

Concept and epidemiology of sudden death (SD) in athletes

Sudden death (SD) is defined as the death that is not traumatic, not violent, unexpected, which occurs within the first 6h without a prior manifestation of cardiac disease (**Maron 1986**). SDs in young competitive athletes are tragic events, with high public visibility. A 'paradox of sport' is that in addition to the undisputed health benefits of physical activity, vigorous exertion may transiently increase the risk of acute cardiac events. In general, the risk of SD approximately doubles during physical activity and is 2- to 3-fold higher in athletes compared to nonathletes. (**Schmied 2014**).

The importance of race and gender with respect to sport and the diagnosis and causes of SD in athletes has generated substantial interest.

Prevalence Estimated between young athletes of secondary school, as 1 in 200,000 per year (**Maron 1996, 1998**).

Incidence: Rates of SD under the age of 40 varied from 1:917,000 to 1:3000. Studies with higher methodological quality consistently yielded incidence rates in the range of 1:40,000 to 1:80,000. Some athlete subgroups, specifically men, African-American/black athletes and basketball players, appear to be at higher risk. The incidence of SD in athletes is likely higher than traditional estimates which may impact the development of more effective prevention strategies. (**Harmon 2014**).

The incidence of SD in older (≥ 35 years) athletes is higher and may be expected to rise, as more and older individuals take part in organized sports. SD is often the first clinical manifestation of a potentially fatal underlying cardiovascular disorder and usually occurs in previously asymptomatic athletes. In college student-athletes, risk of SD is relatively low, with mortality rates similar to suicide and drug abuse, but less than expected in the general population, although highest in African-American athletes.

A substantial minority of confirmed cardiovascular deaths would not likely have been reliably detected by pre-participation screening with ECGs. Over the 10-year study period, 182 SD occurred, 52 resulting from suicide or drug abuse and 64 probably or likely attributable to cardiovascular causes. Of these 64 athletes, 47 had a confirmed post-mortem diagnosis; the most common were HCM in 21 and congenital coronary anomalies in 8. The 4,052,369 athlete participations (in 30 sports over 10 years) incurred mortality risks as follows: suicide and drugs combined, 1.3/100,000 athlete participation-years (5 deaths/year); and documented cardiovascular disease, 1.2/100,000 athlete participation-years (4 deaths/year). Notably, cardiovascular deaths were 5-fold more common in African-American athletes than in white athletes (3.8 vs. 0.7/100,000 athlete participation-years) but did not differ from the general population of the same age and race. (**Maron 2014**) The US National Registry of SD in Athletes, 1980-2011, was accessed to define the epidemiology and causes of SDs in competitive athletes. A total of 2406 deaths were identified in young athletes aged 19 ± 6 years engaged in 29 diverse sports. Among the 842 athletes with autopsy-confirmed

cardiovascular diagnoses, the incidence in males exceeded that in females by 6.5-fold. HCM was the single most common cause of SD, occurring in 302 of 842 athletes (36%) and accounting for 39% of male SDs, almost 4-fold more common than among females. More frequent among females were congenital coronary artery anomalies (33% vs 17% of males), ARVC (13% vs 4%), and clinically diagnosed LQTS (7% vs 1.5%). The cardiovascular death rate among African Americans/other minorities exceeded whites by almost 5-fold, and HCM was more common among African Americans (42%) than in whites (31%). Male and female basketball players were 3-fold more likely to be African American/other minorities than white. They concluded that within this large forensic registry of competitive athletes, cardiovascular SDs due to genetic and/or congenital heart diseases were uncommon in females and more common in African Americans/other minorities than in whites. HCM is an under-appreciated cause of SD in male minority athletes. (**Maron 2016**). The incidence and cause of SD in athletes is debated with HCM often reported as the most common cause. Studies of high quality and rigor consistently yield an incidence of 1:50,000 athlete-years (Ays) in college athletes and between 1:50,000 and 1:80,000 Ays for high school athletes, with certain subgroups that appear to be at particularly high risk, including the following: **Men, basketball players, both male basketball players and African Americans**. Initial reports suggest that the most common cause of SCD is HCM. However, more comprehensive investigations in the US and international populations-athletes, nonathletes, and military-support that the most common finding on autopsy in young individuals with SD is actually a structurally normal heart autopsy-negative sudden unexplained death(SUD). Current rates of SD appear to be at least 4 to 5 times higher than previously estimated, with men, African Americans, and male basketball players being at greatest risk. Emerging data suggest that the leading finding associated with SCD in athletes is actually a structurally normal heart or autopsy-negative sudden unexplained death. (**Assif 2017**) A database of all National Collegiate Athletic Association deaths (2003-2013) was developed by Harmon et al (**Harmon 2015**), and additional autopsy reports were obtained when possible. Cause of death was adjudicated by an expert panel. There were 4 242 519 athlete-years (Ay) and 514 total student athlete deaths. Accidents were the most common cause of death (257, 50%, 1:16 508 Ay) followed by medical causes (147, 29%, 1:28 861 Ay). The most common medical cause of death was SD (79, 15%, 1:53 703 Ay). Males were at higher risk than females 1:37 790 Ay versus 1:121 593 Ay (incidence rate ratio, 3.2; 95% confidence interval, 1.9-5.5), and black athletes were at higher risk than white athletes 1:21491 AY versus 1:68 354 AY (incidence rate ratio, 3.2; 95% confidence interval, 1.9-5.2). The incidence of SCD in Division 1 male basketball athletes was 1:5200 Ay. The most common findings at autopsy were autopsy-negative sudden unexplained death in 16 (25%), and definitive evidence for HCM was seen in 5 (8%). Media reports identified more deaths in higher divisions (87%, 61%, and 44%), whereas the percentages from the internal database did not vary (87%, 83%, and 89%). Insurance claims identified only 11% of SCDs. The rate of SCD in National Collegiate Athletic Association athletes is high, with males, black athletes, and basketball players at substantially higher risk. The most common finding at autopsy is autopsy-negative sudden SUDS. Media reports are more likely to capture high-profile deaths, and insurance claims are not a reliable method for case identification.

The causes of arrhythmic sudden death in young athletes (average age: 17 years)

I. Entities with structural heart disease

- 1. Hypertrophic cardiomyopathy (HCM)** whether in its obstructive form or in its non-obstructive form (36% of all cases). HCM as the leading cause of SCD among athletes was confirmed in a review of 1866 deaths among young competitive athletes in the USA. (Maron 2009) Furthermore, epidemiological investigations with diverse designs have demonstrated similar estimates for prevalence of around 0.2% (1 in 500) in the general population. (Walker 2010) Although HCM is the most common genetic cardiovascular disease, it often remains clinically undetected in many patients. (Maron 2002) HCM is inherited as an autosomal dominant trait with mutations in 1 of 10 genes encoding proteins involved in contractile or structural elements of the cardiac sarcomere. Despite the diversity of mutations, the physical similarity of the proteins encoded makes it possible to classify the diverse HCM spectrum as one disease. Anatomically, HCM is characterized by marked, asymmetric left ventricular hypertrophy (LVH; >15 mm) identified on echocardiography. In addition, most patients have a disproportionate increase in the thickness of the interventricular septum. Structural heterogeneity is considerable and HCM is not necessarily associated with obstruction of the LVOT, particularly if associated with a distal LVH. Although the changes are usually more extreme in HCM, it can mimic a normal athlete's heart and this can pose a diagnostic dilemma. Reduction in LV wall thickness (by 2e5 mm) following a pause from athletic activity is suggestive of athlete's heart rather than HCM. Similarly, a diagnostic dilemma is posed by the fact that significant overlap in clinical and echocardiographic findings is observed in HCM and hypertensive LVH. Although certain features such as anterior movement of the anterior mitral valve leaflet and asymmetric LVH are sensitive for HCM, they are non-specific and overlap with hypertensive LVH. (Vinereanu 2001) The difference lies in the patchy, regional dysfunction of HCM in comparison with the diffuse dysfunction of hypertension. The regional dysfunction can be demonstrated using myocardial velocity gradients on echo or as areas of late enhancement seen on CMR imaging. (Weidemann 2007)
- 2. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)** it is a condition characterized by lipofibromatous infiltration and dysfunction of the RV. (Hoogsteen 2003) The prevalence of ARVC is 1 in 5000, and in 40% of cases it is inherited as an autosomal dominant trait with variable penetrance and expression. (Fisher 2000) Thus far, a number of genes have been mapped and identified as having potential responsibility of causing the condition (Ahmad 1998). It is a condition that predominantly affects men and occurs typically between 7 and 40 years. Among athletes, it presents with exertional pre-syncope, syncope and most tragically as SCD. The classical presentation is that of a S-VT with a LBBB pattern in most cases. (Walker 2010) A prolonged QRS length (>110 ms) is seen in

2. (cont...) right precordial lead due to delayed depolarization of the RV, which results in the occurrence of an epsilon wave on ECG. Other ECG features include T-wave inversion in leads V1-V3 (observed in 85% of cases) and PVCs, which typically occur in excess of 1000 times per day. RV dilation, bulging of RV during diastole, dyskinesia of inferobasal free wall during systole and dyskinesia of the apex are identified on echo. CMR is often used to provide a comprehensive image of the RV and clearly identifies lipofibromatous infiltration on T1-weighted images albeit with an increased incidence of false-positive findings. **Recommendations** Given its predisposition to ventricular arrhythmias and the recognition of ARVC as a cause for sports-related SD[58(**Peters 1995**) its diagnosis precludes participation in any competitive sports, with a possible exception for sports with a low static and dynamic demand (**Mitchell 2005;Corrado 2005**). The same may apply to asymptomatic gene carriers in families in which a mutation has been detected. Leisure time activities with a moderate to high cardiovascular demand are also contraindicated(**Pelliccia 2005**), but activities with low demand are allowed when electrocardiographic evaluation under treatment has shown absence of arrhythmias and when there are no exercise-related symptoms. The need for ICD should be evaluated based on clinical presentation, electrophysiological findings and family history.
3. **Non-atherosclerotic coronary artery disease and early atherosclerotic coronary artery disease** Non-atherosclerotic coronary pathology was identified in 3% of cases in a retrospective study of 1647 SCDs by Hill and colleagues.(**Hill 2010**) This consisted of anomalous origin of coronary artery (48%), coronary artery dissection (16%), coronary artery vasculitis (12%), coronary artery spasm (12%), idiopathic arterial calcification of infancy (6%), fibromuscular dysplasia (4%) and benign tumor occluding the left coronary ostium (2%). Overall, 20 of the 50 patients (40%) were documented to have experienced cardiac symptoms such as syncope, chest pain on exertion or breathlessness prior to their events. Therefore, coronary artery abnormalities should be considered and screened for in any athlete experiencing symptoms on exertion, particularly when the ECG shows no obvious attributable abnormality.(**Basso 2000**) Anomalous origin of the LCA from the right aortic sinus is the most common coronary artery anomaly.(**Davis 2001**) Its mechanism of causing SCD is unclear. However, the abnormal anatomy of the artery makes it vulnerable to compression particularly during exercise. This leads to hypoperfusion followed by VF and SCD. In someone with suspected coronary artery abnormalities, investigations that directly visualize the aortic root and coronary ostia such as cardiac computerized tomography or CMR may be of additional value. Surgery to re-implant the coronary artery in the correct sinus is the optimum treatment for the management of highest risk anomalous origin of the LCA.
4. **Aorta rupture due to Marfan syndrome(MFS)** Aortic rupture is estimated to account for approximately 5% of SCD cases among athletes. In over half of them, the athlete has an underlying connective tissue disorder known as MFS.(**Germann 2004**) MFS is an autosomal dominant condition affecting 1 in 5000 people.(**Gray 1994**) At the molecular level, MFS is caused by fibrillin 1 (FB1) gene defects and rarely by mutations in transforming growth factor b receptor 2 (TGFbR2).(**Collod-Beroud 2003**) Penetrance is complete however phenotypic heterogeneity is huge as different organs are affected differently in different people. MFS mapped in chromosome 3p24. The entity causes

4. osteo-skeletal, cardiovascular, ocular, skin, pulmonary and nervous anomalies. In the aorta, there is weakness in the aortic wall, which predisposes to dissection, rupture and death. **(Maron 2003)** The diagnosis of MFS is based on the presence of two major clinical features (tall stature with arm span greater than height, arachnodactyly, hyper-flexible joints, scoliosis, high-arched palate, pectus excavatum) and the involvement of a third organ system (Ghent criteria). **(De Paepe 1996)** Echocardiography is used to assess aortic root dilatation and mitral valve prolapse and ophthalmology examinations to identify myopia and ocular lens subluxation. Genetic testing can be used to confirm the diagnosis. **(Pelliccia 2005)**
5. **Primary cardiac Tumors or cardiac masses (10%); (Bajanowski 2012)**
6. **Myocarditis (2%):** Myocarditis is defined as an acute or chronic inflammation of the heart muscle and is now recognized as a cause of SCD (5e22% of cases). To determine the incidence and etiology of sudden cardiac arrest and death (SCA/D) in US high school athletes Harmon et al **(Harmon 2016)** studied a prospective media database of SCA/D was queried for cases aged 14 to 18 years from 7 states over 6 school years (September 1, 2007, to August 30, 2013). Event details were investigated to determine participation on a high school athletic team, sex, sport, and occurrence during school-sponsored activity or exertion. National sports participation numbers were used and a conversion factor was applied to account for multisport athletes. Autopsy reports were reviewed and cause of death was adjudicated by an expert panel. 14% of this universe were myocarditis. The inflammatory nature of the myocardium often leads to disrupted ion transport between myocardial cells and subsequently to malignant ventricular arrhythmias. The myocarditis can also lead to cardiac enlargement and impaired function. The most prevalent cause of myocarditis among athletes who have had SCD is viral infection, notably parvovirus B19 **(Rogo 2014)** and human herpesvirus 6B **(Hakacova 2013)**. It may also be caused by drugs and toxic agents such as cocaine. Clinical presentation of patients with myocarditis is diverse, ranging from asymptomatic to debilitating pain and breathlessness. Durakovic et al **(Durakovic 2005)**, studied four cases were reviewed following SCD secondary to myocarditis. Three of the four cases were asymptomatic and the patient with symptoms experienced mild breath lessness prior to the event. Several tests are available to support the diagnosis of myocarditis. A combination of ECG and clinical features is most often used to make the diagnosis, despite the fact that ECG in myocarditis has a low sensitivity of 47% and physical examination is most often normal. Troponin I shows a high specificity in myocarditis (89%) but a poor sensitivity (34%), and therefore an elevated troponin I can be used to support the diagnosis. Endomyocardial biopsy remains the diagnostic gold standard although is rarely, if ever, performed in clinical practice. CMR provides a good appraisal of myocardial inflammation and is being used with increasing frequency where available as it offers the best balance between sensitivity and specificity (85% and 95%, respectively) of any non-invasive test.

6. **Familial arrhythmogenic syndrome:** ventricular and tachyarrhythmia association (syndrome of Wolff-Parkinson-White), progressive disease of conduction system and cardiac hypertrophy by involvement of regulatory subunit gamma-2 (PRKAG2) of AMP- activated by protein kinase (**Gollob 2002**), The cardiac phenotype observed in humans harbouring genetic mutations in the gamma 2 regulatory subunit (PRKAG2) of AMPK is consistent with abnormal glycogen accumulation in the heart. The perturbation of AMPK activity induced by genetic mutations in PRKAG2 and the resultant effect on muscle cell glucose metabolism may be relevant to the issue of targeting AMPK in drug development for insulin-resistant diabetes mellitus. (**Gollob 2003**)
7. **Familial electrical disease of unknown origin** In some families an inherited pattern of clinical events (unexplained abrupt (pre)syncope, sudden death, documented arrhythmias) can be present but without demonstrable structural heart disease nor ECG indications for any of the above-mentioned conditions. Genotyping may over time lead to the discovery of mutations in other ion channels or regulatory proteins. One recognized phenotypic pattern is that of prominent U-waves, which may be the origin of VPB and malignant ventricular arrhythmias. The ECG characteristics of mutations in KCNJ2, coding the inwardly rectifying background IK1 current have been recognized in this respect; although considered before as a form of LQT7, there have been suggestions to categorize this entity as a different disease (Andersen–Tawil syndrome, ATS1) given its prominent U-waves and noncardiac symptoms (**Zhang 2005**). It is likely that the future will reveal more familial genetically determined arrhythmogenic disorders, of which some can create particular vulnerability during exercise. **Recommendations** for these familial electrical diseases are similar to those for the channelopathies. Moreover, in the absence of specific therapy, the need for ICD implantation should be evaluated in each family.
8. **Mitral valve prolapse syndrome (MVPS)** (2%) frequently associated with prolonged QT interval (**Missov 2015**).
9. **Pulmonary hypertension**
10. **Dilated cardiomyopathy**
11. **Restrictive cardiomyopathy**
12. **Left ventricular outflow tract obstruction**
13. **Postoperative congenital heart disease** include tetralogy of Fallot, transposition with transportation of the great arteries, Fontan operation, hypoplastic left heart syndrome, coarctation of the aorta, cardiac transplantation.

Implantable cardioverter defibrillator, secondary or primary prevention by implantation of an ICD will often be considered in patients with documented VT or channelopathies. Advanced screening techniques and molecular diagnosis in family members is contributing to a rapid increase of this population. The recommendations concerning the underlying pathological conditions have been outlined above and generally include the advice to abstain from competitive sports. Although very effective to prevent SD, ICD implantation should not be regarded as a substitute for such a recommendation (**Maron 1998**). The efficacy of the ICD to interrupt malignant ventricular arrhythmias during intense exercise is unknown and from theoretical considerations probably suboptimal (given the associated metabolic, autonomic and potentially ischemic conditions). Specific data on the benefits and risks of ICD in physically active patients are lacking, explaining a large variability in current recommendations made by physicians to their patients (**Lampert 2006**). **Recommendations** An ICD disqualifies an athlete for competitive sports, except those with a low cardiovascular demand (like golf, billiards or bowling) (**Mitchell 2005**). On the other hand, physicians and patients alike may feel more assured to continue leisure-time physical activities with low to moderate dynamic or static demand if an ICD is on board, which may contribute to physical and psychological well-being (**Vanhees 2004**). In patients with arrhythmias that are particularly sensitive to triggering by exercise, these recommendations should be made with caution. Leisure-time sports resumption is allowed from 6 weeks after implant, preferably after a control stress test. When appropriate or inappropriate ICD interventions occur (antitachypacing or shocks), a 6-week period refraining from sports should be reconsidered to evaluate the effect of changes in medical therapy or ICD programming.

Particular recommendations

- 1) Sports participation with bodily contact is contraindicated given the risk for trauma to the subcutaneously implanted device and its connection with the lead system.
- 2) Given the fact that there is a latency between arrhythmia onset and ICD intervention to terminate it (which may be antitachycardia pacing or shocks), sports activities during which dizziness or (pre)syncope would expose the patient or others to additional risks are relatively contraindicated.
- 3) Extreme ipsilateral arm-movements (like during volleyball, basketball, tennis, racket sports, handball, swimming, gymnastics, ballet) may increase the risk for lead dislocation or lead fracture (due to crush between clavicle and first rib), and therefore should be avoided, certainly during the first 6 weeks after implant.
- 4) Electromagnetic interference with ICD function is very rare. The patient should, however, be instructed about this potentiality if encountering any sports-related exposure to electromagnetic fields, and ICD follow-up should explicitly exclude inappropriate detection. Strong magnetic fields could temporarily (or in certain models permanently) inhibit tachyarrhythmia therapy, although no specific sports related circumstances in which this has occurred have been described.

5. Exercise in young people may result in sinus tachycardia (ST) which exceeds the detection threshold for ICD intervention, leading to inappropriate therapy delivery. Inappropriate shocks are painful and may result in psychological problems like anxiety and unrest, which even may amount to aversion for the ICD protection. They also can trigger real life-threatening ventricular arrhythmias. It is therefore extremely important to tailor ICD settings and recommended exercise levels to the anticipated heart rate during sports activity for any individual patient. Prior exercise and long-term ECG recordings will be important for this assessment. When inappropriate device triggering due to ST is anticipated, clear instructions to the patient concerning activity limitation and/or institution of bradycardic therapy (with β -blockers if possible) are mandatory.
6. Many structural or arrhythmogenic conditions may also increase the risk for AF with possible fast atrioventricular conduction during exercise, again with the risk for inappropriate therapy delivery and thus the need for prophylactic antiarrhythmic or bradycardic drug therapy.
7. The implantation of a dual chamber ICD may be considered with the expectation that atrial electrogram information may increase the specificity of ventricular arrhythmia detection. Studies, however, have indicated that there is no significant difference in the incidence of inappropriate ICD therapy with DDD versus VVI-devices (**Deisenhofer 2001; Sinha 2004**). Dual chamber differentiation becomes also irrelevant during high heart rates, as commonly seen for ICD indication in these patients who rarely present with slow VT. Moreover, given the fact that many of these patients will be young, there is a potential risk for increased long-term lead complications when more leads are implanted. Therefore, restraint needs to be advocated concerning the implantation of a more complex ICD system, and its indication should be weighed in every patient.

The causes of arrhythmic sudden death in young athletes (average age: 17 years)

II) Entities without apparent structural heart disease (2%);

- 1. Drug abuse, e.g. anabolic agents** Doping in sports has been defined as the ‘use of unfair and dangerous performance enhancing drugs that are forbidden by organizations that regulate competitions. Although some studies have reported that performance-enhancing drugs can have serious cardiovascular consequences including SD. Bonetti and colleagues conducted a prospective follow-up study consisting of 20 subjects who were administered a course of anabolic steroids and demonstrated that steroid abuse has a dramatic impact on lipid profile during the 2-year follow-up, most noticeably a significant decrease in blood high-density lipoprotein. It could be speculated that this change promotes atherosclerosis and is therefore a potential contributor to accelerated CAD. However, ECGs revealed no functional or morphological abnormalities in any of the subjects.(**Bonetti 2008**) Further studies are required to determine the role of anabolic steroids and other ergogenic aids in causation of SCD. There is variable evidence for the performance-enhancing effects and side effects of the various substances that are used for doping. Drug abuse in athletes should be addressed with preventive measures, education, motivational interviewing, and, when indicated, pharmacologic interventions.(**Reardon 2014**)
- 2. Ventricular pre-excitation of the Wolff-Parkinson-White syndrome (WPW) type** it has accessory pathway(AP) of short refractory period, not detected previously. The incidence of SD in patients with WPW ranges from 0% to 0.39% annually(**Novella 2014**). The existence of an AP forms the basis of a WPW syndrome. The condition is diagnosed on ECG by a shortened PR interval, delta wave at the beginning of the QRS and secondary alteration of repolarization WPW has a prevalence of 1 in 500 (0.2%) in the general population. Studies demonstrate that the first step involves the development of AF with fast antegrade conduction ventricular response over the AP leading to VF. Symptoms in patients with WPW syndrome are related to the development of arrhythmias that cause palpitations, dizziness, syncope and SCD. Children and adolescents with WPW syndrome have a higher rate of AVRT inducibility than asymptomatic patients. However, no differences between the two groups were found in atrial vulnerability and parameters related to the risk of SCD.(**Di Mambro 2015**). EPS and RFCA are recommended in all cases for athletes with symptoms of paroxysmal AV re-entry tachycardia or AF because the risk of subsequent VF and SCD is higher in comparison with asymptomatic athletes (2.2% vs 0.2%). VF frequently occurs in young, previously asymptomatic people as the first clinical manifestation of WPW syndrome; many other initially asymptomatic or symptomatic people experience benign arrhythmias, recurrences, or remain asymptomatic. Pappone et al(**Pappone 2015**) suggests that, regardless of the presence of symptoms, intrinsic electrophysiologic properties of APs predict the risk of developing malignant arrhythmias or SD and that EPS is the gold standard for stratifying the risk. RFCA of dangerous APs can definitively eliminate the lifetime risk of SD in a subgroup of selected asymptomatic people, in whom RFCA could reasonably be recommended as class IA,

2. as currently recommended for all initially symptomatic patients with WPW regardless of their risk. These authors believe that, in the era of widespread use of RFCA, it has become unacceptable for even in asymptomatic individual with WPW to be at potential risk of dying unexpectedly or experiencing life-threatening arrhythmic events. Asymptomatic athletes without AV re-entry tachycardia or AF pose a therapeutic dilemma as their risk of SCD is considerably low. The individual risk needs to be ascertained through EPS in which the refractoriness of the AP and induction of AF to assess the shortest pre-excited RR interval are performed. A short pre-excitation RR interval, increased refractoriness and easily inducible AF are indicators of increased SCD risk and RFCA is recommended in these cases. The chance of future participation in this group is good as previous studies have demonstrated the success rate of RFCA to be as high as 95%. The procedure, although considered relatively safe, does carry a small risk of complications. Jackman and colleagues performed catheter ablation on 166 patients with AV APs. The relatively low risk makes RFCA an acceptable procedure in athletes with WPW (**Jackman 1991**).
3. **Nonpenetrating chest wall impact (commotio cordis) Cardiac concussion or commotio cordis:** is Latin for ‘disturbance of the heart’ and despite the fact that this condition was first discovered in medical experiments on rabbits in 1932, only recently has it been associated with SCD in humans, especially athletes involved in sport. It has been reported with increased frequency following injuries to athletes caused by a hockey puck, baseball or tackle in rugby. It is a primary VF, resulting from a sudden blunt impact to the anterior chest wall. The blow in most cases causes no structural damage, but results in the initiation of VF. Its incidence is difficult to define due to under-reporting and lack of recognition. However, there have been an estimated 180 cases in the USA from 1996 to 2007. Although it has been reported to occur in a wide range of ages, it appears to have a predilection for children and adolescents. Bode et al. (**Bode 2006**) concluded that sudden myocardial stretch can elicit VF when it occurs during a vulnerable window that is based on repolarization inhomogeneity. Stretch pulses applied during this vulnerable window can lead to nonuniform activation. Repolarization dispersion might play a crucial role in the occurrence of fatal VF. An animal model has been developed and utilized to explore the variables and mechanisms. Impact during a narrow window of repolarization causes VF. Other variables include location, velocity, shape, and hardness of the impact object. Biological characteristics such as gender, pliability of the chest wall, and genetic susceptibility also play a role. The mechanism of VF appears to be an increase in heterogeneity of repolarization caused by induced abnormalities of ion channels activated by abrupt increases in LV pressure. In the setting of altered repolarization a trigger of ventricular depolarization (premature ventricular depolarization caused directly by the chest blow) initiates a spiral wave that quickly breaks down into VF. (**Link 2014**)
4. **Sickle cell trait (HbAS)** Reports from the US emphasize possible health risks for individuals with HbAS including increased incidence of renal failure and malignancy, thromboembolic disorders, splenic infarction as a high altitude complication, and exercise-related SD. (**Goldsmith 2012**)

3. **Channelopathies or primary electrical diseases.** Example long QT syndrome(LQTS), Brugada syndrome(BrS), and catecholaminergic polymorphic ventricular tachycardia(CPVT), and short QT syndrome (SQTS)(**Wever-Pinzon 2009**)

a. **LQTS:** Sudden arrhythmic death syndrome (SADS) is a condition when no definite cause is identified, which occurs in 1 in every 20 cases of SCD despite detailed specialist pathological examination of the heart. In SADS, VT causes cardiac arrest. Four out of ten cases of SADS are caused by rare genetic conditions known as cardiac ion channelopathies where there is disturbance of electrical conduction within the heart with no apparent structural abnormality. Therefore, these rare conditions are only identifiable while the person is alive. Sporadic cases are uncommon and they tend to occur in individuals with strong family history of SCDs of unknown cause. LQTS is transmitted as an autosomal dominant, recessive or de novo trait and is characterized by prolonged and abnormal cardiac repolarization with a prevalence of 0.4% among athletes. Overall, it is estimated to affect 1 in 2500 of the general population. The three most common forms include LQTS type 1, type 2 and type 3. The ESC consensus documents recommend a QT interval diagnostic cut-off of 470 and 480 ms on ECGs for male and female athletes, respectively. However, a more recent study recommends using a 500 ms diagnostic cut-off. Genetic testing is available for people with LQTS on ECG and those with a family history of SCD and is particularly useful in asymptomatic patients. The diagnosis should be considered in any athlete with a history of syncope. . In case of a borderline long QTc interval and a negative personal plus familial history, arrhythmias should further be excluded by exercise testing and long-term ECG recording. Infusion of low doses of epinephrine may reveal a paradoxical increase of the QT interval, which is strongly indicative of LQT1(**Vyas 2006**). Modern mutational analysis can reveal mutations in 70% of the index patients by analysis of the five main genes involved. It remains, however, time-intensive and expensive, and therefore is generally reserved to research-oriented large referral centers. The availability of commercial test kits may change this in the future. It is important to realize, however, that in 30% of cases, no definitive diagnosis can be made by genotyping, stressing the importance of careful phenotypic evaluation.

Recommendations Sympathetic stimulation is well-known to be proarrhythmogenic in patients with a congenital form. Therefore, competitive sports are not allowed in patients with definitive or strongly suspected LQTS. Even activities with low cardiovascular demand may be associated with important changes in autonomic tone, which could lead to malignant ventricular arrhythmias and SCD. Such low-intensity sports could only be allowed in proven SCN5A mutation carriers, since they are mainly at risk for malignant arrhythmias at rest. No firm data exist concerning the exercise-related risk of silent mutation carriers: family members without overt phenotype but with a proven mutation. Given the fact that SD has been described in such carriers(**Priori 2003**), it seems advisable for them to also refrain from competitive sports, especially when there is a family history of sudden death or a manifestly prolonged QTc interval. β -blockers remain the mainstay therapy, but are no substitute for recommendations regarding sports participation.

- a. Recommendations (cont)** regarding leisure-time activity should weigh the benefits of physical activity (including psychological well-being and self-assurance) against the risks of sports participation. Considerations should include the risk for syncope or cardiac arrest due to LQTS; increased risk if presyncope occurs during sports, activities like diving or driving, free weight-lifting, climbing and others are relatively contraindicated; avoidance of sports with a high cardiovascular demand or high adrenergic tone; and avoidance of potential triggering conditions. This last advice may be more specific when the underlying genotype is known: LQT1 patients (KCNQ1 mutations) are susceptible for arrhythmia-development after sudden exposure to cold water (swimming, diving), while sudden unexpected auditory stimuli may trigger polymorphic VT in patients with the LQT2 subtype (i.e. HERG/KCNE2 mutations). In those without known underlying genotype, all restrictions should be considered. In athletes who have experienced a previous out-of-hospital cardiac arrest or a LQTS-related syncopal episode, only exercise with low static and dynamic demand is allowed, regardless of QTc or underlying genotype. For high-risk patients, the implantable ICD offers an effective therapeutic option to reduce mortality.
- b. Short QT syndrome** Short QT syndrome is a very rare but severe condition caused by mutations in one of three genes (KCNH2, KCNQ1 and KCNJ2), leading to a gain in function of the channels and therefore a shortened QT interval. The definitive association between SQTS and familial SD was described by Gaita and colleagues, with a clinical report of two families with SQTS and a high incidence of SCD or paroxysmal AF. Despite this proven link between short QT and SCD, there are no cases of SCD in an athlete with SQTS to date. This is reflected in the fact that acknowledges the limited knowledge of the disease among athletes, advising global restriction of competitive sporting participation until the phenotype is better understood. The ESC document does not make any recommendations on SQTS. Patients with this condition have QT interval duration ≤ 330 ms on ECG in combination with tall, peaked T waves. Patients with SQTS are prone to AF, which may cause symptoms such as palpitations and syncope that warrants investigation, particularly among young athletes. Genetic testing is appropriate in the context of affected family members. Due to the association of SCD among patients with SQTS, ICDs are recommended for the management of this condition. Although anti-arrhythmic medications such as sotalol and procainamide have been proposed as a therapy. the data to support this approach are insufficient at present.
- Recommendations** Competitive sports are not allowed except for those with low static or dynamic demand (**Pelliccia 2005**). Until more clinical data become available, restraint should be used to even allow moderate leisure-time activity, certainly avoiding sudden bursts of activity. As with the LQTS, short-lasting arrhythmic episodes may result in (pre)- syncope: therefore, sports activity in which dizziness leads to increased risk of the patient or others are relatively contraindicated. In many affected individuals, an ICD will be recommended until more specific therapy may become available.

- c. **Brugada syndrome** it is another cardiac ion channelopathy. Like LQT3, it is an autosomal dominant mutation of the SCN5A on chromosome 3 gene present in 30% of cases consisting of syncopal episodes and/or SD among patients with apparent structurally normal heart and a characteristic ECG. It is relatively uncommon in the West in comparison with Southeast Asia. A recent study by Donohue and colleagues in the western USA showed a prevalence of 0.14% (1 in 674) affecting most commonly young and middle-aged men. BrS is diagnosed based on a characteristic ECG pattern with ST segment elevation convex upward followed by a negative T wave in the right precordial leads. However, slight variants of the known mutations produce different ECG patterns. The characteristic changes can often be concealed and provocation testing using antiarrhythmic drugs such as ajmaline or flecainide may be useful to demonstrate the ECG features suggestive of the condition. Antiarrhythmic drugs do not lower the incidence of SD in symptomatic or asymptomatic individuals. ICD is advocated among patients with spontaneous type 1 ECG and symptoms as BrS traditionally carries a poor prognosis (10% death rate per year). **Recommendations** Patients with a BrS (i.e. with a distinctive spontaneous or induced type 1 ECG, symptoms of cardiac arrest or syncope, or inducibility at EPS) most often will receive an ICD and should be restricted from all competitive sports except those with low cardiovascular demand (**Pellica 2005**). Also in others, primary or secondary ICD implantation may be proposed based on a combination of personal or familial history of SD or unexplained syncope, the presence of a spontaneous type 1 ECG, male sex, or inducible ventricular arrhythmias during EPS (**Antzelevitch 2005**). In these, the recommendations for ICD recipients apply. When in patients with a Brugada-like ECG the risk for malignant ventricular arrhythmias and SD is judged to be low based on such a combined evaluation, all noncompetitive sports activity can be allowed. Patients should, however, be convinced that re-evaluation is urgently needed in case of symptoms of hemodynamic impairment (even when a specific). It is also advisable that family data are centralized in referral genetic centers, so that any familial event can be communicated to all patients/physicians concerned and appropriate adjustments to recommendations can easily be disseminated to all family members at risk. Finally, it is unclear at present which recommendations should be made for phenotypically negative family members that have been identified as carriers (by class-1 antiarrhythmic drug provocation or genotyping). It seems prudent to restrict them too from competitive sports but to allow all leisure-time activities with close follow-up.
- d. **Catecholaminergic polymorphic ventricular tachycardia (CPVT)** it is a channelopathy of the endoplasmic reticulum or intracellular channelopathies. It is autosomal dominant or recessive arrhythmogenic condition that occurs in structurally normal hearts and can be fatal. (**Joshi 2005**) A number of genetic mutations have been associated with CPVT. These genes encode proteins responsible for the maintenance of intracellular calcium ion levels, notably cardiac ryanodine receptor proteins and calsequestrin. Increased calcium loading of cardiac myocytes predisposes an athlete to VT or VF when combined with physical or emotional stress. The VT may have a polymorphic appearance or have a bidirectional pattern.

- d. Recommendations** Competitive and even moderate leisure-time sports are formally contraindicated. β -blockers form the therapy of first choice but are not always effective and pose an extra risk when intake is forgotten. Therefore, in many patients an ICD will be advised. When electrocardiographic (stress test) follow-up under treatment shows absence of recurrence, low to moderate leisure-time sports can be performed, with immediate re-evaluation if symptoms recur. In the presence of an ICD, the ICD related recommendations apply.
- e. Idiopathic ventricular fibrillation (IVF);**
- f. Progressive familial heart block type I; progressive “idiopathic” disease of the His-Purkinje system or Lenègre;**
- g. Mixed forms or with overlapped phenotypic aspects:** Brugada disease and variant 3 of congenital LQTS; BrS and Lenègre disease;
BrS and sinus node dysfunction; association of BrS, LQTS and progressive conduction disorder;
- h. Early repolarization Syndrome(ERS)**
- i. J-wave syndrome**
- j. Some sudden infant death syndromes (SIDS)**
- k. Some sudden unexpected nocturnal death syndromes (SUNDS)**

Ventricular Premature Beats (VPBs):

Recommendations Athletes with VPBs and underlying abnormalities should not participate in competitive sports, since even activities with low cardiovascular demand may be associated with important changes in autonomic tone, which could lead to malignant ventricular arrhythmias and SCD. Only when cardiovascular abnormalities can effectively be excluded, when there are no frequent VPBs ($< 2000/24$ h) and no exercise-induced increase of VPB or VBP-related symptoms (without or with treatment), all competitive and leisure-time sports activity are allowed. A yearly follow-up for re-evaluation is advised or earlier on the occurrence of symptoms, even when a specific. In a majority of athletes with frequent VPBs, deconditioning for 3–6 months may result in a substantial decrease in the number of VPBs, which may confirm good prognosis (**Biffi 2004**). Whether this is also true for athletes with proven underlying cardiovascular abnormalities, remains to be confirmed. It is recommended that athletes who after deconditioning remain symptomatic or keep having a clear increase in VPB frequency by exercise (even in the absence of underlying disease) should refrain from competitive sports and only participate in light to moderate leisure-time activity. A 6-monthly follow-up is warranted to exclude progression or the development of symptoms during recreational activity.

Nonsustained or sustained ventricular tachycardia(NSVT) Documentation of more complex NSVT (≥ 3 consecutive beats at ≥ 120 bpm) or SVT (≥ 30 s or requiring earlier cardioversion due to hemodynamic compromise) requires stringent evaluation to exclude underlying cardiovascular disease and to evaluate risk. Only slow idioventricular rhythms (< 100 – 150 bpm) in the absence of structural heart disease are benign and can be approached as outlined for VPB above. Evaluation should include imaging techniques like echo (to rule out dilated, HCM and ARVC, pulmonary hypertension or valve disease), nuclear scintigraphy and coronary angiography (to rule out coronary abnormalities(**Basso 2000**) or premature atherosclerosis) and CMRI (to rule out ARVC). Imaging, however, may not be able to rule out unequivocally mild RV structural changes, which could however confer an ominous prognosis in some cases (**Heidbuchel 2003**) nor underlying inherited arrhythmogenic conditions. Therefore, careful assessment of electrophysiological data is warranted. It will help to categorize the cause, anatomic origin and mechanism of the ventricular arrhythmia. Repolarization abnormalities are very commonly observed on a ECG in a young and athletic population (**Balady 1984**). Their presence therefore is often nonspecific. Negative T-waves in the right precordial leads, however, may herald underlying ARVC (**Pelliccia 2000**) and deep negative T-waves in the left precordial leads must raise suspicion of pathologic LVH(**Corrado 1998**). Hence, when these repolarization abnormalities are seen, a more thorough cardiovascular examination to exclude these pathological entities is warranted. Late activation of the RV may lead to slightly wider QRS complexes in V1 or V2, sometimes with a characteristic epsilon-wave appearance or a prolonged S-wave upstroke in V1 to V3 (≥ 55 ms) (**Nasir 2004**). These findings may point to ARVC.

There should be attempts to document a ECG of the ventricular arrhythmias: a LBBB pattern with negative QRS-complexes in V1, electrical transition between V2–V3 or V3–V4, a QS-complex in aVL and dominant inferiorly directed QRS-complexes is pathognomonic for origin in the RVOT. It is a very common form of idiopathic VT, often described as ‘repetitive monomorphic VT’ (**Buxton 1984**). Similar morphology but with earlier precordial transition may indicate origin in the LVOT. These arrhythmias are not usually associated with heart disease, in which case they have a benign prognosis. A rare clinical entity is VT with a RBB morphology and left axis (rarely right axis). If structural or arrhythmogenic heart disease is ruled out, it is pathognomonic for origin in the left posterior fascicle (‘fascicular VT’, ‘Belhassen VT’) (**Belhassen 1981**). It carries no adverse prognosis unless associated with (pre)syncope during exercise. Polymorphic VT or VT with alternating complexes (‘bidirectional VT’), especially when induced during exercise, carries a high risk of SD. This ECG manifestation may point to an CPVT. Some authors have suggested that in the absence of epsilon-waves on the surface-ECG, late potentials recorded on a signal-averaged ECG may be a sign of delayed (right) ventricular activation and of a proarrhythmogenic substrate (**Jordaens 1994**). Late potentials may be a subtle but definite criterion for ARVC.

Holter recordings have to be performed during periods of intense physical activity and preferably whenever the athlete is performing her or his specific sport activity. The recordings may show abundant unifocal ectopy (even with couplets, triplets or runs), which may point to automaticity as the underlying arrhythmia mechanism, as seen in typical idiopathic RVOT-VT.

Exercise testing with sport-specific and special protocols may result in the induction of arrhythmias. Polymorphic VT during exercise always carries a bad prognosis, since it may point to an underlying inherited electrophysiological disorder or to underlying structural disease (like ARVC or HCM, which may phenotypically not be evident from imaging examinations). Repetitive monomorphic bouts of VPBs, especially with the typical LBBB-type ECG pattern as described above indicating an RVOT origin, reveal an automatic focus as the underlying cause of arrhythmia. Often, these arrhythmias increase in frequency at the beginning of exercise, disappear at peak-exercise and re-appear during recovery. Finally, an EPS may be warranted in selected patients to evaluate the inducibility of Sustained VT, to differentiate supraventricular tachycardia with aberrant conduction, and to assess the arrhythmia mechanism (automaticity or reentry). There are many theoretical data and some cohort evidence that reentry arrhythmias confer a more ominous prognosis since they occur in structurally altered myocardium with the potential for development of more life-threatening arrhythmias, whereas automatic and unifocal arrhythmias may be idiopathic and are usually benign (**Heidbuchel 2003**). Spontaneous VT with rates below 100–150 bpm are generally also focal in nature and carry a good prognosis in the absence of underlying heart disease. The difficulty of drawing a line, however, between ‘idiopathic’ and ‘no underlying structural heart disease’ is exemplified by the fact that a more careful morphological evaluation of non-athletic patients with RVOT revealed, in rare cases, minor structural abnormalities indicative for ARVC (**Globits 1997**). This overlap is even more prominent in athletes who often have cardiac structural adaptations and electrophysiological changes (e.g. repolarization variants) (**Serra-Grima 2000**) as part of the athlete’s heart secondary to training and competition. This overlap is also illustrated by the observation that some athletes with manifest signs of structural abnormalities may, however, present with clearly automatic foci

(and even without inducible reentrant arrhythmias during EPS) (**Heidbuchel 2003**). Recommendations NSVT disqualify for competitive sports except for the particular case when there is absence of any familial antecedents of SD, no indication of any underlying structural pathology, a typical presentation of idiopathic RVOT ectopy or fascicular VT (or another idiopathic form of automatic and slow VT ≥ 150 bpm) with nonsustained bouts of tachycardia (eight to ten or fewer beats), and no symptoms of hemodynamic compromise during exercise. When such patients require drug treatment for suppression, more caution should be used since the extreme conditions of competition can never fully be reproduced during noninvasive or invasive testing. Also in rare cases with a manifest transient cause (like myocarditis or electrolyte disturbances) and after complete resolution is confirmed (including absence of any inducible arrhythmias during exercise or EPS), resumption of competitive sports can only be considered after a 3–6-month period. It should be noted in this regard that there are indications that these patients may remain at higher risk for SD, even after resolution of the transient cause (especially when it is ischemic in origin) (**Wyse 2001**). Prospective studies should be awaited to confirm this, but caution and close follow-up of these athletic patients is advisable in case they want to resume competitive sports. In some athletes implantation of an ICD may be warranted, especially when EPS has shown inducibility of life threatening ventricular arrhythmias in the presence of underlying structural heart disease.

Recommendations for such patients are spelled out below. Competitive sports are not allowed except those with a low cardiovascular demand (like golf, billiards or bowling) (**Pellica 2005**). Therefore, the ICD is no substitute for prohibition from performing competitive or high-intensity leisure-time sports. Idiopathic ventricular arrhythmias (as from RVOT or fascicular VT) and some other automatic VTs are amenable to RFCA, with a reasonable success. The procedures, however, carry a small risk of perforation, thrombo-embolic complications or aortic valve damage. Noninducibility during EPS may preclude ablation, although newer mapping techniques may be able to localize the ablation target in some of these patients (**Joshi 2005**). After successful ablation and absence of any recurrent symptoms during a 6-week to 3-month period, resumption of competitive or leisure-time athletic activity can be permitted in patients without underlying structural disease. Close early follow-up is warranted, however, (every 3 months for the first year, and immediately after recurrence of symptoms) and also later (at least yearly), since some may have underlying slowly progressive cardiac disease which will only manifest itself over time. There are no data to indicate that resumption of athletic activity after successful ablation of reentrant ventricular arrhythmias is safe, since the underlying substrate likely is still present. It seems to be advisable that only light-to-moderate recreational sports are allowed (with close follow-up as mentioned above) but competitive sports are prohibited. In all other patients with documented VT, only light-to-moderate leisure-time activity can be allowed, provided that there is proven arrhythmic control with installed therapy, both based on exercise ECG and long-term ECG recordings (preferably during these sports activities) and that the patients have no symptoms of hemodynamic compromise. Supervised activity as in rehabilitation programs may provide added assurance for these patients (**Vanhees 2004**). Burst physical activity and sports in extreme circumstances (like skiing in unusual circumstances or high altitude) should be avoided given the unpredictable autonomic or electrolyte changes they may provoke. VF/resuscitated SD Unless a clearly

identifiable reversible condition can be defined and treated (like AF with rapid conduction over an AP which is subsequently ablated), many of these athletes will require implantation of an ICD. Recommendations for such patients are spelled out below. In others without definitive guarantee that the resolved transient cause will never recur, competitive sports are contraindicated in any case, given the concern that these patients may remain at higher risk for sudden death, as outlined above (**Wyse 2001**).

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