted for 149 (42%) of deaths. Myocardial disease was present in 130 cases (35%). Among these, idiopathic LVH and/or fibrosis accounted for 59 deaths (16%), followed by arrhythmogenic right ventricular cardiomyopathy (ARVC) (n=48, 13%) and hypertrophic cardiomyopathy (HCM) (n=23, 6%). The majority of individuals with ARVC also demonstrated LV involvement with 17 cases (35% of the ARVC subgroup) exhibiting fibro-fatty infiltration of the LV and 41 cases (85% of the ARVC subgroup) showing evidence of LV fibrosis. Coronary artery pathology constituted 7% of cases, with coronary artery anomalies accounting for the majority of the cases.

**Causes of death by age and gender**

The prevalence of specific cardiac pathologies varied with age (Figure 2). SADS was most common in younger cases and showed a reducing trend with increasing age (Figure 3). A normal heart was reported in 56% of children and adolescents (<18 years), 44% of young adults (18-35 years) and 26% of older (>35 years) individuals (p<0.001 between <18 and >35, p=0.004 between 18-35 years and >35 years). Coronary artery abnormalities were also more prevalent in younger individuals, accounting for 11% of deaths in children and adolescents compared to only 2% in adults > 35 years. In contrast, diseases of the myocardium were more common in older athletes (Figure 3). Idiopathic LVH and/or fibrosis was present in only 10% of individuals <18 years but in 26% of those >35 years (p=0.01), while ARVC was detected in only 4% of individuals <18 years but in 18% of those >35 years (p=0.009).

The mean heart weight was 421 ± 110 g. Seventy (20%) athletes exhibited an absolute value of > 500 g. Of these, the majority were diagnosed with idiopathic LVH with or without fibrosis (n=30, 42%), followed by HCM (n=13, 19%) and ARVC (n=12, 17%) (Figure 4).

There were only 27 females in our cohort. The majority (55%) showed a normal heart at the PM. Idiopathic fibrosis accounted for 11%, ARVC for 7% and HCM for 4% of the other deaths. None of the female athletes showed idiopathic LVH.

**Circumstances of death**

The majority of athletes died during exertion (n=219, 61%), including a small proportion of individuals (n=14, 4%) who died during emotional stress (altercation). Of the 137 subjects who died at rest, 47 (34%) died during sleep. The age and gender distribution between athletes who died during exertion and those dying at rest was similar and only a minority of subjects (8%) had a family history of sudden death. Patients who died at rest were more likely to demonstrate a normal heart at post mortem examination (Table 2). Conversely, athletes dying during exertion were more likely to have ARVC (20% vs 3%, p<0.001), LV fibrosis (39% vs 22%, p<0.001) and coronary artery anomalies (7 vs 1%, p=0.01).

Multivariate analysis identified ARVC (HR: 6.01, 95% CI 1.97 to 18.32, p=0.001) as the strongest independent predictor of SCD during exercise, followed by LV fibrosis (HR: 2.11, 95% CI 1.15 to 3.88, p=0.01) (Table 3).

**DISCUSSION**

This study reports on a large number of young athletes dying suddenly in the UK where all post-mortem examinations were conducted by a cardiac pathologist with expertise in conditions predisposing to SCD. In comparison to a smaller study published by our group([6](#_ENREF_6)), the large sample size of almost 70% competitive athletes allows for a greater degree of certainty relating to the impact of specific pathologies associated with SCD during intensive exercise.

**Causes of SCD in athletes**

In agreement with our earlier study([6](#_ENREF_6)) and with studies in US collegiate athletes ([15](#_ENREF_15)) and young military personnel([16](#_ENREF_16)) a normal heart indicative of a diagnosis of SADS was present in a significant proportion of athletes. In this study a structurally normal heart accounted for 42% of the overall cohort, compared to the 23% we reported previously (6). Although the high prevalence of SADS in our cohort may be partly explained by a referral bias, its high prevalence in the US cohorts (31% in collegiate athletes([15](#_ENREF_15)) and 41% in young military personnel([16](#_ENREF_16))) underscores the importance of inherited primary arrhythmia syndromes as a major cause of SCD in athletes([15](#_ENREF_15),[16](#_ENREF_16)).

Myocardial disease accounted for 40% of cases. Idiopathic LVH and/or fibrosis and ARVC were the predominant diagnoses. The significance of idiopathic LVH is uncertain. The entity may be an innocent bystander, however the possibility of pathological LVH, such a variant of HCM, cannot be excluded, particularly in the presence of LV fibrosis ([10](#_ENREF_10)). Idiopathic LVH may also be a trigger for arrhythmia in individuals with underlying primary arrhythmia syndrome. In a recent study by our group, familial evaluation of victims of SCD with autopsy findings consistent with idiopathic LVH, identified primary arrhythmia syndromes in 6 out of 13 (46%) families and probable HCM in only 1 family ([10](#_ENREF_10)). In such circumstances a false diagnosis of HCM has potentially significant implications for surviving relatives who may be subjected to targeted screening for cardiomyopathy rather than the extensive evaluation, including pharmacological provocation tests, to detect primary arrhythmia syndromes([17](#_ENREF_17)).

In this study HCM constituted only 6% of deaths which is in contrast to established perception that HCM is the commonest cause of SCD in athletes ([4](#_ENREF_4)). This may partly reflect the stringent diagnostic criteria applied by our group, which requires the presence of > 20% of myocardial disarray in at least two tissue blocks of 4 cm2(14). In contrast, non-specialist pathologists may attribute exercise-induced adaptations such as LVH to HCM ([7](#_ENREF_7)) without conducting a detailed histological analysis of the heart. This probability highlights the importance that post-mortem examinations in athletes should be performed by pathologists with high level of experience in conditions predisposing to SCD. We cannot disregard the possibility of a selection bias, as general pathologists may be less inclined to refer diseases such as HCM to our center if they are confident about the diagnosis.

An important minority (8%) showed idiopathic fibrosis. Possible explanations include healed myocarditis or incomplete expression of a cardiomyopathy. However, it is also possible that long standing intense exercise may be a causal factor. Studies have previously reported raised serum concentration of biomarkers of myocyte injury following endurance events, an increased prevalence of myocardial fibrosis on cardiac magnetic resonance (CMR) in endurance veteran athletes and a higher burden of atrial and ventricular arrhythmias([25-27](#_ENREF_25)). Over 80% of athletes died suddenly without a preceding warning symptoms, underscoring the possible limitations of cardiac screening based only on medical history and physical examination([22](#_ENREF_22)).

**Effect of age**

In agreement with previous studies,([6](#_ENREF_6),[28](#_ENREF_28)) SADS exhibited a significant age predilection and accounted for more than half of all deaths in children and adolescents but for only 26% of deaths in individuals older than 35 years of age. In contrast, myocardial disease was more prevalent with advancing age. ARVC, a condition commonly associated with SCD in young athletes, was rarely (4%) detected in children and adolescents but accounted for almost a fifth (18%) of deaths in individuals >35 years. Our results are consistent with a large autopsy study in 200 cases of ARVC ([29](#_ENREF_29)), where the average age of death was 33 years and almost 40% of deaths occurred in individuals >35 years. Interestingly, ARVC was associated with an increased heart weight in 25% of cases.

**Relation of sudden cardiac death to exercise**

As reported previously ([4](#_ENREF_4),[30](#_ENREF_30)), we demonstrated that SCD in athletes occurs more frequently during exercise. The strongest predictor for SCD during exertion was ARVC. Athletes with ARVC were 6 times more likely to die on exertion compared to those with other cardiac pathologies, with 92% experiencing SCD on the athletic field. LV fibrosis was also an independent predictor of exercise-induced SCD. Coronary abnormalities were a rare cause of SCD, but the majority of deaths occurred during exertion. Although HCM is considered the leading cause of exercise induced SCD in athletes, deaths from HCM in our cohort did not show any predilection for exercise. Our results, however, should be interpreted with caution given the relatively low numbers of HCM-related deaths in this study. In agreement with the current literature, SADS accounted for the majority of deaths at rest (54%) compared to a third (34%) of deaths during exertion.

**Clinical implications**

Our study reinforces the notion that preventative strategies such as pre-participation screening and emergency response planning, including the use of AEDs in sporting arenas should complement each other. Given that almost 40% of athletes died outside the context of exercise and 13% during sleep, it is highly unlikely that the provision of AEDs in public venues would have prevented these deaths. Considering that many of the SCD during rest were related to SADS, where possible causes are primary arrhythmia syndromes, often detectable with an ECG in asymptomatic individuals, pre-participation screening may be useful in this scenario. Using ARVC as an example, ECG based pre-participation screening can be effective at detecting athletes with the condition, as the ECG may be abnormal in 55% to 75% of cases ([31-33](#_ENREF_31)). However, based on the results of this study, the availability of an AED could be potentially life-saving for cases that were not detected during pre-participation screening. Finally, LV fibrosis is increasingly recognised in athletes but is not considered in isolation as a reason for exercise restriction. This study suggests that LV fibrosis is a trigger for exercise induced fatal arrhythmias in some athletes and warrants longitudinal assessment of asymptomatic athletes with isolated LV fibrosis([34](#_ENREF_34)).

**Limitations**

The CRY Centre for Cardiac Pathology at St George’s University of London is more likely to receive hearts from subjects where the clinical history is suggestive of an inherited cardiac disease and local pathologists are more likely to refer challenging cases, such as athletes with ambiguous autopsy or athletes where an obvious cause of death cannot be established. These facts introduce a potential referral bias; therefore it is probable that pathologies such as coronary artery atherosclerosis and HCM may be under-represented in this cohort. Similarly, the prevalence of less well-defined entities such as idiopathic LVH and a morphologically normal heart may be overestimated. Nevertheless, we receive a high volume of unexpected SCD referrals (> 400 per year) and 58% are in individuals < 35 years at death including athletes. Considering that SCD in young athletes is a rare event, the large number of post-mortem examinations performed in our unit in this cohort suggests that the results are a genuine representation of the type and frequency of cardiac diseases implicated in SCD in young athletes.

It is possible that subtle or incomplete expressions of cardiomyopathy may have been misclassified as SADS, however, considering our thorough laboratory protocol, it is highly unlikely that such cases accounted for a significant proportion of deaths attributed to SADS.

Our study is a pure pathology series, therefore we do not have any data relating to survivors of sudden cardiac arrest (SCA). As such it is possible that the results are biased towards lethal causes of SCA such as cardiomyopathies and primary arrhythmia syndromes, while diseases more amenable to survival following cardiac arrest are under represented([8](#_ENREF_8),[9](#_ENREF_9)).

**CONCLUSIONS**

Conditions predisposing to SCD in sport demonstrate significant age predilection. Sudden arrhythmic death syndrome accounts for the majority of deaths in the very young, whereas cardiomyopathies predominate with increasing age. Although the majority of athletes die during exertion, almost 40% die at rest, highlighting the need for complementary preventative strategies, in addition to AED provision. The strong association of ARVC with exercise induced SCD reinforces the need for competitive sport restriction in athletes with the condition. Finally, the high prevalence of idiopathic LVH or fibrosis underscores the need for further research in the field in order to delineate their significance.

**PERSPECTIVES:**

COMPETENCY IN MEDICAL KNOWLEDGE: The aetiologies underlying sudden death in athletes are highly variable according to age. Sudden arrhythmic death syndrome is prevalent in children and adolescents, while cardiomyopathies are the most common cause of death in adults. Arrhythmogenic right ventricular cardiomyopathy is strongly associated with sudden death during exertion.

TRANSLATIONAL OUTLOOK: A better understanding of causes and circumstances of sudden death in athletes may improve the strategies aimed at preventing such tragedies.

**REFERENCES:**

1. Meyer L, Stubbs B, Fahrenbruch C et al. Incidence, causes, and survival trends from cardiovascular-related sudden cardiac arrest in children and young adults 0 to 35 years of age: a 30-year review. Circulation 2012;126:1363-72.

2. Sharma S, Merghani A, Gati S. Cardiac Screening of Young Athletes Prior to Participation in Sports: Difficulties in Detecting the Fatally Flawed Among the Fabulously Fit. JAMA internal medicine 2014.

3. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? Journal of the American College of Cardiology 2003;42:1959-63.

4. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. Circulation 2009;119:1085-92.

5. Roberts WO, Stovitz SD. Incidence of sudden cardiac death in Minnesota high school athletes 1993-2012 screened with a standardized pre-participation evaluation. Journal of the American College of Cardiology 2013;62:1298-301.

6. de Noronha SV, Sharma S, Papadakis M, Desai S, Whyte G, Sheppard MN. Aetiology of sudden cardiac death in athletes in the United Kingdom: a pathological study. Heart 2009;95:1409-14.

7. de Noronha SV, Behr ER, Papadakis M et al. The importance of specialist cardiac histopathological examination in the investigation of young sudden cardiac deaths. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2014;16:899-907.

8. Drezner JA, Rogers KJ, Horneff JG. Automated external defibrillator use at NCAA Division II and III universities. British journal of sports medicine 2011;45:1174-8.

9. Kim JH, Malhotra R, Chiampas G et al. Cardiac arrest during long-distance running races. The New England journal of medicine 2012;366:130-40.

10. Papadakis M, Raju H, Behr ER et al. Sudden cardiac death with autopsy findings of uncertain significance: potential for erroneous interpretation. Circulation Arrhythmia and electrophysiology 2013;6:588-96.

11. Koplan BA, Stevenson WG. Sudden arrhythmic death syndrome. Heart 2007;93:547-8.

12. Mellor G, Raju H, de Noronha SV et al. Clinical characteristics and circumstances of death in the sudden arrhythmic death syndrome. Circulation Arrhythmia and electrophysiology 2014;7:1078-83.

13. Bowker TJ, Wood DA, Davies MJ et al. Sudden, unexpected cardiac or unexplained death in England: a national survey. QJM : monthly journal of the Association of Physicians 2003;96:269-79.

14. Pfister GC, Puffer JC, Maron BJ. Preparticipation cardiovascular screening for US collegiate student-athletes. Jama 2000;283:1597-9.

15. Harmon KG, Drezner JA, Maleszewski JJ et al. Pathogeneses of sudden cardiac death in national collegiate athletic association athletes. Circulation Arrhythmia and electrophysiology 2014;7:198-204.

16. Eckart RE, Shry EA, Burke AP et al. Sudden death in young adults: an autopsy-based series of a population undergoing active surveillance. Journal of the American College of Cardiology 2011;58:1254-61.

17. Behr ER, Dalageorgou C, Christiansen M et al. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. European heart journal 2008;29:1670-80.

19. Sheppard MN. Aetiology of sudden cardiac death in sport: a histopathologist's perspective. British journal of sports medicine 2012;46 Suppl 1:i15-21.

20. Sharma S, Elliott PM, Whyte G et al. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. Journal of the American College of Cardiology 2000;36:864-70.

21. Finocchiaro G, Haddad F, Knowles JW et al. Cardiopulmonary responses and prognosis in hypertrophic cardiomyopathy: a potential role for comprehensive noninvasive hemodynamic assessment. JACC Heart failure 2015;3:408-18.

22. Margey R, Roy A, Tobin S et al. Sudden cardiac death in 14- to 35-year olds in Ireland from 2005 to 2007: a retrospective registry. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2011;13:1411-8.

23. Risgaard B, Winkel BG, Jabbari R et al. Burden of sudden cardiac death in persons aged 1 to 49 years: nationwide study in Denmark. Circulation Arrhythmia and electrophysiology 2014;7:205-11.

24. Harmon KG, Asif IM, Maleszewski JJ et al. Incidence, Cause, and Comparative Frequency of Sudden Cardiac Death in National Collegiate Athletic Association Athletes: A Decade in Review. Circulation 2015;132:10-9.

25. Jensen-Urstad K, Bouvier F, Saltin B, Jensen-Urstad M. High prevalence of arrhythmias in elderly male athletes with a lifelong history of regular strenuous exercise. Heart 1998;79:161-4.

26. O'Hanlon R, Grasso A, Roughton M et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. Journal of the American College of Cardiology 2010;56:867-74.

27. Mohlenkamp S, Lehmann N, Breuckmann F et al. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. European heart journal 2008;29:1903-10.

28. Mellor G, Raju H, de Noronha SV et al. Clinical Characteristics and Circumstances of Death in the Sudden Arrhythmic Death Syndrome. Circulation Arrhythmia and electrophysiology 2014.

29. Tabib A, Loire R, Chalabreysse L et al. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. Circulation 2003;108:3000-5.

30. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. The New England journal of medicine 1998;339:364-9.

31. Dalal D, Nasir K, Bomma C et al. Arrhythmogenic right ventricular dysplasia: a United States experience. Circulation 2005;112:3823-32.

32. Steriotis AK, Bauce B, Daliento L et al. Electrocardiographic pattern in arrhythmogenic right ventricular cardiomyopathy. The American journal of cardiology 2009;103:1302-8.

33. Peters S, Trummel M. Diagnosis of arrhythmogenic right ventricular dysplasia-cardiomyopathy: value of standard ECG revisited. Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc 2003;8:238-45.

34. Schnell F, Claessen G, La Gerche A et al. Subepicardial delayed gadolinium enhancement in asymptomatic athletes: let sleeping dogs lie? British journal of sports medicine 2015.

35. Maron BJ, Friedman RA, Kligfield P et al. Assessment of the 12-lead ECG as a screening test for detection of cardiovascular disease in healthy general populations of young people (12-25 Years of Age): a scientific statement from the American Heart Association and the American College of Cardiology. Circulation 2014;130:1303-34.

36. Marijon E, Uy-Evanado A, Reinier K et al. Sudden cardiac arrest during sports activity in middle age. Circulation 2015;131:1384-91.

37. Berdowski J, de Beus MF, Blom M et al. Exercise-related out-of-hospital cardiac arrest in the general population: incidence and prognosis. European heart journal 2013;34:3616-23.

38. Varnava AM, Elliott PM, Sharma S, McKenna WJ, Davies MJ. Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. Heart 2000;84:476-82.

**Figure legends:**

**Figure 1:** Causes of sudden cardiac death in the overall population (A), and presented by age: subjects <18 years of age (B), subjects 18-35 years (C) and subjects >35 years of age (D).

In the overall population the subgroup classified as “Other” (n=43) comprised of: mitral valve abnormalities/prolapse; n=7, myocardial infarction with normal coronaries; n=4, bicuspid aortic valve; n=3, aortic dissection; n=3, cocaine/steroid use; n=2, cardiac sarcoidosis; n=1, atrium septal defect (ASD). In the remaining 22 cases the cause of death could not be attributed to a single disease entity or condition and the PM findings were considered of uncertain significance.

**Figure 2:** Histogram depicting the age distribution of deaths with morphologically normal hearts (SADS) compared to deaths with findings indicative of cardiomyopathy (including HCM, idiopathic LVH and/or fibrosis, ARVC, DCM and myocarditis).

**Figure 3:** Histogram depicting the heart weight distribution in the overall cohort. Individuals with a heart weight of ≥ 500 g are represented in red columns. The pie chart presents the cause of death in individuals with a heart weight of ≥ 500 g (n=70).

**Table 1. Pathological macroscopic and microscopic criteria defining main underlying diseases.**

|  |  |  |
| --- | --- | --- |
|  | Macroscopic | Microscopic |
| Hypertrophic cardiomyopathy | Left ventricular wall thickness >15 mm circumferentially or focally and/or heart weight >500 g\*∞ | Myocyte hypertrophy, myocyte disarray (> 20% of myocardial disarray in at least two tissue blocks of 4 cm2) and interstitial fibrosis |
| Idiopathic left ventricular hypertrophy | Left ventricular wall thickness >15 mm and heart weight >500 g\* | Myocyte hypertrophy +/-fibrosis in the absence of myocyte disarray |
| Idiopathic left ventricular fibrosis | Normal heart weight and wall thickness with/without scarring macroscopically | Fibrosis with no myocyte disarray |
| Arrhythmogenic right ventricular cardiomyopathy | Right or left ventricular thinning, fatty replacement, fibrosis on the epicardial surface or outer wall | Fat and fibrosis in the wall of the right and/or left ventricle, particularly in outer wall |
| Myocarditis | Normal or dilated ventricles | Inflammation with myocyte  necrosis |
| Anomalous coronary artery | Anomalous origin of the coronary artery,  coronary artery atresia, stenosis | Fibrosis/acute/chronic infarction in the left  ventricle |
| Coronary atherosclerosis | Atherosclerosis with estimated luminal narrowing >75% | Acute or chronic infarction in  the left ventricle |
| Dilated cardiomyopathy | Increase in heart weight (> 500 g in males, > 400 g in females) with dilated left ventricle (> 4cm) and thin wall (<10mm). Absence of coronary artery disease. | Diffuse interstitial and replacement fibrosis in the left ventricle |
| Mitral valve prolapse | Prolapse of mitral valve above the atrio-ventricular junction with ballooning between chordae in one or both leaflets | Myxoid degeneration with expansion in spongiosa of leaflets and destruction of fibrosa layer |
| Bicuspid aortic valve | Fusion of two aortic cusps, with or without presence of a raphe |  |
| Morphologically normal heart | Normal | Normal |

\*heart weight > 400 g in women

∞in the cohort studied the heart weight was normal in 39% of HCM cases. In a small proportion of cases HCM was diagnosed based on the presence of Myocyte hypertrophy, myocardial disarray and fibrosis on microscopy despite a normal heart weight and wall thickness on macroscopic evaluation.

**Table 2. Characteristics of the population according to circumstances of death.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total  (n=357) | Died on exertion (n=219) | Died at rest (n=138) | P |
| Age (years) | 28±12 | 29±12 | 29±11 | 0.944 |
| Male n (%) | 326(92) | 201(92) | 125(91) | 0.673 |
| FH of SD n (%) | 28(8) | 17(8) | 11(8) | 0.911 |
| Heart weight (g) | 421±110 | 413±107 | 434±115 | 0.086 |
| LV fibrosis n (%) | 115(32) | 85(39) | 30(22) | <0.001 |
| SADS n (%) | 149(42) | 75(34) | 74(54) | <0.001 |
| HCM n (%) | 23(6) | 13(6) | 10(7) | 0.237 |
| ARVC n (%) | 48(13) | 44(20) | 4(3) | <0.001 |
| Idiopathic LVH and/or fibrosis n (%) | 59(16) | 34(15) | 25(18) | 0.548 |
| Coronary anomalies n (%) | 18(5) | 16(7) | 2(1) | 0.01 |
| Coronary atheroma n (%) | 8(2) | 6(3) | 2(1) | 0.521 |

SADS: sudden arrhythmic death syndrome; FH: family history; HCM: hypertrophic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; LVH: left ventricular hypertrophy

**Table 3. Multivariate analysis for death during exercise**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Univariate analysis | | Multivariate analysis | |
|  | HR (95% CI) | P | HR (95% CI) | P |
| Male gender | 1.29 (0.58 to 2.81) | 0.534 |  |  |
| Age at death | 0.99 (0.98 to 1.12) | 0.946 |  |  |
| Caucasian ethnicity | 1.09 (0.43 to 2.72) | 0.85 |  |  |
| Family history of SD | 0.96 (0.43 to 2.12) | 0.93 |  |  |
| Competitive athlete | 1.13 (0.71 to 1.8) | 0.59 |  |  |
| LV fibrosis | 2.43 (1.48 to 4.01) | <0.001 | 2.11 (1.15 to 3.88) | 0.01 |
| Heart weight\* | 0.96(0.95 to 0.97) | 0.001 |  |  |
| ARVC | 8.36 (2.93 to 23.84) | <0.001 | 6.01 (1.97 to 18.32) | 0.001 |
| Coronary anomaly | 5.32 (1.20 to 23.51) | 0.008 |  |  |
| SADS | 0.44 (0.29 to 0.68) | 0.002 |  |  |
| HCM | 0.80 (0.34 to 1.88) | 0.613 |  |  |

ARVC: arrhythmogenic right ventricular cardiomyopathy, LV: left ventricle, HCM: hypertrophic cardiomyopathy, SADS: sudden arrhythmic death, SD: sudden death.

\*for 10 g of increase