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Cardiac arrest at rest and during sport activity: causes and prevention

Cristina Basso*, Stefania Rizzo, Elisa Carturan, Kalliopi Pilichou, and Gaetano Thiene

UOC Patologia Cardiovascolare, Azienda Ospedaliera-Università di Padova

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In the Western Countries, cardiovascular diseases are still the most frequent cause of death, which is often sudden. Sudden death (SD) in the young population occurs at a rate of 1/100 000/year and carries a profound social impact both for the young age of the victims and the unanticipated occurrence. Physical effort is a triggering risk factor, in fact SD occurs three times more frequently in athletes than in non-athletes. The screening for sport activity fitness can identify apparently healthy subjects carrying a silent abnormality able to trigger sudden cardiac death during sport activity, thus the fitness screening could be lifesaving. The spectrum of cardiovascular conditions identified at post-mortem examination is quite extensive, and include: coronary, myocardial, valvular diseases, as well as conduction system abnormalities. In 20% of the cases, the heart is normal, and sudden cardiac death is ascribed to ionic channel disease. The diagnosis of cardiomyopathy is possible with the integration of electrocardiogram and echography, thus decreasing significantly the occurrence of SD of athletes in Italy, but early diagnosis of coronary artery disease still remains challenging. The best strategy to further decrease sudden cardiac death during sport activities consists in combining early diagnosis with widespread availability of defibrillators on site.

Introduction

Sudden death (SD) is in 80–85% of cases of cardiovascular origin.[1] Exercise performed regularly and continuously can protect against the risk of SD, but it can increase the risk if there is an occult pathology that is unmasked during the effort.[2]

In a study on the incidence in the Veneto Region of SD in young people and athletes aged between 12 and 35 years, a rate of 1 per 100 000 subjects/year was calculated, and in most cases was not preceded by premonitory signs or symptoms.[2] By analysing the data and dividing it into two groups, athletes and non-athletes, the SD rate was almost three times higher in young athletes (2.3/100 000 vs. 0.9/100 000).

*Corresponding author. Email: cristina.basso@unipd.it

Mechanisms of sudden cardiac death

The physiopathological mechanisms of cardiovascular SD are essentially two: ‘mechanical’, when there is a sudden impediment to blood progression (e.g. cardiac tamponade, pulmonary embolism), and ‘electrical’ due to arrhythmia (ventricular fibrillation, ventricular tachycardia, or asystole), where the substrate can be represented by congenital or acquired pathologies and the triggering event (‘trigger’) is represented by physical exercise, emotions, electrolytic alterations, drug intake, etc. In 90% of SD cases, the mechanism is electrical.[1–3]

Heart disease at risk of sudden death in young people

Aorta

The aorta can tear spontaneously and suddenly during exertion leading to massive bleeding. Young subjects at risk

of SD due to aortic rupture can be hypertensive (main risk factor in adult-advanced age), but more often they are carriers of Marfan syndrome and bicuspid aortic valve with or without isthmic coarctation.[1] Syndrome of Marfan is an inherited autosomal dominant disease due to the mutation of the fibrillin gene,[1] a glycoprotein that plays a crucial role in the interaction between elastic fibres and smooth muscle cells of the media. In a subgroup of patients with bicuspid valves, an 'aortopathy' is associated, so echocardiography is recommended not only for the diagnosis but also for the subsequent monitoring of the ascending aorta to assess progressive dilation and elasticity.

Coronary artery diseases

Coronary atherosclerosis

In the young man, fibro-cellular or fibro-atheroma atherosclerotic plaques are often found, often with a fibrous cap, uncomplicated, achieving a critical stenosis, mostly at the level of the anterior descending branch (*Figure* 1A *and B*). The most likely mechanism at the base of fatal ventricular fibrillation is vasospasm with temporary occlusion and subsequent reperfusion after reopening of the coronary artery, unlike in adults where coronary thrombotic occlusion is most frequent[4] ischaemia often does not alter the ECG at rest and under stress, so the young athlete can achieve sporting fitness certification. Only the use of non-invasive imaging techniques for the study of the coronary artery tree, such as magnetic resonance imaging (MRI) or computerized tomography, can help identify those at risk.

Congenital anomalies of the coronary arteries

The anomalous origin of the coronary artery from the pulmonary trunk is a serious malformation, highly symptomatic from childhood, and exceptionally observed in the young and in the athlete. Other apparently minor malformations, such as the anomalous origin of the coronary artery from the opposed sinus (right coronary artery from the left sinus, left coronary artery from the right sinus), are at risk of SD especially during exertion.[5] The coronary artery, which originates from the wrong sinus, has an acute angle and an intramural anomalous course of the first tract between aorta and pulmonary artery which makes it difficult to sustain the increase in blood flow during exercise with consequent ischaemic episodes, which lead to damage of the myocardium and substitution with fibrotic scar tissue, source of menacing ventricular arrhythmias, and ventricular fibrillations (*Figure* 1C *and D*). The origin of the left coronary artery from the right sinus appears to be the worst condition because the area of ventricular myocardium at risk is wider. This malformation can escape during pre-competitive ECG screening both at rest and under stress, but in the presence of symptoms, such as angina, syncope, or palpitations, exploration of the aortic root with non-invasive methods such as ECO 2D, the MRI, or computed tomography can be of great help.

Cardiomyopathies

The right ventricular arrhythmogenic cardiomyopathy (RVAC) in the experience of the Veneto Region turns out to be the second cause of SD in the young and the first in the young athlete.[1,2] The disease is characterized by tachyarrhythmias originating from the right ventricle as a consequence of cardiomyocytes damage, with phenomena of necrosis or apoptosis, and subsequent fibroadipose substitution (*Figure* 2A *and B*).[6] Genetic investigation has identified the alteration of genes that encode for desmosomal proteins up to 50% of the cases.[7] ECO 2D and MRI can identify the dilatation of the right ventricle, the contractile depression, and aneurysms in the so-called 'triangle of dysplasia'. At the ECG, pathognomonic alterations of the disease can be observed: inversion of the T wave in the right precordial, widening of the QRS (>110 ms), and presence of the epsilon wave. The formulation of diagnostic criteria has allowed the feasibility of the diagnosis and identification of affected patients. In recent years, the left variant of RVAC has become increasingly frequent, which is difficult to diagnose due to the often absence of functional and electrocardiographic alterations, unless advanced imaging techniques with tissue characterization are used (*Figure* 2C *and D*).

Hypertrophic cardiomyopathy (HCM) is characterized by mostly asymmetric hypertrophy of the left ventricle, usually anteroseptal, more rarely apical, not due to ventricular pressure overload. In the USA, it has been identified as the main cause of SD in athletes, while in Italy it is almost always identified in the screening with consequent non-suitability of the athletes affected.[8] The resting ECG is easily suspected when the QRS voltage increase occurs, the inverted T waves in the left precordial, the Q waves. These alterations are not specific for the HCM, and the ECO 2D is obligatory, as the protocol for the suitability to the sport activity demands. Hypertrophic cardiomyopathy is an inherited autosomal dominant disease and genetic studies have identified mutations in genes coding for proteins of the contractile apparatus to the point that HCM is called 'sarcomeric disease'. The HCM is highly arrhythmogenic and the arrhythmic substrate resides in cardiac hypertrophy, myocardial disarray, and post-ischaemic scars that are created following the compression of the small intramural arteries due to the increase in diastolic intramyocardial pressure and reduced coronary reserve.[9]

Myocarditis is an inflammatory cardiomyopathy causing SD in about 10% of young people. Even a form of focal myocarditis, with preserved pump function, can trigger a fatal ventricular arrhythmia. Respiratory or gastroenteric infections of viral aetiology can lead to myocardial involvement. The aetiological diagnosis can be obtained *in vivo* from endomyocardial biopsies, with the use also of molecular techniques.[1,3] Stress is a trigger for arrhythmias and should therefore be avoided during feverish states.

Diseases of the valves

Arrhythmic SD can occur in conditions of valvular disease such as aortic stenosis and mitral valve prolapse, in the absence of heart failure.[1]

The aortic stenosis in the young usually develops on the bicuspid valve. It is an arrhythmogenic disease to the extent that ventricular hypertrophy due to stenosis of the aortic orifice with systolic overload causes subendocardial ischaemia, with necrosis and scarring, which are aggravated by repeated efforts. Affected patients are easily

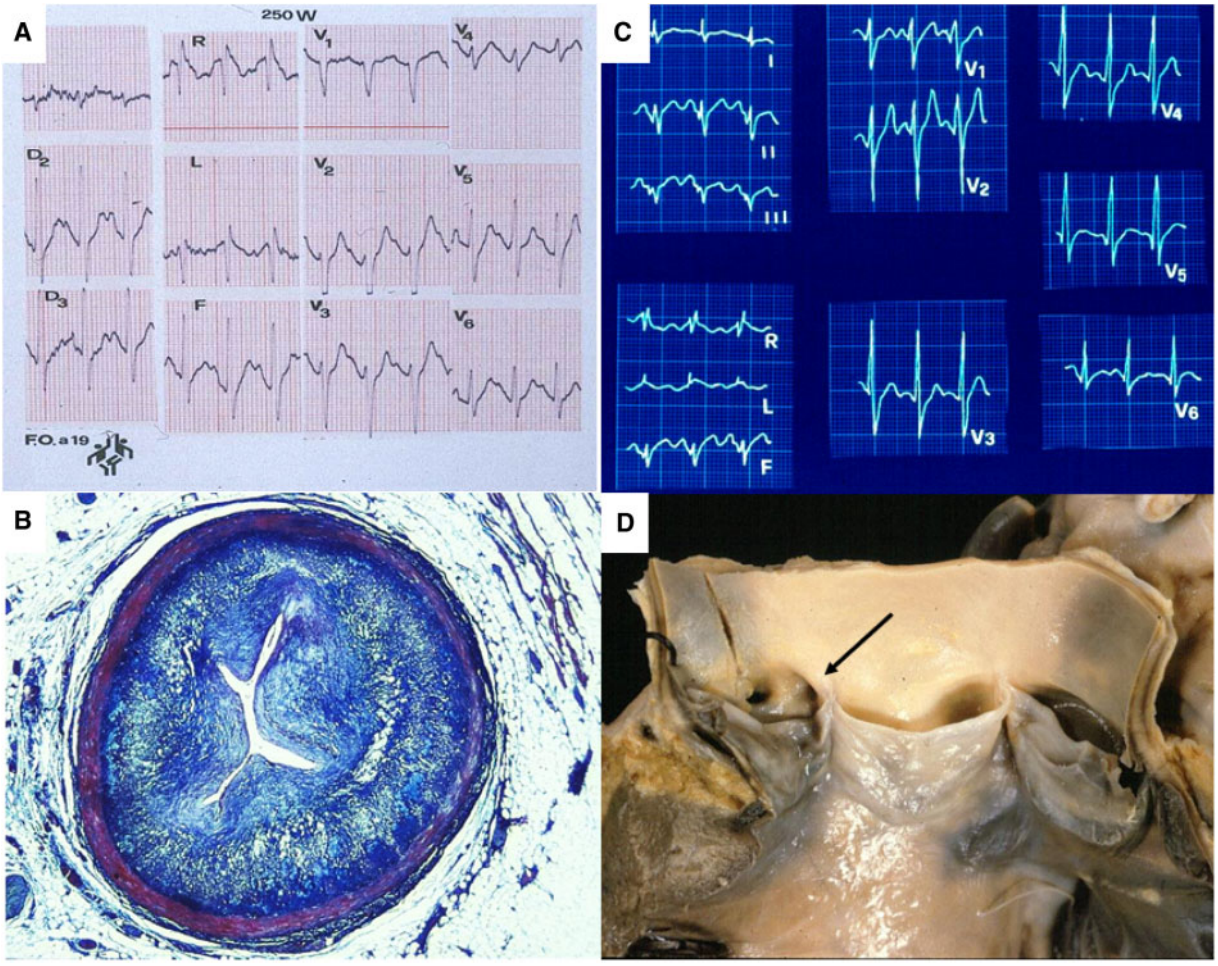

Figure 1 Coronary artery disease causing sudden death under stress in the athlete (negative competitive fitness test). (*A*) Coronary atherosclerosis of the first section of the anterior descending branch. (*B*) Normal effort ECG trace (same patient in *A*). (*C*) Anomalous origin of the right from the left coronary sinus of Valsalva; (*D*) normal effort ECG trace (same patient in *C*).

identifiable by systolic murmurs and therefore recognizable by 2D ECO and consequently considered unsuitable for sports activities.

Mitral valve prolapse is a disease that afflicts young women the most and can remain silent in the absence of valvular incontinence or present with ventricular arrhythmias. Arrhythmic substrates often consist of areas of fibrous substitution at the papillary muscles and of the postero-basal wall, as a result of mechanical damage by traction of the leaflets/cords.[10]

Disorders of the conduction system

A ventricular pre-excitation can be observed, as in Wolff-Parkinson-White syndrome (WPW) where atrioventricular (AV) accessory fascicles occur which bypass the specialized tissue of the normal conduction system. Since the accessory fasciculus consists of ordinary myocardium, this pathology leads to a loss of the normal AV delay, so that an episode of atrial fibrillation can turn into a ventricular fibrillation.[11] These syndromes can be congenital or acquired and lead to SD (43). A short PQ interval with a classic delta wave is observed in ECG in WPW subjects. It is possible to ablate the aberrant fasciculus, interrupting the anomalous AV connection, which may represent the ventricular atrial or atrial ventricular re-entry pathway.

Lenègre's disease is characterized by a progressive fibrosis of the AV junction. It can remain hidden and manifest with an apparently innocent right bundle branch block or it can be sudden and fatal.

Diseases of ion channels

In about 10–20% of juvenile SD, the heart appears to be structurally normal at macroscopic, histological, and ultrastructural investigation and is called unexplained SD or 'mors sine materia'.[1,3] The cause often lies in an electrical defect of the cardiac ion channels and are characterized by very distinct and recognizable clinical pictures *in vivo*. These syndromes have abnormal basal ECG therefore they should be easily diagnosed or suspected. They are hereditary diseases with autosomal dominant transmission and genetic investigations have identified mutations in the genes that encode sodium and potassium channels. The exception is the catecholaminergic syndrome with polymorphic ventricular tachycardia which presents with normal

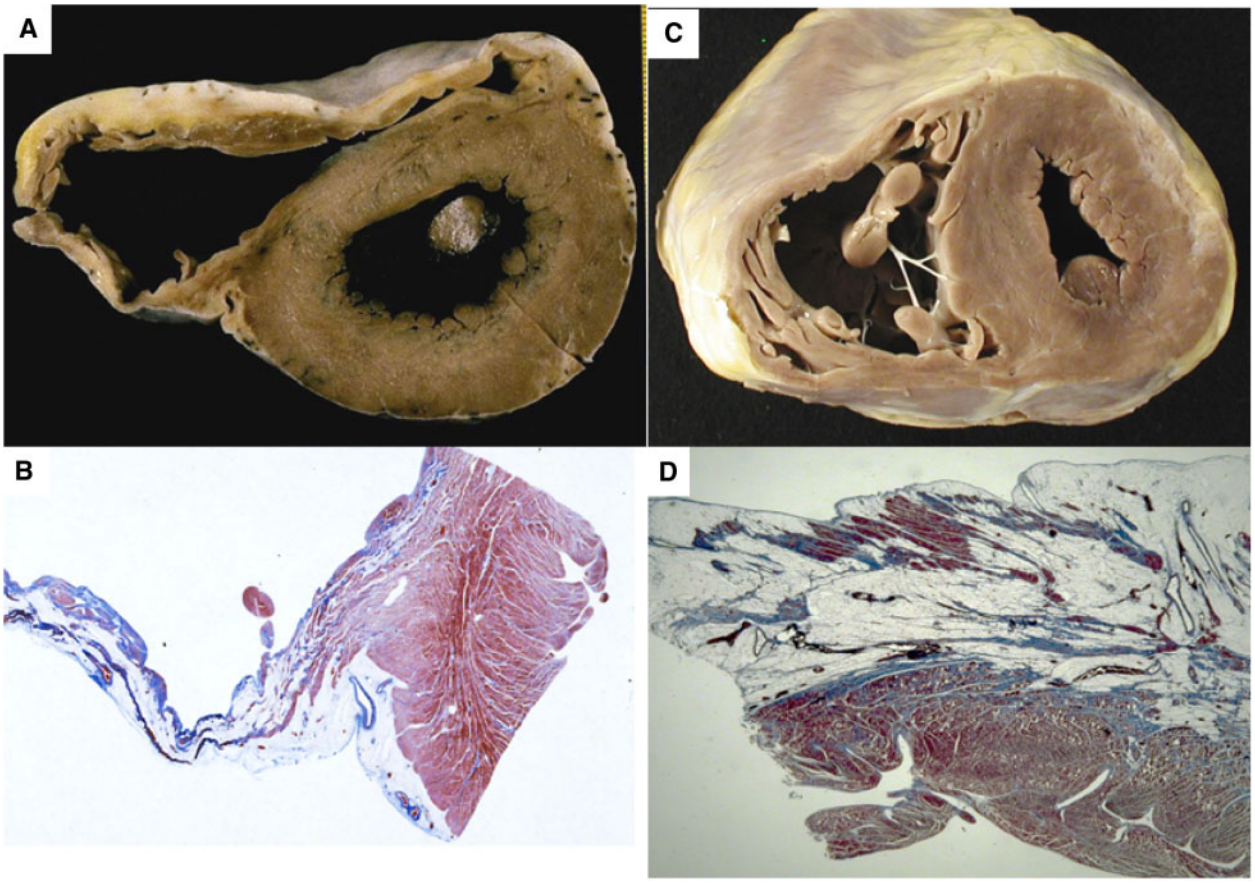

Figure 2 Arrhythmogenic cardiomyopathy of the right ventricle vs. left form. While the identification of the classical variant (*A*, *B*) with transmural fibroadipose substitution and aneurysms, with typical ECG alterations, is today possible at screening for agonistic suitability. The identification of the left forms (*C*, *D*) with subepicardial fibroadiposis, without thinning and aneurysms, and often normal ECG remains difficult.

resting ECG and is characterized by arrhythmias that occur during physical effort or emotional stress when the heart rate exceeds the threshold of 120–130 beats/min. It is a hereditary disease and molecular investigations have identified mutations in the genes that code for calcium receptors, responsible for calcium homeostasis during electromechanical coupling.

Autopsy can be the first opportunity to diagnose ion channel disease by solving unexplained cases of SD.

The use of molecular techniques in autopsy has become necessary to reduce the cases of SD that remain undiagnosed and recently the guidelines for the SD study defining the modality of the study with a sequential approach have been defined by the European Association of Cardiovascular Pathology as well as the correct modalities for collection of samples.[12]

Prevention of sudden cardiac death in young people and athletes

Different methods allow prevention of SD. The external defibrillator, if used promptly within 2–3 min of collapse, can be effective in order to prevent irreversible brain damage. These tools should be made mandatory in all public places (schools, gyms, discos, and playgrounds). Implantable cardioverter-defibrillator (ICD) is usually indicated for secondary prevention, following an episode of life-threatening arrhythmias and syncope. The ICD is able to intervene at the onset of a ventricular fibrillation, delivering an electric discharge, and converting back to a sinus rhythm. Risk stratification is mandatory in these patients to choose the best treatment for SD prevention, up to the use of ICD in primary prevention.

A fairly simple way to prevent SD is to change one's lifestyle, i.e. to avoid physical exertion. Screening for fitness to sport is the only opportunity in the young person to undergo a careful and systematic medical examination, in order to identify asymptomatic or poorly symptomatic subjects. In Italy in 1982, a law was introduced that makes clinical screening mandatory to obtain fitness for sports.[13] As for the cardiovascular system, control is composed of a personal family history, a clinical examination with blood pressure measurement, as well as instrumental investigations, such as resting ECG. If the results are doubtful, 2D echo becomes mandatory. This investigation protocol is quite different from that used in the USA, where only family history and physical examination are usually collected by nurses. In Italy, the SD in athletes with HCM was defeated, with sports disqualification. The same is almost true for RVAD, when the diagnostic criteria are strictly applied. Sudden death in athletes has decreased by 90%, from

4 to 0.4%/100 000 per year in Italy since the introduction times of pre-participation screening and therefore with the preventive diagnosis.[13] It has been suggested that a similar pre-competitive screening protocol should be adopted in other European countries and in North America.

In the field of cardiomyopathies, there remains the problem of the difficult identification of non-ischaemic left scar forms (outcome of previous myocarditis? Left forms of RVAD?) that often present normal ECG or with alterations not yet codified in the diagnostic criteria and with often negative echocardiogram, where the only diagnostic weapon is often the MRI with contrast.[14] The early detection of coronary heart disease, both acquired and congenital, is still almost prohibitive, since these disorders often do not show signs of abnormality during the ECG at rest or under stress. The use of new non-invasive coronary imaging techniques, such as computerized tomography and MRI, could aid in the recognition of these morbid entities and prevent SD, as well as routine examination of serum cholesterol levels.

Given the variability of existing data in the literature, for an accurate collection of data at international level, it becomes increasingly necessary to adopt a common protocol in the various reference centres.[15]

Conclusions

Many advances have been made in the prevention of SD in young people and athletes. The main cause of SD in young people is of a cardiovascular nature. The effort is the triggering factor, and the SD is triple in athletes vs. non-athletes, and sports disqualification is life-saving in itself. The identification of hidden cardiomyopathies is possible with ECG and echocardiography and has led to a marked decrease in SD in the athlete in Italy. The systematic evaluation of the risk factor for atherosclerosis and disease and non-invasive coronary imaging techniques in selected cases will help to identify young people with hidden coronary artery disease who are still not diagnosed.

Conflict of interest: none declared.

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